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Phosphorus Fluorides

G.I.Drozd

Advances in the chemistry of compounds containing P–F bonds, published during the past three or four years, are surveyed. Methods of synthesising several novel and some previously known products containing phosphorus and fluorine are reported, together with their chemical properties and the results of structural investigations using optical spectroscopy, nuclear magnetic resonance spectroscopy, and electron diffraction. The Review covers recent investigations on the stereochemistry of fluorides of five-coordinated phosphorus, and also problems of the complexing power of P[III] and P[V] fluorides, which have been widely studied during recent years. Progress in the chemistry of the phosphorus fluorides will help to solve such important and continuing problems as the degree of hybridisation and the nature of the phosphorus-substituent bond in five-coordinated phosphorus compounds, the mechanism of chemical reactions involving phosphorus compounds of various coordination numbers, the possibility and the character of interference between substituents, etc. A list of 188 references is given.

CONTENTS

I. INTRODUCTION

In 1965 a review by Schmutzler appeared in the series "Advances in Fluorine Chemistry"[1], which surveyed the main results of investigations on the fluorides of phosphorus varying in coordination, made from the time of Moissan's discovery of phosphorus trifluoride to 1964 inclusive. The present Review is based on work published during 1965–1968, and reflects both the increasing intensity of research in this field and the shift in the centre of attention from fluorides of four-coordinated phosphorus P[IV] to compounds in which the coordination number of phosphorus is either three (P[III]) or five (P[V]). The latter feature depends upon the widespread possibilities of modern physicochemical methods for identifying and investigating structure. This has given the most significant results in the study of the stereochemistry of the molecules PF_5, CH_3PF_4, and $(CH_3)_2PF_3$, for which the previously suggested configuration of a trigonal bipyramid has been quite rigorously confirmed.

II. METHODS OF PREPARATION AND CHEMICAL PROPERTIES

1. Fluorides of Three-coordinated Phosphorus

Phosphorus trifluoride, mixed halides, and fluoride pseudohalides of P[III]. It has recently been proposed to prepare phosphorus trifluoride by double decomposition between the halides $PHal_3$ (Hal = Cl, Br) and salts of hexafluorosilicic acid[2], which are considerably more readily available than the fluorides of arsenic, antimony, lead, and calcium which are usually employed[1].

During this period, however, research workers have paid greater attention not to phosphorus trifluoride itself but to its derivatives XPF_2 (X = I, Br, Cl, CN, NCO, NCS), which open up possibilities for the preparation of interesting new compounds. In particular, immediately after Cavell's reported[3] preparation of phosphorus iodide difluoride by treating *NN*-dimethylphosphoramidous difluoride with hydrogen iodide, publications appeared[4-6] confirming his results and developing the chemistry of phosphorus iodide difluoride. Reaction of the latter with mercury yielded the previously unknown tetrafluorodiphosphine[6], attempts to prepare which from tetrachloro- or tetraiododiphosphine had been unsuccessful[7]. The preparation of tetrafluorodiphosphine was conducted in a vacuum (residual pressure ~50 mmHg), since at higher pressures the initial phosphorus iodide difluoride disproportionates into the trifluoride and the tri-iodide of phosphorus.

Analysis of the mass spectrum of tetrafluorodiphosphine led to the conclusion[6] that the product contained pyrophosphorous tetrafluoride as impurity, which might have been formed by the hydrolysis of tetrafluorodiphosphine:

$$2\,P_2F_4 + H_2O \rightarrow 2\,PHF_2 + F_2POPF_2\,.$$

This compound has been prepared from phosphorus iodide difluoride and copper(I) oxide[6,8]. It is unstable, and at room temperature it decomposes slowly in conformity with the equation

$$F_2POPF_2 \rightarrow PF_3 + (POF)_n\,.$$

Phosphorus iodide difluoride reacts with cuprous cyanide to form phosphorus cyanide difluoride[6]:

$$IPF_2 + CuCN \rightarrow PF_2CN + CuI\,.$$

This compound is stable only below 0°C. Above −20°C it probably undergoes exchange interactions with the more stable phosphorus trifluoride and phosphorus tricyanide.

The previously unknown phosphorus di-isothiocyanate fluoride has been obtained, together with the difluoride $P(NCS)F_2$, by exchange between the tri-isothiocyanate and antimony trifluoride[9]:

$$2\,P(NCS)_3 + SbF_3 \rightarrow F_2P(NCS) + FP(NCS)_2 + Sb(NCS)_3\,.$$

The quite substantial difference in the boiling points reported[9,10] for phosphorus isothiocyanate difluoride indicates that the earlier investigation[10] had dealt not with $P(NCS)F_2$ but with a phosphorus fluoride of greater coordination number—most probably $SP(NCS)F_2$.

Fluorides of the type XPF_2 (where X = Br, I, H) exhibit an interesting peculiarity on reaction with hexafluoroacetone. Unlike most other P[III] derivatives, which form 1 : 2 adducts, in which the coordination number of the phosphorus is five, these fluorides give with hexafluoroacetone 1 : 1 adducts having the structure of phosphorodifluoridous esters of the type $(CF_3)_2CX.OPF_2$.[11] Quite recently Lustig[12] has obtained $(CF_3)_2C(CN)OPF_2$ by the reaction between phosphorus bromide difluoride and hexafluoroacetone in the presence of sodium cyanide. This involves the initial formation of $(CF_3)_2C(CN)O^-Na^+$, which then reacts with $BrPF_2$ to yield the final product.

Phosphorofluoridous amides and esters. Synthetic work in this field is distinguished by a broader study of the chemical properties of derivatives of phosphorofluoridous acids, which previously had hardly been investigated.

An interesting result is obtained from the reaction of phosphorodifluoridous esters and amides with primary amines. In both cases hydrides of P[V] are among the main products[13,14]:

$$XPF_2 + H_2NR \rightarrow XF_2PH(NHR) \quad (X{=}OR,\ NR_2)\,.$$

Nevertheless, the phosphorus-31 nuclear magnetic resonance spectra indicate that no P[V] derivatives are formed in the reactions of amides R_2NPF_2 and esters $ROPF_2$ or $(RO)_2PF$ with alcohols. Only after prolonged heating of an alcohol and a phosphorofluoridous diester do signals from $(RO)_2POH$ appear in the spectra. Amides of phosphorodifluoridous acid react readily with alcohols even at room temperature, to form a series of P[III] derivatives, among which phosphorofluoridous diesters have been identified by their ^{31}P and ^{19}F n.m.r. spectra. When, however, the fluorides $ROPF_2$ are treated with secondary amines, at least three products—an amide R_2NPF_2, a phosphoramidous ester R_2NPFOR, and a diester $(RO)_2PF$—are formed. There are grounds for supposing that this reaction involves the initial formation of hydrides $RO(R_2N)PHF_2$, which at elevated temperatures may break down into R_2NPF_2 and $R_2N(RO)PF$, whereas the formation of diesters $(RO)_2PF$ may be a consequence of subsequent reactions in the phosphoramidous esters $R_2N(RO)PF$ in the multicomponent reaction mixture. The higher stability of hydrides containing an NHR group may be a consequence of intramolecular hydrogen bonding[13,14].

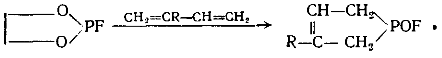
The addition of chlorine to phosphoramidous difluorides was first noted by Ivanova[15]. It has since been established[13,16,17] that chlorine and bromine form with these derivatives liquid 1 : 1 adducts, which in several cases can be distilled in a vacuum, their spectral characteristics indicating that they are P[V] derivatives. Furthermore, dimethylaminodichlorodifluorophosphorane has been obtained by treating the corresponding phosphoramidous difluoride with copper(II) chloride[16]:

$$(CH_3)_2NPF_2 + 2\,CuCl_2 \rightarrow \text{Complex} \rightarrow (CH_3)_2NPF_2Cl_2 + 2\,CuCl\,.$$

The formation of 1 : 1 adducts has been established also in the reactions of diamides $(R_2N)_2PF$ and amides $R(R_2N)PF$ with halogens, but the products are probably ionic, not pentacovalent structures[13,17]. It is obvious that 1 : 1 adducts are formed also in the initial stage of the interaction of P[III] fluorides with cyanogen bromide[13,18].

At temperatures up to 50−60°C amides and esters of phosphorofluoridous acids do not react with simple ketones. Nevertheless, the amides R_2NPF_2 and the diesters $(RO)_2PF$ react exothermally with hexafluoroacetone to form 1 : 2 adducts containing a five-coordinated phosphorus atom. Phosphorodifluoridous esters do not react with hexafluoroacetone under the same conditions[19]. As already mentioned, fluorides of the type XPF_2 (X = I, Br, H) form 1 : 1 adducts with hexafluoroacetone, which have been regarded as phosphorodifluoridous esters[11].

The condensation of cyclic phosphorofluoridous esters with diene hydrocarbons led to the isolation of four-coordinated phosphorus compounds[20], which are probably decomposition products of the initially formed P[V] fluorophospholens:



The first attempt to isolate difluorodihalogenophosphoranes of the type $ROPF_2X_2$ (X = Cl, Br) were unsuccessful[21], the reaction of phosphorodifluoridous esters with halogens yielding instead halide fluorides $XPOF_2$, which have since been proved[13] to be products of the rearrangement of the difluorodihalogenophosphoranes (P[V]):

$$ROPF_2 + Hal_2 \rightarrow ROPF_2Hal_2 \rightarrow HalPOF_2 + RHal \quad (Hal{=}Cl,\ Br).$$

More stable addition products are obtained from halogens and phosphorofluoridous esters containing ArO groups or the phosphorus atom in a five-membered phospholan ring.

Among work on the synthesis of phosphorofluoridous amides and esters themselves we must first note the development of a process for preparing the previously unknown amides $RN(PF_2)_2$, which have been obtained in good yield by the reaction of their chlorine-containing analogues with antimony trifluoride[22]. The same type of reaction has been used to synthesise several new dialkylamides of phosphorodifluoridous acid[15] and cyclic phosphorofluoridous esters[20]. A previously unknown phosphorodifluoridous ester has recently been obtained by Lustig[12] by means of the reaction

$$BrPF_2 + OC(CF_3)_2 + NaOCN \xrightarrow[-CO]{} (CF_3)_2C{=}NC(CF_3)_2{-}OPF_2\ .$$

Difluorophosphines and dialkylfluorophosphines. In 1965 Rudolph and Parry reported the synthesis of the first member HPF_2 of the series of difluorophosphines, by the reaction of phosphorus iodide difluoride with hydrogen iodide in the presence of mercury[23]:

$$F_2PI + Hg + IH \rightarrow HPF_2 + Hg_2I_2\ .$$

Later the same workers noted[6] that difluorophosphine is formed by the reaction of tetrafluorodiphosphine with water or with hydrogen iodide:

$$2\,P_2F_4 + H_2O \rightarrow 2\,HPF_2 + F_2POPF_2$$

$$P_2F_4 + HI \rightarrow HPF_2 + IPF_2\ .$$

Little work has yet been done on the chemical properties of difluorophosphine, although available information shows that they are unusual in the quite high lability of the P–H bond, as indicated both by the above reaction with hexafluoroacetone[11] and by the hydrolysis of difluorophosphine, the latter accompanied by the evolution of hydrogen[23]:

$$PHF_2 + H_2O \rightarrow HOPF_2 + H_2\ .$$

A theoretical yield of hydrogen is not obtained, this being attributed[23] to secondary processes accompanying the cleavage of P–F bonds.

Difluorophosphine is more basic than phosphine and phosphorus trifluoride towards borine. Its adduct $F_2PH.BH_3$ (b.p. 6.2°C) is stable to decomposition up to 25°C at a pressure of ~1 atm.[24] Under comparable conditions $F_3P.BH_3$ and $H_3P.BH_3$ will dissociate into the initial components.

The first alkyl(or aryl)difluorophosphines were described in 1959 by Kulakova and her coworkers[25]. However, owing to a misprint in this paper—the boiling point of $C_6H_5PF_2$ was printed 74–70°, whereas actually it is 74°C at 70 mmHg—the possibility of obtaining these compounds by reaction between their chloro-analogues and antimony trifluoride was open to doubt. A more detailed investigation of the reaction of alkyl(or aryl)dichlorophosphines with antimony trifluoride showed that, under certain conditions, it could be successfully used for the preparation of difluorophosphines. In particular, 80–85% yields of gaseous methyl- and ethyl-difluorophosphines are formed by the reaction of their chloro-analogues with the complex $SbF_3.2C_5H_5N$,[26,27] and high-boiling difluorophosphines can be obtained in 40–60% yield by exchange between the corresponding dichlorophosphines and antimony trifluoride in dialkylaniline in a vacuum[26,27].

The fluorophosphines CH_3PF_2 [29] and $(CH_3)_2PF$ [30] have been prepared by exchange between the chloro-analogues and the highly active potassium fluoride in a vacuum. Sodium fluoride has been successfully used in thiolan 1,1-dioxide medium for the preparation of $C_6H_5PF_2$.[31]

Fluorinated phosphines can be obtained also by the elimination of hydrogen fluoride from the hydrides $RPHF_3$ [26,32] and R_2PHF_2.[33] Better results are given by heating the monohydride aryltrifluorophosphoranes with potassium fluoride[26,32], whereas alkyldifluorophosphines could not be obtained in this way[26]. The elimination of hydrogen fluoride from unsubstituted alkyltrifluorophosphoranes and dialkyldifluorophosphoranes can be accomplished by means of tertiary amines[26,33], but the yields of the final compounds are low, since the reaction is accompanied by secondary processes.

In assessing existing methods for the preparation of fluorophosphines, we note that, in order to obtain gaseous compounds, it is advisable to use the reaction of chlorophosphines with the complex $SbF_3.2C_5H_5N$, which requires only simple apparatus and ensures high yields of the final products. For the preparation of high-boiling fluorophosphines it is more convenient to use the reaction between chlorophosphines and sodium fluoride in thiolan 1,1-dioxide, since in this case the purest fluorophosphines are obtained.

The study of the chemical properties of alkyldifluorophosphines has revealed that the reaction of three-coordinated phosphorus fluorides with reagents of the type H–X (where X = NHR, OR, F, Cl) may yield hydrides containing five-coordinated phosphorus[27,30,34-42]. The resulting hydrides $RPHF_2X$ vary greatly in thermal stability depending on the structure of the radical X. In particular, the hydrides $RPHF_2NHR$ [37,38], $RPHF_2OR$ [34-36], and $RPHF_3$ [39,40] can in several cases be distilled even at atmospheric pressure, whereas the hydrides in which X = NR_2, Cl [42] possess far lower thermal stability. Formation of the hydride $CH_3PHF_2SC_2H_5$ in a mixture of CH_3PF_2 and C_2H_5SH could not be detected at temperatures between −30° and +20°C by means of the ^{31}P n.m.r. spectra[41].

Both alkyl- and aryl-difluorophosphines add chlorine and bromine to form alkyl(or aryl)difluorodihalogenophosphoranes RPF_2Hal_2, which are extremely unstable even below 0°C, with a tendency to intermolecular exchange of ligands[13]. With rise in temperature the exchange processes become more intense, so that it is possible to isolate from the reaction mass alkyl(or aryl)tetrafluorophosphoranes and crystalline products approximating closely in composition to alkyl(or aryl)fluorotrihalogenophosphoranes[13,17].

Alkyl(or aryl)phosphonofluoridous amides and O- and S-esters. Compounds of this type have been described quite recently, and their chemical properties have not yet been adequately studied. The most detailed investigations have been made on alkyl(or aryl)phosphonofluoridous amides, rather less work has been done on O-alkyl alkylphosphonofluoridites, and the *S*-alkyl analogues of the latter have been the least studied.

It has been noted above that at low temperatures alkyldifluorophosphines form with secondary amines the hydrides $RPHF_2NR'_2$ [42], which, with rise in temperature to 50–60°C in the presence of excess of the amine, eliminate hydrogen fluoride to give 40–60% yields of *NN*-dialkylamides of alkylphosphonofluoridous acids. The same compounds can be obtained by treating the amides $RPClNR'_2$ [38,43] with antimony trifluoride or pentafluoride in an inert solvent (ether, benzene), but the results were more satisfactory when this exchange interaction was accomplished in a dialkylaniline, the products containing phosphorus and fluorine being distilled off under a vacuum[38]. Prolonged heating of the hydrides $RPHF_2NHR'$ with tributylamine gives 10–15% yields of monoalkylamides of alkylphosphonofluoridous acids[44]. The single example has also been reported of the synthesis of the *NN*-dibutylamide of methylphosphonofluoridous acid from methylchlorofluorophosphine and dibutylamine[38]. Most of the above reactions are suitable also for the synthesis of arylphosphonofluoridous amides. However, it has been noticed[28] that, although the products of the interaction of aryldifluorophosphines with secondary and even with primary amines contain signals from arylphosphonofluoridous amides in their ^{31}P n.m.r. spectra, vacuum distillation enables only their adducts with hydrogen fluoride to be isolated (the structure of the latter was not investigated).

Amides of alkyl(or aryl)phosphonofluoridous acids are relatively stable compounds: in sealed ampoules they can be kept for several months without any signs of change in structure. In air the substances are slowly oxidised to the corresponding alkyl(or aryl)phosphonofluoridic amides. Prolonged heating with antimony trifluoride oxidises them to alkyl(or aryl)trifluoroaminophosphoranes[38]. Like the phosphorofluoridous amides they form liquid 1 : 1 adducts with chlorine and bromine, which as a result of intermolecular exchange of ligands yield the trifluorophosphoranes $RPF_3NR'_2$, and on hydrolysis form the amides $RPOFNR'_2$ [17,45]. Hydrogen chloride causes rupture of the P–N bond in alkyl(or aryl)phosphonofluoridous amides with the formation of alkyl(or aryl)chlorofluorophosphines[27,38,46]. With α-diketones the alkylphosphonofluoridous amides form 1 : 1 products, which on the basis of spectral investigations are regarded as dioxophospholens containing a five-coordinated phosphorus atom[47].

O-Alkyl (or aryl) alkylphosphonofluoridites were first reported in 1968.[35,41] They can be obtained by—(1) treating the hydrides $RPHF_2OR'$ with ammonia or a tertiary amine[35,41], (2) the reaction of alkyldifluorophosphines with sodium alkoxides[48], or (3) exchange interaction between alkylphosphonochloridous esters and antimony trifluoride[48]—but in all cases the yields are low, since the reactions are accompanied by secondary reactions. The purest products are formed from difluorophosphines and sodium alkoxides[48].

Alkylphosphonofluoridous esters are oxidised comparatively easily by oxygen, and add sulphur to form the corresponding phosphonofluoridates[48]. In the presence of alkyl halides[49] or of halogens[50] they undergo a Michaelis–Arbuzov type of rearrangement, with the formation of dialkylphosphinic fluorides and alkylphosphonofluoridic halides respectively. Like other compounds containing a three-coordinated phosphorus atom, alkylphosphonofluoridous esters react with trifluoromethyl azide to form phosphazo-compounds $R(R'O)PF:NCF_3$.[51]

The only *S*-alkyl alkylphosphonofluoridite known at present has been obtained by the reaction of methyldifluorophosphine with butanethiol in the presence of triethylamine[52].

Complex compounds containing fluorides of three-coordinated phosphorus as ligands. In the general development of the chemistry of complex compounds comprehensive investigations have been made during recent years on a series of complexes containing fluorides of three-coordinated phosphorus as ligands. Methods of preparation, chemical and physical properties, structure, and spectroscopic results, as well as theoretical aspects of the problem of transition metal–PF_3 (ligand) complexes, have been discussed in a review by Kruck[53], who covered work published up to 1967 inclusive. Schmutzler's review[1] considers the same aspects of the chemistry of complex compounds containing other phosphorus-containing ligands as well as the trifluoride. We recommend that the reader, who wishes to be fully informed on this research, refer first to these two reviews[1,53], and the small amount of work not covered by them will be discussed below.

To estimate the electron-donor capacity of difluorophosphine Rudolph and Parry[24] studied its reaction with diborane to form the complex $HPF_2.BH_3$, which does not decompose below 25°C. The same complex can be obtained by substituting HPF_2 for the phosphorus-containing ligand in the complexes $F_3P.BH_3$ and $H_3P.BH_3$. Substitution of the PF_3 ligand takes place even between −78° and −45°C, whereas replacement of the PH_3 ligand requires considerably more severe conditions. From these results it was concluded[24] that HPF_2 is more basic than PF_3 and PH_3 towards the Lewis acid BH_3. This fact was explained on the hypothesis that difluorophosphine contains an intramolecular hydrogen bond (FHF interaction).

Tetrafluorodiphosphine reacts at 25°C with diborane to form the complex $P_2F_4.BH_3$. At room temperature this decomposes slowly in conformity with the equation[54]

$$F_2P{-}PF_2\cdot BH_3 \rightarrow F_3P\cdot BH_3 + (PF)_n,$$

Deewer and Ritter[55] have recently been able to obtain the relatively stable complex $B_2H_4(PF_3)_2$ by the reaction of B_3H_7 with PF_3. The reaction was conducted in dimethyl ether at −15°C under pressure (35 atm). The adduct $B_3H_7.O(CH_3)_2$, formed initially, then reacted with PF_3 to give diborane–bistrifluorophosphine. Hydrogenation of the latter yielded $BH_3.PF_3$.

Complexes of fluorides of three-coordinated phosphorus with zerovalent nickel NiL_4 are usually obtained from the corresponding phosphorus fluoride and tetracarbonylnickel[1,53,56]. A disadvantage of this method for obtaining NiL_4 complexes is the necessity of isolating them from a mixture of products of all degrees of substitution, which in several cases is a difficult task. A more convenient method in this respect is that proposed by Nixon, who prepared several such complexes by the reaction of π-dicyclopentadienylnickel with fluorides of three-coordinated phosphorus[57]:

$$\pi\text{-}(C_5H_5)_2\,Ni + 4\,X_n\,PF_{3-n} \rightarrow Ni\,(X_n\,PF_{3-n})_4 + (2\cdot C_5H_5)$$
$$X{=}F,\ CCl_3,\ (C_2H_5)_2\,N,\ C_5H_{10},\quad n = 1;\ X{=}CF_3,\ n = 1.\ 2$$

In order to prepare $Ni(PF_3)_4$ and $Pd(PF_3)_4$ Kruck et al.[58] used the direct reaction of the metals with phosphorus trifluoride in the presence of iodine as catalyst. Under the same conditions platinum gives only traces of $Pt(PF_3)_4$ with phosphorus trifluoride. When cobalt was treated under pressure with a mixture of phosphorus trifluoride and hydrogen, the hydride $HCO(PF_3)_4$ was obtained.

A large number of complexes of the type $Ni(CO)_nL_{4-n}$ (n = 0–3), $Mo(CO)_3L$ [$L = RPF_2$, $ROPF_2$, R_2NPF_2, $(RO)_2PF$, R_2PF, $R(R_2N)PF$, $(R_2N)_2PF$], and $Mn_2(CO)_n(PF_3)_{10-n}$ (n = 7–9) have been obtained by replacing carbonyl groups in the complexes $M(CO)_4$ (M = Ni, Mo) and $Mn_2(CO)_{10}$ by the appropriate phosphorus-containing ligands[56,57,59–61].

2. Fluorides of Four-coordinated Phosphorus

Phosphoryl fluoride, mixed halides and fluoride pseudohalide, phosphorofluoridic esters, and their derivatives. Fluorides of the type ZPF_nX_{3-n} (where Z = O, S; X = Cl, Br, NCO, NCS; n = 1–3) are usually obtained by double decomposition between ZPX_3 and the metal fluorides[1]. Phosphoryl and thiophosphoryl fluorides can also be obtained by the reaction of P_2O_5 and P_2S_5 with CaF_2, SF_4, HF, or IF_5.[1] These methods have been somewhat developed during recent years. In particular, the possibility has been reported of using fluorosilicates in the exchange reaction with the halides $ZPHal_3$ (Z = O, S) in order to obtain phosphoryl and thiophosphoryl fluorides. In view of the accessibility of the starting materials, this method can probably be used on an industrial scale. A 40% yield of phosphoryl fluoride has been obtained by heating a mixture of P_2O_5 and NF_3 (1 : 2) in a nickel autoclave to 480°C. However, the reaction is complicated by secondary processes leading to the formation of $NOPF_6$.[62]

Useful results have been obtained in the search for new methods of synthesising halide fluorides POF_2Hal (where Hal = Cl, Br), which will be convenient in laboratory practice. All three new reactions which can be used to obtain these compounds provide good yields and require only simple apparatus, so that the choice of method of synthesis in the laboratory may be governed merely by the availability of particular starting materials:

$$(1)\quad ROPF_2 \xrightarrow{Hal_2} OPF_2Hal + RHal\ ^{21}$$

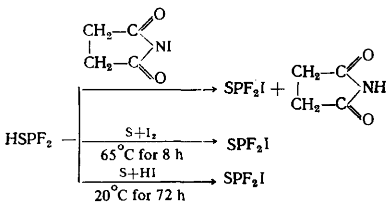
$$(2)\quad F_2POOOPF_2 \xrightarrow{PHal_5\ \text{или}\ MHal_3} OPF_2Hal\ ^{63}\quad (Hal{=}Cl,\ Br;\ \ M{=}Al)$$

$$(3)\quad HOPOF_2 \xrightarrow{PHal_5} OPF_2Hal + OPHal_3 + HHal\ ^{63}\ .$$

An attempt to prepare $OPIF_2$ by reaction (1) was unsuccessful. Nor was this product obtained on treating phosphorodifluoridic amides with hydrogen iodide. Although this compound is probably formed in the initial stages, only phosphorodifluoridous acid can be isolated, which, like $HSPF_2$ obtained in a similar manner, contains a four-coordinated phosphorus atom[64],[65]:

$$ZPF_2(NR_2) + 3\,HI \rightarrow ZPF_2H + R_2NH\cdot HI + I_2\quad (Z{=}O,S)\,.$$

Charlton and Cavell[66] have since reported that $SPIF_2$ can be obtained by treating phosphorodifluoridothious acid with the following reagents:



Thiophosphoryl iodide difluoride, unlike PIF_2, is thermally stable, and can be distilled at atmospheric pressure almost without decomposition. Only 5% of the substance had decomposed after the sample had been heated at 150°C for 4 days[66].

Treichell and his coworkers[67] reported that phosphorodifluoridous acid is formed also as a result of interaction between tetrafluorophosphorane and glass.

The chemistry of pseudohalide fluorides of P[IV] has been considerably extended during recent years. Roesky[63],[68-70] investigated the chemical properties of the tetrafluoride of pyrophosphoric acid, and found a convenient method of synthesising OPF_2NCS, $OPF(NCO)_2$, and OPF_2NCO, which consisted in reaction of the tetrafluoride with potassium isothiocyanate and isocyanate respectively. It was found that phosphoryl di-isothiocyanate fluoride is formed by disproportionation of the initially formed OPF_2NCS:

$$F_2POOOPF_2 \xrightarrow[25^\circ C\ \text{for}\ 12\ h]{KNCS} OPF_2(NCS)\quad (\text{yield } 50\%)$$

$$2\,OPF_2(NCS) \xrightarrow[65^\circ C\ \text{for}\ 1\ h]{} OPF(NCS)_2 + OPF_3.$$

Treatment of thiophosphoryl tri-isothiocyanate with antimony trifluoride at elevated temperatures yields thiophosphoryl fluoride isothiocyanates[9],[68]:

$$SP(NCS)_3 + SbF_3 \rightarrow SPF_2(NCS) + SPF(NCS)_2 + Sb(NCS)_3$$

and phosphoryl fluoride isocyanates have been obtained[71] by the reaction

$$OPCl(NCO)_2 \xrightarrow{SbF_3} OPF(NCO)_2 + OPF_2(NCO)\,.$$

An interesting method for obtaining OPF_2NCO, consisting in the reaction at elevated temperatures of silicon tetraisocyanate with phosphoryl trifluoride, has been proposed by Glemser and his coworkers[72], and a good yield of the di-isothiocyanate $SPF(NCS)_2$ is given by the reaction between $SPFCl_2$ and potassium isothiocyanate[73].

It should be noted that the boiling point given in Ref. 9 for SPF_2NCS is identical with that reported previously[10] for PF_2NCS, so that doubt is cast on the three-coordinated structure of the latter compound.

The new fluorides OPF_2OSO_2F and $OPF(OSO_2F)_2$, which are essentially mixed anhydrides of fluorosulphuric acid and the corresponding acids of phosphorus, have been obtained by heating $OP(OSO_2F)_3$ to 100°C for 2 h.[74]

Investigation of the chemical properties of P[IV] fluoride pseudohalides has shown that they react with alcohols and amines primarily at the NCO or NCS group[71],[73]:

$$OPF(NCO)_2 \;-\!\!\left[\begin{array}{l} \xrightarrow{ROH} OPF(NHCOOR)_2 \\ \xrightarrow{RNH_2} OPF(NHCONHR)_2 \end{array}\right.$$

$$RO(S)PF(NCS) \xrightarrow{RNH_2} RO(S)PF(NHCSNHR)\,.$$

NN'-Dialkoxy(or aroxy)carbonylphosphorodiamidic fluorides are able to react further with alcohols and phenols to give the corresponding phosphorodiamidate esters.

Phosphoryl difluoride isocyanate reacts similarly to the monofluoro-derivative with alcohols and amines. The resulting difluorides $OPF_2NHCONHAr$ on treatment with phosphorus pentachloride form *N*-difluorophosphonyl-*N'*-aryl-*C*-chloroformamidines. Similar treatment of OPFClNHCONHAr yields *N*-chlorofluorophosphonyl-*N'*-aryl-*C*-chloroformamidines[75]. These compounds are hydrolysed to phosphoric acid, although phosphorofluoridic acids may be formed at an intermediate stage:

$$ArNHC({=}NPOF_2)Cl + 5\,H_2O \rightarrow ArNH_2\cdot NF + NH_3\cdot NCl + HF + CO_2 + H_3PO_4.$$

Study of the chemical properties of phosphoryl and thiophosphoryl fluorides has shown that they react with alkali-metal fluorides to form salts containing the anions $[PO_2F_2]^-$ and $[PS_2F_2]^-$. The salt KPS_2F_2 can be obtained also, together with potassium hexafluorophosphate, by the reaction between thiophosphoryl chloride and potassium fluoride[76]:

$$2\,MF + 2\,ZPF_3 \rightarrow MPZ_2F_2 + MPF_6\quad (M{=}Cs,\ K;\ Z{=}O,\ S)$$

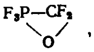
$$8\,KF + 2\,SPCl_3 \rightarrow KPS_2F_2 + KPF_6 + 8\,KCl\,.$$

The caesium salt $CsPS_2F_2$ has been used for the preparation of $(C_6H_5)_4AsPS_2F_2$ and $[(C_6H_5)_3P]_2NPS_2F_2$. Onium compounds of nitrogen, phosphorus, and arsenic containing the anion $[POSF_2]^-$ can be obtained by the reaction[77]

$$SPF_3 + (R_3R'Z)OH \rightarrow [R_3R'Z]^-[POSF_2)^-\quad (Z{=}N,\ P,\ As).$$

Ammonium salts containing the anions $[POSF_2]^-$ and $[PO_2SF]^{2-}$ have been obtained by treating with hydrogen fluoride salts containing the anions $[POSNH_2]^-$ and $[PO_2SNH_2]^{2-}$.[78] In water P_4S_{10} reacts with sodium fluoride[79] to form a salt containing the doubly charged anion $[S_2PF-S-PS_2F]^{2-}$.

An interesting reaction takes place between phosphoryl fluoride and difluorocarbene. The latter acts as both reducing and fluorinating agent, first adding to the P=O bond and then forming OCF_2 and PF_3 or F_4PCOF. It is assumed[80] that the latter compound is formed by migration of a fluorine atom from the carbonyl carbon to the phosphorus atom in the initially formed trifluorophosphorane



accompanied by cleavage of the P–O bond.

Among work on phosphorofluoridates the greatest interest attaches to the synthesis of the silyl esters and to the study of their chemical properties. Bistrialkyl(or aryl)-silyl phosphorofluoridates have been obtained by the reaction between silver phosphoromonofluoridate and the corresponding chlorosilanes[81]:

$$2\,R_2R'SiCl + Ag_2PO_3F \rightarrow (R_2R'SiO)_2POF + 2\,AgCl.$$

An analogous type of reaction has been used for the synthesis of silylene diphosphorodifluoridates[82]:

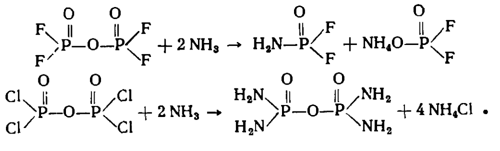
$$RR'SiCl_2 + 8\,NH_4PO_2F_2 \rightarrow RR'Si\,[OP(O)F_2]_2 + RR'Si\,[OP(O)F_2]\,F + RR'SiF_2.$$

It is interesting that with alkali-metal alkoxides silylene diphosphorodifluoridates yield salts of phosphorodifluoridic acid. The hydroloysis of silyl phosphorofluoridates is accompanied by the formation of fluorosilanes, disiloxanes, and $[PO_3F]^{2-}$ anions[81,82].

Several new phosphorofluoridates have been obtained by Roesky by the widely applied reaction of mixed halide fluorides of four-coordinated phosphorus with alcohols or thiols in the presence of tertiary amines[63].

Canadian workers[83] have described a new synthesis of dialkyl phosphorofluoridates based on cleavage of the P–N bond in phosphoroamidates by means of hydrogen fluoride. Phosphorofluoridates $(RO)_2PZF$ (where Z = O, S) can be obtained[84] by the reaction of salts of phosphorodithioic and the corresponding *SS'*-diethyl acids with aromatic and heterocyclic fluorides.

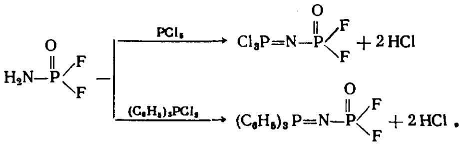
Heating the compound OPF_2OPOF_2 with ammonia leads to the formation of phosphoramidic difluoride and the salt $[NH_4]^+[PO_2F_2]^-$: i.e. the reaction involves cleavage of a P–O bond which has been weakened by the displacement of electrons towards the highly electronegative fluorine atoms[85]. This explanation for the rupture of a P–O bond in OPF_2OPOF_2 appears to be sound, since the compound $OPCl_2OPOCl_2$ reacts with ammonia without cleavage of such a bond[86,87]:



$$F_2P(O){-}O{-}P(O)F_2 + 2\,NH_3 \rightarrow H_2N{-}P(O)F_2 + NH_4O{-}P(O)F_2$$

$$Cl_2P(O){-}O{-}P(O)Cl_2 + 2\,NH_3 \rightarrow (H_2N)_2P(O){-}O{-}P(O)(NH_2)_2 + 4\,NH_4Cl\,.$$

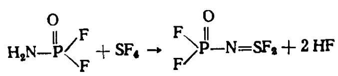
The compound H_2NPOF_2 obtained in this way has been used for the synthesis of phosphazophosphoryl fluorides[85]:



$$H_2N{-}P(O)F_2 \xrightarrow{PCl_5} Cl_3P{=}N{-}P(O)F_2 + 2\,HCl$$

$$H_2N{-}P(O)F_2 \xrightarrow{(C_6H_5)_3PCl_2} (C_6H_5)_3P{=}N{-}P(O)F_2 + 2\,HCl\,.$$

Glemser and his coworkers[88] obtained the compound $OPF_2N:SF_2$ from H_2NPOF_2 and sulphur tetrafluoride:



$$H_2N{-}P(O)F_2 + SF_4 \rightarrow F_2P(O){-}N{=}SF_2 + 2\,HF$$

The previously unknown aroxydifluorophosphazoiminoaryls[89] and alkoxydifluorophosphazosulphonylaryls[90] have been obtained by the reaction of phosphorodifluoridic esters with *N*-chloroarenamines and with dichloroamides of arenesulphonic acids respectively. The P–N bond in the first group of compounds is ruptured by the action of water, to give arenesulphonamides, and treatment with aqueous potassium carbonate yields the salts $ArSO_2NKPFOOR$, which can also be obtained by replacing a fluorine atom by an alkoxy-radical in potassium arenesulphonylamidophosphorodifluoridates[90].

Several new phosphorofluoridates of the type $(CF_3)_2CXOPZF_2$ (X = CN, N_3 and Z = O, S) have recently been obtained by Lustig[12] by the reactions

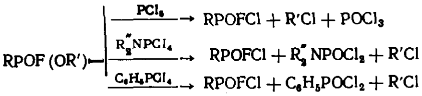
$$ZPF_2Br + [(CF_3)_2C(CN)O]^-\,Na^+ \rightarrow (CF_3)_2C(CN){-}O{-}P(Z)F_2 + NaBr$$
$$(Z{=}O,\ S;\ \text{yield } 60{-}87\%)$$

$$OPF_2Br + [(CF_3)_2CO + NaN_3] \rightarrow (CF_3)_2C(N_3){-}O{-}P(O)F_2 + NaBr\,.$$
$$(\text{yield } 64\%)$$

The above compounds have been characterised by nuclear magnetic resonance using the ^{31}P and ^{19}F nuclei, by their infrared spectra, and by their mass spectra; there is no doubt about their structure.

A recent paper by Shreeve[91] records the preparation of $SPIF_2$ by the addition of sulphur to PIF_2 at 80–90°C (duration of contact of reactants 1 h). The yield of the final product was ~50%, which is extremely surprising in view of the tendency of PIF_2 to disproportionate at elevated temperatures.

Fluorides of four-coordinated phosphorus containing a C–P bond. Here we must first note the development of new syntheses of mixed halides of alkylphosphonic acids and the investigation of their chemical properties. Good yields of CH_3POClF, C_6H_5POClF, and also several previously unknown chloride fluorides have been obtained by the reaction of alkylphosphonofluoridic esters with the chlorides $XPCl_4$ (X = Cl, R_2N, C_6H_5):[92]



$$RPOF(OR') \xrightarrow{PCl_5} RPOFCl + R'Cl + POCl_3$$

$$RPOF(OR') \xrightarrow{R''_2NPCl_4} RPOFCl + R''_2NPOCl_2 + R'Cl$$

$$RPOF(OR') \xrightarrow{C_6H_5PCl_4} RPOFCl + C_6H_5POCl_2 + R'Cl\,.$$

When phosphorus pentachloride is used, the temperature of the reaction mass must be kept between 30° and 40°C, since considerable quantities of the dichlorides $RPOCl_2$ are formed at higher temperatures. Under laboratory conditions the choice of a particular chloride $XPCl_4$ is governed not only by its accessibility but also by the relative boiling points of the phosphorus-containing products formed. In particular, it is inadvisable to use phosphorus pentachloride to obtain chloride fluorides $RPOClF$ whose boiling points are close to that of phosphoryl chloride, which would make it difficult to separate the final products by distillation.

The same workers[92] have used the reaction

$$RPSF(OR') + Cl_2 \rightarrow RPOFCl + SCl_2 + R'Cl$$

to obtain alkylphosphonic chloride fluorides. This probably involves the intermediate formation of the dichlorofluorophosphorane $RPCl_2FOR'$ (as is observed in the reaction of the amides R_2NPSF_2 with chlorine), which, being unstable, splits off R'Cl to form $RPOClF$.

Under the influence of thionyl chloride, phosphorus pentachloride, or phosphorus pentabromide alkylphosphonofluoridic acids, like phosphorodifluoridic acid[63], are able to replace their hydroxyl by Cl or Br, to form the corresponding mixed halides RPOHalF, among which the bromine-containing products can be obtained also by treating alkylphosphonofluoridous esters with bromine[50,92]:

$$\mathrm{RPOF(OH)} \xrightarrow{\mathrm{SOCl_2}} \mathrm{RPOFCl}$$
$$\mathrm{RPOF(OH)} + \mathrm{PBr_5} \rightarrow \mathrm{RPOFBr} + \mathrm{HBr} + \mathrm{OPBr_3}$$
$$\mathrm{RPF(OR')} + \mathrm{Br_2} \rightarrow [\mathrm{RPFBr_2(OR')}] \rightarrow \mathrm{RPOFBr} + \mathrm{R'Br}.$$

On hydrolysis all the fluorides RPOHalF (where Hal = F, Cl, Br) produce initially alkylphosphonofluoridic acids, these being followed by alkylphosphonic acids[50]. The differing activities of the halogen atoms in alkylphosphonic chloride fluorides have been used in the preparation of the previously unknown alkylphosphonisocyanatidic and alkylphosphon(isothiocyanatidic) fluorides[92]:

$$\mathrm{RPOFCl} - \begin{cases} \xrightarrow{\mathrm{NaOCN}} \mathrm{RPOF(NCO)} + \mathrm{NaCl} \\ \xrightarrow{\mathrm{KSCN}} \mathrm{RPOF(NCS)} + \mathrm{KCl}. \end{cases}$$

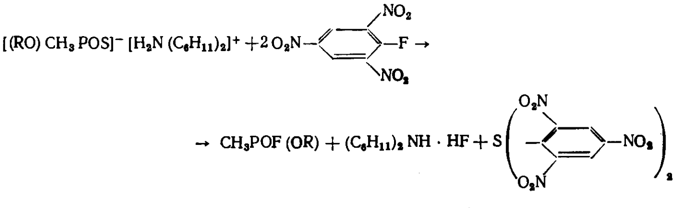
The yield of alkylphosphon(isothiocyanatidic) fluorides exceeds 50% in this reaction, whereas, among the considerably more unstable derivatives containing an isothiocyanato-group, only $\mathrm{CH_3PO(NCS)F}$ has been isolated, in 10% yield.

Trichloromethylphosphonisocyanatidic fluoride has been obtained by double decomposition between $\mathrm{CCl_3PO(NCO)Cl}$ and antimony trifluoride. The use of excess of the latter reagent makes it possible to conduct the reaction so that it yields exclusively trichloromethylphosphonic difluoride[93] (the latter is formed as a byproduct in the reaction of $\mathrm{Cl_3CPCl_4}$ with antimony trifluoride).

Investigation of the chemical properties of the alkylphosphonisocyanatidic and alkylphosphon(isothiocyanatidic) fluorides has shown that their reactions with primary amines and alcohols involve firstly the NCO and NCS groups[92,93]:

$$\mathrm{RPOF(NCO)} - \begin{cases} \xrightarrow{\mathrm{ArNH_2}} \mathrm{RPOF(NHCONHAr)} \\ \xrightarrow{\mathrm{R'OH}} \mathrm{RPOF(NHCOOR')} \end{cases}$$
$$\mathrm{RPOF(NCS)} \xrightarrow{\mathrm{ArNH_2}} \mathrm{RPOF(NHCSNHAr)}.$$

An interesting synthesis of alkyl methylphosphonofluoridates has been suggested recently by Boter and Berg[94], who used the reaction between the ammonium salts $[(\mathrm{C_6H_{11}})_2\mathrm{NH_2}]^+[\mathrm{CH_3PSOOR}]^-$ and fluorotrinitrobenzene:



This method has been successfully used[94] to prepare t-butyl methylphosphonofluoridate, which is difficult to obtain by other methods, since it decomposes appreciably even at room temperature.

Several new phosphonofluoridates containing P–O–El bonds (where El = Si, Ge, As) have been obtained by the reaction of methylphosphonic difluoride with oxides of the type $\mathrm{R_nEl{-}O{-}ElR_n}$.[95]

3. Fluorides of Five-coordinated Phosphorus

Phosphorus pentafluoride and the mixed halides $\mathrm{PHal_nF_{5-n}}$ ($n = 1-4$). Phosphorus pentafluoride is usually obtained[1] by double decomposition between the pentachloride and such fluorides as $\mathrm{AsF_3}$, HF, AgF, and $\mathrm{C_6H_5COF}$. In the laboratory it is convenient to use the reaction between phosphorus pentachloride and antimony pentafluoride, which guarantees a relatively high yield of the final product[13]. The recently patented[2] preparation by treating phosphorus pentachloride with salts of hexafluorosilicic acid is evidently a promising method for industrial application.

Phosphorus trifluoride is readily oxidised[1] to the pentafluoride by elementary fluorine, molybdenum hexafluoride, and $\mathrm{O_2F_2}$. Lustig showed[96] that difluorohydrazine also reacts under comparatively mild conditions (room temperature for 17 h) with phosphorus trifluoride to form the pentafluoride. It is interesting that phosphoryl fluoride can also be converted into phosphorus pentafluoride by the action of difluorohydrazine:

$$\mathrm{PF_3} + \mathrm{N_2F_2} \rightarrow \mathrm{PF_5} + \mathrm{N_2}$$
$$\mathrm{OPF_3} + \mathrm{N_2F_2} \rightarrow \mathrm{PF_5} + \mathrm{N_2} + \mathrm{O_2}.$$

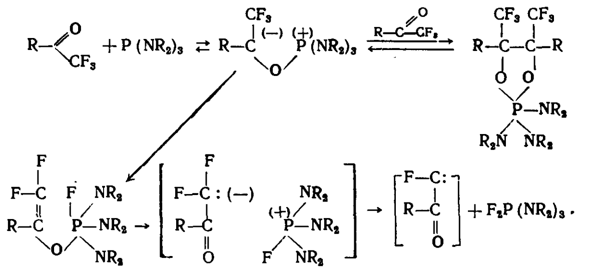
Among the mixed halides $\mathrm{PHal_nF_{5-n}}$ those in which n has the values 1 and 4 have been the least studied. Only in 1965 did Carter and Holmes[97] obtain $\mathrm{PClF_4}$ by the reaction of $\mathrm{PCl_2F_3}$ with antimony trifluoride. Phosphorus chloride tetrafluoride is a gas having an extrapolated boiling point of –43.4° and a melting point of –132°C. When kept at room temperature, it slowly decomposes to form a solid deposit on the walls of the vessel together with gaseous phosphorus pentafluoride and phosphorus dichloride trifluoride. It has since been shown[13,98] that $\mathrm{PClF_4}$ and $\mathrm{PBrF_4}$ can be obtained from dialkylaminotetrafluorophosphoranes and the corresponding hydrogen halides. It has not proved possible to obtain $\mathrm{PIF_4}$ by this method.

Phosphorus tetrachloride fluoride was first obtained by Kolditz[99] by the vacuum sublimation of $[\mathrm{PCl_4}]^+[\mathrm{PF_6}]^-$. The product exists in two forms—covalent and ionic $[\mathrm{PCl_4}]^+\mathrm{F}^-$—and the former can be converted into the latter merely when allowed to warm to room temperature from –40° to –50°C, at which the covalent form is preserved for quite a long time. The compound was obtained directly in the ionic form by Kesavadas and Payne[100] by the gas-phase reaction of phosphorus trichloride with fluorine in nitrogen. The structure $[\mathrm{PCl_4}]^+\mathrm{F}^-$ is supported by X-ray examination.

Many papers have appeared during recent years on the donor–acceptor properties of phosphorus pentafluoride and some of its derivatives. Investigation of the reaction of the pentafluoride with secondary amines has confirmed the initial formation of 1 : 1 adducts, which at high temperatures yield dialkylaminotetrafluorophosphoranes[101]. With excess of the secondary amine bisdialkylaminotrifluorophosphoranes can also be obtained[13,101]. The original conclusion reached by Brown and his coworkers[102], that only bisdimethylaminotrifluorophosphorane can be obtained in this way, is incorrect, since the corresponding bisdiethylamino-derivative has been obtained by heating a mixture (1 : 4) of phosphorus pentafluoride and diethylamine from –180° to 110–130°C.[13]

As a consequence of the sharp decrease in electron-acceptor power on passing from phosphorus pentafluoride to bisdialkylaminotrifluorophosphoranes, the latter do not react with secondary amines even at 100–120°C.[13,101] The triaminodifluorophosphoranes which might be expected in this reaction have been obtained in a different way—by treating the amides $(\mathrm{R_2N})_3\mathrm{P}$ with fluorinated ketones[103,104]—the initially formed 1 : 1 adducts being able below 0°C to add a further molecule of the ketone to form dioxophospholans containing a five-coordinated phosphorus atom.

Above 100°C the 1 : 1 adducts undergo reduction and defluorination to yield trisdialkylaminodifluorophosphoranes:



The adducts formed by phosphorus pentafluoride with trimethylamine and acetonitrile, as well as the adducts $AsF_5.CH_3CN$ and $SbF_5.CH_3CN$, are electrically conducting, this being explained[105] by self-ionisation:

$$2AF_5 \cdot L \rightleftarrows AF_4L_2^+ + AF_6^- \quad (A{=}P,\ Sb,\ As).$$

From a study of the ^{19}F nuclear magnetic resonance spectra, however, Tebbe and Muetterties concluded[106] that no appreciable self-ionisation occurs in these systems. Their results seem to be convincing, and the electrical conductivity of the complexes investigated by Kolditz and Rehak was probably due, not to self-ionisation, but to ionisation resulting from the initial formation of an F^- ion (this may be caused by partial hydrolysis of the complexes), which attacks the complexes by an S_N1 or S_N2 mechanism.

Phosphorus pentafluoride forms an adduct with thiolan. Determination of the molecular weight of the adduct has shown that ~ 50% of the pentafluoride is bound into a 1 : 1 complex. The ^{19}F n.m.r. spectrum indicates complete loss of P–F splitting in this complex, which may be due to partial ionisation of the pentafluoride with rapid exchange of ligands between ionised and non-ionised forms[107].

The adducts $(CH_3)_2O.PF_5$ and $(CH_3)_2S.PF_5$ both undergo rearrangement even at room temperature in conformity with the equation[108]

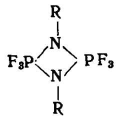
$$3(CH_3)_2O \cdot PF_5 \rightarrow 2[(CH_3)_3O]^+[PF_6]^- + POF_3$$
$$3(CH_3)_2S \cdot PF_5 \rightarrow [(CH_3)_3S]^+[PF_6]^- + [(CH_3)_2SSCH_3]^+[PF_6]^- + PF_3\,.$$

Several properties of the resulting saltlike compounds have been studied[108]. The oxonium compound $[(CH_3)_3O]^+[PF_6]^-$ reacts with acetone and dimethylformamide. It dissolves satisfactorily in acetonitrile, but in time reacts even with this solvent. It reacts with water with the evolution of hydrogen fluoride. The n.m.r. spectra of a rapidly cooled acetonitrile solution indicate the formation of a saltlike product $[(CH_3)_2CN]^+[PF_6]^-$.

Aminofluorophosphoranes and aminofluorohalogenophosphoranes. It has already been noted that dialkylaminotetra- and bisdialkylaminotri-fluorophosphoranes have been obtained by the reaction between phosphorus pentafluoride and secondary amines[101], and trisdialkylaminodifluorophosphoranes by interaction of the corresponding phosphorous amides with $(CF_3)_2CO$ or $CF_3COC_6H_5$.[103,104] Dialkylaminotetrafluorophosphoranes are formed also as a result of intermolecular exchange of ligands in the difluorodihalogenophosphoranes $R_2NPHal_2F_2$ (where Hal = Cl, Br).[13,45] Treatment of the latter with antimony pentafluoride in a solvent while the temperature is gradually raised from –30° to 20–25°C may give 30–70% yields of the dialkylaminotetrafluorophosphoranes[13]. The quite considerable fluctuations in the yield of the final products are probably associated with the thermal stability of the initial dialkylaminodifluorodihalogenophosphoranes, which increases appreciably on passing from the brominated to the chlorinated products, and reaches a maximum in the fluorophosphoranes

(the fluorophosphoranes $R_2NPF_2Cl_2$, where R = CH_3, C_2H_5, C_4H_9, are less stable at corresponding temperatures).

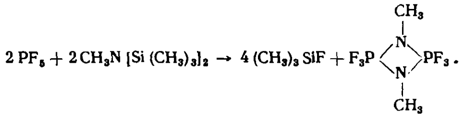
A more detailed investigation of the interaction between phosphorus pentafluoride and primary amines has recently been reported[109]. Compounds $RNHPF_4$ cannot be isolated or even detected here, cyclic derivatives of the type



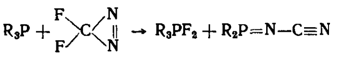
and salts $[RNH_3]^+[PF_6]^-$ being formed. Dehydrofluorination of the adduct $NH_3.PF_5$ by means of triethylamine gives a low yield of phosphonitrile fluoride, the main product being a partly dehydrofluorinated oil.

The reaction of dialkylaminodifluorodihalogenophosphoranes with secondary and primary amines gives the corresponding triaminodifluorophosphoranes[13]. The trifluorophosphoranes $(R_2N)_2PF_3$ or R_2NPF_3NHR' were also isolated, their formation evidently being a consequence of intermolecular exchange of ligands either in the final triaminodifluorophosphoranes during distillation or in the intermediate chlorodifluorophosphoranes $(R_2N)_2PClF_2$ or R_2NPClF_2NHR'. The trifluorophosphoranes R_2NPF_3NHR' can be obtained also by the reaction between dialkylaminotetrafluorophosphoranes and primary amines.

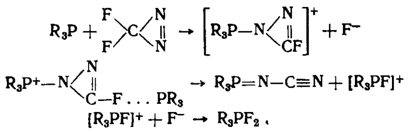
The reaction of phosphorus pentafluoride with silazanes can be successfully used to obtain aminofluorophosphoranes. Dimethyl- and diethyl-aminotetrafluorophosphoranes have been obtained in this way[110,111]. The reaction involves intermediate formation of a 1 : 1 adduct stable at –78°C. At room temperature the adduct breaks down into R_2NPF_4 and R_3SiF. 2,2,2,4,4,4-Hexafluoro-1,3-dimethyl-1,3-diazadiphosphetan can easily be obtained by a reaction of similar type[110]:



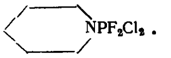
A large number of fluorophosphoranes, including some containing R_2N, RO, RS, and mixed functional groups attached to the phosphorus atom, have been obtained by reaction of the corresponding P[III] derivatives with difluorodiazirine[112]:



where R = Alk, Ar, RO, RS, R_2N. The amide $[(CH_3)_2N]_3P$ reacts the most easily with difluorodiazirine (at –78°C), with the formation of $[(CH_3)_2N]_3PF_2$ (the same worker[112] obtained the product by the reaction of $[(CH_3)_2N]_3P$ with tetrafluorohydrazine). Compounds containing more electronegative substituents react under more severe conditions with difluorodiazirine. The reaction is assumed to have an ionic mechanism, in conformity with the probable scheme



The fact that phosphorodifluoridous amides are able to add chlorine to form adducts, which can be converted by sulphur dioxide into phosphorodifluoridic amides, was first noted by Ivanova[15]. Later work has established that both chlorine and bromine, in a solvent at low temperatures, react with the amides R_2NPF_2 [13,16,17], $(R_2N)_2PF$ [13,17,45], and $RPFNR_2$ [13,17,45] to give 1 : 1 adducts, in most cases liquid and soluble in the usual organic solvents, among which the chlorinated adducts $(CH_3)_2NPCl_2F_2$, $(C_2H_5)_2NPCl_2F_2$, and



have been isolated in the pure state by distillation[13,17]. The phosphorus-31 n.m.r. spectra confirm the pentacovalent structure of the adducts $R_2NPHal_2F_2$ (Hal = Cl, Br), but saltlike structures of the type $[X_2PHalF]^+Hal^-$ are more probable in the case of the adducts $(R_2N)_2PHal_2F$ and $RPHal_2FNR_2$.

All the above addition products can be kept satisfactorily only below 0°C. At room temperature they undergo intermolecular exchange of ligands, with the formation of both mixed fluorohalogenophosphoranes and phosphoranes containing only one halogen. The fluorine-19 n.m.r. spectra have shown[45] that diethylaminodibromodifluorophosphorane forms the bromotrifluorophosphorane $(C_2H_5)_2NPBrF_3$ and the tetrafluorophosphorane $(C_2H_5)_2NPF_4$ as a result of exchange. The adducts $RPHal_2FNR_2$ gradually form trifluorophosphoranes RPF_3NR_2 and probably the halides $RPHal_3NR_2$ even below 0°C. Exchange processes are appreciably accelerated by raising the temperature to 40–60°C, and at 100–150°C phosphorus(III) halides in particular are formed, evidently as a result of redox reactions.

Emeléus and Onak have recently proposed[113] a new synthesis of aminofluorohalogenophosphoranes, consisting in the reaction of P[III] fluorides with compounds containing a nitrogen–chlorine bond. They have obtained the previously unknown fluorohalogenophosphoranes $(CF_3)_2NPClF_3$ and $(CF_3)_2NPCl_2F_2$ by the reaction of *N*-chlorobistrifluoromethylamine with phosphorus trifluoride and phosphorus chloride difluoride.

Several investigations have shown[13,16,17,113] that the hydrolysis of aminofluorodihalogenophosphoranes results in formation of the corresponding phosphorofluoridic amides. The same products result from the interaction of these phosphoranes with carboxylic anhydrides. The reaction of $(C_2H_5)_2NPClF_2$ with ethanethiol in the presence of triethylamine yields the difluorophosphorane $(C_2H_5)_2NPF_2(SC_2H_5)_2$, and interaction of the same difluorodihalogenophosphorane with alcohols in the presence of tertiary amines produces the fairly unstable fluorophosphoranes $R_2NPF_2(OR')_2$.[13] Monitoring both reactions by means of the n.m.r. spectra revealed also partial formation of the amides R_2NPXF_2 (X = O, S), which may be due to rearrangement of the products of the first stage of substitution:

$$R_2NPF_2Cl_2 \xrightarrow{HXR',\ NR'''_3} R_2NPF_2Cl(XR') \rightarrow R_2NP(X)F_2 + R'Cl \quad (X{=}O,\ S).$$

On treatment with antimony trifluoride, adducts of all types form either tetra- or tri-fluorophosphoranes[13]. The same type of interaction has been used[13] for the synthesis of $(C_2H_5)_2NPF_3CN$ from $(C_2H_5)_2NPBrF_2CN$, and Clune and Cohn[18] have isolated $(CH_3)_2NPF_3CN$, formed by the disproportionation of $(CH_3)_2NPBrF_2CN$.

Fluorophosphoranes containing a C – P bond. The most widely used syntheses of fluorophosphoranes containing a carbon–phosphorus bond have been described in Schmutzler's reviews[1,114]. However, immediately after publication of these reviews Treichel and Goodrich proposed[115] a new and extremely promising synthesis of alkyltetrafluorophosphoranes based on the reaction between phosphorus pentafluoride and tetra-alkyl stannates. Yields of 15–19% of methyltetrafluorophosphorane are obtained when the duration of the reaction is 1–2 days. Increasing the time of contact of the initial reactants increases the yield to 60–70%. This synthesis of alkyltetrafluorophosphoranes is attractive in that the initial phosphorus-containing compound used is the readily available phosphorus pentafluoride, not the alkyldichlorophosphines from which alkyltetrafluorophosphoranes are usually obtained.

The reaction of phosphonothionic and phosphinothionic halides with antimony trifluoride has been proposed[116] for the preparation of alkyl(or aryl)tetra- and dialkyltri-fluorophosphoranes. A reaction of similar type had previously[114] been used for the synthesis of trialkyldifluorophosphoranes. The possibility of converting thione derivatives of four-coordinated phosphorus into fluorophosphoranes is of the greatest value for the synthesis of dialkyltrifluorophosphoranes, which are mostly obtained by the reaction of antimony trifluoride with dialkylchlorophosphines, these being considerably less readily available substances than their thione derivatives.

Triphenyldifluorophosphorane has been obtained by the reaction of triphenylphosphine with dinitrogen tetrafluoride[117], perfluoropiperidine, and nitrogen trifluoride[118]. The reaction between diphenylphosphine and tetrafluorohydrazine might be expected to yield the hydride $(C_6H_5)_2PHF_2$, but diphenyltrifluorophosphorane is said[117] to be formed (though in a later patent[119] the same workers state that reaction of the appropriate phosphines with tetrafluorohydrazine yields the hydrides R_2PHF_2).

It has not proved possible to isolate alkyl(or aryl)difluorodihalogenophosphoranes in the pure state[13,45]. Thermally the compounds are considerably less stable than their analogues[1] containing perfluoroalkyl radicals, and their formation in the reaction of alkyl(or aryl)difluorophosphines with chlorine or bromine has been detected[13] by means of the low-temperature fluorine-19 n.m.r. spectra. Even below 0°C they form, as a result of intermolecular ligand exchange, fluorophosphoranes $RPHalF_3$, RPF_4, and solids, insoluble in most organic solvents, whose composition is close to that of alkyl(or aryl)fluorotrihalogenophosphoranes (on treatment with antimony trifluoride the latter also give RPF_4).[13] Trichlorofluorotrifluoromethylphosphorane CF_3PCl_3F has been obtained as the desired product by Griffiths[120] by the addition of chlorine fluoride to dichlorotrifluoromethylphosphine.

During the past three or four years a large amount of work has been done on alkyl(or aryl)mono(or di)alkylaminofluorophosphoranes, among which the trifluorophosphoranes $ArPF_3NR_2$ were reported originally[121], and then other members of the series of alkyl(or aryl)aminotrifluorophosphoranes[40,122–126]. Alkyldiaminodifluorophosphoranes have recently been obtained[127] by the reaction of trifluorophosphoranes RPF_3NR_2 or RPF_3NHR with primary or secondary amines. Alkyl(or aryl)mono(or di)alkylaminotrifluorophosphoranes have been synthesised by the following methods:

(1) $RPF_4 + 2\,H_2NR' \rightarrow RPF_3(NHR') + HF \cdot H_2NR'$[40,122–124]

(2) $2\,RPF_4 + 2\,HNR'_2 \rightarrow RPF_3(NR'_2) + [R_2NH_2]^+[RPF_5]^-$[122,123,125]

(3) $RPF_3Cl + 2\,HNR'_2 \rightarrow RPF_3(NR_2) + HCl \cdot HNR_2$[121,125]

(4) $RPHal(N{<}) \xrightarrow{SbF_3} RPF_3(N{<})$ (Hal=Cl, F)[40,122,123,125]

(5) $RPF_4 + (CH_3)_3Si{-}NR'_2 \rightarrow RPF_3(NR'_2) + (CH_3)_3SiF$[122,123,126]

Arylaminotrifluorophosphoranes are most conveniently obtained by reaction (3), since the initial arylchlorotrifluorophosphoranes can easily be prepared by treating aryltrifluorophosphoranes with chlorine, the latter being comparatively readily available compounds. Reaction (4) is advisable for the preparation of alkyldialkylaminotrifluorophosphoranes, and reaction (1) for their monoalkylamino-derivatives.

Study of the hydrolysis of alkyl(or aryl)aminotrifluorophosphoranes by means of the ^{19}F n.m.r. spectra has shown[13,128] that the addition even of catalytic quantities of water results in formation of the anion $[RPF_5]^-$, whose concentration initially increases as fresh portions of water are added, reaches a maximum at a ratio of the initial reactants of ~1 : 1, and then diminishes until signals due to $[RPF_5]^-$ have completely disappeared from the spectrum. Ultimately, as had been noted previously[121], hydrolysis yields the salts $[HN{<}]^+[RPO_2F]^-$, which can be obtained also by the direct reaction between alkylphosphonofluoridic acids and amines[13].

In a series of papers Schmutzler and Reddy have shown[129–131] that on storage the fluorophosphoranes $C_6H_5PF_3N(CH_3)_2$ and $CH_3PF_3N(CH_3)_2$ undergo rearrangement accompanied by formation of the ionic compound $[RPF(N(CH_3)_2)_2]^+[RPF_5]^-$. Other workers have found[13,128] that the anions $[RPF_5]^-$ are formed also on the storage of most fluorophosphoranes RPF_3NHR, although the formation of cations containing phosphorus has not been established in this case.

The first attempts to obtain the trifluorophosphoranes RPF_3OR' from tetrafluorophosphoranes and siloxanes did not give the results expected[1,114]: instead of compounds of five-coordinated phosphorus, the phosphonic fluorides $RPOF_2$ and $RPFOOR'$ were isolated, among which at least the former product might be formed by the rearrangement

$$RPF_3(OR') \rightarrow RPOF_2 + R'F.$$

Investigation of the reaction of methyl- and ethyl-tetrafluorophosphoranes with siloxanes by means of the low-temperature ^{19}F n.m.r. spectra has shown the actual formation in this case of the trifluorophosphoranes RPF_3OR', which are stable only at subzero temperatures. On warming up to room temperature the signals from the trifluorophosphoranes disappeared, and signals appeared from the phosphonic fluorides $RPOF_2$ and $RPFOOR'$. Formation of the latter compounds may be due either to reaction of the difluorides $RPOF_2$ with the siloxanes or to rearrangement of alkyldialkoxydifluorophosphoranes

$$RPF_2(OR')_2 \rightarrow RPOF(OR') + R'F,$$

which may be formed both by interaction of the trifluorophosphoranes RPF_3OR' with siloxanes and as a consequence of intermolecular exchange in the alkylalkoxytrifluorophosphoranes themselves

$$2\,RPF_3(OR') \rightarrow RPF_2(OR')_2 + RPF_4.$$

The relatively stable difluorophosphoranes $RPF_2(OC_6H_5)_2$ and $(C_6H_5)_2PF_3OC_6H_5$ have recently been obtained by reaction of the corresponding tetra- and tri-fluorophosphoranes with siloxanes[132]. Fluorophosphoranes containing alkylthio- or arylthio-groups attached to the phosphorus atom have been described[13,132,133].

The attention of research workers has long been attracted to the acceptor properties of fluorophosphoranes. Alkyl(or aryl)tetrafluorophosphoranes are weaker acceptors of electrons than is phosphorus pentafluoride, but nevertheless they exhibit this property quite distinctly. Thus phenyltetrafluorophosphorane forms relatively stable complexes with dimethylformamide and with pyridine. The temperature variation in the parameters of the ^{19}F n.m.r. spectra observed in solutions of these complexes may be due to the partial dissociation[134]

$$C_6H_5PF_4.\text{Donor} \rightleftharpoons C_6H_5PF_4 + \text{Donor}.$$

According to Muetterties and Mahler[134] donor–acceptor interaction is not observed in solutions of phenyltetrafluorophosphorane in acetonitrile and triethylamine. Alkyltetrafluorophosphoranes undergo an exothermic interaction with many organic bases, but at room temperature the resulting complexes are in considerable measure dissociated. According to their acceptor power the fluorides of five-coordinated phosphorus form the sequence[134]

$$PF_5 > ArPF_4 > AlkPF_4 \gg R_2PF_3 > R_3PF_2$$

which reflects the diminution in the relative positive charge on the phosphorus atom when the fluorine atom is replaced by less electronegative substituents. Steric factors probably play an important part also.

Phenyltetrafluorophosphorane forms with dimethyl sulphoxide a complex, which at 25°C dissociates with increase in the electrical conductivity of the solution. Spectroscopic investigation indicates that the reversible process

$$C_6H_5PF_4 \cdot OS(CH_3)_2 \rightleftarrows C_6H_5PF_4 + (CH_3)_2SO$$

is accompanied in the solution by another interaction involving formation of the anion $[RPF_5]^-$ and of $RPOF_2$ (the role and the fate of the dimethyl sulphoxide in this process have not been ascertained)[134].

Alkyltetrafluorophosphoranes react irreversibly with dimethyl sulphoxide. The products contain the anions $[RPF_5]^-$ and alkylphosphonic difluorides. The ^{19}F n.m.r. spectrum of these anions varies with temperature, this being attributed to exchange with F^- ions[134].

It has come to be accepted[1,114,134] that the donor properties of fluorides of five-coordinated phosphorus may be due either to ionisation $PX_5 \rightleftharpoons PX_4^+ + X^-$ or to the presence of lone pairs of electrons on the atoms attached to the phosphorus. All derivatives of phosphorus pentafluoride possess donor properties, although it is unknown which of the above causes is operative. Alkyl- and aryl-tetrafluorophosphoranes form colourless crystalline 1 : 1 complexes with strong acceptors such as boron trifluoride, antimony pentafluoride, and phosphorus pentafluoride. The complexes of dialkyltrifluorophosphoranes with the same acceptors are usually more stable than those of alkyltetrafluorophosphoranes [the dissociation pressure for the complex $PF_5.(CH_3)_2PF_3$ is less than 1 mm at 25°C, whereas for $CH_3PF_4.PF_5$ it is ~10 mm at –61°C].[134]

Hydrides of five-coordinated phosphorus. The first hydrides containing a five-coordinated phosphorus atom were described in 1961[135,136]: tetra- and tri-fluorophosphorane were obtained by the reaction of orthophosphorous and hypophosphorous acids with hydrogen fluoride, and treatment of aryldichlorophosphines with potassium hydrogen fluoride gave aryltrifluorophosphorus monohydrides. Treichell and his coworkers have since found[67] that the hydrides HPF_4 and H_2PF_3 can be obtained by the gas-phase reaction of phosphorus pentafluoride with trimethylstannane [the deuteriated derivatives DPF_4 and D_2PF_3 have been prepared by the use of $(CH_3)_3SnD$]. Available data indicate[67,137,138] that both compounds are monomeric in the vapour state, whereas in the liquid state the H_2PF_3 molecules are in considerable measure associated. The chemical properties of these compounds have not been studied. It is known only that HPF_4 reacts with glass or quartz to form the unstable phosphorodifluoridous acid[67].

The hydrides methyl- and ethyl-trifluorophosphorane were first described in the patent literature[39]. Their synthesis and also several chemical properties have since been reported[13,35,38,40,139-141]. Both alkyl- and aryltrifluorophosphoranes (monohydrides) can be obtained in 80–90% yield by the low-temperature reaction between the halides $RPHal_2$ (where Hal = Cl, Br, F) and hydrogen fluoride[13,39,40,140,141]. The reaction of methyl- and ethyltetrafluorophosphoranes with trimethylstannane has also been used to prepare the alkyl derivatives[139].

All the trifluorophosphorus monohydrides investigated are relatively low-boiling liquids, which distil satisfactorily in an atmosphere of nitrogen, are easily hydrolysed, and react with glass. The compounds can be stored for a long time in vessels of an inert material (quartz, polyethylene, polytetrafluoroethylene). With tertiary amines they form alkyl(or aryl)difluorophosphines and salts $[NHR_3]^+[R'PHF_4]^-$ [26,38,40,141]. By the action of sodium alkoxides on aryltrifluorophosphoranes (monohydrides) the fluorine atom can be replaced by an alkoxy-group[35,141,142], and the action of primary amines on the corresponding alkyl monohydrides yields the alkyl-alkylaminodifluorophosphoranes $RPHF_2NHR'$ [38,41,141]. The latter compounds, as well as the hydrides $AlkPHF_2OR$, can also be obtained by the reaction of alkyldifluorophosphines with alcohols and with primary amines respectively[13,34-38,141,143]. The hydrides $AlkPHF_2NR_2$ are formed also in the first stage of interaction between alkyldifluorophosphines and secondary amines[13,42]. However, these compounds break down at high temperatures to form alkylphosphonofluoridous amides, and it proved extremely difficult to isolate them in the pure state by distillation.

Somewhat obscure results have been obtained for the reaction of aryldifluorophosphines and aryltrifluorophosphoranes with primary and secondary amines[38]. The formation of amides $ArPFN\langle$ in these cases is established by the ^{31}P n.m.r. spectra, whereas on distillation only their adducts with hydrogen fluoride, corresponding formally in composition to the hydrides $ArPHF_2N\langle$, can be isolated.

The previously unknown hydrides $ROPHF_2NHR'$ and R_2NPHF_2NHR' have been obtained from the corresponding fluorides XPF_2 and primary amines[14]:

$$XPF_2 + H_2NR' \rightarrow XPHF_2(NHR') \quad (X{=}OR,\ NR_2)$$

and the hydrides R_2PHF_2 (R = Alk, Ar) by reaction of the halides R_2PCl and R_2PF with hydrogen fluoride[13,107].

The above cases of the formation of hydrides of five-coordinated phosphorus by the reaction of fluorides of three-coordinated phosphorus with alcohols, amines, and hydrogen halides have several common features, which suggest that the initial step in this process is the reaction of a weak n-base with an acid HX (where X = F, Cl, OR, NHR, NR_2). The driving force in this stage of the reaction should be the high electronegativity of X. Where the electronegativity of X is small, systems may be formed containing a hydrogen bond $\rangle$P:...H:X, the strength of which depends on the state of the lone pair of electrons of the base. When, however, X is strongly electronegative, and the phosphorus is combined with substituents of low electronegativity, the H–X bond may be ruptured with formation of the ion-pair $[\rangle PH]^+X^-$. The presence on the phosphorus atom of highly electronegative substituents, tending to lower the energy and localise the d-orbitals, is evidently a necessary condition for conversion of the initially formed system $\rangle$P:...H:X into a hydride of five-coordinated phosphorus.

It may be supposed then that the hydrides HPF_3X (where X = F, Cl, OR, NHR, etc.) will be fairly difficult to obtain by direct reaction of the compounds HX with phosphorus trifluoride, owing to the weak donor power of the latter. This conclusion is supported by the well known experimental fact that the hydride PHF_4 is not formed as a result of contact between phosphorus trifluoride and hydrogen fluoride. Replacement of one of the fluorine atoms in phosphorus trifluoride by a less electronegative substituent is sufficient for the compound to react exothermally with HX to form, as is shown experimentally, hydrides of five-coordinated phosphorus. On the whole it is obvious that, in the series PF_3, YPF_2, Y_2PF, and Y_3P (where Y is a substituent other than fluorine), the last compound will react most easily with the acid HX. However, if the reaction can produce a five-coordinated molecule thanks to the presence of highly electronegative substituents in the compounds YPF_2 and to a less extent Y_2PF, such possibilities should be limited in the latter compounds. This conclusion also is supported by the experimental results available at present. In particular, the fluorophosphines RPF_2 and R_2PF form with hydrogen fluoride hydrides of five-coordinated phosphorus, whereas the products of the interaction of hydrogen fluoride with trialkyl(or aryl)phosphines have a clearly ionic structure[144].

III. PHYSICOCHEMICAL INVESTIGATIONS

The wide use of modern physicochemical methods of investigation, primarily n.m.r. spectroscopy, has had an exceptionally fruitful influence on the development of the chemistry of the fluorides of phosphorus. The most significant result has been obtained from a combined study (by electron diffraction, and n.m.r. and vibrational spectroscopy) of the structure of P[V] compounds, which are in most cases found to have a trigonal–bipyramidal configuration.

Another important result of work done during recent years is the evaluation of the true parameters of the ^{31}P and ^{19}F n.m.r. spectra for the fluorides of three-coordinated phosphorus, and in particular for derivatives of alkylphosphonofluoridous acids, which exhibit abnormally small chemical shifts δ_P.

Particular attention will be paid here to the results of n.m.r. and vibrational spectroscopy, and also to the investigation of the structure of the fluorides of phosphorus by electron diffraction.

1. Phosphorus-31 and Fluorine-19 n.m.r. Spectra

^{31}P and ^{19}F n.m.r. spectra of the fluorides of three-coordinated phosphorus. The fluorides C_2H_5PFX (where X = F, Cl, iso-OC_3H_7) were among the first organophosphorus compounds to be investigated by means of the ^{31}P n.m.r. spectra. Unfortunately, the relevant paper[145] contained a mistake, these compounds being attributed the spectral characteristics of more highly coordinated fluorides of phosphorus. Only eight years later[146] was the error in the original results demonstrated, and subsequently the true parameters of the ^{31}P and ^{19}F n.m.r. spectra have been determined[26-29,33,41,49,52,147] for these types of compounds (see Table 1), which were found to possess abnormally low δ_P values, disproving the theory of "group shifts"[145].

Quite a large amount of experimental information has now accumulated providing knowledge of the values of δ_P, δ_F, and J_{P-F} for about a hundred phosphorus(III) fluorides. However, it has not yet proved possible to use this information in developing theoretical aspects of the problem of screening and spin–spin interaction in the series of compounds considered. Solution of these problems is complicated by the absence of any well-developed regularities in the variation of these parameters with the structure of the compounds. Only in narrow series of closely related derivatives, where the variation in structure seemingly does not involve substantial variation in angles and bond lengths, is it possible to detect a more or less well defined inverse relation (e.g. for compounds 15–19 in Table 1) and occasionally even a direct relation (compounds 8–10, 12, and 13) between the values of δ_P and the aggregate electronegativities of the substituents. However, when broader series of compounds are considered, e.g. fluorides of the type XPF_2 (compounds 1–13, Table 1) and XYPF (compounds 14–24), this relation breaks down, probably because of the considerable fluctuations in the valency angles within series of these compounds.

Not only δ_P but also the chemical shifts of the ^{19}F nuclei vary over a wide range. Thus for compounds of the type RPFX (Table 1, compounds 12–19) the range of variation in δ_P is ~90 ppm, while the chemical shifts δ_F vary over the range 522–626 ppm. The screening of the ^{31}P nuclei changes with the nature of X in the sequence $F < Cl < OR \simeq SR < R < NR_2$, which differs from the sequence of variation in δ_F in the same compounds (the screening of ^{19}F nuclei varies in the sequence $OR < F < NR_2 < SR < R$). The constants J_{P-F} increase in the sequence $R < NR_2 < SR < Cl < OR < F$, which differs from both δ_P and δ_F sequences.

It must be noted in conclusion that ^{31}P nuclei are usually considerably less screened in P[III] fluorides than in the corresponding derivatives containing P[IV] or P[V], whereas ^{19}F nuclei, on the other hand, are more screened in P[III] fluorides than in the P[IV] compounds. In virtue of these facts phosphorus(III) fluorides can often be easily identified by means of the ^{31}P and ^{19}F n.m.r. spectra not only in the pure state but also when mixed with more highly coordinated phosphorus compounds.

Phosphorus-31 and fluorine-19 n.m.r. spectra of complex compounds. An interesting paper appeared recently[60] on the investigation by means of the ^{31}P and ^{19}F n.m.r. spectra of complex compounds containing P[III] fluorides as ligands. It contains extensive experimental results, and makes an analysis of possible factors influencing the variation in the parameters of the n.m.r. spectra on passing from the free ligands to the complex compounds. In the complexes the ^{31}P nuclei are deshielded in comparison with the free ligands ($\Delta\delta_P$ = 6–55 ppm); the ^{19}F nuclei also become less well screened ($\Delta\delta_F$ = 17–46 ppm). The constants J_{P-F} are, with rare exceptions, smaller in the complexes than in the free ligands. It has also been noted that, the better screened are the ^{31}P nuclei in the free ligands and complexes, the smaller is $\Delta\delta_F$ accompanying complex formation.

Analysis of these results led to the conclusions[60] that complex formation is accompanied by an increase in the paramagnetic contribution to the screening constants of the ^{31}P and ^{19}F nuclei, and this contribution is greater in molybdenum complexes than in nickel complexes. Part of this contribution is due to $d_\pi - d_\pi$ bonding between the phosphorus atom and the metal. The change in hybridisation of the phosphorus atom accompanying complex formation should also play an important part. However, the absence of data on valency angles and bond lengths, both in the initial phosphorus-containing compounds and in the complexes, prevents serious discussion of this problem. It is clear only that a diminution in the *s*-character of the phosphorus–fluorine bond, which should be observed on complex formation, will lead to a decrease in the J_{P-F} constants in the complexes (and this is actually observed in the vast majority of compounds investigated). In the opinion of the authors, polarisation of the lone pair of electrons on the

Table 1. Parameters of ^{31}P and ^{19}F n.m.r. spectra for various groups of three-coordinated phosphorus compounds*.

No.	Compound	δ_P, ppm	δ_F, ppm	J_{P-F}, c/s	Σ_κ	Refs.
1	PF_3	—97	464	1405	11.7	1
2	$ROPF_2$	—110	~479	~1290	~10.3	1
3	CCl_3PF_2	—131	518	1285	10.64	1
4	$CNPF_2$	—140	519	1267	11.64	6
5	R_2NPF_2	—144	495	1194	10.16	1,14
6	CF_3PF_2	—158	536	1250	11.26	1
7	$ClPF_2$	—176	468	1390	10.80	1
8	$ClC_6H_4PF_2$	—197	—	1118	—	26
9	$CH_3C_6H_4PF_2$	—206	521	1099	10.24	26
10	$C_6H_5CH_2PF_2$	—224	527	1191	—	26
11	$F_2P—PF_2$	—226	—	1130	—	6
12	$C_2H_5PF_2$	—245	533	1162	10.08	33
13	CH_3PF_2	—251	522	1157	10.07	1.29
14	$CH_3PF(NR_2)$	~—165	~540	~920	~8.53	33,38
15	$(CH_3)_2PF$	—185	626	823	8.44	30,33
16		(—187)		(830)		
17	$CH_3(C_2H_5)PF$	—182	—	820	8.45	33
18	$CH_3(OR)PF$	~—214	~530	~1120	8.70	33,35,41
19	$CH_3(SR)PF$	~—214	~580	~960	8.56	33.42
	$CH_3(Cl)PF$	—240	—	1040	9.17	33
20	$(RO)_2PF$	~—130	495	1215	~8.96	1.14
21	$RO(R_2N)PF$	~—151	~500	~1125	~8.80	14
22	$(R_2N)_2PF$	~—151	~530	~1050	~8.60	14
23	Cl_2PF	—224	487	1320	9.90	1
24	Br_2PF	—255	500	1301	9.30	148.149

* Chemical shifts δ_P given relative to H_3PO_4, and δ_F relative to F_2.

central atom of the free ligand by the unsymmetrical field of the substituents should promote descreening of the ^{31}P nuclei in the compounds XPF_2 and X_2PF. This effect should be considerably weaker in the complexes, since the "lone" pair in them is already bound, and therefore less subject to polarisation.

Nuclear magnetic resonance of fluorides of four-coordinated phosphorus. Until recently data on the parameters of the ^{31}P and ^{19}F n.m.r. spectra of P[IV] fluorides were extremely limited (a 1965 review[1] gave the spectral characteristics of forty compounds). Shortly after this the characteristics of about eighty more compounds were recorded, including the thiophosphoryl derivatives SPF_nX_{3-n} ($n = 1-3$ and X = Cl, Br, NCS, H, NR_2, SR, OR) [12,64,68,150-152], isocyanates and isothiocyanates of phosphorofluoridic acids[68], phosphazofluorides[153,154], the mixed halides XPOHalF (X = R, NR_2, Hal and Hal = Cl, Br) [14,50,155], and also a large number of phosphorofluoridates[66,147,148] and phosphonofluoridates[156,157].

A paper[156] giving the spectral characteristics of about thirty compounds of the type XYPOF, some new and many which had been investigated previously, noted that all the compounds can be divided into three groups, within each of which the chemical shifts δ_P and δ_F increase linearly with the sum of the electronegativities of the substituents X and Y. The first group comprises molecules in which X and Y ≠ F, Cl, or OH (Table 2, compounds 1–18); in the second group X = F, Cl, OH (compounds 20–27); and in the third group X and Y = F, Cl, OH (compounds 28–30). In each group δ_P and δ_F vary in the same sense, the dialkylphosphinic fluorides constituting an exception. The occurrence of such groups may be due to a slight variation in valency angles within each series of compounds.

On the whole, methods at present available for the quantum-chemical calculation of the parameters of the ^{31}P and ^{19}F n.m.r. spectra do not provide quantitative estimates of δ_P and δ_F. Moreover, there is no generally accepted view on the main factors responsible for the variation in the chemical shifts in these compounds[158-161].

Nuclear magnetic resonance of fluorides of five-coordinated phosphorus. Among phosphorus compounds the P[V] fluorides are some of the most interesting subjects for investigation by n.m.r. spectroscopy on ^{31}P and ^{19}F nuclei. However, theoretical aspects of screening and spin–spin interaction are still less developed for these compounds than for P[III] and P[IV] fluorides, which makes it important to seek purely empirical rules for the variation in the parameters of the spectra for different groups of these compounds.

The number of P[V] fluorides which have been investigated by the n.m.r. method now exceeds a hundred. They include most of the structures from XPF_4 to X_4PF which are conceivable in practice, the spectral data for which, with rare exceptions, are satisfactorily interpreted on the basis of a trigonal–bipyramidal model. Such exceptions include in particular the spectral characteristics of certain adducts of P[III] fluorides with halogens (Table 3), which have been investigated quite recently[13,16,17,45,162].

In spite of the formal similarity in structure, these compounds (Table 3) give an extraordinarily wide range of variation in δ_P (from +110 to −80 ppm); the majority have very low values of δ_F, and the constants J_{P-F} are unusually large for axial fluorine atoms. However, the low-temperature ^{19}F n.m.r. spectra proved the trigonal–bypyramidal configuration (with an axial conformation of the two fluorine atoms) of compounds 1 and 2 [162] and 3–13 [13] (Table 3) (an axial arrangement of the fluorine atoms was confirmed for compounds of the type $R_2NPF_2Hal_2$ by examining the ^{19}F n.m.r. spectra of compounds 5 and 11 at various temperatures). In view of the closeness of the spectral characteristics, compounds 21–31 can also be assigned to the same molecular model. Compounds 14–20 most probably have an ionic structure, especially in view of their very low δ_P values.

Another unexpected result, which at first glance seems to contradict the trigonal–bipyramidal model of the molecules, has been obtained for the structure of the trifluorophosphoranes RPF_3NHR' [13,40,125,128,163]. As was first shown for methylisobutylaminotrifluorophosphorane[40], the

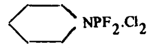
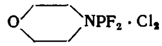
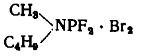
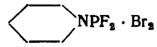
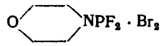
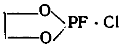
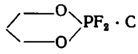
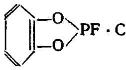
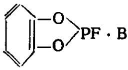
Table 2. Parameters of ^{31}P and ^{19}F n.m.r. spectra for compounds of type $\begin{matrix}X\\Y\end{matrix}\!\!>\!POF$ in comparison with sum of electronegativities of X and Y*.

No.	Compound		δ_P, ppm	δ_F, ppm	J_{P-F}, c/s	$\kappa_X + \kappa_Y$
	X	Y				
			R_2POF			
1	CH_3	CH_3	−66.7	495	968	4.54
2	CH_3	C_4H_9	−65.2	502	975	4.55
3	C_2H_5	C_6H_5	−53.4	507	1014	4.77
4	C_3H_7-*i*	C_3H_7-*i*	−78.2	529	1069	4.56
5	C_6H_5	C_6H_5	−40.5	—	1020	4.98
			R(RO)POF			
6	CH_3	C_3H_7O	−26	490	1035	~4.8
7	C_2H_5	CH_3O	−32.9	501	1078	4.96
8	C_2H_5	C_2H_5O	−33.1	498	1056	4.81
9	$CH_2=CH$	*i*-C_4H_5O	−15.5	497	1031	~4.9
10	C_6H_5	C_2H_5O	−14.9	495	1031	5.02
			R(RS)POF			
11	CH_3	C_2H_5S	−61.5	472	1064	4.66
12	C_2H_5	CH_3S	−67.0	484	1066	4.73
13	C_3H_7-*i*	C_2H_5S	−74.0	—	1107	4.67
			$(RO)_2POF$, RO(RS)POF, $(R_2N)_2$ POF			
14	C_2H_5O	C_2H_5O	9.2	512	963	5.06
15	*i*-C_4H_9O	*i*-C_4H_9O	9.0	513	969	—
16	C_6H_5O	C_6H_5O	20.3	509	997	5.36
17	C_2H_5O	C_2H_5O	−26.6	—	1127	4.92
18	$(CH_3)_2N$	$(CH_3)_2N$	−23.9	—	954	4.80
			Hal(R)POF, Hal(RO)POF, Hal(R_2N)POF, Hal_2POF			
19	F	CH_3	−27.4	491	1093	6.17
20	F	C_2H_5	−29.2	—	1130	6.18
21	F	$ClCH_2$	−12.0	—	1142	6.37
22	Cl	$ClCH_2$	−32.0	490	1014	5.47
23	OH	CH_3	−32.2	490	1014	5,78
24	F	C_2H_5O	20.9	—	1015	6.43
25	F	C_6H_5O	27.1	—	1030	6.58
26	Cl	CH_3O	5.4	477	1110	5.68
27	F	$(C_2H_5)_2N$	3.6	—	1004	6.26
28	F	F	35.5	523	1080	7.80
29	F	Cl	15.0	477	1138	6,90
30	OH	OH	8.0	504	954	7.02

*Chemical shifts δ_P given relative to H_3PO_4, and δ_F relative to F_2. Data taken from Ref. 156.

^{19}F n.m.r. spectra of compounds of this type have a pattern indicating the magnetic non-equivalence of all three fluorine atoms in the molecule, whereas the fluorine resonance spectra of the trifluorophosphoranes X_2PF_3 investigated previously indicated interaction of phosphorus nuclei with two magnetically equivalent (axial) ^{19}F nuclei and one ^{19}F nucleus differing from them. A more detailed investigation of the ^{19}F and ^{31}P n.m.r. spectra of the trifluorophosphoranes RPF_3NHR' showed[13,125,128,163] that the signals from these compounds in the fluorine resonance spectra can also be divided into signals from an equatorial and two axial fluorine atoms, because of the fact that under normal conditions the ^{31}P nuclei do not "sense" the non-equivalence of the two less well screened (axial) fluorine atoms, and preserve the normal pattern of the ^{31}P n.m.r. spectrum.

Table 3. Parameters of ^{31}P and ^{19}F n.m.r. spectra of 1 : 1 adducts of phosphorus(III) fluorides with halogens.

No.	Compound	δ^*_P, ppm	$\delta^*_{F_{ax}}$, ppm	$\delta^*_{F_{eq}}$, ppm	$J_{P-F_{ax}}$, c/s	$J_{P-F_{eq}}$, c/s	J_{F-F}, c/s	Refs
1	$PF_3\cdot Cl_2$	—	364	472	1023	1085	142	162
2	$PF_3\cdot Br_2$	—	327	465	1141	1143	124	162
3	$(CH_3)_2NPF_2\cdot Cl_2$	+44	381	—	960	—	—	16,17
4	$(C_2H_5)_2NPF_2\cdot Cl_2$	+42	375	—	962	—	—	17
5**	 $\mathrm{(CH_3)(C_4H_9)NPF_2\cdot Cl_2}$	—	378/383	—	945	—	—	13
6		+48	388	—	970	—	—	13
7		+46	—	—	950	—	—	13
8	$(CH_3)_2NPF_2\cdot Br_2$	+103	354	—	1020	—	—	17
9	$(C_2H_5)_2NPF_2\cdot Br_2$	+108	356	—	1025	—	—	17
10	$(C_4H_9)_2NPF_2\cdot Br_2$	—	355	—	1030	—	—	13
11**	 $\mathrm{(CH_3)(C_4H_9)NPF_2\cdot Br_2}$	—	352/356	—	1050	—	45	13
12		—	353	—	1050	—	—	13
13		+110	—	—	1030	—	—	17
14***	$[(CH_3)_2N]_2PF\cdot Cl_2$	−40	480	—	1135	—	—	13,17
15***	$[(CH_3)_2N]_2PF\cdot Br_2$	−32	489	—	1130	—	—	13,17
16***	$(CH_3)_2N[(C_2H_5)_2N]PF\cdot Br_2$	—	491	—	1130	—	—	13
17***	$CH_3[(C_2H_5)_2N]PF\cdot Cl_2$	—	479	—	1122	—	—	13,17
18***	$C_6H_5[(C_2H_5)_2N]PF\cdot Cl_2$	−67	486	—	1150	—	—	13,17
19***	$CH_3[(C_2H_5)_2N]PF\cdot Br_2$	−80	473	—	1164	—	—	13,17
20***	$C_6H_5[(C_2H_5)_2N]PF\cdot Br_2$	−57	—	—	1200	—	—	13,17
21	$CH_3OPF_2\cdot Cl_2$	—	378	—	960	—	—	13,21
22	$C_4H_9OPF_2\cdot Cl_2$	—	376	—	910	—	—	13,21
23	$C_6H_5OPF_2\cdot Cl_2$	+35	374	—	1020	—	—	13,21
24	$C_6H_5OPF_2\cdot Br_2$	+96	345	—	1025	—	—	13,21
25		—	375	—	915	—	—	13,21
26		—	373	—	930	—	—	13,21
27		—	379	—	940	—	—	13,21
28		—	345	—	975	—	—	13,21
29	$CH_3PF_2\cdot Cl_2$	—	356	—	980	—	—	13
30	$C_6H_5PF_2\cdot Cl_2$	—	377	—	965	—	—	13
31	$C_6H_5PF_2\cdot Br_2$	—	348	—	1000	—	—	13

* Values of δ_P given relative to H_3PO_4, and of δ_F relative to F_2.

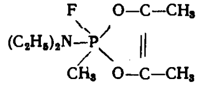
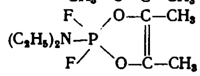
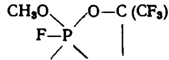
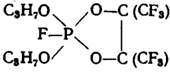
** Axial fluorines are magnetically non-equivalent (recorded at −50°C).

*** Values of δ_F and J_{P-F} arbitrarily attributed to axial fluorine atoms.

Likewise the equatorial fluorine atoms do not "sense" the non-equivalence of the axial fluorine atoms.

It was subsequently established[13,164] that magnetically non-equivalent axial fluorine atoms are present not only in trifluorophosphoranes containing an NHR group attached to the phosphorus atom but also in fluorophosphoranes containing NR^1R^2 and SR groups. There are grounds for assuming that the cause of this phenomenon is the relatively high energy barrier to internal rotation about the P–N and P–S bonds[13,163,164].

Table 4. Parameters of ^{31}P and ^{19}F n.m.r. spectra of fluorophosphoranes containing alkoxy- and alkylthio-groups attached to the phosphorus atom.

No.	Compound	δ^*_P, ppm	$\delta^*_{F_{ax}}$, ppm	$\delta^*_{F_{eq}}$, ppm	$J_{P-F_{ax}}$, c/s	$J_{P-F_{eq}}$, c/s	J_{F-F}, c/s	Refs.
1	CH_3OPF_4	+65	498	—	—	870	—	166
2	$CH_3PF_3(OC_2H_5)$	—	456	502	840	990	64	131
3	$C_2H_5PF_3(OC_2H_5)$	—	460	500	855	1010	62	131
4	$CH_3PF_3(OC_6H_5)$	—	448	—	825	—	—	132
5	$C_6H_5PF_2(OC_6H_5)_2$	—	465	—	829	—	—	132
6	$(C_6H_5)_2PF_2(OC_6H_5)_2$	—	463	—	797	—	—	132
7	$(CH_3O)_3PF_2$	—	503	—	706	—	—	112
8	$(C_6H_5O)_3PF_2$	—	503	—	721	—	—	112
9	$CH_3PF_2(SC_2H_5)_2$	+15	—	—	690	—	—	131
10	$C_6H_5PF_3(SCH_3)$	—	445	502	942	1042	60	132
11**	$C_6H_5PF_3(SC_2H_5)$	+21	446	501	938	1049	59	132,164
12	$C_6H_5PF_3(SC_6H_5)$	—	444	501	970	1060	60	132
13	$(C_6H_5)_2PF_2(SCH_3)$	—	455	—	760	—	—	132
14	$(C_6H_5)_2PF_2(SC_2H_5)$	—	455	—	752	—	—	132
15	$(C_6H_5)_2PF_2(SC_6H_5)$	—	456	—	796	—	—	132
16	$(C_4H_9S)_3PF_2$	—	502	—	713	—	—	112
17	$(C_2H_5)_2NPF_2(SC_2H_5)_2$	+31	437	—	845	—	—	13
18		+28	471	—	785	—	—	47
19		+50	489	—	810	—	—	19
20		+81	—	—	915	—	—	19
21		+83	—	—	930	—	—	19

* Chemical shifts δ_P given relative to H_3PO_4, and δ_F relative to F_2.

** At −50°C the axial fluorine atoms exhibit magnetic non-equivalence: $\delta'_{F_{ax}} = 450$ ppm and $\delta''_{F_{ax}} = 442$ ppm; $J'_{P-F_{ax}} = 940$ c/s and $J''_{P-F_{ax}} = 1030$ c/s [13,164]. A similar phenomenon cannot be observed in compounds containing RO-groups[13].

A large number of fluorophosphoranes containing alkoxy- and alkylthio-groups attached to the phosphorus atom have recently been investigated by means of the ^{19}F n.m.r. spectra (Table 4). Compounds of this type are in most cases unstable, and their spectral characteristics are therefore especially important for identifying newly prepared products. Table 4 makes it clear that these compounds are characterised by positive chemical shifts δ_P, spin–spin interaction constants $J_{P-F_{eq}}$ exceeding 1000 c/s, and large fluctuations in the values of $J_{P-F_{ax}}$ (from 690 to 970 c/s). An appreciable increase in screening of the axial fluorine atoms is noteworthy on passing from fluorophosphoranes containing a carbon–phosphorus bond (Table 4, compounds 2–6 and 9–15) to compounds containing more electronegative substituents (e.g. compounds 7, 8, and 16). The trigonal–bipyramidal configuration of compounds of this type is confirmed by the n.m.r. spectra of the trifluorophosphoranes (compounds 2, 3, and 10–12) containing signals from two (axial and equatorial) groups of fluorine atoms. In several cases, e.g. with the cyclic monofluorophosphoranes 20 and 21, whether the fluorine is located at the equator or in an axial position of the bipyramid remains an open question, since the values of δ_F remain unknown, while those of the constants J_{P-F} are nevertheless large for an axial position, usually occupied by the more electronegative substituents, to be assigned to the fluorine atoms solely on the basis of these data[165]. The spectral characteristics of the recently reported[166] compound CH_3OPF_4 demand special notice (Table 4, compound 1): the ^{31}P nuclei are considerably better screened than in CH_3PF_4 and PF_5, almost to the same extent as in $BrPF_4$ [98]; the quantity δ_F occupies an intermediate position between its values for CH_3PF_4 and PF_5 (but is closer to the latter); while the constant J_{P-F} is considerably smaller than in the above compounds.

The parameters of the n.m.r. spectra for all the phosphorus(V) hydrides other than the monohydride phenyltrifluorophosphorane[167] have been given in papers published since 1964. During this time n.m.r. spectroscopy has been used to examine about fifteen compounds having various types of structure, beginning from HPF_4 and H_2PF_3 and ending with the hydrides $XYPHF_2$ (where X and Y are substituents other than fluorine). The parameters (Table 5) and the character of the ^{31}P and ^{19}F n.m.r. spectra of the phosphorus hydrides investigated indicate that they have a five-coordinated structure, and are well interpreted on the basis of a trigonal–bipyramidal model. The compounds are characterised by positive values of the chemical shifts δ_P, reaching ±70 ppm for the hydrides $ROPHF_2NHR'$ (Table 5, compound 13) and extremely large numerical values of the constants J_{P-H}, exceeding by more than 100 c/s the constants $J_{P-F_{ax}}$. There is also a tendency for the constants J_{P-H} to increase with increase in the sum of the electronegativities of the substituents attached to the phosphorus atom.

2. Electron Diffraction

An examination of phosphorus pentafluoride, methylphosphorus tetrafluoride, and dimethyphosphorous trifluoride, made in 1965 by Bartell and Hansen[165], confirmed the trigonal–bipyramidal structure of the molecules and led to the following important conclusions: (1) the more electronegative substituents occupy the vertices of the bipyramid; (2) axial bonds are more polar and longer than equatorial bonds; and (3) the replacement of fluorine atoms by alkyl and other less electronegative substituents results in an increase in the difference $r_{ax} - r_{eq}$. The results can be satisfactorily explained both on the basis of Rundle's model[168–170], which postulates that axial bonds are three-centred and have a bond order of ~ 0.5, and by means of Gillespie's model[171–174], in which the stereochemistry of the molecule is determined by the repulsion of electron pairs. It is difficult to give preference to either model, for, as Bartell remarked[175], they both require additional postulates to explain all the details found for the five-coordinated structure.

3. Vibrational Spectra

Vibrational spectroscopy has also been fairly widely used for analysing the structure of the fluorides of phosphorus. The most significant results have been obtained when the vibrational spectra have been used to solve structural problems in the fluorides of five-coordinated phosphorus. The infrared and Raman spectra of HPF_4 [67,137], H_2PF_3 [67,137,138], and the fluorophosphoranes $(CH_3)_nPF_{5-n}$ (n = 1 – 3) [176] have been interpreted in terms of a trigonal–bipyramidal molecular model in which the less electronegative substituents occupy equatorial positions. In the vapours all the compounds are found to be monomeric,

Table 5. Parameters of ^{31}P and ^{19}F n.m.r. spectra of hydrides of five-coordinated phosphorus*.

No.	Compound	δ_P, ppm	$\delta_{F_{ax}}$, ppm	$\delta_{F_{eq}}$, ppm	$J_{P-F_{ax}}$, c/s	$J_{P-F_{eq}}$, c/s	J_{P-H}, c/s	J_{F-F}, c/s	$J_{H-F_{eq}}/J_{H-F_{ax}}$	Refs.
1**	HPF_4	+53.6	~480***		~980***		1100	—	91	67,137
2**	H_2PF_3	+24	401	484	770	824	841	—	80	67,137
3	CH_3PHF_3	+10	446	530	795	965	850	19	120/30	42,139,140
4	$C_2H_5PHF_8$	—			810	976	862	22.7	121/30	139
5	CH_3PHF_2Cl	—	446	—	785	—	—	—	121	42
6	$CH_3PHF_2[N(C_2H_5)_2]$	—	469	—	832	—	—	—	132	42
7	$CH_3PHF_2(HNC_4H_9\text{-}i)$	+44.5	—	—	622	—	760	—	—	37,38
8	$CH_3PHF_2(HNCH_2{-}CH{=}CH_2)$	+42	—	—	609	—	739	—	—	37,38
9	$CH_3PHF_2(OC_2H_5)$	+20	—	—	757	—	850	—	—	34,35
10	$CH_3PHF_2(OC_3H_7\text{-}i)$	—	452	—	725	—	—	—	120	34,35
11	$\text{NH}{-}PHF_2(CH_3)$ $\text{NH}{-}PHF_2(CH_3)$	+44	—	—	610	—	780	—	120	143
12	$CH_3C_6H_4PHF_3$	+30	$\Delta\delta_F$ = 53 ppm		815	950	—	34	118/34	13,40
13	$CH_3O(C_2H_5NH)PHF_2$	+70	490	—	670	—	818	—	122	14
14	$(CH_3)_2N(C_2H_5NH)PHF_2$	—	488	—	712	—	—	—	127	14
15	$(CH_3)_2PHF_2$	+31.7	458	—	535	—	733	—	98	140

* Chemical shifts δ_P given relative to H_3PO_4, and δ_F relative to F_2.
** The n.m.r. spectra of the deuteriated derivatives are given in Ref. 67.
*** Axial and equatorial fluorine atoms indistinguishable.

whereas in the liquid state the phosphorane PH_2F_3 is associated by means of hydrogen bonds. It is interesting that in the liquid state the hydride HPF_4 is either considerably less or not at all associated.

Investigation by means of the vibrational spectra of phosphorus hydrides of different degrees of coordination has shown that the P–H stretching frequencies appear over a wide range from 2233 cm^{-1} (in HPF_2)[23] to 2545 cm^{-1} (in H_2PF_3). The most significant are the frequencies ν_{P-H} and the constants J_{P-H}, which vary in parallel with the former on passing from the phosphorus(III) fluorides to the four- and five-coordinated compounds (for HPF_2 [23], $HPOF_2$ [64], and HPF_4 [67] we have 2233, 2500, and 2485 cm^{-1} for ν_{P-H}, and 182, 844, and > 1000 c/s for J_{P-H}). Within groups of four- and five-coordinated compounds there is a tendency for ν_{P-H} and J_{P-H} to increase with the electronegativity of the substituents attached to the phosphorus atom (e.g. on passing from $HPSF_2$ [20] to $HPOF_2$ [20] the frequencies ν_{P-H} and the constants J_{P-H} increase by 42 cm^{-1} and 119 c/s respectively, and on passing from HPF_4 [67] to $RPHF_3$ [40,139] by ~40 cm^{-1} and ~150 c/s).

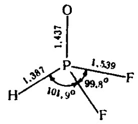
Table 6. Spin–spin interaction constants $J_{P-F_{ax}}$ and P–F stretching frequencies compared with lengths of $P-F_{ax}$ bond for the fluorophosphoranes X_nPF_{5-n}.

No.	Compound	ν_s^{P-F}, cm^{-1}	ν_{as}^{P-F}, sm^{-1}	Mean	$J_{P-F_{ax}}$, c/s	$P-F_{ax}$ bond length, Å
1	PF_5	640	945	793	—	1.577
2	CH_3PF_4	596	843	720	—	1.612
3	$(CH_3)_2PF_3$	540	755	648	772	1.643
4	$(CH_3)_3PF_2$	500	670	585	541	—

* Data taken from Ref. 176.

Increase in the sum of the electronegativities of the substituents in the series of fluorophosphoranes X_nPF_{5-n} ($n = 0-3$) has been shown[176] to be accompanied by contraction of the $P-F_{ax}$ bonds together with an increase in the frequencies of the symmetric and antisymmetric vibrations $\nu_{P-F_{ax}}$ (see Table 6). A similar relation between the sum of the electronegativities of the substituents and the frequencies ν_{P-F} is observed also for several series of compounds of four-coordinated phosphorus[148,149] [for the main results on the vibrational spectra of phosphorus(IV) fluorides see Refs. 148, 149, and 177–184].

Quite recently[185] the microwave spectrum has yielded for $HPOF_2$ the parameters



∠OPF = 116.5°
∠OPH = 117.9°
Dipole moment 2.65 ± 0.03 D

Vibrational and especially microwave spectroscopy has been used very rarely to solve structural problems in the phosphorus(III) fluorides, the number and significance of papers published during the period in which we are interested being fairly limited[186–188].

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U. D. C. 546.18

Cyclodiphosphazanes

A.F.Grapov, N.N.Mel'nikov, and L.V.Razvodovskaya

The chemistry of four-membered cyclic compounds containing both nitrogen and phosphorus, which may find application in the preparation of thermostable plastics and the synthesis of biologically active compounds, has been widely investigated in recent years. This review deals with problems concerning the determination of the structure, the investigation of the physical and chemical properties of cyclodiphosphazanes containing trivalent tetraco-ordinate and pentaco-ordinate phosphorus atoms, and the methods of their synthesis and chemical reactions.

20 The bibliography includes 103 references.

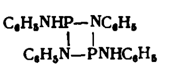
CONTENTS

I. INTRODUCTION

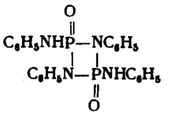
Towards the end of the 19th and the beginning of the 20th century, Michaelis[1,2] described for the first time compounds containing a four-membered ring with alternating phosphorus and nitrogen atoms. The work of Michaelis and his school led to the development of the simplest methods for the synthesis of such compounds. Then for a long time this class of organic phosphorus derivatives remained sidetracked from the mainstream of the development of organic chemistry. It was not until a few years ago that four-membered ring compounds containing both phosphorus and nitrogen atoms again attracted the attention of investigators. The year 1959 must be regarded as the start of the new period in the study of these compounds, when Kirsanov and Zhmurova published their investigation of dimeric trichlorophosphazoarenes[3]. In recent years new synthetic methods have been developed for these compounds, their reactivity has been investigated, and physicochemical studies have been made to determine their structure and to elucidate the mutual effects of the atoms.

Four-membered ring compounds containing both trivalent and tetraco-ordinate and pentaco-ordinate phosphorus atoms have now been obtained.

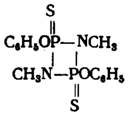
There is no agreement as regards the nomenclature of such cyclic systems. In Sasse's monograph[4] they are referred to as derivatives of imidophosphorous, imidophosphoric, imidophosphonic, imidothiophosphoric, and imidothiophosphonic acids. In chemical literature in English they are sometimes called 1,3,2,4-diazadiphosphetidines[5]. The term "dimeric phosphazo-compounds" is fairly frequently encountered. The name cyclodiphosphazanes proposed by Shaw et al[6] and also by Davydova and Voronkov[7] is the most apt. For example:



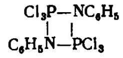
2,4-dianilino-1,3-diphenylcyclodiphospha(III)azane



2,4-dianilino-2,4-dioxo-1,3-diphenylcyclodiphosphazane



1,3-dimethyl-2,4-diphenoxy-2,4-dithionocyclodiphosphazane



2,2,2,4,4,4-hexachloro-1,3-diphenylcyclodiphosphazane

This nomenclature will in fact be adhered to in the present review.

II. THE STRUCTURE OF THE CYCLODIPHOSPHAZANE RING

To establish the structure of cyclodiphosphazanes, various physicochemical methods have been used: X-ray diffraction measurements of dipole moments, infrared and ultraviolet spectroscopy, Raman spectroscopy, and nuclear magnetic resonance (NMR). The data obtained made it possible not only to establish the relative positions of the atoms in the molecule but also to arrive at certain conclusions concerning the nature of the nitrogen–phosphorus bond.

Unfortunately almost all studies of this kind deal with compounds with tetra- and penta-co-ordinate phosphorus atoms. There are no physicochemical data in the literature for cyclodiphosphazanes with a trivalent phosphorus atom.

1. Vibration and Electronic Spectra

Most investigators attribute the intense absorption in the region 850–865 cm^{-1} in the infrared spectra of dialkyl- or diaryl-hexachlorocyclodiphosphazanes to P–N vibrations of the four-membered ring[8-10]. The intense band at 1160–1165 cm^{-1} may be assigned to N-alkyl vibrations[11] but not to P–N–P bridge vibrations or P–N stretching vibrations[8-12].

The vibration frequencies in the infrared and Raman spectra of hexafluorodimethylcyclodiphosphazane have been assigned (Table 1)[13] by analogy with the spectra of alkylfluorophosphoranes[14,15].

The spectra of dithionocyclodiphosphazanes have been investigated in greatest detail[11]. The intense absorption bands in the region 850–900 cm^{-1} in the infrared spectra 1,3-dialkyldithionocyclodiphosphazanes are due to antisymmetric vibrations of the four-membered ring. The replacement of the *N*-alkyl group by an *N*-aryl group leads to an increase of the vibration frequency by about 100 cm^{-1}. The symmetrical vibrations of the ring are revealed only in the Raman spectrum in the region 430–570 cm^{-1}. The infrared spectroscopic data for bis(diphenylthiophosphono)-*N*-alkylamines are satisfactorily consistent with these results. The P–N–P antisymmetric vibration band in their spectra lies in the region 912–928 cm^{-1}, while the band due to the P–N–P symmetrical vibrations is in the region[16] 528–583 cm^{-1}.

The absorption bands at 1150–1180 cm^{-1} in the infrared spectra of 1,3-dialkyl-2,4-dithionocyclodiphosphazanes have been assigned to N–C (alkyl) vibrations. In the spectra of the *N*-aryl analogues these bands occur at 1250–1270 cm^{-1}. 2,4-Dialkyl-2,4-dithionocyclodiphosphazanes absorb in the region 615–630 cm^{-1}, which may be attributed to P=S vibrations. In the spectrum of 2,4-diphenyl-2,4-dithionocyclodiphosphazane the absorption shifts to the region 650–670 cm^{-1}. Such as increase in the P=S vibration frequency as a function of the immediate environment of the phosphorus atom is consistent with the available data[17,18].

Table 1. Infrared and Raman spectra of hexafluorodimethylcyclodiphosphazane

Frequencies of band maxima, cm^{-1}		Assignment
i.r. (vapour)	Raman (liquid)	
1264	1202	C–N antisymmetric
~964	960	C–N symmetrical
934	904	$P-F_{eq}$ antisymmetric
858	839,5	$P-F_{eq}$ symmetrical
807	741,5	$P-F_{ax}$
614	626	$P-N_{eq}$
535	563	$P-N_{ax}$

The ultraviolet spectra 2,4-dialkyl-1,3-diaryl-2,4-dithionocyclodiphosphazanes are virtually identical with those of the dianilides of methylthiophosphonic [methylphosphonothioic? (Ed. of Translation)] acid[11] (Table 2).

Compared with the spectra of *NN'*-dialkyldiaminophenylphosphonothioates, those of 1,3-dialkyl-2,4-diphenyl-2,4-dithionocyclodiphosphazanes show a bathochromic shift of the nearest absorption band [band at the lowest frequency? (Ed. of Translation)] together with an increase in its intensity, and an additional maximum appears at 245 nm.

2. Nuclear Magnetic Resonance Spectra

The ^1H-NMR spectra of hexachlorodimethylcyclodiphosphazane show a 1 : 2 : 1 triplet at 3.00 p.p.m.† with a spin–spin interaction constant $J_{P-N-C-H} = 20$ Hz.[8,19]

The signal due to H–C–N–P protons in the homologues of this compound occurs in the region 3.29–3.58 p.p.m. with an interaction constant of 28–29 Hz. In the NMR spectra of the fluoro-analogues $[CH_3NPF_2X]_2$, where X = F, alkyl, or aryl, the chemical shift of the protons is 2.32–2.48 p.p.m. with an interaction constant J = 12.5–12.9 Hz {for $[CH_3NPF_3]_2$, $J_{P-N-C-H}$ = 14.5 Hz[19,20]}.

The ^{31}P chemical shifts in the spectra of $[RNPCl_3]_2$ and $[CH_3NPF_2C_6H_5]_2$ are +78.2–79.8 and +56.1 p.p.m. respectively (relative to 30% of phosphoric acid)[8,21], i.e. the phosphorus nucleus in chlorocyclodiphosphazanes is more screened than in the fluoro-derivatives. The marked shift indicates that the phosphorus atom in these compounds has a co-ordination number of 5 (for PCl_5, I = +80 p.p.m.).[22]

Table 2. Positions and intensities of the ultraviolet absorption bands of solutions in heptane

Compound		λ_{max}, nm	ϵ_{max}
$[CH_3P(S)NCH_3]_2$	(I)	220	10500
$[CH_3P(S)NC_2H_5]_2$	(II)	222	11000
$[CH_3P(S)NC_6H_5]_2$	(III)	236,280	29000,1500
$[CH_3P(S)NC_6H_4CH_3-4]_2$	(IV)	239,280	42000,1800
$[CH_3P(S)NC_6H_4Cl-4]_2$	(V)	243,285	42800,1900
$[CH_3P(S)NC_6H_4OCH_3-4]_2$	(VI)	238,282	40000,2700
$[CH_3P(S)NC_6H_4OC_2H_5-4]_2$	(VII)	238,282	47000,2500
$[C_6H_5P(S)NCH_3]_2$	(VIII)	220,242,283	20000,11500 s, 8500
$[C_6H_5P(S)NC_3H_7\text{-изо}]_2$	(IX)	220,245,292	25000,12800,9000
$[C_6H_5P(S)NC_6H_5]_2$	(X)	236,265,300	41700,9500, 3000 s
$[C_6H_5P(S)NC_6H_4OC_2H_5-4]_2$	(XI)	236,270,295	41200,9000,4000 s
$C_6H_5P(S)[NHC_3H_7\text{-изо}]_2$	(XII)	255	2500
$CH_3P(S)(NHC_6H_5)(NHC_2H_5)$	(XIII)	238,278	177000,1300
$CH_3P(S)(NHC_6N_5)_2^*$	(XIV)	238,278	28000,2300

*In alcohol. The letter s denotes a shoulder.

In the spectra of 1,3-dialkyl-2,4-dioxocyclodiphosphazanes the constant for the spin–spin interaction of the proton with the phosphorus nucleus via three H–C–N–P bonds is 13.0–16.3 Hz, the chemical shift of the proton signal amounting to 2.6–3.37 p.p.m.[19]

In the ^{31}P-NMR spectra there is a signal in the region between −7.0 and +5.7 p.p.m.,[10,19] which is characteristic of the P=O group[23].

In the ^1H-NMR spectrum of 1,3-dimethyl-2,4-diphenyl-2,4-dithionocyclodiphosphazane Trippett[24] observed a 1 : 2 : 1 triplet (δ = 2.32 p.p.m., J = 14 Hz) and a second triplet, 10 times less intense, at 2.56 p.p.m. (J = 15.5 Hz). According to Mel'nikov et al.[11], the NMR spectrum of a preparation obtained by a different method contains 1 triplet at 2.52 p.p.m. (J = 15 Hz). The ^1H-NMR spectrum of the 1,3-dibenzyl analogue of this compound was found to have two triplets of approximately equal intensity at 4.14 and 3.99 p.p.m. (J = 15.0 and 18.0 Hz). The two triplets are probably due to the presence in the specimens investigated of *cis*- and *trans*-isomers of 1,3-dimethyl- and 1,3-dibenzyl-2,4-diphenyl-2,4-dithionocyclodiphosphazanes. These data agree satisfactorily with the results of the measurements of the dipole moment of 1,3-dimethyl-2,4-diphenyl-2,4-dithionocyclodiphosphazane[25].

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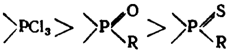
† In the ^1H-NMR spectra the chemical shifts are given in terms of the δ scale relative to tetramethylsilane as an internal standard.

The chemical shifts in the ^{31}P-NMR spectra of dithionocyclodiphosphazanes are in the range between −51.5 and −60 p.p.m.,[10] i.e. the screening of the phosphorus atom decreases in the sequence



$$>PCl_3 > \; >P\begin{smallmatrix}O\\R\end{smallmatrix} \; > \; >P\begin{smallmatrix}S\\R\end{smallmatrix}$$

3. Bond Lengths and Valence Angles

Hess and Forst[26] and also Hoard and Jacobson[27] determined by X-ray diffraction the angles and bond lengths in 2,2,2,4,4,4-hexachloro-1,3-dimethylcyclodiphosphazane. Cox and Corey[28] and Weiss and Hartmann[29] made similar measurements (Table 3) for 2,2,4,4-tetrafluoro-1,3-dimethyl-2,4-diphenylcyclodiphosphazane $[MeNPF_2Ph]_2$ and a compound which was isolated by Becke-Goehring et al.[10] (see p. 27).

Table 3. Bond lengths (in ångstroms) and angles (in degrees).

Bonds and angles	Ref.26	Ref.27	Ref.28	Ref.29
Bonds				
P—Cl axial	2.152	2.133	—	2,16
P—N axial	1.776	1.769	1.78	1,71
P—F axial			1.62	
P—Cl radial	2.022; 2.018	2.026		2.05
P—N radial	1.629	1.635	1.64	1.66
P—F radial			1.57	
P—C			1.79	
N—C	1.476	1.475	1.44	
Angles				
P—N—P	98.3	99.5	99.4	99.1
N—P—N	81.7	80.5	80.6	80.7

A centrosymmetric structure with a planar four-membered ring is characteristic of the molecules of cyclodiphosphazanes with a pentacovalent phosphorus atom (see Figure). Each phosphorus atom exhibits dsp^3 hybridisation and consists of a trigonal bipyramid. In such hybrid structures the axial orbitals are longer than the radial orbitals by a factor of 1.1–1.2. This ratio is 1.05–1.07 for P–Cl bonds, 1.085–1.09 for P–N bonds, and 1.08 for P–F bonds. The P–N–P and N–P–N angles are 98.3–99.5°C and 80.5–81.7°C respectively.

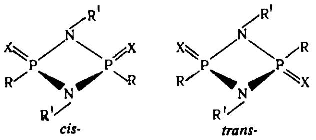
In 2,4-dichloro-1,3-dimethyl-2,4-dithionocyclodiphosphazane containing an sp^3-hybridised phosphorus atom, P–N bonds are of the same length (1.67 Å), i.e. they assume the average value for the radial and axial bond lengths[30]. The lengths of other bonds and the angles between them are given below.

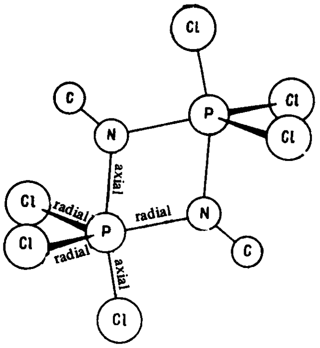
Bond length	P—S (Cl)*	1.93 A
	N—C	1.46 A
Angle	N—P—N	84.0°
	P—N—P	96.0°
	N—P—S (Cl)	114.7°
	S—P—Cl	111.5°

*Weiss and Hartmann do not distinguish S and Cl; usually the P–Cl bond length is 0.01 Å.[23]

4. Dipole Moments

Cyclodiphosphazanes with a tetraco-ordinate phosphorus atom can exist as *cis*- or *trans*-isomers[25]:





The occurrence of *cis*- and *trans*-isomerism in the series of 2,4-dithionocyclodiphosphazanes has been fairly convincingly confirmed by the measurements and calculations of their dipole moments (Table 4), although the calculations were based on a simplified scheme and the extrapolated results of a relatively small number of measurements by different investigators. The considerable deviation of experimental dipole moments of the *trans*-isomers from zero may be explained by their partial inversion in solution.

Table 4. Dipole moments of certain dithionocyclodiphosphazanes.

R	R′	μ_{exp}	$\mu_{cis.\,calc}$
CH_3	CH_3	6.11	7.18
C_6H_5	C_6H_5	5.84	6.70
CH_3	C_6H_5	1.82	7.18
C_6H_5	CH_3	0.7	6.70
Cl	C_6H_5	1.32	3.57

5. Bond Energies

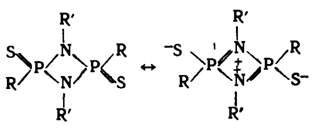
Only one study has been made on the thermochemistry of cyclodiphosphazanes, namely that of Fowell and Mortimer[31], who found that the average P–N bond energy in 2,2,2,4,4,4-hexachloro-1,3-dimethylcyclodiphosphazanes is 74.3 kcal mole^{-1} according to measurements of the heat of hydrolysis. This is close to the P–N bond energy in cyclotriphosphazenes (72.3 kcal mole^{-1}) and cyclotetraphosphazenes (72.5 kcal mole^{-1})[32] and greatly exceeds the energy of the same bond in tri(diethylamino)phosphine (66.8 kcal mole^{-1}).[33] The fact that the formation of the cyclodiphosphazane ring is favoured by thermodynamic factors is indicated also by chemical data. The reaction of tri(diethylamino)phosphine with aniline yields the corresponding cyclodiphospha(III) azane[34].

The P–Cl bond energy is 63.1 kcal mole^{-1},[31] i.e. is smaller by 13.1 kcal mole^{-1} than in PCl_5.[35]

6. The Nature of the Phosphorus–Nitrogen Bond

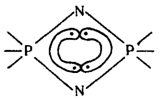
The available physicochemical data on the structure of cyclodiphosphazanes permit certain conclusions concerning the nature of the P–N bond. The shortening of the P–N bond, the planarity of the dimer, the location of the N atoms in the same plane (according to X-ray diffraction analysis), the thermochemical data, and the relatively high stability of the ring in cyclodiphosphazanes with tetra- and penta-co-ordinate phosphorus atoms (see sections IV and V) are evidence of an additional interaction between nitrogen and phosphorus atoms.

The idea that dithionocyclodiphosphazane molecules are stabilised by isomerisation, described by the resonance of the structures[24]



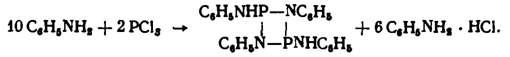
is not confirmed by physicochemical investigations.

It is most probable that the molecules of cyclodiphosphazanes are stabilised by the interaction of the unshared electron pairs of the nitrogen atoms with the *d* orbitals of the adjacent phosphorus atoms[26,36] via three-centre *π*-molecular orbitals[37,38]:



III. CYCLODIPHOSPHAZANES WITH TRICO-ORDINATE PHOSPHORUS ATOMS

The reaction of phosphorus trichloride with aromatic amines in a non-polar solvent yields 2,4-diaminocyclodiphospha(III) azanes[39,40]:



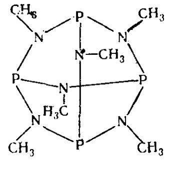
$$10\,C_6H_5NH_2 + 2\,PCl_3 \rightarrow \begin{array}{l} C_6H_5NHP{-}NC_6H_5 \\ \quad\;\; | \quad\; | \\ C_6H_5N{-}PNHC_6H_5 \end{array} + 6\,C_6H_5NH_2 \cdot HCl.$$

An excess of the amine introduced into the reaction or a tertiary amine may be used as the acceptor of hydrogen chloride[5]. Phenyldichlorophosphine reacts similarly[39].

The reaction of phosphorus trichloride with ammonia and primary aliphatic amines does not take place unambiguously. With ammonia, a number of products are formed, according to the following mechanism[41,42]:

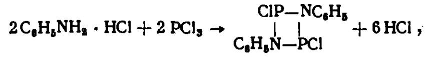
$$PCl_3 + NH_3 \rightarrow P(NH_2)_3 \rightarrow [HNP(NH_2)]_n \rightarrow (PNH)_n \rightarrow PN.$$

The reaction of phosphorus trichloride with methylamine gives a compound with a urotropine-like structure[43,44]:

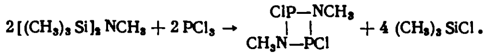


When straight-chain primary amines containing two and more carbon atoms are introduced into the reaction, the corresponding cyclodiphospha(III) azanes are formed[40].

The reaction of aniline hydrochloride with phosphorus trichloride yields 2,4-dichloro-1,3-diphenylcyclodiphospha(III) azane[45]. Its 1,3-dimethyl analogue has been obtained by the amination of phosphorus tetrachloride with heptamethyldisilazane[46]:



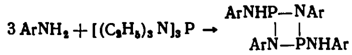
$$2\,C_6H_5NH_2 \cdot HCl + 2\,PCl_3 \rightarrow \begin{array}{l} \quad\;\; ClP{-}NC_6H_5 \\ \qquad\;\; | \quad\; | \\ C_6H_5N{-}PCl \end{array} + 6\,HCl,$$



$$2\,[(CH_3)_3Si]_2NCH_3 + 2\,PCl_3 \rightarrow \begin{array}{l} \quad\; ClP{-}NCH_3 \\ \qquad | \quad\; | \\ CH_3N{-}PCl \end{array} + 4\,(CH_3)_3SiCl.$$

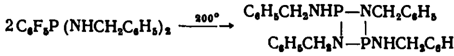
It is noteworthy that the reaction of *N*-ethylhexamethyldisilazane with phosphorus trichloride yields a mixture containing 2,4,6-trichloro-1,3,5-triethylcyclotriphosphazane and 2,4,6,8-tetrachloro-1,3,5,7-tetraethylcyclotetraphosphazane[47].

The reaction of tri(triethylamino)phosphine with aniline or *p*-toluidine at 60–70°C leads to the formation of 2,4-dianilino-1,3-diarylcyclodiphospha(III) azanes[34]:



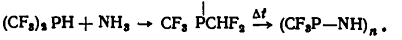
$$3\,ArNH_2 + [(C_2H_5)_2N]_3P \rightarrow \begin{array}{l} ArNHP{-}NAr \\ \quad\;\; | \quad\; | \\ \quad ArN{-}PNHAr \end{array}.$$

The synthesis of 1,3-dibenzyl-2,4-di(benzylamino)cyclodiphospha(III)azane by the thermal dissociation of the di(benzylamide) of pentafluorophenylphosphonus acid[48] is interesting:



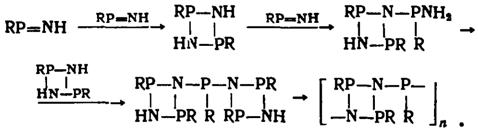
$$2\,C_6F_5P(NHCH_2C_6H_5)_2 \xrightarrow{200^\circ} \begin{array}{l} C_6H_5CH_2NHP{-}NCH_2C_6H_5 \\ \qquad\qquad\quad | \quad\; | \\ \quad C_6H_5CH_2N{-}PNHCH_2C_6H_5 \end{array}$$

Cyclodiphosphazanes can form part of certain polymeric compounds. Thus the thermal decomposition of the amides of pentafluorodimethylphosphinous acid, obtained by the ammonolysis of di(trifluoromethyl)phosphine with liquid ammonia at −78°C, yields linear and cross-linked polymers:

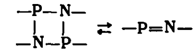


$$(CF_3)_2PH + NH_3 \rightarrow CF_3\overset{\displaystyle NH_2 \atop |}{P}CHF_2 \xrightarrow{\Delta t} (CF_3P{-}NH)_n.$$

The mechanism of their formation is probably as follows[49]:



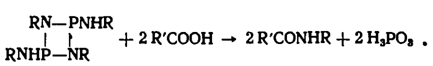
Cyclodiphosphazanes containing a trivalent phosphorus atom are present in solution with a corresponding phospha(III)azo-compounds. On raising the temperature and increasing the polarity of the solvent, the equilibrium shifts to the right[5,40]:



$$\begin{array}{c} {-}P{-}N{-} \\ |\quad\; | \\ {-}N{-}P{-} \end{array} \rightleftarrows {-}P{=}N{-}.$$

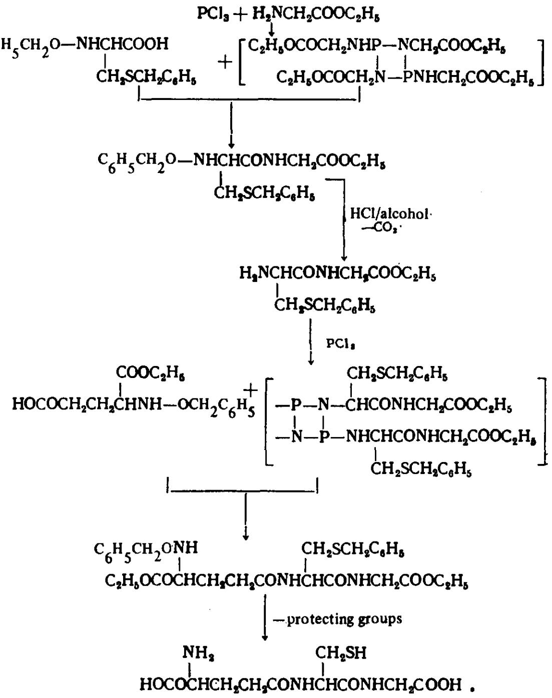
This equilibrium accounts to a large extent for the ease of the dissociation of the cyclodiphosphazane ring under the action of nucleophilic reagents.

When water reacts with diaminocyclodiphospha(III)azanes, diamides of phosphorous acid are formed. Inorganic acids decompose cyclodiphosphazanes to phosphorous acids and substituted ammonium salts. Organic acids react with formation of carboxylic acid amides[45,50,51]:

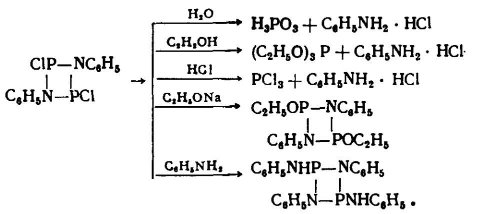


$$\begin{array}{l} \quad RN{-}PNHR \\ \qquad | \quad\; | \\ RNHP{-}NR \end{array} + 2\,R'COOH \rightarrow 2\,R'CONHR + 2\,H_3PO_3.$$

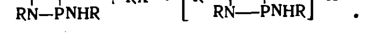
The salts of carboxylic acids do not react with cyclodiphosphazanes. Preparative methods for the synthesis of acid amides, substituted ureas, and di-, tri-, and tetrapeptides have been developed on the basis of these data[50-56]. In the synthesis of peptides, amino-acid derivatives are allowed to react with phosphorus trichloride, the reaction mass being subsequently treated with the amino-acid without isolating the cyclodiphospha(III)azane in a pure form. The following elegant synthesis of glutathione may be quoted as an example[51]:



2,4-Dichloro-1,3-diphenylcyclodiphospha(III)azane also readily reacts with nucleophilic reagents, undergoing ring rupture, under the conditions of acid catalysis. It undergoes substitution reactions with alkaline nucleophilic reagents (sodium alkoxides, piperidine, aniline)[45,56]:



Cyclodiphospha(III) azanes also enter into addition reactions with electrophilic reagents via the unshared electron pairs. Thus in the reaction with alkyl halides, arylalkyl halides, and halogenomethyl ethers, 1,3-dialkyl-2,4-di(alkylamino)cyclodiphosphazanes are converted into the corresponding salts[5]:



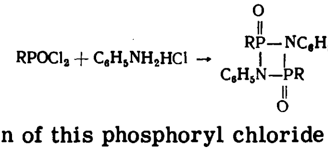
The charge distribution in this molecule has not been investigated.

N-Methylaniline has been isolated after the reaction of 2,4-dianilino-1,3-diphenylcyclodiphosphazane with methylmagnesium iodide and dimethyl sulphate[53].

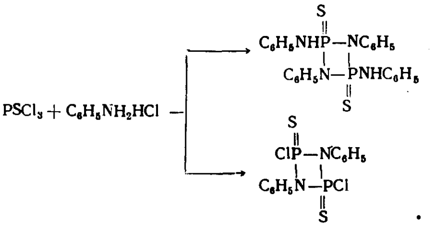
IV. CYCLODIPHOSPHAZANES WITH TETRACO-ORDINATE PHOSPHORUS ATOMS

Cyclodiphosphazanes with tetraco-ordinate phosphorus atoms are obtained both from linear molecules and from pre-formed cyclic structures.

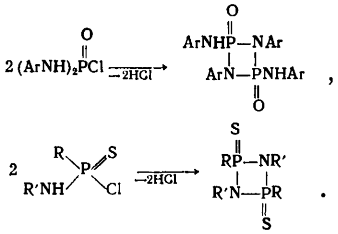
When the hydrochlorides of aromatic amines[2,57,58] or the free amines themselves[59] are heated for many hours with phosphorus oxychloride, phosphoramidic dichlorides, aryl phosphorodichloridates, or phenylphosphonic dichlorides in xylene, 2,4-dioxocyclodiphosphazanes are obtained:



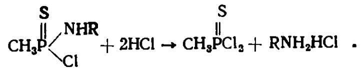
The reaction of this phosphoryl chloride with aniline hydrochloride leads to 2,4-dianilino-1,3-diphenyl or 2,4-dichloro-1,3-diphenyl-2,4-dithionocyclodiphosphazanes depending on the reactant ratio and the process conditions[60]:



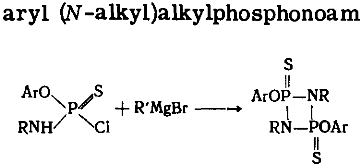
The thermal dehydrochlorination of the chlorides of pentavalent phosphorus acid amides containing a primary or a secondary nitrogen atom results in the formation of the corresponding 2,4-dioxo- or 2,4-dithionocyclodiphosphazanes[1,11,58]:



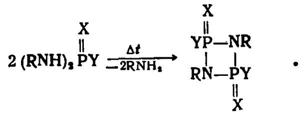
The last reaction is carried out at a reduced pressure of 100–200 mmHg and 120–150°C. Methylphosphonothionic dichloride and the hydrochloride of the corresponding amine were isolated as side products. Their formation may be explained by the following mechanism[11]:



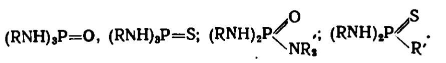
The attempts to employ tertiary amines as acceptors for hydrogen chloride in this process were unsuccessful. However, quite unexpectedly, it was found that organomagnesium compounds may be used as dehydrochlorinating agents. Thus the reaction of butyl- or pentyl-magnesium bromide with aryl *N*-alkylphosphoramidochloridothionates led to the corresponding dithionocyclodiphosphazanes together with aryl (*N*-alkyl)alkylphosphonoamidothionates[61]:



The most general method for the synthesis of dioxo- and dithiono-cyclodiphosphazanes of different structures is thermal deamination of the amides of phosphorus acids containing at least two secondary amide groups[1,24,58,62-66]:



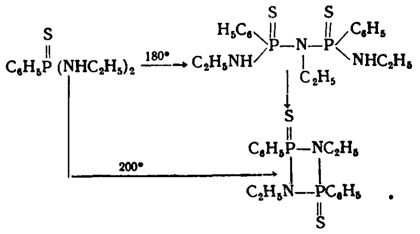
Compounds of the following types have been used as the starting materials:



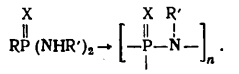
$(RNH)_3P{=}O,\ (RNH)_3P{=}S;\ (RNH)_2P({=}O)NR_2;\ (RNH)_2P({=}S)R'.$

The reaction is carried out in a stream of an inert gas at 200–300°C. The derivatives of thioic acids usually decompose at a lower temperature and give higher yields of the final products than oxygen analogues. When phosphorothionic tri(isobutylamide) was heated in the temperature range 260–280°C, the corresponding dithionocyclodiphosphazane was isolated in a 56% yield. The preparation of the oxygen analogue required a temperature of 280–295°C and the yield fell to 21%.[64]

Ibrahim and Shaw[65] obtained data demonstrating indirectly that thermal cyclisation of phosphorus acid amides takes place in steps. Thus on heating to 180°C phenylphosphonothionic di(ethylamide) is converted into di-*N*-ethylphenylphosphonamidothionylethylamine, while the reaction at 200°C leads to the formation of the corresponding dithionocyclodiphosphazane:

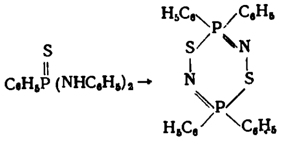


The synthesis of dioxo- and dithiono-cyclodiphosphazanes by the thermal deamination of the amides of phosphorus acid is accompanied by a side process—polycondensation involving the formation of polymers with phosphorus—nitrogen bonds[67-69]:

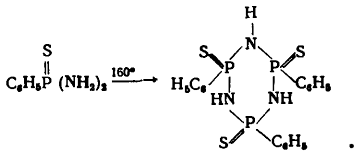


$RP(X)(NHR')_2 \rightarrow \left[-\overset{X}{\underset{|}{P}}-\overset{R'}{N}-\right]_n.$

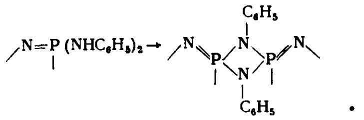
Cleavage of the dianilide of phenylphosphonothionic acid at 265°C leads to the formation of 1,1,4,4-tetraphenyl-2,5-diaza-3,6-dithia-1,4-diphosphacyclohexa-1,4-diene[65] and not tetraphenyldithionocyclodiphosphazane:



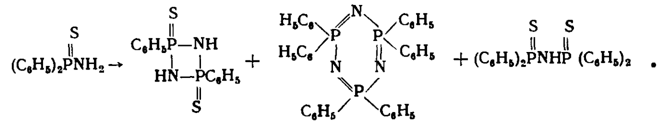
Thermal deamination of phenylphosphonothionic diamide at 160°C results in the formation of 2,4,6-triphenyl-2,4,6-trithionocyclotriphosphazane, while *N*-alkyl homologues yield under these conditions dithionocyclodiphosphazanes[65]:



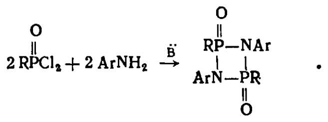
Probably the polymeric products formed in the thermal condensation of hexa-anilinocyclotriphosphazenes include cyclodiphosphazane structures[70]:



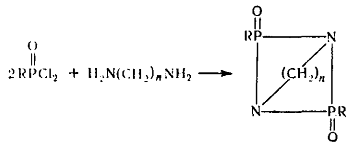
2,4-Diphenyl-2,4-dithionocyclodiphosphazane in a yield of 17% together with bisdiphenylphosphonothionic imide and 2,2,4,4,6,6-hexaphenylcyclotriphosphazene were isolated from a mixture obtained on thermal decomposition of diphenylphosphinothionic amide at 280°C for 30 min[71]:



The reaction of the dichlorides of alkyl(aryl)phosphonic acids with primary aliphatic or aromatic amines in the presence of bases (molar ratios of the reactants 1 : 1 : 2) in inert solvents constitutes a convenient method for the synthesis of 1,3-dialkyl(aryl)-2,4-dialkyl(aryl)-2,4-dioxocyclodiphosphazanes[66,72-76]:

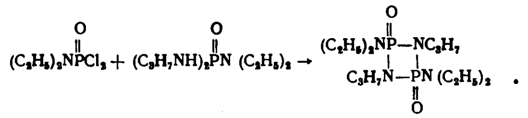


According to Binder and Heinle[72], the reaction of one mole of an alkylenediamine with two moles of a phosphonic acid dichloride can lead to the formation of dioxocyclodiphosphazanes with an alkylene bridge between the nitrogen atoms:

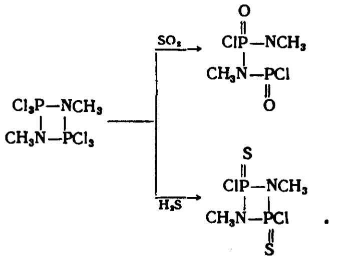


However, the structure of the compound obtained was not proved.

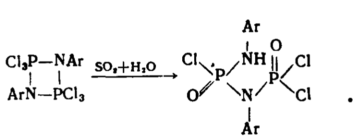
Bock and Wiegrabe[64] proposed an interesting method for the synthesis of dioxocyclodiphosphazanes with various substituents at the nitrogen atom. When the dichloride of *NN*-diethylphosphoramidic acid was heated with phosphoric *NN*-diethyldi(*N'*-propyl)triamide in benzene in the presence of triethylamine, the product was 1,3-dipropyl-2,4-di(diethylamino)-2,4-dioxocyclodiphosphazane:



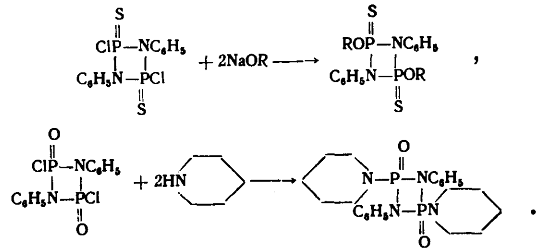
The conversion of 2,2,2,4,4,4-hexachlorocyclodiphosphazanes into 2,4-dichloro-2,4-dioxo- or 2,4-dichloro-2,4-dithiono-cyclodiphosphazanes takes place when the former compounds are treated with sulphur dioxide or hydrogen sulphide in the presence of pyridine[10,19].



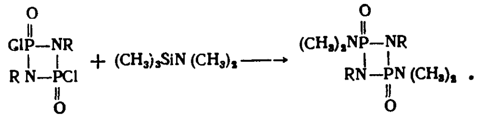
Treatment of hexachlorocyclotriphosphazanes with sulphur dioxide in the presence of moisture in phosphorus oxychloride results in ring rupture and the formation of *NN'*-diaryl-*N*-(dichlorophosphinyl)phosphorodiamidic chloride[77]:



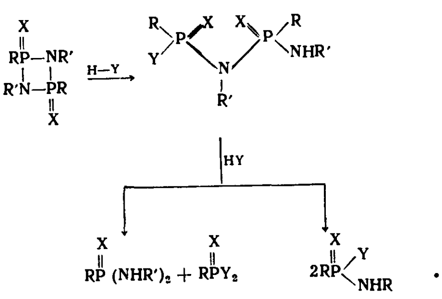
Substitution of a halogen in 2,4-dichloro-2,4-dioxo- or 2,4-dichloro-2,4-dithiono-cyclodiphosphazanes may be used for the introduction of various substituents into the molecule. Thus the reaction with sodium alkoxides or phenoxides under mild conditions leads to the formation of 2,4-dialkoxy-derivatives. The reactions with amines or anilines yield 2,4-diamino-derivatives of 2,4-dioxo- or 2,4-dithiono-cyclodiphosphazanes[2,60]:



Halogen substitution in 2,4-dichloro-2,4-dioxocyclodiphosphazanes by dialkylamino- and alkylthio-groups has also been achieved by reaction with dialkylamino- and alkylthio-trimethylsilanes respectively[19]:

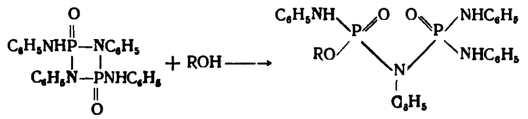


Cyclodiphosphazanes with tetraco-ordinate phosphorus atoms are fairly stable. However, nucleophilic reagents with a labile hydrogen atom, such as water, alcohols, phenols, amines, β-diketones, esters of β-keto-acids, etc. at a high temperature rupture the four-membered ring[1,2,8,62,63,78,79]. The process takes place in steps:

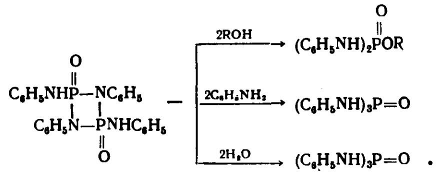


Initially one P–N bond dissociates and an unsymmetrical diphosphoric imide (or a diphosphonic imide or their thio-analogues) is formed and reacts with a molecule of the nucleophilic reagent with dissociation of the second P–N bond. This may result in the formation of both symmetrical and unsymmetrical compounds[63,79].

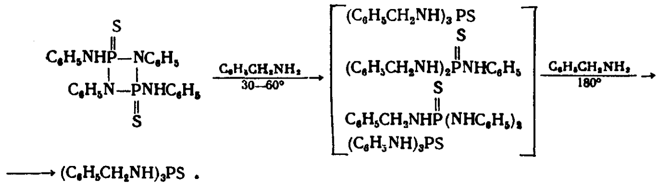
The cleavage reactions of 2,4-dioxocyclodiphosphazanes have been investigated in greater detail. Michaelis[1,2] showed that the process may also be stopped at the first stage. For example, when one mole of phenol, ethyl alcohol, or sodium alkoxide reacts with 2,4-dianilino-1,3-diphenyl-2,4-dioxocyclodiphosphazane, the corresponding diphosphoric imides are formed[2,58]:



Esters of *NN*-diphenylphosphorodiamidic acid have been isolated after reaction with two moles of phenol or alcohol. The reaction with two moles of water gives phosphoric trianilide. The latter was also isolated after the reaction with aniline:

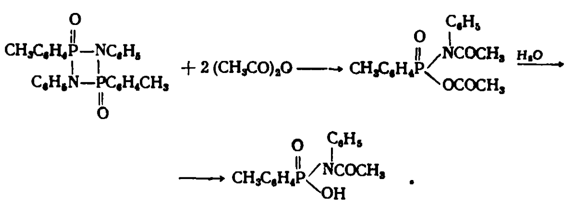


The reaction of 2,4-dianilino-1,3-diphenyl-2,4-dithionocyclodiphosphazane with benzylamine at 30–60°C leads to a mixture of phosphorothionic triamides, which could not be separated. If the mixture is heated with an excess of benzylamine at 180°C, transamination takes place and phosphorothionic tri(benzylamide) is formed[63]:

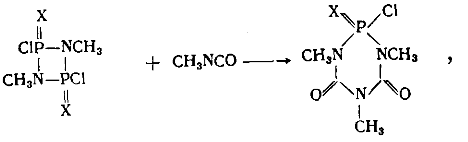


The reaction of 2,4-dimethyl-1,3-diphenyl-2,4-dithionocyclodiphosphazane with butylamine in a sealed tube at 160–170°C for several hours yielded a mixture of products containing the dianilide, *N*-butyl-*N'*-phenyl-diamide, and di-(n-butylamide) of methylphosphonothionic acid. The mixture could be separated by thin-layer and column chromatography[79].

The reaction of acetic anhydride with 1,3-diphenyl-2,4-ditolyl-2,4-dioxocyclodiphosphazane gave the *N*-acetylated mixed anhydride of phosphonic and acetic acids, which is readily hydrolysed by water and yields the corresponding phosphonoamidic acid[2]:



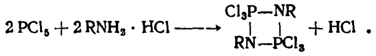
The reaction of 2,4-dichloro-1,3-dimethyl-2,4-dioxocyclodiphosphazane or its sulphur analogue with methyl isocyanate results in the formation of 1-chloro-2,4,6-trimethyl-1,2,4,6-phosphatriazane-1,3,5-trione. The process is carried out in a sealed tube in dry benzene at 100°C for several days[80]:



where X = O or S.

V. CYCLODIPHOSPHAZANES WITH PENTACO-ORDINATE PHOSPHORUS ATOMS

The simplest and most general method for the synthesis of 1,3-dialkyl- or 1,3-diaryl-2,2,2,4,4,4-hexachlorocyclodiphosphazanes consists in the reaction between phosphorus pentachloride and primary aliphatic amines and also the hydrochlorides of aliphatic and aromatic amines[3,8,81-87]:



$$2\,PCl_5 + 2\,RNH_2\cdot HCl \longrightarrow \begin{array}{c} Cl_3P-NR \\ |\quad\ \ | \\ RN-PCl_3 \end{array} + HCl\ .$$

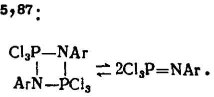
This reaction was discovered by Kirsanov and Zhmurova[3] in 1959. The reaction of phosphorus pentachloride with aniline hydrochloride was first investigated by Gilpin[88], but the latter was unable to establish the structure of the compound produced.

Whether or not the reaction occurs depends on the basicity of the initial amines. An empirical rule has been deduced from experimental data for substituted anilines, according to which hexachlorocyclodiphosphazanes are formed only if the basicity constant of the initial aniline is higher than 1×10^{-13}.

With less basic anilines, the reaction leads to the formation of trichlorophosphazoarenes[85,87]:

$$PCl_5 + RNH_2\cdot HCl \rightarrow Cl_3P{=}NR + 3\,HCl\ .$$

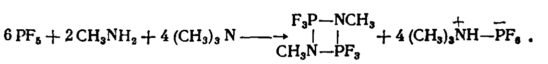
On heating in benzene solution or without solvent up to 150°C and above, hexachlorodiarylcyclodiphosphazanes are frequently converted into phosphazo-compounds, which on evaporation of the solution dimerise and are reconverted into cyclic products[85,87]:



$$\begin{array}{c} Cl_3P-NAr \\ |\quad\ \ | \\ ArN-PCl_3 \end{array} \rightleftarrows 2Cl_3P{=}NAr\,.$$

In the case of aliphatic amines, the structure of the aliphatic chain plays an important role rather than the basicity of the compound[8,82-84]. While amines with an unbranched chain and their hydrochlorides form hexachlorodialkylcyclodiphosphazanes in the reaction with phosphorus pentachloride, amines with substituents in α- and β-positions yield as a rule trichlorophosphazoalkanes. Substituents in the γ-position do not have a significant effect on the reaction.

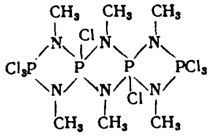
$C_6H_5PCl_4$ can react with aliphatic and aromatic amines[89,90] to form 1,3-dialkyl(diaryl)-2,2,4,4-tetrachloro-2,4-diphenylcyclodiphosphazanes. Amines react with phosphorus pentafluoride in the presence of tertiary amines:



$$6\,PF_5 + 2\,CH_3NH_2 + 4\,(CH_3)_3\,N \longrightarrow \begin{array}{c} F_3P-NCH_3 \\ |\quad\ \ | \\ CH_3N-PF_3 \end{array} + 4\,(CH_3)_3\overset{+}{N}H-\overset{-}{P}F_6\ .$$

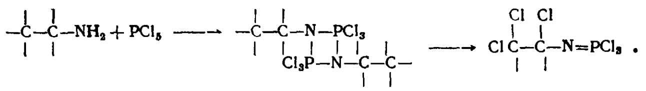
In many cases it is convenient to employ adducts of amines and phosphorus pentafluoride. Thus the 1 : 3 adduct of aniline with phosphorus pentafluoride yields hexafluoro-2,4-diphenylcyclodiphosphazane[91,92].

As regards side reactions, mention should be made of the formation of a tricyclic spirane when phosphorus pentachloride reacts with methylamine hydrochloride[10]:

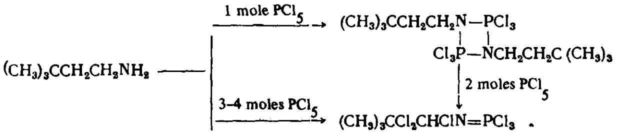


(I)

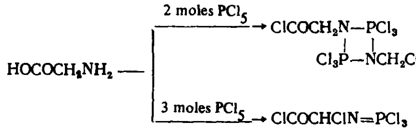
Another side process is the chlorination of the carbon chain of the amine by the excess phosphorus pentachloride. For example, aliphatic amines can be chlorinated simultaneously in the α- and β-positions, This process consists of many stages. A cyclodiphosphazane evidently forms initially and is then chlorinated in stages and converted into a trichlorophosphazochloroalkane[93]:



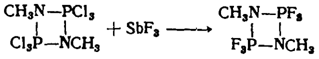
This mechanism is confirmed indirectly by experimental data. Thus the reaction of $\gamma\gamma$-dimethylbutylamine with one mole of phosphorus pentachloride leads to the formation of the corresponding cyclodiphosphazane and the reaction with 3–4 moles of phosphorus pentachloride yields $\alpha\beta\beta$-trichloro-trichlorophosphazo-$\gamma\gamma$-dimethylbutane. The latter has also been isolated as the product of the reaction between two moles of phosphorus pentachloride and 2,2,2,4,4,4-hexachloro-1,3-di-($\gamma\gamma$-dimethylbutyl) cyclodiphosphazane:



Similarly the reaction of glycine with two moles of phosphorus pentachloride leads to the formation of hexachloro-1,3-di(chlorocarbonylmethyl)cyclodiphosphazane. When the amount of phosphorus pentachloride is increased, the product is trichlorophosphazochlorocarbonylchloromethane[84,93].



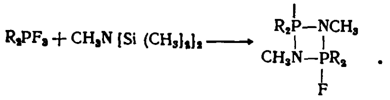
Hexafluorocyclodiphosphazanes can be synthesised in high yields by double decomposition of hexachlorocyclodiphosphazane with antimony trifluoride[94]:



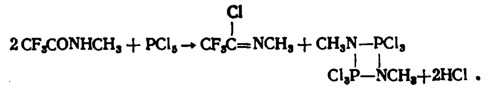
$$\begin{array}{c} CH_3N-PCl_3 \\ |\quad\ \ | \\ Cl_3P-NCH_3 \end{array} + SbF_3 \longrightarrow \begin{array}{c} CH_3N-PF_3 \\ |\quad\ \ | \\ F_3P-NCH_3 \end{array}.$$

Fluorination can be also achieved with KSO_2F in nitrobenzene but the yields are low[95].

An interesting method for the synthesis of fluorinated cyclodiphosphazanes is the reaction of heptamethyldisilazane with phosphorus pentafluoride, alkyl- and aryltetrafluorophosphoranes, or dialkyl- and diaryl-trifluorophosphoranes[96,97]:

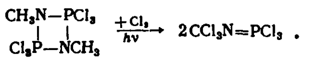


When the methylamide of trifluoroacetic acid was heated with phosphorus pentachloride, dimethylhexachlorocyclodiphosphazane and 1-chloro-2,2,2-trifluoro-*N*-methylethylideneimine were isolated[98]:

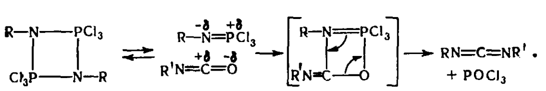


All hexachloro- or tetrachloro-diphenylcyclodiphosphazanes are white crystalline materials readily soluble in organic solvents and readily hydrolysed by atmospheric moisture.

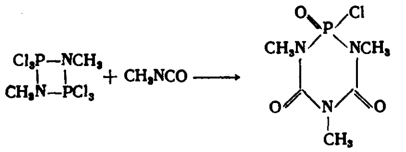
Photochemical chlorination converts hexachlorodimethylcyclodiphosphazane into monomeric trichlorophosphazotrichloromethane[94]:



Hexachlorocyclodiphosphazanes readily react with compounds having a polarised double bond[99]. The reaction takes place above 150°C. Under these conditions, cyclodiphosphazanes probably dissociate to phosphazo-compounds. For example, the reaction of hexachlorodimethylcyclodiphosphazane with phenyl isocyanate in *o*-dichlorobenzene at 175–180°C yields methylphenylcarbodi-imide. Similarly diphenylcarbodi-imide is obtained from hexachlorodiphenylcyclodiphosphazane. The corresponding isothiocyanates and isocyanates are formed analogously in the reaction with carbon disulphide and carbon dioxide. The reaction probably involves the formation of a four-membered cyclic intermediate:

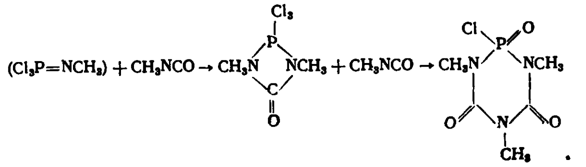


1-Chloro-2,4,6-trimethyl-1,2,4,6-phosphatriazane-1,3,5-trione was obtained on prolonged heating of hexachlorodimethylcyclodiphosphazane with methyl isocyanate in a sealed tube with dry benzene at 100°C:[80]

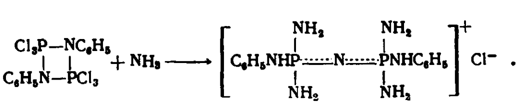


Phosphorus oxychloride and *N*-methyliminophosgene were formed as side products.

To account for the mechanism of this reaction, one may suppose that methyl isocyanate attacks the "intact" four-membered ring with formation of a cyclic system comprising a large number of units as the result of the addition of one or several methyl isocyanate molecules. Transannular double decomposition reaction with other methyl isocyanate molecules yields a six-membered cyclic system which is energetically more favoured. The dissociated bonds are reformed and the process can be repeated. On the other hand, one may suppose that monomeric trichlorophosphazomethane reacts with methyl isocyanate:

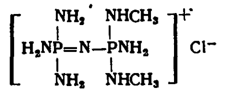


The reactions of hexachlorocyclodiphosphazanes with sulphur dioxide and hydrogen sulphide in the presence of bases were considered in the preceding section. The reaction of hexachlorodiphenylcyclophosphazane with liquid ammonia yields a phosphonium salt (II) in a yield of 41%:[100]



(II)

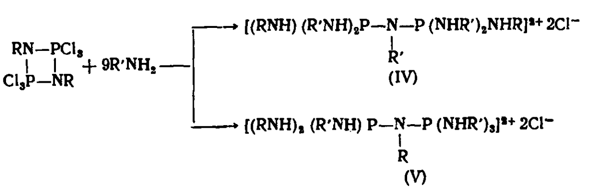
Hexachlorodimethylcyclodiphosphazane reacts similarly with ammonia: both chlorine atoms are substituted with simultaneous cleavage of the ring and the formation of the salt (III), the structure of which has been confirmed by X-ray diffraction analysis[102, 103]:



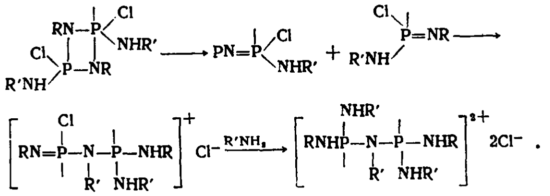
(III)

The reaction of methylamine and hexachlorodiphenylcyclodiphosphazane leads to a polymer with a molecular weight of 1450 and a melting point of 58°C; dimethylamine yields monomeric products[101] with the general formula $C_6H_5N{-}PCl_n[N(C_2H_5)_2]_{3-n}$.

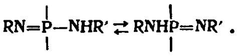
Hexachlorodialkylcyclodiphosphazanes react with an excess of primary amines to form bisphosphonium salts, the structure of which has not, however, been demonstrated[104]:



Two mechanisms have been proposed for the aminolysis of hexachlorocyclodiphosphazanes[104]. In the first of these the initial formation of a phosphazo-structure is postulated:

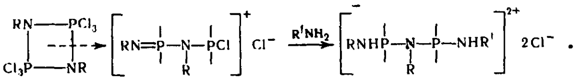


Compounds with the structure (IV) can also be formed by this mechanism if one takes into account the possibility of the tautomerism of the intermediate phosphazo-compound:



$$RN{=}P{-}NHR' \rightleftarrows RNHP{=}NR' .$$

The second mechanism involves the dissociation of one phosphorus–nitrogen bond at a definite stage in the substitution of chlorine atoms by alkylamino-groups:



The available experimental data are more consistent with this mechanism; it also agrees with the mechanism proposed for the reaction of cyclodiphosphazanes having tetraco-ordinate phosphorus atoms with nucleophilic reagents[79].

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All-Union Research
Institute for Chemical
Plant Protection Agents,
Moscow

U. D. C. 541.515

Interactions between Atoms and Radicals in the Liquid Phase

E.T.Denisov

CONTENTS

The review presents a compilation and an analysis of the results of quantitative kinetic studies on liquid-phase interactions between atoms and free radicals. Problems such as the diffusion mechanism for the recombination of atoms in solution, the competition between recombination and disproportionation reactions of alkyl radicals in the liquid phase, the mechanisms of the reactions of secondary and tertiary peroxy-radicals, the effect of the viscosity, internal pressure, and dielectric constant of the liquid on the rate constant for the interaction between the radicals, and also the role of radical hydrogen bonds are discussed. The rate constants for 142 interactions of atoms and radicals in different solvents are quoted.
The bibliography includes 165 references.

I. INTRODUCTION

The interactions of atoms and radicals play an important role in a wide variety of free-radical reations. In chain reactions such as polymerisation, oxidation, and halogenation the elementary steps involving interactions between free radicals are responsible for chain termination (in the absence of inhibitors). For this reason, the concentration of free radicals and hence the rate of the chain process depend on the rate constants for these reactions. Atoms and radicals arise in the liquid phase under the action of light and penetrating radiation. Very frequently in such cases the reactions between free radicals determine not only the rate of formation of products but also their composition.

Reactive free radicals and atoms interact with one another very rapidly; this retarded the quantitative study of these processes for a long time. The development and extension of the kinetic methods for the investigation of fast reactions constituted an important pre-condition for the vigorous development of studies on radical reactions in the last twenty years. A large amount of data has accumulated on the kinetics of recombination and disproportionation reactions of free radicals. The interest in these reactions is not fortuitous, since they constitute an example of the interaction of chemically highly reactive species and occupy an important place in chain processes. The aim of the present review is to examine the experimental data and theoretical concepts concerning the interactions of atoms and radicals in solution.

The rate constants for the reactions of atoms and radicals are measured by the following methods: electron spin resonance (ESR), method of the non-steady-state kinetics of chain reactions (NKR), the method of intermittent illumination—the rotating sector method (RSM), flash photolysis (FP), pulse radiolysis (PR), flow methods (FM), the method of photochemical space intermittency (PSI), and the method of competing reactions (MCR). These methods have been described in monographs and individual papers [1-8].

II. RECOMBINATION OF ATOMS IN SOLUTION

In the gas phase atoms recombine in triple collisions of two atoms with a third particle (molecule or atom) which partially deactivates the excited molecule formed from the atoms. In solution a third particle (solvent molecule) is always present. Therefore the rate of recombination of atoms in solution is limited solely by their diffusion. The rate constants for the recombination of hydrogen, bromine, and iodine atoms are similar (Table 1) and lie in the range $1 \times 10^{10}-3 \times 10^{10}$ litre mole^{-1} s^{-1}. Since in each elementary recombination step two atoms disappear and one molecule is formed, in the steady state $w_i = 2k[x]^2$, where w_i is the rate of initiation and k the recombination rate constant. Table 1 and other tables list the values of $\lg(2k)$, the dimensions of k being throughout litre mole^{-1} s^{-1}.

Table 1. Rate constants for the recombination of atoms in solution ($\theta = 4.57T/1000$).

Atom	Solvent	t, °C	lg(2k)	Method	Refs.
H	H_2O, pH=3	25	10.08	PR	9
H	H_2O, pH=0,4—3	25	10.415	PR	10
H	H_2O, pH=0,1—1,0	25	10.48	PR	11
H	H_2O, pH=2	25	10.30	PR	12
	mean value		10.30±0.13		
Br	CCl_4	25	10.6	FP	13
I	CCl_4	15—35	14.40—5.6/θ	RSM	14
I	CCl_4	25	10.06	FP	15
I	CCl_4	25—50	12.49—3,2/θ	FP	16
I	CCl_4	25	10.64	FP	17
I	CCl_4	25	10.30	FP	18
	mean value for	25	10.28±0.15		
I	n-C_6H_{14}	15—35	12.20—2.4/θ	RSM	14
I	n-C_6H_{14}	25	10.30	RSM	18
I	n-C_6H_{14}	25	10.64	RSM	17
I	n-C_6H_{14}	25	10.56	RSM	16
I	$Cl_2C{=}CCl{-}CCl{=}CCl_2$	15—35	12.50—3.3/θ	RSM	14

The rate constant for diffusion is related to the diffusion coefficient by Smoluchowski's equation[19]: $k_D = 4\pi\sigma DN/1000$, where σ is the diameter of the diffusing species (cm), N the Avogadro number, and D the diffusion coefficient (cm^2 s^{-1}); k_D is expressed in litre mole^{-1} s^{-1}. The diameter of the iodine atom is 4.3 Å. Table 2 lists the diffusion coefficients of iodine atoms[14] calculated from the experimental values of k, and includes for comparison the experimental diffusion coefficients of iodine molecules[20,21].

Table 2. Diffusion coefficients of atomic[14] and molecular[20,21] iodine.

Solvent	t, °C	$10^5 D_I$, cm^2 s^{-1}	$10^5 D_{I_2}$, cm^2 s^{-1}
n-C_6H_{14}	15	3.5	—
n-C_6H_{14}	25	4.0	4.05
CCl_4	17.5	2.1	1.30
CCl_4	25	2.5	1.50
CCl_4	38	4.1	1.84
$CCl_2{=}CCl{-}CCl{=}CCl_2$	15	1.4	—
$CCl_2{=}CCl{-}CCl{=}CCl_2$	25	1.9	—
$CCl_2{=}CCl{-}CCl{=}CCl_2$	35	2.1	—

Using the Stokes–Einstein equation $D = kT/3\pi\eta\sigma$, it is possible to calculate k_D from the viscosity η: $k_D = 8RT/3000\eta$. According to this expression, the product $k_D\eta T^{-1}$ for different solvents should be constant. However, in fact $k_D\eta/T$ for iodine atoms varies from solvent to solvent[14]: at 25°C it is 1.29×10^5 in n-hexane, 2.22×10^5 in carbon tetrachloride, and 6.15×10^5 in hexachloroethane. Consequently the Stokes–Einstein equation does not hold rigorously for the diffusion of atoms in liquids. This can be explained by the fact that the viscosity depends on the dimensions of solvent molecules and the interaction forces between them, while the diffusion coefficient is determined by the interaction between the diffusing species and solvent molecules.

III. DISPROPORTIONATION AND RECOMBINATION OF ALKYL RADICALS

Alkyl radicals interact in two ways: they recombine with formation of a new C–C bond and disproportionate with the abstraction of a hydrogen atom by one radical from another with formation of an olefin and an alkane. The interaction between methyl and ethyl radicals may serve as an example:

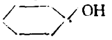
$$CH_3^{\cdot} + C_2H_5^{\cdot} \rightarrow CH_3CH_2CH_3 + 80.5 \text{ kcal mole}^{-1}$$
$$CH_3^{\cdot} + C_2H_5^{\cdot} \rightarrow CH_4 + CH_2{=}CH_2 + 64 \text{ kcal mole}^{-1}$$

The heats of these reactions have been calculated from the heats of formation of the radicals quoted in Ref. 22. The ratio of the disproportionation and recombination rate constants of alkyl radicals has been measured experimentally in the following way. An azo-compound was decomposed photochemically in a solvent; this resulted in the following reactions:

$$R{-}N{=}N{-}CH_2CH_2R' \xrightarrow{h\nu} \overline{R' + R'CH_2CH_2^{\cdot}} + N_2 \,,$$
$$\overline{R^{\cdot} + CH_2CH_2R'} \xrightarrow{k_d} RH + CH_2{=}CHR' \,,$$
$$\overline{R^{\cdot} + \cdot CH_2CH_2R'} \xrightarrow{k_r} RCH_2CH_2R' \,.$$

The radicals disproportionated and recombined in a solvent cage. Since the olefin $CH_2{=}CHR'$ was obtained only by the disproportionation reaction and the hydrocarbon RCH_2CH_2R' by the recombination reaction, analysis of the products for the relative amounts of the olefin and the alkane yields the ratio of the rate constants: $k_d/k_r = [CH_2{=}CHR^{\cdot}]/[RCH_2CH_2R']$. Table 3 shows that this ratio depends on the structure of the reacting radicals and is in the range 0.1–1. The difference between the activation energies for recombination and disproportionation in the reactions between a methyl and an ethyl radical and between two ethyl radicals is $E_r - E_d = 0.4$ kcal mole^{-1}. In the solid state, in contrast to solution, $\lg(k_d/k_r)$ is independent of temperature[26].

Table 3. Relative contributions of the disproportionation and recombination of radicals with a free valence at a carbon atom ($\theta = 4.57T/1000$).

Radical	Solvent	t, °C	$\lg(k_d/k_r)$	Refs
$CH_3^{\cdot}+C_2H_5^{\cdot}$	n-C_7H_{16}+$CH_2{=}CHC_6H_5$	–75–100	$\bar{2}.416+0{,}40/\theta$	23
$CH_3^{\cdot}+C_2H_5^{\cdot}$	$(CH_3)_2CHCH_2C(CH_3)_3$	0	$\bar{2}.875$	21
$CH_3^{\cdot}+C_2H_5^{\cdot}$	$CH_2(OH)CH_2OH$	0	$\bar{2}.965$	24
$2C_2H_5^{\cdot}$	$(CH_3)_2CHCH_2C(CH_3)_3$	65	$\bar{1}.16$	25
$2C_2H_5^{\cdot}$	$(CH_3)_2CHCH_2C(CH_3)_3$	0	$\bar{1}.25$	26
$2C_2H_5^{\cdot}$	$C_6H_5CH_3$	0	$\bar{1}.27$	26
$2C_2H_5^{\cdot}$	$(CH_3)_2CHOH$	0	$\bar{1}.305$	26
$2C_2H_5^{\cdot}$	$CH_2(OH)CH_2OH$	0	$\bar{1}.415$	26
$2C_2H_5^{\cdot}$	$CH_2(OH)CH_2OH$	65	$\bar{1}.38$	25
$2C_2H_5^{\cdot}$	gas phase	0	$\bar{1}.115$	26
$2C_2H_5^{\cdot}$	n-C_7H_{16}	–75–99	$\bar{2}.94+0.37/\theta$	27
$2C_6H_5(CH_3)_2C^{\cdot}$	$C_6H_5CH(CH_3)_2$	20–60	$\bar{2}.73$	28
2 cyclo-$C_6H_{11}^{\cdot}$	cyclo-C_6H_{12}	23	0.04	29
$2CH_3\dot{C}HOH$	H_2O	23	$\bar{1}.40$	30
	cyclo-$C_6H_{11}OH$	25	0.30	31
$2{\sim}CH_2\dot{C}(CH_3)COOCH_3^{-}$	$CH_2{=}C(CH_3)COOCH_3$	0–60	$1.99-2.26/\theta$	32

The recombination of hydroxyalkyl radicals results in the formation of a diol and their disproportionation yields an alcohol and a carbonyl compound. For example:

$$2\,CH_3\dot{C}HOH \begin{cases} \xrightarrow{k_r} CH_3CH(OH)CH(OH)CH_3 \\ \xrightarrow{k_d} CH_3CHO + CH_3CH_2OH \,. \end{cases}$$

The rate constant ratios k_d/k_r have been calculated from the composition of the products formed in the radiolysis of the corresponding alcohols. The relative contributions of the disproportionation and recombination of alkyl radicals vary from solvent to solvent owing to the effect of the internal pressure of the liquid on k_d and k_r. With increase of the internal pressure in the solvent, k_d/k_r for ethyl radicals increases from 0.13 in the gas phase to 0.26 in ethylene glycol at 0°C.[26] There is a satisfactory linear relation between $\lg(k_d/k_r)$ for ethyl radicals and $P_s^{1/2}$, where P_s is the internal pressure of the solvent[25]:

$$\lg(k_d/k_r) = -1.08 + 4.76 \times 10^{-3} P_s^{1/2} \,.$$

The explanation is that the volume of the activated complex in the disproportionation process is somewhat smaller than in recombination. For ethyl radicals, $V_r^{\ddagger} - V_d^{\ddagger} = 2.4$ cm^3 mole^{-1} at 0°C.[26]

Table 4. Overall rate constants for the interactions of radicals having a free valence at a carbon atom.

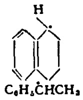
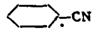
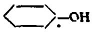
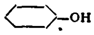
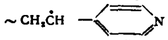
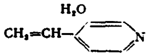
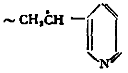
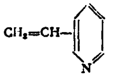
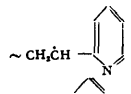
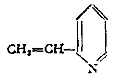
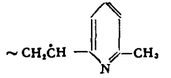
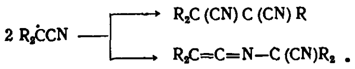
Radical	Solvent	t, °C	lg(2k)	lg(2A)	E, kcal mole^{-1}	Method	References
$C_2H_5^{\bullet}$	C_2H_6	−140—170	9.51 (30°)	10,11	0,83	PR	33
$CH_3(CH_2)_3CH_2^{\bullet}$	n-C_5H_{12}	25	9.30	—	—	RSM	34
$C_6H_5CH_2^{\bullet}$	$C_2H_5OH+(CH_2OH)_2CHOH$	25	7.60	—	—	PR	35
$C_6H_5CH_2^{\bullet}$	alkane	23	7.90	—	—	FP	36
$C_6H_5CH_2^{\bullet}$	$C_6H_5CH_3$	25	9.91	—	—	RSM	34
$CCl_3^{\bullet}$	$CHCl_3$	24	7.845	—	—	RSM	37
$CCl_3^{\bullet}$	$CH_2{=}CHOCOCH_3$	25	8.025	—	—	NKR	38
$CCl_3^{\bullet}$	$CH_2{=}CHOCOCH_3$	25	7.725	—	—	RSM	38
$CCl_3^{\bullet}$	$CHCl_3$	25	8.21	—	—	RSM	38
$CCl_3^{\bullet}$	$CH_2{=}CHOCOCH_3$	25	8.00	—	—	RSM	39
$CCl_3^{\bullet}$		25	8.00	—	—	NKR	40
	RH	25	6.85	—	—	RSM	41
$C_6H_5\dot{C}HCH_3$	RH	60	8.30	—	—	NKR	42
$CH_3(CH_2)_4CH{=}CH{-}\dot{C}H$ $C_2H_5OCO(CH_2)_7CH{=}CH$	RH	25	7.18	—	—	NKR	43
$CH_2{=}C(CH_3)(CH_2)_2C(CH_3){=}CH{-}\dot{C}H{-}CH_2$ $CH_2{=}(CH_3)C(CH_2)_2CH_2C{=}CH$	RH	25	8.415	—	—	NKR	43
$(CH_3)_3C^{\bullet}$	cyclo-C_6H_{12}	25	9.30	—	—	RSM	44
$C_6H_5C^{\bullet}(CH_3)_2$	RH	60	~6.70	—	—	NKR	42
$(CH_3)_2\dot{C}CN$	C_6H_5Cl	60	~8.30	—	—	NKR	42
$(CH_3)_2\dot{C}CN$	C_6H_6	25	9.64	—	—	ESR	45
	C_6H_6	25	9.64	—	—	ESR	45
$CH_3\dot{C}HOH$	H_2O	23	9.04	—	—	PR	30
$CH_3\dot{C}HOH$	H_2O	23	9.15	—	—	PR	46
$CH_3\dot{C}HOH$	H_2O	23	9.30	—	—	PR	47
	RH	25	8.53	—	—	PR	31
	$RH+CH_2{=}C(CH_3)_2$	25	8.32	—	—	PR	31
$(C_6H_5)_2\dot{C}OH$	$(CH_3)_2CHOH$	25	7.77	—	—	FP	48
$\sim CH_2{-}CH_2^{\bullet}$	C_6H_6	83	9.02	—	—	RSM	49
$\sim CH_2{-}CH_2^{\bullet}$	$CH_2{=}CH_2$	−20	8.66	—	—	RSM	50
$C_6H_5\dot{C}HCH_2\sim$	$CH_2{=}CHC_6H_5$	0—25	6.45 (25°)	8.505	2.8	NKR	51
$C_6H_5\dot{C}HCH_2\sim$	$CH_2{=}CHC_6H_5$	28	6.78	—	—	NKR	52
$C_6H_5\dot{C}HCH_2\sim$	$CH_2{=}CHC_6H_5$	15—25	6.48 (25°)	7.875	1.9	NKR	53
$C_6H_5\dot{C}HCH_2\sim$	$CH_4{=}CHC_6H_5$	0—60	7.86 (60°)	9,27	2.4	RSM	54
		mean value		8.85	1.5		3
p-$CH_3OC_6H_4\dot{C}H_2\sim$	$CH_2{=}CHC_6H_4OCH_3$	0	6.025	—	—	NKR	55
$\sim CH_2\dot{C}HCOOCH_3$	$CH_3COOC_2H_5$	26—50	6.55	—	—	RSM	56
$\sim CH\dot{C}HCOOCH_3$	$CH_3COOC_2H_5$	30—60	6.63 (30°)	10.45	5.3	RSM	57
$\sim CH_2\dot{C}HCOOCH_3$	$CH_3COOC_2H_5$	28	8.00	—	—	NKR	52
$\sim CH_2\dot{C}HCOOC_4H_9$	$CH_2{=}CHCOOC_4H_9$	25	6.92	—	—	NKR	58
$\sim CH_2\dot{C}HCOOC_4H_9$	$CH_2{=}CHCOOC_4H_9$	25	8.52	—	—	NKR	59
$\sim CH_2\dot{C}HCOOC_4H_9$	$CH_2{=}CHCOOC_4H_9$	25	4.255	—	—	RSM	60
$\sim CH_2\dot{C}HCOOC_4H_9$	$CH_2{=}CHCOOC_4H_9$	28	7.53	—	—	NKR	52
$\sim CH_2\dot{C}(CH_3)COOCH_3$	$CH_2{=}C(CH_3)COOCH_3$	30—60	7.39 (30°)	9.41	2.8	RSM	61
$\sim CH_2\dot{C}(CH_3)COOCH_3$	$CH_2{=}C(CH_3)COOCH_3$	24—50	7.82 (24°)	8.555	1.0	RSM	62
$\sim CH_2\dot{C}(CH)_3COOCH_3$	$CH_2{=}C(CH_3)COOCH_3$	28	7.41	—	—	NKR	52
		mean value	7.69	7.69	0.4		3
$\sim CH_2\dot{C}(CH_3)COOC_3H_7$	$CH_2{=}C(CH_3)COOC_3H_7$	30	7.65	—	—	RSM	63
$\sim CH_2\dot{C}(CH_3)COOC_4H_9$	$CH_2{=}C(CH_3)COOC_4H_9$	28	8.255	—	—	NKR	52
$\sim CH_2\dot{C}(CH_3)COOC(CH_3)_3$	$CH_2{=}\overset{\displaystyle CH_3}{\overset{\vert}{C}}CO_2C(CH_3)_3$	20—90	7.15 (30°)	7.95	1.1	RSM	64
$\sim CH_2\dot{C}(CH_3)CH_2CH(CH_3)_2$	$CH_2{=}\overset{\displaystyle CH_3}{\overset{\vert}{C}}CH_2CH(CH_3)_2$	30	7.08	—	—	NKR	65
$\sim CH_2\dot{C}(CH_3)CH(CH_3)_2$	$CH_2{-}\overset{\displaystyle CH_3}{\overset{\vert}{C}}CH_2CH(CH_3)_2$	28	8.00	—	—	NKR	52
$\sim CH_2\dot{C}HCl$		25—55	9.07 (30°)	12.115	4.2	RSM	66
$\sim CH_2\dot{C}HCN$	$HCON(CH_3)_2$	13—40	6.26	—	—	NKR	67
$\sim CH_2\dot{C}HCN$	$HCON(CH_3)_2$	0—60	7.94 (60°)	10.11	3.7	RSM	68
$\sim CH_2\dot{C}HCN$	$HCON(CH_3)_2$	60	8.89	—	—	RSM	69
$\sim CH\dot{C}HCN$	$CH_2{=}CHCN$	25	7.09	—	—	NKR	70
$\sim CH_2\dot{C}(CH_3)CN$	$CH_2{=}C(CH_3)CN$	60—80	6.23 (30°)	9.855	5.00	RSM	71
$\sim CH_2\dot{C}HCONH_2$	H_2O	25	7.16	—	—	RSM	72
$\sim CH_2\dot{C}HCONH_2$	H_2O	10—40	7.21 (30°)	10.11	4.0	RSM	73
		25	6.48	—	—	NKR	74
		25	7.52	—	—	RSM	75

Table 4 (cont'd).

Radical	Solvent	t, °C	lg(2k)	lg(2A)	E, kcal mole^{-1}	Method	References
		25	6.95	—	—	NKR	75
	CHON (CH$_3$)$_2$	25	6.545	—	—	NKR	67
$\sim CF_2-CF_2^\bullet$	H_2O	30—70	1.12 (30°)	1.26	0.2	NKR	76
$\sim CF_2-CF_2^\bullet$	H_2O	40—60	1.79 (30)°	4.14	3.25	inhib. method	77

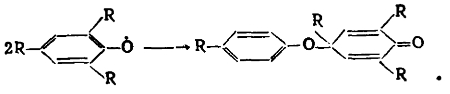
Kinetic methods make it possible to measure the overall rate constants for the interactions between alkyl radicals, which are listed in Table 4 [$k = k_d + k_r$, the values of lg(2k) are listed]. Table 4 shows that the radicals $C_2H_5^\bullet$,[33] $(CH_3)_3C^\bullet$,[44] $C_6H_5CH_2^\bullet$,[34] and $CH_3\dot{C}HOH$,[30,46,47] interact with very high rate constants in the range 1×10^9–5×10^9 litre mole^{-1} s^{-1}, which are equal [lg(2k)] or close to the rate constants for the diffusion of radicals. The radicals $R_2\dot{C}CN$ recombine with formation of a C–C or C–N bond[78]:



Tetralyl, cumenyl, and trichloromethyl radicals interact with rate constants which are significantly smaller than the diffusional rate constants. The problems associated with the interactions of macroradicals with one another in polymerisation processes have been examined in monographs[3,79] and in a review[80].

IV. REACTIONS OF HO$^\bullet$ AND RO$^\bullet$ RADICALS

The rate constant for the recombination of hydroxy-radicals is equal to the diffusion rate constant (Table 5). On the other hand, phenoxy-radicals substituted in the 2-, 4-, and 6-positions recombine very slowly. The recombination of substituted phenoxy-radicals is mainly of the "head to tail" type[81]:

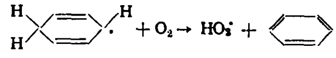


V. REACTIONS BETWEEN PEROXY-RADICALS

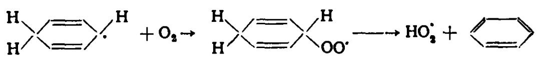
1. The Hydroperoxy-radical

The $HO_2^\bullet$ radical has amphoteric properties and in aqueous solution can be present in the forms $HO_2^\bullet$, O_2^-, and $H_2O_2^{\bullet+}$ depending on the pH. At pH ⩾ 5 the equilibrium $HO_2^\bullet \rightleftharpoons H^+ + O_2^-$ is displaced to the right[92]: $pK_{HO_2^\bullet} = 4.4 \pm 0.4$ at 23°C.[92] The rate constant for the reaction $O_2^- + O_2^- \rightarrow O_2 + O_2^{2-}$ is 1.5×10^7 litre mole^{-1} s^{-1} at 23°C.[92] At pH ⩽ 2 the equilibrium is displaced to the left and under these conditions the disproportionation of the HO$^\bullet$ radicals takes place: $HO_2^\bullet + HO_2^\bullet \rightleftharpoons O_2 + H_2O_2$; $k = 2.2 \times 10^6$ litre mole^{-1} s^{-1} at 23°C.[92] It is interesting to note that the electron transfer process between two O_2^- radical-ions which bear the same charge is much faster than the adiabatic reaction with transfer of a hydrogen atom between two neutral $HO_2^\bullet$ radicals. In strongly acid media at pH < 1, $HO_2^\bullet$ is protonated: $HO_2^\bullet + H^+ \rightleftharpoons H_2O_2^{\bullet+}$; at 23°C $pK = 1.0 \pm 0.4$.[93] In this pH range the rate constant for the reaction of $HO_2^\bullet$ radicals depends on the ionic strength of the solution, which is characteristic of an ion–ion type of reaction. The rate constants[93] are $k = 3 \times 10^6$ litre mole^{-1} s^{-1} for the reaction between $HO_2^\bullet$ and $H_2O_2^{\bullet+}$ and $k = 0.5 \times 10^6$ litre mole^{-1} s^{-1} for the reaction between $2H_2O_2^{\bullet+}$ species.

In organic solvents the formation of hydroperoxy-radicals is postulated in the oxidation of cyclohexadiene, dihydronaphthalene, and 9,10-dihydrophenanthrene:



or



This is proved by the fact that in the oxidation of the above hydrocarbons hydrogen peroxide is formed and also by the similarity of the disproportionation rate constants for the peroxy-radicals derived from the hydrocarbons. For example, in chlorobenzene at 30°C $k = 6.3 \times 10^8$ litre mole^{-1} s^{-1} in the oxidation of cyclohexadiene and $k = 3.5 \times 10^8$ litre mole^{-1} s^{-1} in the oxidation of dihydronaphthalene. The sharp difference between the rate constants for the disproportionation of hydroperoxy-radicals in organic solvents and in water can be accounted for by the fact that in water $HO_2^\bullet$ radicals are linked by hydrogen bonds of the type $HO_2^\bullet \ldots HOH$ and $^\bullet O_2H \ldots O\langle^{H}_{H}$, which sharply reduces the rate of their interaction. In a hydrocarbon solvent the rate constant for the interaction of $HO_2^\bullet$ radicals is close to the diffusional rate constant (Table 7).

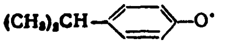
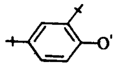
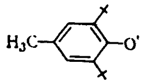
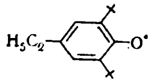
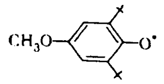
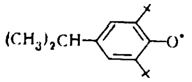
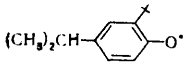
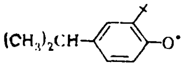
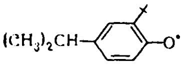
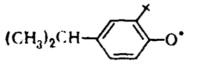
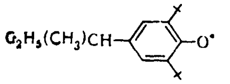
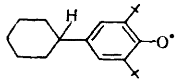
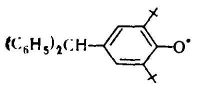
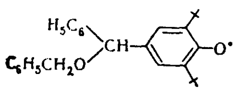
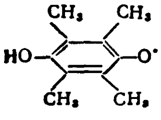
2. Tertiary Peroxy-radicals

The reaction between tertiary peroxy-radicals has been investigated in detail for cumenyl peroxy-radicals. Among the products of the initiated oxidation of cumene, Blanchard[94] detected a peroxide acetophenone and proposed the following reaction mechanism:

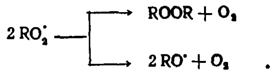
$$2RO_2^\bullet \rightarrow [ROOOOR] \rightarrow 2\overline{RO^\bullet} + O_2\,,$$
$$2\overline{RO^\bullet} \rightarrow ROOR\,,$$
$$RO^\bullet \rightarrow CH_3^\bullet + CH_3COC_6H_5\,.$$

The formation of oxygen in the reaction $RO_2^\bullet + RO^*O^{\bullet *} \rightarrow ROO^*R + OO^*$ was demonstrated by Bartlett and Traylor[95,96] in experiments with heavy oxygen (oxygen-18). Oxygen

Table 5.

Radical	Solvent	t, °C	lg (2k)	lg(2A)	E, kcal mole^{-1}	Method	Refs
$HO^{\bullet}$	H_2O, pH=7	25	9.9	—	—	MCR	82
$HO^{\bullet}$	H_2O, pH=0.4÷3	25	10.08	—	—	PR	83
$(CH_3)_3CO^{\bullet}$	CCl_4	10—55	8.32	8.32	0	RSM	84
$C_6H_5O^{\bullet}$	H_2O	20	9.03	—	—	FP	85
	cyclo-C_6H_{12}	25	0.92	—	—	kinetic	86
p-$HOC_6H_4O^{\bullet}$	H_2O, pH=7	25	9.34	—	—	PR	87
	alkane	20	7.60	—	—	FP	85
	CCl_4	20	8.48	—	—	FP	85
	CCl_4	20	7.42	—	—	FP	85
	$CHCl_3$	—30	5.70	—	—	NMR	88
	C_6H_6	10—50	0.41 (10°)	5.24	6.23	kinetic	89
	cyclo-C_6H_{12}	10—50	0.75 (10°)	4.91	5.50	ditto	89
	p-$CH_3OC_6H_4OH$	10—50	0.55 (10°)	6.13	7.20	»	89
	C_6H_5CN	10—50	0.70 (10°)	7.02	8.16	»	89
	C_6H_5Cl	10—50	0.50 (10°)	5.88	6.94	»	89
	C_6H_6	10—50	1.78 (10°)	5.22	7.04	»	90
	C_6H_6	10—50	0.10 (10°)	6.23	7.93	»	90
	cyclo-C_6H_{12}	25	0.62	—	—	»	86
	cyclo-C_6H_{12}	25	0.145	—	—	»	86
	alkane	25	9.00	—	—	FP	91
	$H_2O+C_2H_5OH$	25	9.20	—	—	FP	91

was passed through cumene undergoing oxidation and containing together with $^{16}O{=}^{16}O$ molecules also 1–6% of $^{18}O{=}^{18}O$. At the outlet from the reactor the oxygen was analysed mass-spectrometrically and the presence of $^{16}O{=}^{18}O$ molecules was established, thus demonstrating the occurrence of the reaction $R{-}^{16}O{-}^{16}O^{\bullet} + {}^{18\bullet}O{-}^{18}O{-}R \rightarrow R^{16}O^{\bullet} + {}^{16}O{=}^{18}O + R^{18}O^{\bullet}$. In experiments on the sensitised oxidation of cumene under conditions such that the chains are short it was established that the amount of oxygen evolved as a result of the reaction between two peroxy-radicals exceeds by a factor of 1.7–2.6 the number of elementary steps involving the disappearance of free radicals in this reaction[98]. Consequently the interaction of two tertiary peroxy-radicals has the following mechanism:



$$2\,RO_2^{\cdot} \rightarrow \begin{cases} ROOR + O_2 \\ 2\,RO^{\cdot} + O_2 \end{cases} .$$

The recombination of alkoxy-radicals and their liberation into the bulk phase has been investigated in the decomposition of di-t-butyl peroxyoxalate[97]:

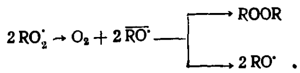
$$(CH_3)_3COOCOCOOOC\,(CH_3)_3 \rightarrow 2\,(CH_3)_3CO^{\cdot} + 2\,CO_2\ ,$$
$$\overline{2\,(CH_3)_3CO^{\cdot}} \longrightarrow (CH_3)_3COOC\,(CH_3)_3\ ,$$
$$\overline{2\,(CH_3)_3CO^{\cdot}} \longrightarrow 2\,(CH_3)_3CO^{\cdot},$$
$$(CH_3)_3CO^{\cdot} + RH \rightarrow (CH_3)_3COH + R^{\cdot},$$
$$(CH_3)_3CO^{\cdot} \rightarrow CH_3COCH_3 + CH_3^{\cdot}\ ,$$

The decomposition products are a peroxide and an alcohol. Table 6 shows that, with increase in the viscosity of the solvent, the yield of the peroxide increases at the expense of a reduced yield of the alcohol (temperature 45°C).[97]

Table 6. Products of decomposition of di-t-butyl peroxalate in various solvents.

Solvent	Viscosity, cP	Yield of ROOR, %	Yield of ROH, %
n-C_5H_{12}	2.20	3.9	94.6
C_6H_6	5.6	5.5	53
$(CH_3)_3COH$	46	10	...
Nujol	1000	76.8	23.2

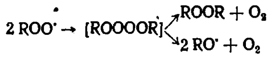
Evidently a similar situation arises in reactions between peroxy-radicals:



$$2\,RO_2^{\cdot} \rightarrow O_2 + \overline{2\,RO^{\cdot}} \rightarrow \begin{cases} ROOR \\ 2\,RO^{\cdot} \end{cases} .$$

This mechanism of the interaction between tertiary peroxy-radicals has been demonstrated for t-butylperoxy-radicals[98] in a study of the decomposition of t-butyl hydroperoxide initiated with azobisisobutyronitrile. It was established that the rate of decomposition of the hydroperoxide w, measured from the amount of oxygen evolved, is directly proportional to the rate of initiation w_i and the ratio w/w_i is significantly greater than unity: it is 9 at 65°C and 4 at 36°C. The rate constant for the reaction $2RO_2^{\cdot} \rightarrow 2RO^{\cdot} + O_2$ is 19.5×10^2 litre mole^{-1} s^{-1} at 22°C with $E = 15.5$ kcal mole^{-1}, while for the reaction $2RO_2^{\cdot} \rightarrow ROOR + O_2$, $k = 3.9 \times 10^2$ mole^{-1} s^{-1} (also at 22°C) with $E = 10.2$ kcal mole^{-1}.

The data for the isotope effect in the oxidation of cumene with deuterated methyl groups are somewhat inconsistent with the above mechanism[99]. The mechanism leads to the expectation that the replacement of a CH_3 group in cumene by CD_3 should not affect the rate of reaction between two $RO_2^{\cdot}$ radicals and consequently also the rate of oxidation. However, experiments have shown that [CD_3]cumene is oxidised somewhat faster owing to a lower rate of chain termination. This contradiction can be accounted for by postulating a more complex mechanism for chain termination in cumene undergoing oxidation, in particular by the participation in these processes of the radicals $CH_3OO^{\cdot}$ (and $CD_3OO^{\cdot}$). The overall mechanism of chain termination of cumene undergoing oxidation is as follows[100]



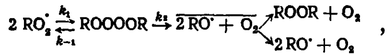
$$2\,R\dot{O}O^{\cdot} \rightarrow [ROOO\dot{O}R] \begin{cases} \nearrow ROOR + O_2 \\ \searrow 2\,RO^{\cdot} + O_2 \end{cases} ,$$
$$RO^{\cdot} + RH \rightarrow ROH + R^{\cdot}\ ,$$
$$RO^{\cdot} \rightarrow CH_3^{\cdot} + CH_3COC_6H_5\ ,$$
$$CH_3^{\cdot} + O_2 \rightarrow CH_3OO^{\cdot}\ ,$$
$$CH_3OO^{\cdot} + ROO^{\cdot} \rightarrow ROH + O_2 + CH_2O\ ,$$
$$RO^{\cdot} + ROOH \rightarrow ROH + ROO^{\cdot}\ .$$

The involvement of methylperoxy-radicals in chain termination can be avoided by introducing into cumene, cumenyl hydroperoxide at a concentration such that the following rapid transfer reaction takes place[101]:

$$CH_3OO^{\cdot} + ROOH \rightarrow CH_3OOH + RO_2^{\cdot}\ .$$

The rate constants for the reactions of tertiary peroxy-radicals are in the range 10^3–10^5 litre mole^{-1} s^{-1}.

The reaction of ozone with $KOOC(CH_3)_3$ at −78°C yielded a solid[102] soluble in pentane which decomposes at −30°C with formation of t-butyl peroxide and O_2. It is suggested that it is the tetroxide ROOOOR. The reaction of t-butyl hydroperoxide with lead tetra-acetate in dichloromethane at a low temperature[103] gives rise to a substance which decomposes reversibly to peroxy-radicals on raising the temperature from −110° to −85°C. At a higher temperature (in excess of −82°C) it decomposes with evolution of O_2 and irreversible destruction of free radicals. The results have been interpreted as follows[103]:



$$2\,RO_2^{\cdot} \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} ROOOOR \xrightarrow{k_2} \overline{2\,RO^{\cdot} + O_2} \begin{cases} \nearrow ROOR + O_2 \\ \searrow 2\,RO^{\cdot} + O_2 \end{cases} ,$$
$$K = \frac{k_{-1}}{k_1},\ \lg K = 3.55 - 6.0/\theta,\ \lg k_2 = 9.27 - 11.0/\theta\ ,$$
$$\theta = 4.57\,T/1000.$$

3. Secondary Peroxy-radicals

The C–H bond is involved in the elementary reaction step between two secondary peroxy-radicals[104] as shown by the reaction products and the isotope effect. The interaction of two peroxy-radicals derived from ethylbenzene yields one molecule of acetophenone[104], while in the interaction of cyclohexylperoxy-radicals the principal products are cyclohexanol and cyclohexanone in equal amounts[31]. The isotope effect in the reaction between two $RO_2^{\cdot}$ radicals amounts to 1.9 (at 60°C) in the case of ethylbenzene[104], while for the peroxy-radicals derived from styrene and α-deuterostyrene $k_H/k_D = 3.9$ (30°C) with $E_D - E_H = 1.9$ kcal mole^{-1}.[105] These results agree well with the mechanism proposed by Russell[104]:

$$2R_2CHOO^{\cdot} \rightarrow R_2C{=}O + O_2 + HOCHR_2\ .$$

A reaction of this kind can take place in two ways: via a cyclic activated complex or via the intermediate formation of the tetroxide. Calculation shows[2] that the formation of a cyclic activated complex should involve a high negative entropy of activation, which leads to the calculated constant $k \simeq 1$. The pathway via the intermediate formation of the tetroxide should be faster:

$$2\,R_2CHOO^{\cdot} - R_2CHOOOOCHR_2 \rightarrow R_2C{=}O + R_2CHOH + O_2\ .$$

This mechanism was recently confirmed by Howard and Ingold[105] in the following way. According to this mechanism and the spin conservation rule, the reactions between two peroxy-radicals should result in the formation of singlet oxygen. Singlet oxygen is known to react rapidly with 9,10-diphenylanthracene with formation of an *endo*-peroxide. Secondary peroxy-radicals were obtained in benzene solutions by the reaction of s-butyl hydroperoxide with Ce^{4+} ions. The addition of 9,10-diphenylanthracene to this type of system leads to the formation of an *endo*-peroxide. This demonstrates the formation of singlet oxygen by the reaction

$$2\,R_2CHOO^{\cdot} \rightarrow R_2CHOOOOCHR_2 \rightarrow R_2C{=}O + R_2CHOH + {}^1O_2\,.$$

If instead of a secondary hydroperoxide, a tertiary hydroperoxide is introduced, an *endo*-peroxide does not form in agreement with the mechanism

$$2\,RO_2^{\cdot} \rightarrow ROOOOR \rightarrow 2\,\overline{RO^{\cdot}} + {}^3O_2\,.$$

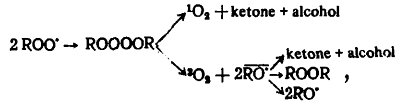
The rate constants for the reactions of secondary peroxy-radicals are of the order of 10^7–10^8 litre $mole^{-1}\,s^{-1}$. This mechanism can be revised slightly on the basis of data for the decomposition of peroxy-macroradicals derived from polyethylene[106]. It has been established that bond dissociation in the sensitised oxidation of linear polyethylene takes place in the peroxy-radical stage by the following reactions

$$RO_2^{\cdot} \rightarrow \text{dissociation of C-C bond}$$
$$2\,RO_2^{\cdot} \rightarrow \text{dissociation of C - C bond,}$$

The dissociation of the C–C bond following the reaction between two $RO_2^{\bullet}$ radicals can be accounted for by postulating the formation of alkoxy-macroradicals, which subsequently break down with dissociation of the C–C bond:

$$2\,RO_2^{\cdot} \rightarrow O_2 + 2RO^{\cdot}\,,$$
$$RO^{\cdot} \rightarrow \text{aldehyde} + R'^{\cdot}\,.$$

The linear polyethylene contained virtually no tertiary C–H bonds and therefore the alkoxy-radicals were obtained by the reaction between secondary peroxy-radicals, for which the following general mechanism may be proposed:



$$2\,ROO^{\cdot} \rightarrow ROOOOR \begin{cases} \nearrow {}^1O_2 + \text{ketone + alcohol} \\ \searrow {}^3O_2 + 2\overline{RO^{\cdot}} \begin{cases} \nearrow \text{ketone + alcohol} \\ \rightarrow ROOR \\ \searrow 2RO^{\cdot} \end{cases} \end{cases},$$

$$RO^{\cdot} + RH \rightarrow ROH + R^{\cdot}\,,$$
$$RO^{\cdot} \rightarrow \text{aldehyde} + R''\,.$$

Quantitative measurements show that in polyethylene undergoing oxidation in chlorobenzene at 115°C there are six C–C bond dissociation steps for each 100 elementary reaction steps between two $RO_2^{\bullet}$ radicals[106]. Thus for macroradicals also the reaction $2RO_2^{\bullet} \rightarrow$ alcohol + ketone + $^1O_2$ appears to predominate.

Among the reaction products from cyclohexylperoxy-radicals obtained by pulse radiolysis in cyclohexane at 25°C, cyclohexene and a hydroperoxide were detected, together with an alcohol and ketone, with radiation-chemical yields of 1.14 and 1.10 respectively[31]. Under these conditions (low temperature, high $RO_2^{\bullet}$ concentration), the hydroperoxide could not form in an appreciable amount by the reaction of the peroxy-radical with cyclohexane. One may postulate the formation of cyclohexene by disproportionation between two cyclohexyl radicals. Then dicyclohexyl, for which $k_d/k_r = 1$ (Table 7), should form with the same radiation-chemical yield. However, experiments have established that for dicyclohexyl $G = 0.3$, i.e. is 4 times smaller than for cyclohexene. This suggests a new disproportionation reaction of peroxy-radicals:

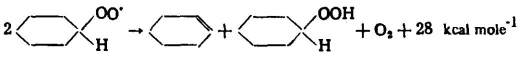


Table 7. Rate constants for the interactions of peroxy-radicals.

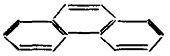
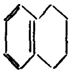
Radical	Solvent	t, °C	lg (2k)	lg(2A)	E, kcal mole^{-1}	Method	Refs.
$HO_2^{\cdot}$	H_2O, pH=0,5–1,5	1–43	6.82 (30°)	11.08	5.9	FM	107
$HO_2^{\cdot}$	H_2O, pH=2,7	25	6.40	—	—	FP	108
$HO_2^{\cdot}$	H_2O, pH=2	23	6.64	—	—	PR	90
$HO_2^{\cdot}$	H_2O, pH=2	23	6.74	—	—	PR	109
$HO_2^{\cdot}$	H_2O, pH=2	–10–50	6.40 (30°)	9.8	4.7	FM	110
$HO_2^{\cdot}$	CCl_4	30	10.05	—	—	RSM	111
$HO_2^{\cdot}$	C_6H_5Cl	30	9.10	—	—	RSM	111
$HO_2^{\cdot}$	C_6H_5Cl	30	8.85	—	—	RSM	111
$HO_2^{\cdot}$	CH_3CN	30	6.935	—	—	RSM	111
$HO_2^{\cdot}$	n-$C_{10}H_{22}$	30	9.43	—	—	RSM	111
$HO_2^{\cdot}$		30	7.78	—	—	RSM	112
$HO_2^{\cdot}$		30	7.82	—	—	RSM	111
$CH_3(CH_2)_3OO^{\cdot}$	CH_3OH	7	7.48	—	—	FM	110
$CH_3(CH_2)_3OO^{\cdot}$		30	7.60	—	—	RSM	113

Table 7 (cont'd).

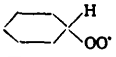
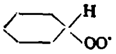
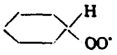
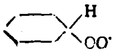
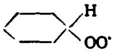
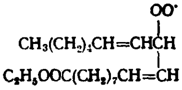
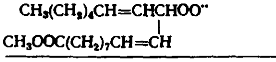
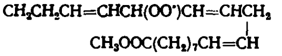
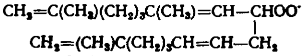
Radical	Solvent	t, °C	lg (2k)	lg(2A)	E, kcal mole^{-1}	Method	Refs.
$(CH_3)_2C{=}\overset{CH_3}{C}CH_2OO^{\cdot}$	RH	30	5.805	—	—	RSM	113
$C_6H_5CH_2OO^{\cdot}$	RH	30	8.48	—	—	RSM	112
m-$CH_3C_6H_4CH_2OO^{\cdot}$	RH	30	8.48	—	—	RSM	112
o-$CH_3C_6H_4CH_2OO^{\cdot}$	RH	30	8.18	—	—	RSM	112
p-$CH_3C_6H_4CH_2OO^{\cdot}$	RH	30	8.48	—	—	RSM	112
$CH_3\overset{OO^{\cdot}}{C}HCH_2CH_3$		30	6.18	—	—	RSM	113
$(CH_3)_2\overset{OO^{\cdot}}{C}CH(CH_3)CH(CH_3)_2$	RH	42—78	5.545	—	—	RSM	114
	RH	23	6.505	—	—	PR	115
		30	6.30	—	—	RSM	113
		40—70	6.68 (30°)	7.84	1.6	NKR	116
	$CH_3COOC_2H_5$	40—70	5.37 (30°)	9.64	5.9	NKR	116
	CH_3COOH	40—70	5.31 (30°)	9.72	6.1	NKR	116
$(CH_3)_2C{=}CH\overset{OO^{\cdot}}{C}HC_2H_5$	RH	40—60	6.48 (30°)	7.415	1.2	NKR	117
$CH_2{=}CH\overset{OO^{\cdot}}{C}H(CH_2)_4CH_3$	RH	25	7.08	—	—	PR	31
$CH_2{=}CH\overset{OO^{\cdot}}{C}H(CH_2)_4CH_3$	RH	30	8.41	—	—	RSM	113
$CH_2{=}CH\overset{OO^{\cdot}}{C}H(CH_2)_6CH_3$	RH	25—40	5.3	—	—	NKR	118
$CH_2{=}CH\overset{OO^{\cdot}}{C}HCH{=}CH_2$	RH	30	9.03	—	—	RSM	119
$C_2H_5CH{=}CH\overset{OO^{\cdot}}{C}HC_2H_5$	RH	30	6.84	—	—	RSM	119
 $CH_3(CH_2)_4CH{=}CH\overset{OO^{\cdot}}{C}H$ $C_2H_5OOC(CH_2)_7CH{=}CH$	RH	11	5.70	—	—	RSM	118
	RH	25	5.48	—	—	NKR	118
$CH_3(CH_2)_7\overset{OO^{\cdot}}{C}HCH{=}CH(CH_2)_7CO_2CH_3$	RH	30	6.02	—	—	RSM	119
$(CH_3)_2C{=}CH\overset{OO^{\cdot}}{C}HCH_2\overset{CH_3}{C}{=}CHCH_3$	RH	0	5.59	—	—	NKR	118
$(CH_3)_2C{=}CH\overset{OO^{\cdot}}{C}HCH_2\overset{CH_3}{C}{=}CHCH_3$	RH	15	5.72	—	—	RSM	118
$(CH_3)_2C{=}CH\overset{OO^{\cdot}}{C}HCH_2\overset{CH_3}{C}{=}CHCH_3$	RH	25	5.72	—	—	NKR	118
 $CH_3(CH_2)_4CH{=}CHCHOO^{\cdot}$ $CH_3OOC(CH_2)_7CH{=}CH$	RH	30	6.945	—	—	RSM	119
 $CH_2CH_2CH{=}CHCH(OO^{\cdot})CH{=}CHCH_2$ $CH_3OOC(CH_2)_7CH{=}CH$	RH	30	7.555	—	—	RSM	119
 $CH_2{=}C(CH_3)(CH_2)_3C(CH_3){=}CH{-}CHOO^{\cdot}$ $CH_2{=}(CH_3)C(CH_2)_3CH{=}CH{-}CH_2$	RH	25	5.45	—	—	NKR	118
		40	5.00			NKR	118
$CH_3(CH_2)_2C{\equiv}C\overset{OO^{\cdot}}{C}H(CH_2)_2CH_3$	RH	30	7.145	—	—	RSM	118

Table 7 (cont'd).

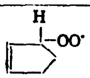
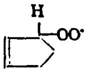
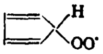
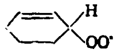
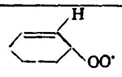
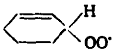
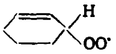
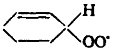
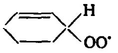
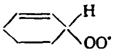
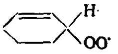
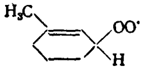
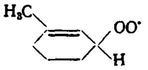
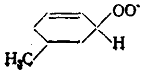
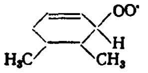
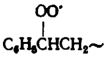
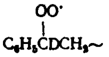
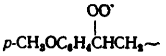
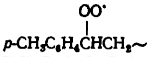
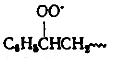
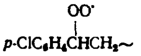
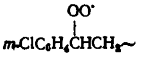
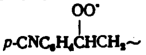
Radical	Solvent	t, °C	lg (2k)	lg(2A)	E, kcal mole^{-1}	Method	Refs.
	CH_3OH	30	7.175	—	—	FM	100
	RH	30	6.79	—	—	RSM	119
	RH	30	9.03	—	—	RSM	119
	RH	15	5.98	—	—	RSM	118
	RH	20—50	6.20	—	—	NKR	121
	RH	56	6.30	—	—	RSM	122
	RH	15	5.855	—	—	RSM	123
		30	6.75	—	—	RSM	120
	RH	30	6.42	—	—	NKR	124
	RH	mean value	6.25	—	—		
	CH_3OH	30	6.45	10.8	6.0	FM	110
	RH	15	5.70	—	—	RSM	118
	RH	40	5.935	—	—	NKR	121
	RH	40	6.52	—	—	NKR	125
	RH	40	6.43	—	—	NKR	125
$C_6H_5CH(CH_3)OO^{\cdot}$	RH	50—90	7.28	—	—	RSM	126
$C_6H_5CH(CH_3)OO^{\cdot}$	RH	30	7.60	—	—	RSM	120
$C_6H_5CH(CH_3)OO^{\cdot}$	RH	30	7.60	—	—	NKR	127
 $C_6H_5\overset{OO^{\cdot}}{\overset{\mid}{C}}HCH_2\sim$	C_6H_5Cl	13—50	7.71 (30°)	9.01	1.8	RSM	128
 $C_6H_5\overset{OO^{\cdot}}{\overset{\mid}{C}}DCH_2\sim$	C_6H_5Cl	13—50	7.12 (30°)	9.80	3.7	RSM	105
 $p\text{-}CH_3OC_6H_4\overset{OO^{\cdot}}{\overset{\mid}{C}}HCH_2\sim$	C_6H_5Cl	40	7.64	—	—	RSM	105
 $p\text{-}CH_3C_6H_4\overset{OO^{\cdot}}{\overset{\mid}{C}}HCH_2\sim$	C_6H_5Cl	40	7.75	—	—	RSM	105
 $C_6H_5\overset{OO^{\cdot}}{\overset{\mid}{C}}HCH_2\sim$	C_6H_5Cl	40	7.86	—	—	RSM	105
 $p\text{-}ClC_6H_4\overset{OO^{\cdot}}{\overset{\mid}{C}}HCH_2\sim$	C_6H_5Cl	40	7.99	—	—	RSM	105
 $m\text{-}ClC_6H_4\overset{OO^{\cdot}}{\overset{\mid}{C}}HCH_2\sim$	C_6H_5Cl	40	8.03	—	—	RSM	105
 $p\text{-}CNC_6H_4\overset{OO^{\cdot}}{\overset{\mid}{C}}HCH_2\sim$	C_6H_5Cl	40	9.45	—	—	RSM	105

Table 7 (cont'd).

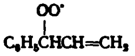
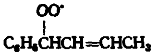
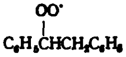
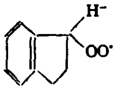
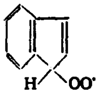
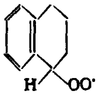
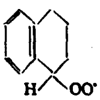
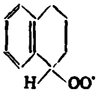
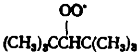
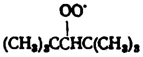
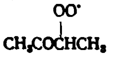
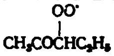
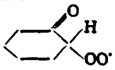
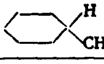
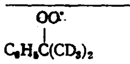
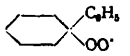
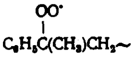
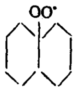
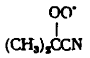
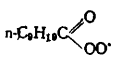
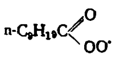
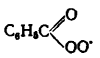
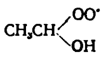
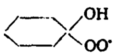
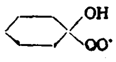
Radical	Solvent	t, °C	lg (2k)	lg(2A)	E, kcal mole^{-1}	Method	Refs.
 $C_6H_5\overset{OO^{\cdot}}{C}HCH(CH_3)\sim$	C_6H_5Cl	30	7.505	—	—	RSM	129
 $C_6H_5\overset{OO^{\cdot}}{C}HCH{=}CH_2$	C_6H_5Cl	30	8.645	—	—	RSM	120
 $C_6H_5\overset{OO^{\cdot}}{C}HCH{=}CHCH_3$	RH	30	6.58	—	—	RSM	119
$(C_6H_5)_2CHOO^{\cdot}$	RH	30	8.20	—	—	RSM	120
$(C_6H_5)_2CDOO^{\cdot}$	RH	30	8.06	—	—	RSM	120
 $C_6H_5\overset{OO^{\cdot}}{C}HCH_2C_6H_5$	RH	30	7.30	—	—	RSM	112
	RH	30	6.91	—	—	RSM	112
	C_6H_5Cl	30	7.70	—	—	RSM	129
	RH	25	7.33	—	—	RSM	130
	RH	40	6.98	—	—	NKR	124
	RH	13—50	6.82 (30°)	9.93	4.3	RSM	120
	CH_3OH	—10—50	6.67 (30°)	10.0	4.6	FM	110
$C_6H_5(n\text{-}C_3H_7)CHOO^{\cdot}$	RH	30	7.70	—	—	RSM	112
 $(CH_3)_3C\overset{OO^{\cdot}}{C}HC(CH_3)_3$	CH_3OH	—10—50	3.92 (30°)	11.0	9.8	FM	110
 $(CH_3)_3C\overset{OO^{\cdot}}{C}HC(CH_3)_3$	C_6H_6	—10—50	4.18 (30°)	9.2	7.0	FM	110
 $CH_3CO\overset{OO^{\cdot}}{C}HCH_3$	RH	35—75	6.35 (30°)	7.48	1.7	NKR	116
 $CH_3CO\overset{OO^{\cdot}}{C}HC_2H_5$	RH	35—75	6.32 (30°)	7.48	1.6	NKR	116
	RH	75	6.43	—	—	NKR	131
$(CH_3)_3COO^{\cdot}$	CH_3OH	—10—50	3.54 (30°)	10.4	9.2	FM	110
$(CH_3)_3COO^{\cdot}$	CH_3OH	36—65	2.59 (22°)	10.56	10.2	FM	98
$(CH_3)_3COO^{\cdot}$	C_6H_6	—10—50	3.11 (30°)	6.4	4.5	FM	110
$(CH_3)_3COO^{\cdot}$	$C_6H_5CH(CH_3)_2$	25—65	3.15 (35°)	9.8	7.0	NKR	132
$(CH_3)_3COO^{\cdot}$	$n\text{-}C_6H_{14}$	—41	4.115	9.145	7.2	ESR	133
$(CH_3)_3COO^{\cdot}$		+48— —24	4.06 (41°)	9.99	8.5	ESR	133
$(CH_3)_3COO^{\cdot}$		+48— —24	4.19 (41°)	10.12	8.5	ESR	133
$(CH_3)_3COO^{\cdot}$	$C_2H_5CH(CH_3)C_2H_5$	+48— —24	4.26 (41°)	10.12	8.4	ESR	133
$(CH_3)_3COO^{\cdot}$	$(CH_3)_3COOH$	—38—0	4.00 (41°)	9.79	8.3	ESR	101
$(CH_3)_3COO^{\cdot}$	$C_6H_5CH(CH_3)_2$	30	3.11	—	—	FM	101
$(CH_3)_3CCH_2C(CH_3)_2OO^{\cdot}$	$C_6H_5CH(CH_3)_2$	30	4.01	—	—	FM	101

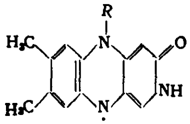
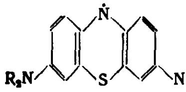
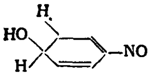
Table 7 (cont'd).

Radical	Solvent	t, °C	lg (2k)	lg(2A)	E, kcal mole^{-1}	Method	Refs.
$C_6H_5(CH_3)_2COO^\cdot$	RH	56	5.155	—	—	NKR	122
$C_6H_5(CH_3)_2COO^\cdot$	RH	50	4.45	—	—	RSM	134
$C_6H_5(CH_3)_2COO^\cdot$	RH	65	4.52	—	—	RSM	134
$C_6H_5(CH_3)_2COO^\cdot$	RH	23	4.64	—	—	ESR	135
$C_6H_5(CH_3)_2COO^\cdot$	RH	40	4.38	—	—	NKR	124
$C_6H_5(CH_3)_2COO^\cdot$	RH	60	4.68	—	—	NKR	127
$C_6H_5(CH_3)_2COO^\cdot$	RH	30	4.175	—	—	RSM	112
$C_6H_5(CH_3)_2COO^\cdot$	CH_3OH	—10—50	5.09 (30°)	10.7	7,8	FM	110
$C_6H_5(CH_3)_2COO^\cdot$	C_6H_6	—10—50	4.57 (30°)	8.8	5.8	FM	110
$C_6H_5(CH_3)_2COO^\cdot$	RH	25—65	4.27 (30°)	8.58	5.96	RSM	132
 $C_6H_5\overset{OO^\cdot}{C}(CD_3)_2$	RH	30	4.08			RSM	136
p-$CH_3OC_6H_4C(CH_3)_2OO^\cdot$	RH	30	4.60	—	—	RSM	136
m-$CH_3OC_6H_4C(CH_3)_2OO^\cdot$	RH	30	4.90	—	—	RSM	136
o-$CH_3OC_6H_4C(CH_3)_2OO^\cdot$	RH	30	4.48	—	—	RSM	136
$(C_6H_5)_2(CH_3)COO^\cdot$	RH	30	4.97	—	—	RSM	112
$(C_6H_5)_2(CH_3)COO^\cdot$	RH	30	4.81	—	—	RSM	101
$(C_6H_5)_2(CH_3)COO^\cdot$	RH	50—88	5.98 (30°)	11.04	7.0	ESR	137
$(C_6H_5)_2(CH_3)COO^\cdot$	C_6H_6	—10—50	6.34 (30°)	8.1	2.5	FM	110
$C_6H_5(CH_3)(C_2H_5)COO^\cdot$	CH_3OH	—10—50	5.46 (30°)	9.4	5.5	FM	110
$C_6H_5(CH_3)(C_2H_5)COO^\cdot$	RH	30—56	4.43 (30°)	8.48	5.6	RSM	101
$C_6H_5(CH_3)(n\text{-}C_3H_7)COO^\cdot$	RH	30	5.64	—	—	RSM	112
	RH	30	5,20	—	—	RSM	112
 $C_6H_5\overset{OO^\cdot}{C}(CH_3)CH_2\sim$	C_6H_5Cl	13—50	5.82 (30°)	8.50	3.7	RSM	129
	RH	60	5.18	—	—	NKR	127
 $(CH_3)_2\overset{OO^\cdot}{C}CN$	C_6H_5Cl	80	7.20	—	—	NKR	138
$CH_3COC(CH_3)_2OO^\cdot$	RH	35—75	6.32 (30°)	7.48	1.6	NKR	116
	n-$C_{10}H_{22}$	5	7.53	—	—	RSM	139
	RH	5	6.875	—	—	RSM	139
	RH	5	8.32	—	—	RSM	140
	RH	23	8.08	—	—	PR	141
	RH	23	7.255	—	—	PR	31
	RH	75—90	5.37 (30°)	7.10	2.4	NKR	142

VI. REACTIONS OF MOLECULES WITH FREE VALENCES AT NITROGEN AND TIN ATOMS

Aromatic radicals with a free valence at a nitrogen atom interact very rapidly (Table 8). Very high rate constants have been obtained for the radicals R_3Sn.[44]

Table 8. Rate constants for the interactions of radicals having free valences at nitrogen and tin atoms.

Radical	Solvent	t, °C	lg (2k)	Method	References
$C_6H_5\dot{N}H$	H_2O	25	9.18	FP	143
	H_2O	25	8.48	FP	144
 Methylene Blue semiquinone	H_2O	25	9.38	FP	145
	H_2O	25	9.18	FP	146
	H_2O	25	8.78	PR	147
$(C_6H_5)_3Sn^\cdot$	cyclo-C_6H_{12}	25	9.48	RSM	44
$(n\text{-}C_4H_9)_3Sn^\cdot$	cyclo-C_6H_{12}	25	9.18	RSM	44

VII. REACTIONS BETWEEN FREE RADICALS OF DIFFERENT TYPES

The reactions between $H^\cdot$ and $OH^\cdot$, between $H^\cdot$ and $HO_2^\cdot$, and between $HO^\cdot$ and $HO_2^\cdot$ radicals are very rapid and their rates are limited by diffusion (Table 8). The rate of recombination of alkyl radicals with peroxy-radicals is not limited by diffusion but the reaction takes place as a rule with higher rate constants than the reaction between two peroxy-radicals (Table 9). In particular this is the reason for the inhibiting effect of triphenylmethane when the latter is introduced, for example, into cumene undergoing oxidation. The $C-O_2^\cdot$ bond in the radical $(C_6H_5)_3COO^\cdot$ is weak, its energy amounting to only 9 kcal mole^{-1}, [148] and under oxidation conditions the following equilibrium obtains:

$$(C_6H_5)_3COO^\cdot \rightleftarrows (C_6H_5)_3C^\cdot + O_2 .$$

Therefore in a hydrocarbon undergoing oxidation there is always a fairly high concentration of triphenylmethyl radicals (the higher the temperature the higher the concentration) and there is rapid chain termination by the reaction

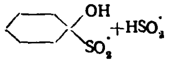
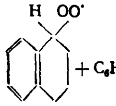
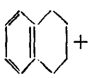
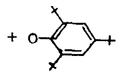
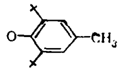
$$RO_2^\cdot + (C_6H_5)_3C^\cdot \rightarrow ROOC\,(C_6H_5)_3 .$$

VIII. EFFECT OF THE SOLVENT. VISCOSITY OF THE SOLVENT

If atoms or free radicals interact very rapidly so that $k > k_D$, diffusion limits the rate of the process and the diffusional rate constant k_D is measured experimentally. Then the viscosity of the solvent affects k_D: the higher the viscosity, the lower is the value of k_D. For low-molecular-weight radicals, $k_D \simeq 10^9-10^{10}$ litre mole^{-1} s^{-1}. Macroradicals diffuse much more slowly, so that even in not very viscous media diffusion may be rate-limiting for the reaction between two macroradicals. Since the viscosity of the solution increases as polymerisation proceeds, this entails a decrease of the rate constant for chain termination[79]. Data for the photopolymerisation of methyl methacrylate at 32 °C may be quoted as an example[59]:

% polymer.	0	15	25	35
$10^{-4}k$, litre mole^{-1} s^{-1}	570	140	35	8.8

Table 9. Rate constants for the interactions of radicals of different types.

Reaction	Solvent	t, °C	lg k	Method	Refs;
$H^\cdot + {}^\cdot OH$	H_2O	25	10.08	PR	9
$H^\cdot + {}^\cdot OH$	H_2O, pH = 0,4 ÷ 3	25	10.505	PR	10
$H^\cdot + {}^\cdot OH$	H_2O, 0,8 N H_2SO_4	25	9.85	PR	149
$H^\cdot + {}^\cdot OH$	H_2O, 0,4 N H_2SO_4	25	10.65	PR	15
$H^\cdot + HO_2^\cdot$	H_2O, acid medium	25	10.30	PR	151
$HO^\cdot + HO_2^\cdot$	H_2O, pH = 0,4 ÷ 3	25	10.175	PR	10
$HO^\cdot + HO_2^\cdot$	H_2O	25	10.04	PR	151
$HO^\cdot + HO_2^\cdot$	H_2O, pH = 0,5 ÷ 6,7	25	9.85	PR	152
$C_6H_5CH_2^\cdot + CH_3^\cdot CHOH$	$C_2H_5OH + HOCH_2CH(OH)CH_2OH$	25	8.30	PR	35
	cyclo-$C_6H_{11}OH$	25	8.45	PR	31
$(CH_3)_3C^\cdot + (n\text{-}C_4H_9)_3Sn^\cdot$	cyclo-C_6H_{12}	25	9.30	RSM	44
$(C_6H_5)_3C^\cdot + (C_6H_5)_3COO^\cdot$	$(C_6H_5)\,CH(CH_3)_2$	30	8.175	RSM	101
$R^\cdot + RO_2^\cdot$	(in ethyl linoleate)	25	7.70	NKR	118
$R^\cdot + RO_2^\cdot$	(in digeranyl)	25	7.00	NKR	118
 $+ C_6H_5\overset{OO^\cdot}{\overset{\vert}{C}}(CH_3)_2$	 $+ C_6H_5CH\,(CH_3)_2$	90	6.78	MCR	153
$C_6H_5COOO^\cdot + n\text{-}C_9H_{19}COOO^\cdot$	$C_6H_5CHO + n\text{-}C_9H_{19}CHO$	5	7.93	MCR	154
$C_6H_5\overset{OO^\cdot}{\overset{\vert}{C}}(CH_3)_2 + C_6H_5\overset{OO^\cdot}{\overset{\vert}{C}}HCH_3$	$C_6H_5CH\,(CH_3)_2 + C_6H_5C_2H_5$	60	5.87	MCR	155
$C_6H_5\overset{OO^\cdot}{\overset{\vert}{C}}(CH_3)_2 + C_6H_5\overset{OO^\cdot}{\overset{\vert}{C}}HCH_3$	$C_6H_5CH\,(CH_3)_2 + C_6H_5C_2H_5$	80	5.945	MCR	155
$p\text{-}CH_3OC_6H_4O^\cdot$ + 	C_6H_5Cl	24	7.725	SFT*	156
$p\text{-}CH_3OC_6H_4O^\cdot$ + 	C_6H_5Cl	24	8.00	SFT*	156

*The significance of the Russian abbreviation (TsINR, not explained in the text) is obscure, but the authors quoted used a stop-flow technique (SFT) (Ed. of Translation).

1. Internal Pressure of the Liquid

Since recombination of two radicals to give one molecule is accompanied by a decrease of free volume, an increase of the rate constant for the reaction between two free radicals with increasing internal pressure of the liquid is to be expected. Unfortunately there have been no systematic studies on this problem. A distinct effect of the internal pressure of the liquid on the reaction between two radicals has been established for the process involving the competition between the disproportionation and recombination reactions of ethyl radicals[25], where a linear relation between $\lg(k_d/k_r)$ and $\Delta P_S^{1/2}$ has been demonstrated, P_S being the internal pressure of the solvent.

2. Non-specific Solvation

A free radical with a dipole moment is solvated in a polar solvent, i.e. it is surrounded by a "coating" of polar solvent molecules. If the solvent molecules do not form hydrogen bonds or π-complexes (specific solvation) with the free radical, then the solvation of a polar radical is due to electrostatic forces between its dipole and the polar medium. The rate constant for the reaction between polar species depends on the dielectric constant of the medium. If the dipole moment of the activated complex is higher than for the initial species, the reaction is faster in more polar media. The quantitative relation between the reaction rate constant and the dipole moments of the initial species and the activated complex on the one hand and the dielectric constant of the medium on the other is expressed by the following formula due to Kirkwood[157]:

$$\ln k = \ln k_0 - \frac{1}{\mathrm{k}\,T}\,\frac{\varepsilon-1}{2\varepsilon+1}\left(\frac{\mu_A^2}{r_A^3}+\frac{\mu_B^2}{r_B^3}-\frac{\mu_{\neq}^2}{r_{\neq}^3}\right),$$

where k is the Boltzmann constant, ϵ the dielectric constant of the medium, r_A, r_B, and $r_{\neq}$ are the radii of the initial species and of the activated complex, and μ_A, μ_B, and $\mu_{\neq}$ are their dipole moments. This formula was derived on the assumption that the medium surrounding the species is isotropic and the macroscopic dielectric constant ϵ holds also for the interaction between the species and the solvent molecules. Since strictly speaking this is not true, the above formula is approximate. The effect of non-specific solvation on the interaction between free radicals was investigated in detail by Zaikov, Maizus, and Emanuel' in the case of peroxy-radicals[116,158-160].

It was established that, when ethyl methyl ketone is diluted with various solvents (benzene, carbon tetrachloride, acetic acid, decane, and p-dichlorobenzene), the rate constant for the reaction between the peroxy-radicals derived from ethyl methyl ketone increases with ϵ and Kirkwood's formula holds satisfactorily:

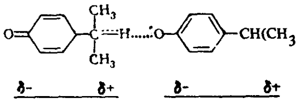
$$\lg k = A + B\,\frac{\varepsilon-1}{2\varepsilon+1}\ .$$

At 60°C $A = 3.36$ and $B = 6.0$. By extrapolation to $\epsilon = 0$ and $1/\epsilon \to 0$, the activation energies $E_{\epsilon\to 0} = 6.5$ kcal mole^{-1} and $E_{\epsilon\to\infty} = 1.2$ kcal mole^{-1} were obtained.

A linear relation between E and $(\epsilon - 1)/\epsilon$ holds for the disproportionation reaction of 2,6-di-t-butyl-4-isopropylphenoxy-radicals[89]:

$$E = E_0 + A\,\frac{\varepsilon-1}{\varepsilon}\ .$$

This relation is consistent with theoretical calculations. The reaction of two phenoxy-radicals constitutes, from the electrostatic standpoint, the interaction of two dipoles of the "head to tail" type:



When the dielectric constant changes from ϵ_1 to ϵ_2, the energy of this interaction is altered by an amount:

$$\Delta E = -\frac{28.9\,\mu_A\mu_B\Delta\varepsilon}{\varepsilon_1\varepsilon_2 r^3},$$

or on transition from $\epsilon = 1$ to $\epsilon = \epsilon$ with $\mu_A = \mu_B$, we obtain

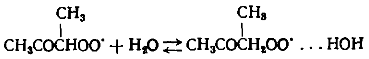
$$\Delta E = \frac{28.9\,\mu^2(\varepsilon-1)}{\epsilon r^3}\ ,$$

which agrees with the experimental relation.

3. Specific Solvation

Radicals with a free valence at nitrogen and oxygen atoms can form a hydrogen bond of the type Y...H–X, which should be reflected in their reactivity. A hydrogen bond of the type ROO...H–X has been suggested[161] and its formation has been proved by Zaikov, Maisuz, and Emanuel'.[116,162-164]

According to Zaikov et al.[162], the equilibrium constant for the reaction

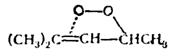


$$\mathrm{CH_3CO\overset{\overset{\displaystyle CH_3}{|}}{C}HOO^{\bullet} + H_2O \rightleftarrows CH_3CO\overset{\overset{\displaystyle CH_3}{|}}{C}H_2OO^{\bullet}\ldots HOH}$$

corresponds to $\lg K = 4.88 + 4.8/\theta$, where $\theta = 4.57T/1000$ (K is expressed in litre mole^{-1}).

The radical hydrogen bond appreciably retards the reaction between two peroxy-radicals[162,163]. However, for the peroxy-radical derived from ethyl methyl ketone[163], $2k(\mathrm{RO_2^{\bullet}} + \mathrm{RO_2^{\bullet}}) = 18\times10^5$ litre mole^{-1} s^{-1} and $2k(\mathrm{RO_2^{\bullet}}\ldots\mathrm{HOH} + \mathrm{RO_2^{\bullet}}\ldots\mathrm{HOH}) = 0.70\times10^5$ litre mole^{-1} s^{-1} at 60°C, $E_{\mathrm{RO_2^{\bullet}}} = 1.6$ kcal mole^{-1}, $E_{\mathrm{RO_2^{\bullet}}\ldots\mathrm{HOH}} = 4.6$ kcal mole^{-1}, $\lg 2A_{\mathrm{RO_2^{\bullet}}} = 7.30$, and $\lg 2A_{\mathrm{RO_2^{\bullet}}\ldots\mathrm{HOH}} = 7.86$. The existence of the hydrogen bond has been demonstrated kinetically for the cyclohexylperoxy-radical and t-butyl alcohol[116], the equilibrium constant corresponding to $\lg K = \bar{3}.69 + 3.5/\theta$ with $\theta = 4.57T/100$ (K expressed in litre mole^{-1}).

The rate constants for the interaction of cyclohexylperoxy-radicals do not differ greatly for solvated and unsolvated radicals[116]: $2k_{\mathrm{RO_2^{\bullet}}} = 5.0\times10^6$ and $2k_{\mathrm{RO_2^{\bullet}}\ldots\mathrm{MOR'}} = 1.6\times10^6$. Thus a hydrogen bond to a free radical lowers the rate of its destruction by reaction with other radicals and consequently increases the steady-state concentration of radicals in the system. However, the overall rate of the chain reaction usually falls in the presence of a solvent forming hydrogen bonds, since the hydrogen bond also retards the chain propagation reaction. Thus, as a result of the formation of hydrogen bonds in the system, free radicals become less active but their steady-state concentration increases. An interesting exception are the peroxy-radicals of 2-methylpent-2-ene[165], the rate constants for the interaction of which with one another and with the hydrocarbon increase as alcohol is added to the hydrocarbon. This has been explained by the formation of an intramolecular π-bond:



which in the presence of an alcohol dissociates as a result of the formation of the hydrogen bond; the hydrogen-bonded peroxy-radicals are apparently less active than the radicals with the intramolecular π-bond.

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Institute of Chemical Physics
of the USSR Academy of
Sciences,
Chernogolovka Branch

U.D.C. 547.321

Vinyl Fluoride

V.A.Korin'ko, M.I.Levinskii, E.A.Chaika, and A.L.Englin

The review deals with the methods of preparation, physical and chemical properties, and polymerisation and copolymerisation of vinyl fluoride with various unsaturated compounds as well as the properties, stabilisation, processing, and applications of its polymers and copolymers based on the data published up to the end of 1968.
The bibliography includes 299 references.

CONTENTS

I. INTRODUCTION

Numerous studies dealing with the synthesis, polymerisation, and copolymerisation of vinyl fluoride have been published. Polymers and copolymers of vinyl fluoride are of great interest because they have many valuable properties: high thermal stability, resistance to the action of light, chemical reagents, and radiation, and exceptional resistance to weathering.

Certain results of studies dealing with vinyl fluoride were described in the 1951 review by Knunyants and Fokin[1] on the polymerisation of fluoro-olefins and in a later monograph by Vaculik[2] on the chemistry of monomers.

II. METHODS OF PREPARATION OF VINYL FLUORIDE

Vinyl fluoride (VF) was obtained for the first time by Swarts[3,4] in 1901:

$$BrCH_2{-}CHBr_2 \xrightarrow[100,180^\circ]{SbF_3,Br_2} \left[\begin{array}{l} BrCH_2{-}CHF_2 \\ BrCH_2{-}CHBrF \end{array}\right. \xrightarrow[C_2H_5OH]{Zn} H_2C{=}CHF$$

Later he synthesised it[5] in 98% yield from 1, 1-difluoro-2-iodoethane:

$$F_2CH{-}CH_2I \xrightarrow[\text{ether}]{C_2H_5MgBr} H_2C{=}CHF\ .$$

1. Preparation of Vinyl Fluoride by Hydrofluorination of Acetylene

Investigators have devoted most attention to the synthesis of vinyl fluoride by the hydrofluorination of acetylene. In the absence of a catalyst and high pressures vinyl fluoride is not formed at temperatures ranging from −70° to 0°C [6]. The possibility in principle of obtaining vinyl fluoride from acetylene and hydrogen fluoride under pressure was mentioned in patents as early as the 1920's[7], but the process itself was achieved much later by Grosse and Linn[6] with a conversion of acetylene of about 15%:

$$HC{\equiv}CH \xrightarrow[20^\circ,72\ h]{8-12\ atm} H_2C{=}CHF + CH_3{-}CHF_2\ .$$

The catalytic method is more effective. A number of catalysts have been proposed for the vapour-phase process, among which mercury compounds have become most widely known: HgO and $HgCl_2$ on activated charcoal[8], in the presence of hydrogen chloride[9] or hydrogen chloride and iron(III) chloride[10]. Newkirk[11], who used as catalyst mercury(II) chloride on activated charcoal promoted with barium chloride, obtained an 82% yield of vinyl fluoride at 97−104°C. Under the same conditions in the absence of barium chloride, the yield of vinyl fluoride fell to 51.5%. Dolgopol'skii et al.[12] used HgO in liquid paraffin as a catalyst. Acetylene was passed through a vessel with anhydrous hydrogen fluoride and then through a suspension of HgO in liquid paraffin. At 0°C, for a molar ratio $C_2H_2 : HF = 1 : 3.48$ and an acetylene flow rate of 6 litre h^{-1}, the yield of vinyl fluoride was 68.4%. Using mercury acetate on activated charcoal at 40°C and a molar ratio $C_2H_2 : HF = 1 : 1.5$, it proved possible to obtain vinyl fluoride in 86% yield[13]. Other mercury compounds on activated charcoal have also been used as catalysts, for example nitrates[14-17] (at temperatures between 0° and 100°C). Apart from activated charcoal, alumina, graphite[17], or solid organic polymers[16,17] can be used as carriers, which stabilise the catalyst and increase the duration of its activity. A method of preparation of vinyl fluoride in the presence of mercury salts on activated charcoal at 30−40°C in a polypropylene reactor has been described. The catalyst functioned for 240 h without loss of activity[18].

It has been noted that at an elevated temperature activated charcoal reduces mercury salts and deactivates them. The mercury thus produced evaporates and condenses in various parts of the apparatus. Loss of mercury also leads to a decrease of the activity of the catalyst and in addition results in the formation of mercury fluoride, which induces the polymerisation of vinyl fluoride. To prevent the reduction of mercury salts, iron(III) salts or other oxidants are added to the catalyst, which increases its activity and duration of its useful operational life[11].

Mercury nitrate deposited on alumina in an amount of 5−20 wt.% proved to be a long-lived catalyst for the synthesis of vinyl fluoride. After passing a mixture of 48% of acetylene, 50% of hydrogen fluoride, and 2% of nitrogen oxides through the catalyst at 65°C and neutralising the product, a mixture of 66% of vinyl fluoride and 34% of 1, 1-difluoroethane was obtained[17]. Zinc and mercury chromates[19] or mixtures of mercury, zinc, and nickel chromates[20] have also been used as catalysts at temperatures in the range 75–250°C. Boric acid was added to prevent the sintering of the catalyst[19].

The synthesis of vinyl fluoride at 20–100°C with catalysts consisting of mercury(II) oxide on activated charcoal or alumina and also TiO_2 or ZrO_2 on the same carriers, subjected to preliminary irradiation or irradiated during the reaction with γ-rays, has been described[21,22]. The yield of the monomer was 70%.

When activated alumina or aluminium trifluoride were used as catalysts at temperatures in the range 250–400°C, a mixture of vinyl fluoride and 1, 1-difluoroethane was obtained[23-28]. The same compounds were synthesised in the presence of aluminium sulphate[29] or a 3 : 1 mixture of Al_2O_3 and ZnF_2.[30]

Skiles proposed zinc[31] and chromium[32] catalysts. In the first case the catalyst was prepared by mixing zinc oxide with cane sugar in water and the resulting paste was dried and carbonised at 700°C.

Clark[33] obtained vinyl fluoride in the presence of copper cyanide deposited on activated charcoal or other porous carriers inert with respect to hydrogen fluoride. When copper chloride on activated charcoal was tested, the conversion of acetylene was only 0.3%.

The use of fluorosulphonic acid as a catalyst for the hydrofluorination of acetylene has been reported. At 0°C 1, 1-difluoroethane forms in 85% yield and at 80–90°C the product is a mixture of 50% of vinyl fluoride and 40% of 1, 1-difluoroethane[34]. Linn[35] obtained vinyl fluoride in the presence of boron trifluoride.

With cadmium sulphate, nitrate, or acetate on activated charcoal in a stationary or fluidised bed as catalysts, vinyl fluoride was obtained in 98% yield at 300°C. The catalysts functioned for 50 h without loss of activity. The vinyl fluoride contained traces of acetylene and 1, 1-difluoroethane[36].

When the catalyst was aluminium trifluoride with a small amount of BiF_3 or $Bi(OH)_3$, a mixture of 70.3% of vinyl fluoride and 29.6% of 1, 1-difluoroethane was obtained at 200–400°C; the conversion of acetylene was 96.7%[37]. Since vinyl fluoride and acetylene have similar boiling points, there are technical difficulties in the isolation of the pure monomer free from acetylene. McMillan[38] purified vinyl fluoride by azeotropic fractionation of the mixture using ethane, which forms an azeotrope with acetylene. Kalb et al.[39] separated vinyl fluoride from 1, 1-difluoroethane, hydrogen fluoride, and other impurities by distillation. Traces of hydrogen fluoride were removed by passing the monomer through columns filled with sodium carbonate and acetylene was removed by washing the monomer in a scrubber with an ammoniacal solution of copper(I) chloride. Oxygen was removed by repeated distillation at a pressure of 2.8–7 atm at temperatures ranging from −50° to −25°C.

For the removal of acetylene from vinyl fluoride, dimethyl sulphoxide and dimethylformamide or their mixtures[40] as well as *N*-methylpyrrolidinone[41] were proposed as selective solvents for acetylene. It has also been suggested that a mixture of vinyl fluoride, acetylene, and 1, 1-difluoroethane be brominated at 0°C with subsequent distillation of the bromination products; pure vinyl fluoride was obtained by treating 1, 2-dibromo-1-fluoroethane with zinc in alcohol[42]. The purification of vinyl fluoride by the hydrochlorination of the acetylene impurity with subsequent fractionation of the mixture is very promising[43]. Usmanov et al.[44] developed a method for a high degree of elimination of acetylene and difluoroethane from vinyl fluoride in a gas saturator with glass frit gas spreaders consisting of 5 saturators connected in series and two gas-absorption columns. Acetylene was absorbed in a solution of ammonium chloride and copper(I) chloride in aqueous ammonia. The gas flow rate was maintained in the range 10–15 litre h^{-1}. This method made it possible to reduce the acetylene content in the crude monomer to 4×10^{-5}%. Difluoroethane was removed from vinyl fluoride on a column for low-temperature fractionation. The purified monomer contained not more than 1×10^{-4}% of difluoroethane.

2. Preparation of Vinyl Fluoride by the Dehydrofluorination of 1, 1-Difluoroethane

Vinyl fluoride has been obtained[45-47] by the pyrolysis of 1, 1-difluoroethane at 350–1000°C and in the presence of activated charcoal at 300–600°C:

$$CH_3{-}CHF_2 \xrightarrow{-HF} H_2C{=}CHF \ .$$

Pyrolysis of 1, 1-difluoroethane in the presence of 2% of oxygen at 500°C gave a 61% yield of vinyl fluoride[48]. Calcium fluoride, charcoal, and steel filings were used as catalysts at 300–600°C, the yields of vinyl fluoride being 75, 84, and 88% respectively[49]. Vinyl fluoride forms in 32.7% yield at 400–850°C in the presence of a catalyst based on $CrF_3.H_2O$. Without the catalyst, the amount of acetylene increased and the conversion fell to 3.3%[50].

By dehydrofluorinating 1, 1-difluoroethane on activated charcoal at 350°C, a mixture containing 27.8% of vinyl fluoride and 62.7% of 1, 1-difluoroethane was obtained; at a reaction temperature of 400°C the amount of vinyl fluoride rose to 37.2%[51]. 1, 1-Difluoroethane has also been pyrolysed in a steel tube on charcoal or metals and their oxides and salts of Groups I, II, V, and VII,[52,53] at 300–800°C. The yield of vinyl fluoride reached 88%. When 4–6% of nickel oxide on alumina was used as a catalyst at 400°C, the yield of vinyl fluoride rose to 99%[54].

By passing a 1.7 : 1 mixture of 1, 1-difluoroethane and acetylene over aluminium trifluoride at 250–300°C, a mixture containing 64% of vinyl fluoride, 1.6% of acetylene, 0.3% of ethylene, and 1.1% of hydrogen fluoride was obtained. Unsaturated hydrocarbons were removed by catalytic hydrogenation (in the presence of palladium on charcoal) in the form of ethane and vinyl fluoride was isolated by fractional distillation[55].

3. Other Methods for the Preparation of Vinyl Fluoride

Henne and Midgley[56] synthesised vinyl fluoride by treating 1, 2-dichloro-1-fluoroethane with zinc in alcohol. Vinyl fluoride forms in 50% yield from 1, 1-difluoro-2-iodo- or 1, 2-dibromo-1-fluoro-ethane on treatment with magnesium, sodium, or potassium in ether[57]. Benning et al.[58] suggested acetone, pyridine, and dioxan, in addition to alcohol, as the medium for the elimination of halogen atoms with zinc.

Vinyl fluoride was synthesised in 58% yield from 1-chloro-2-fluoroethane by the elimination of hydrogen chloride with soda-lime at 400°C[59]. A high yield of vinyl fluoride in the pyrolysis of 1-chloro-1-fluoroethane at 500–800°C at a reduced pressure[47,60], in a chromenickel tube[61] and in the presence of copper or Cu_2Cl_2 powder[62], has been reported. In the last case the yield was 97.9%.

The fluorination of alkyl halides with hydrogen fluoride at an elevated temperature and pressure on activated charcoal[63] or alumina[64] is accompanied by the elimination of hydrogen halides and the formation of vinyl chloride and fluoride. The latter was also isolated in the pyrolysis of 1,2-difluoroethane on alumina, calcium sulphate, or activated charcoal at 200–400°C [65]. A mixture of ethyl and vinyl fluorides was obtained from ethane on oxidative fluorination in the presence of iron(III) oxide or lead oxide at 325–700°C [66]. The products of the fluorination of ethylene with mercury(II) fluoride at 150–180°C in an autoclave are hexafluoroethane and vinyl fluoride[67]. Vinyl fluoride has also been synthesised from ethylene, hydrogen fluoride, and oxygen, using as a catalyst a mixture of $PdCl_2$, $FeCl_3$, and $CuCl_2$ on activated charcoal[68]. The formation of vinyl fluoride by the reaction of ethylene and alkali metal fluorides in the presence of $PdCl_2$ in an autoclave at 160–190°C has been described; the reaction medium may be benzonitrile, nitrobenzene, dibutyl phthalate, or tetrahydrofuran (THF)[69,70]. After being passed over a Cr_2O_3 catalyst on alumina at 300–400°C, a mixture of 1,2-dichloroethane and hydrogen fluoride was found to contain about 20% of vinyl fluoride[71]. Vinyl fluoride forms in 70% yield when fluorine reacts with a complex of vinylmagnesium chloride and tetrahydrofuran[72].

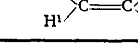
By passing vinyl chloride through a vessel with anhydrous hydrogen fluoride in the presence of oleum at a temperature not exceeding 20°C, a mixture of vinyl chloride, 1-chloro-1-fluoroethane, 1,1-difluoroethane, and hydrogen chloride and fluoride was obtained; this was then pyrolysed at 400–800°C. The gas from the pyrolysis was passed through a fractionating column, where hydrogen chloride and vinyl fluoride were separated and a mixture of hydrogen fluoride, vinyl chloride, and fluoroethanes was returned to the hydrofluorination reactor. The vinyl fluoride did not contain acetylene as an impurity; the yield was 85%[73]. Vinyl fluoride forms when vinyl chloride reacts with a fluorinated anion-exchange resin in the presence of a palladium salt in acetic or propionic acid, tetrahydrofuran, or dimethylformamide at 0–200°C [74]. Vinyl fluoride has been isolated in the photolysis of 1,3-difluoroacetone[75].

III. PHYSICAL PROPERTIES OF VINYL FLUORIDE

At normal temperatures and pressures vinyl fluoride is a colourless gas with a boiling point of −72.2°C, a melting point of −160.5°C, and $d_4 = 0.853$ at −72.2°C. It is insoluble in water and is relatively sparingly soluble in alcohol and acetone[8]. It has not been found to have a narcotic effect[76]. The heat of formation ($-\Delta H$) of vinyl fluoride from the elements in the gaseous state at 25°C has been calculated as +28 kcal mole^{-1}.[7] The experimental dipole moment is $\mu = 1.42 \pm 0.01$ D.[78] The ionisation potential of vinyl fluoride, determined by photoionisation and electron impact methods, has been found to be 10.37 and 10.45 eV respectively[79-82].

In recent years spectroscopic methods have been widely used to study vinyl fluoride. The vibration spectra have been investigated by many workers[83-95], who used them largely to determine and describe the geometrical structure of the vinyl fluoride molecule. A full compilation of all the geometrical parameters is presented in Table 1. The infrared spectrum of vinyl fluoride was obtained for the first time by Torkington and Thompson[92]. Bak and Christensen[94] analysed the infrared spectra of vinyl fluoride and all seven of its deutero-derivatives and assigned the frequencies of the fundamental vibrations of the molecules. The isotopic compounds were isolated from the mixture and freed from non-isotopic admixtures on silica gel at 43°C, the purity of the compounds obtained being checked by infrared spectroscopy. Sverdlov et al.[91] achieved a complete interpretation of the vibration spectra of vinyl fluoride and its deutero-derivatives.

Table 1. Bond lengths (Å) and valence angles in the vinyl fluoride molecule



Bonds and angles	Method		
	microwave spectroscopy Ref.83	microwave spectroscopy, least squares method (Ref.84)	isotopic shift method (Ref.85)
C_1—F	1.348	1.344±0.002	1.347±0.009
C_1—H_1	1.073	1.080±0.005	1.082±0.004
C_2—H_3	1.080	1.075±0.005	1.077±0.003
C_1—C_2	1.333	1.337±0.002	1.329±0.006
C_2—H_2	—	—	1.087±0.003
FC_1H_1	115.4°	—	110.0±1°
$H_1C_1C_2$	123.7°	—	—
$H_2C_2C_1$	121.1°	—	120.9±0.3°
$H_3C_2C_1$	118.5°	—	119.0±0.3°
C_2C_1F	—	121±0.2°	120.8±0.3°

Quite recently the NMR spectra[96-103], electronic spectra[82], and mass spectra[81] of vinyl fluoride were reported. The values and relative signs of the spin–spin interaction constants and chemical shifts have been determined and it has been shown that the variation of the latter with the electronegativity of the atoms is close to linearity. Fogg and Lambert[104] studied the propagation of ultrasonic waves in vinyl fluoride at 100°C.

IV. ANALYSIS OF VINYL FLUORIDE

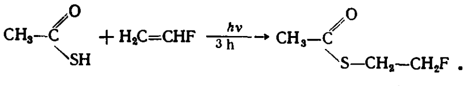
Newkirk[11] determined the density of gaseous vinyl fluoride on an Edwards balance and measured its amount by absorption in bromine water. Of the modern analytical methods, gas chromatography[44,105,106] and infrared spectroscopy[92] may be used. The analysis of the mixture consisting of 1-chloro-1-fluoroethane, 1-chloro-2-fluoroethane, and vinyl fluoride on a laboratory chromatograph of type KhL-3 has been described[105]. A mixture of trifluoromethane, chlorotrifluoromethane, 1,1-dichloro-2,2-difluoroethylene, vinyl fluoride, nitrogen, and oxygen has been separated[106]. Usmanov et al.[44] have proposed a method of analysis by gas–liquid chromatography with a flame-ionisation detector on a column with 25% of liquid paraffin on an INZ-600 carrier as the stationary liquid phase.

V. CHEMICAL PROPERTIES OF VINYL FLUORIDE

Reactions involving the double bond of vinyl fluoride have ionic and radical mechanisms. Reactions of the first type include the addition of halogens[3,42] and hydrogen halides, the latter following the Markovnikov rule with the exception of hydrogen bromide under the conditions of a radical process[107]. Hydrogen fluoride adds to vinyl fluoride with greater difficulty than to unsubstituted ethylenes, which can be accounted for by the effect of the highly electronegative fluorine atom. The addition of hydrogen fluoride to vinyl fluoride is catalysed by the halides of certain metals and also by fluorosulphonic acid[34]. Yakubovich et al.[108,109] showed that nitrosyl chloride adds to vinyl fluoride with formation of 1-chloro-1-fluoro-2-nitrosoethane, which is then oxidised to 1-chloro-1-fluoro-2-nitroethane:

$$H_2C{=}CHF + NOCl \rightarrow [FClCH{-}CH_2NO] \rightarrow FClCH{-}CH_2NO_2 \ .$$

The reaction of vinyl fluoride with thioacetic acid under irradiation with ultraviolet light and in the presence of benzoyl peroxide[110] gave a 75% yield of 2-fluoroethyl thioacetate:



$$CH_3{-}C(=O){-}SH + H_2C{=}CHF \xrightarrow[3\,h]{h\nu} CH_3{-}C(=O){-}S{-}CH_2{-}CH_2F \ .$$

Yarovenko and Vasil'eva[111] obtained a 30% yield of di(2-chloro-2-fluoroethyl) sulphide by irradiating with ultraviolet light a mixture of copper(I) chloride and vinyl fluoride under pressure in the presence of benzoyl peroxide for 200 h at 20°C [111]:

$$H_2C{=}CHF + S_2Cl_2 \xrightarrow{h\nu} S(CH_2{-}CHFCl)_2 + S \ .$$

A number of free-radical reactions involving the addition of perhalogenoalkanes to vinyl fluoride have been investigated. Haszeldine et al.[112] irradiated trifluoroiodomethane and vinyl fluoride with ultraviolet light for 14 days and obtained an 84% yield of 1,1,1,3-tetrafluoro-3-iodopropane as well as a small amount of 1,1,1,3,5-pentafluoro-5-iodopentane:

$$CF_3I + H_2C{=}CHF \xrightarrow{h\nu} F_3C{-}CH_2{-}CHFI + F_3C{-}CH_2{-}CHF{-}CH_2{-}CHFI \ .$$

The addition of dibromodifluoromethane[113] and 1,2-dibromo-2-chloro-1,1,2-trifluoroethane[114] to vinyl fluoride in an autoclave at 100°C in the presence of benzoyl peroxide has been described:

$$\begin{gathered} CBr_2F_2 + H_2C{=}CHF \rightarrow BrCF_2{-}CH_2{-}CHFBr + BrCF_2{-}CH_2{-}CHF{-}CH_2{-}CHFBr \ , \\ BrCF_2{-}CBrFCl + H_2C{=}CHF \rightarrow BrCF_2{-}CFCl{-}CH_2{-}CHFBr + BrCF_2{-}CFCl{-}CH_2{-} \\ {-}CHF{-}CH_2{-}CHFBr \ . \end{gathered}$$

Park et al.[115] showed that the free-radical addition of perfluorovinyl iodide to vinyl fluoride leads to the formation of 1,1,2,4-tetrafluoro-4-iodobut-1-ene:

$$H_2C{=}CHF + F_2C{=}CFI \rightarrow F_2C{=}CF{-}CH_2{-}CHFI \ .$$

The addition of trichloromethyl[116,117] and trifluoromethyl[118,119] radicals to vinyl fluoride has been reported. The free-radical addition of perfluoroacetonitrile to vinyl fluoride has been investigated[120]:

$$H_2C{=}CHF + F_3C{-}CN \rightarrow F_3C{-}CH_2{-}CHF{-}CN \ .$$

It has been shown[121] that the reaction of trichloro-, methyldichloro-, and trimethyl-silane with vinyl fluoride gives a high yield of the corresponding 2-fluoroethylsilanes:

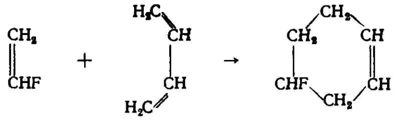
$$SiHCl_3 + H_2C{=}CHF \rightarrow CH_2F{-}CH_2{-}SiCl_3 \ .$$

The kinetics of the radical addition of tetrafluorohydrazine to vinyl fluoride have been studied[122]. It has been noted that the interaction of vinyl fluoride and ClF_3 in the gas phase at 70–125°C results, apart from substitution, in the addition of the decomposition products of chlorine trifluoride (Cl_2, F_2, ClF) to the double bond[123].

Haszeldine et al.[124] attempted to carry out the reaction of trifluoronitrosomethane with vinyl fluoride, but only the starting materials and the conversion products of trifluoronitrosomethane were isolated.

When tetramethyldiborane was allowed to react with vinyl fluoride, a mixture of ethyldimethyl-, diethylmethyl-, trimethyl-, fluorodimethyl-, and difluoromethyl-borane was obtained[125]. By allowing diborane to react with vinyl fluoride, Bartocha et al.[126] obtained a mixture of triethyl-, diethylfluoro-, and ethyldifluoro-borane with the last compound predominating; under these conditions, polymerisation of vinyl fluoride was not observed.

McQueen[127] showed that the reaction of vinyl fluoride with butadiene at 150–300°C and an elevated pressure, in the absence of polymerisation catalysts, gives a low yield of 4-fluorocyclohexene:



Soborovskii and coworkers[128,129] carried out the reaction of phosphorus trichloride with vinyl fluoride and obtained low yields of the chlorides of the isomeric 1-chloro-2-fluoro- and 2-chloro-2-fluoro-ethylphosphonic acids:

$$H_2C{=}CHF + 2PCl_3 + O_2 \rightarrow \begin{matrix} ClCH_2{-}CHF{-}P(O)Cl_2 \\ ClCHF{-}CH_2{-}P(O)Cl_2 \end{matrix}$$

Recently Jones[130] reported that butadiene is formed in high yield when vinyl fluoride is treated with tetraethylammonium trichlorostannate(II) in the presence of $PtCl_2$ and CsF in dimethylformamide, acetonitrile, or dimethyl sulphoxide:

$$CH_2{=}CHF + (C_2H_5)_4NSnCl_3 \xrightarrow[25°]{PtCl_2, CsF} H_2C{=}CH{-}CH{=}CH_2$$

Monofluorocyclopropane and its isomerisation products were obtained by the photolysis of keten in the presence of vinyl fluoride[131].

VI. POLYMERISATION OF VINYL FLUORIDE

The polymerisation of vinyl fluoride was observed for the first time by Starkweather in 1934[132]. Toluene was saturated with the monomer at −35°C, the solution was kept at 67°C and 6000 atm for 16 h, and the polymer was obtained in a low yield. Later, Newkirk[11] described the polymerisation of vinyl fluoride under ultraviolet irradiation in quartz capillaries in the presence of benzoyl, lauroyl, or acetyl peroxides as initiators.

Various methods have been described for the polymerisation of vinyl fluoride: emulsion, solution, suspension, and solid state. Emulsion polymerisation has found the widest application, since it takes place at a high rate at a relatively low temperature, which makes it possible to obtain a polymer with a high average molecular weight. Oxygen-free water or a mixture of water and organic solvents have been used as dispersion media[133–136].

Kalb et al.[39] studied the effect of impurities on the polymerisation of vinyl fluoride and found that, when the process is initiated with 0.2% of benzoyl peroxide at a pressure of 900 atm and a temperature of 80–100°C, 0.05% of oxygen in the monomer inhibits the polymerisation and 0.013% promotes it. Acetylene strongly inhibits the process, a brittle polymer of low molecular weight being formed in a yield of only 3%.

To improve the stability of the emulsions, emulsifying agents such as magnesium lauryl sulphate[137] or sodium bis(tridecyl)sulphosuccinate[138] are added to the system.

Redox systems, alkali metals, and substances which give rise to free radicals on heating have been investigated as initiators. Substances of the last type yielded polymers with the most successful combination of properties[39,139]. Of the peroxy-catalysts, benzoyl[39,136,140–142], dodecanoyl[134], diethyl, di-t-butyl[39] peroxides and t-butyl hydroperoxide[138] have been tested for the polymerisation of vinyl fluoride. When dialkyl percarbonates are used as initiators, the polymerisation takes place at a lower temperature and pressure[143]. Apart from peroxides, azo-compounds have been widely used as initiators: αα′-azo-bis-αγ-dimethylvaleronitrile, αα′-azobisisobutyronitrile[39,144], the hydrochloride of αα′-azobisisobutyramidine[39,145], azodisulphonates of alkali and alkaline earth metals[133], and the dihydrochloride of 2,2′-diamidino-2,2′-azopropane[146–149].

Tri-isobutylborane[134] and the products of the interaction of triethylborane with ammonia, hydrazine, hydroxylamine, and amines[150,151] have also been used for the polymerisation of vinyl fluoride.

The effect of various initiators on the polymerisation process has been studied[39]. Differences have been noted between initiators active at 125°C and above and those which activate polymerisation at 70–85°C. It was found that the polymers obtained at a high temperature had a lower molecular weight and more highly branched chains. The concentration of the initiator also affected the molecular weight of the polymer. With increase of the concentration of benzoyl peroxide in an aqueous medium at 80–90°C and a pressure of 250 atm, the effectiveness of the initiator and the characteristic viscosity of the polymer decreased. Analogous results were obtained when azo-compounds were employed as initiators.

The effect of temperature and pressure on the radical polymerisation of vinyl fluoride has been investigated. It has been established that, with increase of temperature, the effectiveness of the initiator reaches a maximum and then falls, the temperature corresponding to the maximum effectiveness being independent of pressure. As the reaction temperature rises, the viscosity of the poly(vinyl fluoride) (PVF) melt diminishes; an increase of pressure favours the formation of a polymer with a higher molecular weight[39].

Recently a number of continuous polymerisation processes have been developed for vinyl fluoride. Their essential feature consists of a continuous supply of vinyl fluoride, water, and the initiator into the reaction zone. The reaction is carried out in a homogeneous dispersion medium, the PVF formed being continuously removed. The required pressure and temperature are maintained in the reactor[145,146,149]. Processes with recycling of water, in which after the separation of the polymer water is deionised, freed from oxygen, and returned to the cycle, have been proposed[147–149].

In studies on the suspension polymerisation of vinyl fluoride much attention has been devoted to the search for new improved surface-active substances and stabilisers. Methylcellulose[137,152,153], glucose ethers[154], and the copolymers of ethylene[155], vinyl acetate, and allyl alcohol[156] with maleic acid or its anhydride have been suggested as dispersing agents for polymerisation in suspension. Using such compounds, it was possible to obtain highly porous PVF, which readily blends with plasticising agents, exhibits improved stability under illumination, and is a good electrical insulator. When lauroyl peroxide was used as an initiator, a polymer with a particle size of 0.05–2.5 μm was obtained[137]. The polymerisation of vinyl fluoride in the presence of titanium dioxide, yielding a product with a particle size of 0.3 μm, has been described[153].

PVF containing 14.4% of titanium dioxide and consisting largely of particles about 1 μm in diameter has been used in the form of dispersions in dimethylacetamide for coatings on metals.

In polymerisation in solution it is easier to control the reaction temperature, but, because of the lower concentration of the monomer, the polymers produced have a lower molecular weight. A number of organic solvents have been investigated as reaction media, using various polymerisation initiators: benzoyl, acetyl, lauroyl, diethyl, di-t-butyl[39,157,158], and perfluoroacyl[159–161] peroxides.

The search for new catalytic systems suitable for the polymerisation of vinyl fluoride has been vigorously prosecuted in recent years. The following systems have been tested: diethylaluminium bromide or triethyl aluminium–titanium tetrachloride[162,163], tri-isopropylaluminium–tetraisopropyloxytitanium[164], and cadmium and zinc alkyls[142]. Alkyl compounds of boron[165–168] and their coordination compounds with ammonia, hydrazine, hydroxylamine, and amines[150,151,169] have also been used as catalysts, which yielded PVF with a degree of crystallinity in excess of 30%. The polymerisation was carried out in solution, using methylene chloride, ethyl acetate, tetrahydrofuran, isobutyl alcohol, dimethylformamide, dimethyl sulphoxide, etc. as solvents[150]. A continuous process for the polymerisation of vinyl fluoride in carbon tetrachloride using peroxide initiators has been proposed[170]. It has been shown[39] that a common property of organic solvents is a tendency towards interaction (telomerisation) with vinyl fluoride, which leads to a sharp decrease of the molecular weight of the polymer obtained. Films produced from these polymers had a low impact strength.

Recently there has been a continuous increase in the number of experimental studies involving the use of radiation for the polymerisation of vinyl fluoride[171–177].

The use of radiation makes it possible to achieve polymerisation at low temperatures. Vinyl fluoride has been polymerised at a radiation dose rate ranging from 1×10^2 to 1×10^8 r h^{-1}.[73] The yield of PVF varied with the radiation dose and temperature, the maximum yield of the polymer being obtained at 0°C and a radiation dose rate of 10^4 r h^{-1}.[75] The polymerisation of vinyl fluoride at −78°C under γ-irradiation in the presence and absence of benzoyl peroxide has been studied[176].

VII. PROPERTIES OF POLY(VINYL FLUORIDE)

1. Physical Properties and Structure

A change in polymerisation conditions is reflected in the viscosity of the solutions and in the molecular weight of the resulting polymer. It has been shown[39] that the molecular weight is independent of the solvent used in the measurements. When benzoyl peroxide was employed, a decrease of the molecular weight of the polymer with increasing reaction temperature was observed. The molecular weight distribution of the polymer varies within wide limits as a function of the method of preparation, catalyst, and polymerisation temperature. Polymers synthesised using benzoyl peroxide as an initiator in the absence of a telogen melt at about 198°C.

Sapper[178] determined the heat of fusion per crystallising polymer unit, which amounted to 1800 cal.

The crystal structure of PVF has been studied by X-ray diffraction[167,179,180]. The NMR spectra of PVF have been recorded[181–183]. α-Particle absorption by PVF has been studied[184] at temperatures ranging from −59.7° to 42.7°C.

Ellison and Zisman[185] showed that the surface of PVF is readily wetted by solvents capable of forming hydrogen bonds.

2. Chemical Properties

Poly(vinyl fluoride) is resistant to the action of high temperatures, light, chemical reagents, and in particular hydrolysing agents. Characteristics such as tensile strength and modulus of elasticity do not change appreciably after exposure of the polymer to steam for 1500 h. After PVF specimens have been treated with 10% solutions of sodium hydroxide and hydrochloric acid for 7 days at 60°C, no changes in their mechanical properties were observed[186]. The treatment of PVF with nitrogen trifluoride and N_2F_2 at 80–100°C leads to formation of cross-links in the polymer and an improvement of its properties[187,188]. In the manufacture of laminate plastics adhesion between the carrier and the activated PVF layer can be achieved by the formation of OH, COOH, NH_2, etc. groups by treatment with boron trifluoride[189-191], concentrated sulphuric acid, hot alkali, or aluminium chloride[189].

Thermal decomposition of PVF in a vacuum at temperatures between 370°C and 500°C leads to the formation of hydrogen fluoride and fragments with different carbon chain lengths[192].

The telomerisation of vinyl fluoride by chloroformates at different temperatures in the presence of peroxides[193] and by trifluoromethyl iodide[194] has been investigated. The telomers obtained may be used as plasticisers for PVF. Telomers of chloroperfluoro-olefins and carbon tetrachloride have been recommended for the same purpose. Such plasticisers are not "sweated out" and do not cause turbidity of the specimen on bending[195]. Haszeldine et al.[196] carried out the telomerisation of vinyl fluoride with perhalogenoethanes under ultraviolet or X-ray irradiation or in the presence of peroxides at temperatures in the range 20–150°C.

The resistance of fluorine-containing polymers to ionising radiation has been investigated[197]. It has been found that polytetrafluoroethylene retains its structural properties only up to a dose rate of 2 Mrad, while PVF is stable up to 32 Mrad. After irradiation and simultaneous heat treatment the polymers become brittle.

Bro[198] studied the stability of various polymers in relation to amines and found that the PVF film is stable under the action of n-butylamine.

3. Stabilisation

Although PVF is distinguished by a comparatively high resistance to oxidative thermal and light-induced degradation, a number of stabilisers have been proposed for the preparation of compositions based on it which would be stable in various applications and under different processing conditions.

Monoalkyl esters of fumaric and maleic acids[199], glyceryl monolaurate[200], substituted 6-methyleneoctahydronaphthalenes[201], unsaturated terpenes and disulphides[202], alkali metal formates[203], and the copolymer of vinyl fluoride with bicyclo[2, 2, 1]hept-2-ene[204] have been proposed as thermostabilisers for PVF.

Benzophenone[205], *O*-hydroxybenzophenone[206], 2, 2′-dihydroxy-4, 4′-dimethoxybenzophenone[207,208], 2, 2′, 4, 4′-tetrahydroxybenzophenone[209], substituted triazoles[210], poly(2-hydroxy-4-methacryloyloxybenzophenone)[211], and a polyester obtained from the dichloride of adipic acid and 2, 4, 4′-trihydroxybenzophenone[212] proved to be effective photostabilisers under the action of ultraviolet light.

4. Processing and Applications

PVF is processed by the usual methods for thermoplastic materials: by extrusion, by pressing, by casting under pressure at temperatures in excess of 200°C, and also by deposition of coatings from dispersions[39,203,207-211,213-215].

PVF has found wide application in the form of films. Films are most often formed from solutions[39] or dispersions containing various substances which function as latent solvents for PVF[213,215-220]. Dimethylformamide[39], various lactones, for example γ-butyrolactone[213,217,219], tetramethylurea, dimethylacetamide, triethyl phosphate[216], 2-pyrrolidinone, *N*-isopropyl-*N*-methyl-, and 5-methyl-2-pyrrolidinone[218], *N*-formyl- and *N*-acetyl-piperidine[220], and dimethyl sulphoxide[214,215] have been used as solvents. A method has been described for the preparation of electroluminescent films from dispersions containing zinc sulphide[221]. To prepare opaque PVF films and dispersions, 1–35% of titanium dioxide, calcium carbonate, or their mixtures have been added. Pigments, stabilisers, and plasticisers have also been introduced into the films[222-227]. A method has been described[228] for the preparations of transparent films with low reflectivity by adding to PVF 1–5% of silica in the form of homogeneous spherical particles 2–10 μm in diameter. PVF films have been used in the manufacture of laminate plastics with high stability to wear and the effect of light[229-232].

Simril and Curry[186] made a detailed study of the physical, chemical, optical, and electrical properties of PVF films, and also of the effect of diaxial orientation of the films on some of their physical properties. PVF is transparent to visible and ultraviolet light but absorbs strongly in the infrared. PVF films have high tensile, bending, and impact strength, exhibit high resistance to wear, and undergo high relative elongation on stretching.

The principal distinctive feature of PVF is its high resistance to weathering. After exposure to sunlight for 7 years, a PVF film retained 50% of its initial tensile strength and remained flexible[39,233,234]. The permeability of PVF films to water and also to water vapour and various organic compounds and gases has been investigated[234-236]. A relation between the degree of orientation of the films and some of their mechanical properties has been demonstrated[39,237,238]. A highly oriented film shows a higher, tensile, impact, and bending strength and also exhibits a higher tear resistance.

To improve its adhesion to various materials, the film has been treated in a flame for periods ranging from 0.0025 to 0.5 s, with solutions of alkali metals in liquid ammonia, with organic derivatives of aluminium, zinc, and magnesium, and also with a solution of a diazo-compound in toluene, for example ethyl diazoacetate, 4, 4′-bis-(dimethylaminophenyl)diazomethane, etc. with subsequent irradiation of the treated surface by ultraviolet light[239-244].

The preparation of filaments from a dispersed paste containing 20–70% PVF has been described[245]. PVF in the form of films oriented to different extents has found a wide variety of applications in electrical insulation, packing, in the glazing of forcing frames, and in the protection of horticultural crops. Its exceptionally high resistance to the action of ultraviolet radiation makes PVF a very promising material for the protection of surfaces in apparatus designed for the collection of solar energy[246], in the building industry[233,247,248], and for protective coatings on metals[249-254]. The applications of PVF for internal coatings[255], for the preparation of diaphragms in electrolysers for the manufacture of chlorine[256], and also in chemical engineering[257] have been described.

VIII. COPOLYMERS OF VINYL FLUORIDE

Much work has been devoted[258-299] to the preparation, investigation of the properties, and applications of the copolymers of vinyl fluoride with various unsaturated compounds. The methods for the synthesis of vinyl fluoride copolymers are completely analogous to those for the synthesis of PVF. The copolymerisation has been carried out in suspension[155,156,164,268], in emulsion[138,150,152,261,263-265,272,288], in solution[166,167,170,259,262,263,266,288,295,296,299], or in the solid state[150,268,278,288,289]. A list of binary copolymers (comonomers) is given in Table 2.

Table 2. Binary copolymers of vinyl fluoride

Comonomer	References	Comonomer	References
Ethylene	138,150,262,277,279,299	Vinyl butyrate	156,274
Tetrafluoroethylene	142,150,167,168,263,266,279,299	Propene	278,290
Vinyl acetate	159,260,269,270,274,289, 297	Isobutene	152
Vinylidene fluoride	142,167,170,265,274,299	Bicycloheptene	138
Trifluoroethylene	170,268	Diethyl maleate	155,156
Vinyl chloride	150,164,166,168,271,275,276,280,283,289,299	Acrylate and methacrylate esters	159,299
Methylenemalononitrile	267	Vinyl benzoate	156
α-Acetamidoacrylamide	258	Dioctyl fumarate	156
Hydrogen cyanide	259	Vinyl carbonate	284
Chlorotrifluoroethylene	170,261,271,299	Acrylonitrile	156,296,299
Dichlorodifluoroethylene	264	Perfluoropropene	150,285,299
α-Cyanoacrylamide	267	Acrylamide	156
Methylenemalonamide	267	1,1,2,4-Tetrafluorobuta-1,3-diene	286
Fluoromethacrylate esters	273	1,1,2- and 1,1,3-trifluorobutadiene	287
Vinylidene chloride	299	1,1-Difluoroisobutene	288
Vinyl propionate	274,289	Perfluoronitrosomethane	291
		Styrene	299

The copolymers of vinyl fluoride are processed by the same methods as those used for PVF. The copolymers are widely used in the form of films[139,150,260,263,270,279,287,288] and coatings[271,286,287,298]. Coatings made from the copolymer of vinyl fluoride and vinyl chloride make various rubber articles resistant to light. Specimens with such coating remained unchanged after irradiation for 20 h with ultraviolet light, while ordinary rubber withstood only 7.5–25 min of such treatment[282]. The synthesis of foam plastics based on a copolymer of vinyl fluoride and vinyl chloride has been described.

Dimethyl sulphoxide, furfural, tetrahydrofuran, and dichlorobenzene have been used as solvents in the manufacture of fibre from the copolymers of vinyl fluoride and vinyl chloride; the fibre was spun by a wet method[150,270,280]. Copolymers of vinyl fluoride with isobutene and perfluoropropene proved to be resistant to heat, light, and chemical reagents. Extruded sheets of such copolymers are strong, flexible, and transparent, and, by virtue of their capacity for cold draining, can be used for the manufacture of various articles[150,152,155].

The synthesis of ternary copolymers has also been described. Thus the copolymer of vinyl fluoride, tetrafluoroethylene, and chlorotrifluoroethylene has been obtained in aqueous suspension at 80°C in the presence of benzoyl peroxide[292]. The copolymer of vinyl fluoride, tetrafluoroethylene, and vinyl chloride is incombustible and is readily soluble in acetone, ethyl methyl ketone, ethyl acetate, and halogeno-derivatives of hydrocarbons[293]. Copolymers melting without decomposition have been obtained from vinyl fluoride, dialkyl maleates, and vinylidene halides[294]. The copolymerisation of vinylidene fluoride, vinyl fluoride, and chlorotrifluoroethylene on γ-irradiation of the monomers has been described[274].

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Detritylation and Transtritylation Reactions

P.Buckus

This review deals with various reactions involving the cleavage and certain interesting rearrangements of trityl compounds and the use of trityl protecting groups in the synthesis and reactions of glycerides, carbohydrates, nucleosides, nucleotides, and peptides. The lability of the bond between the trityl group and oxygen, sulphur, nitrogen, carbon, and other atoms has been demonstrated.
The bibliography includes 519 references.

INTRODUCTION

The tendency of compounds containing the labile trityl (triphenylmethyl) group to undergo detritylation and transtritylation reactions has been known for a long time. These reactions are of both theoretical and preparative interest. Various reactions involving the cleavage of trityl compounds and interesting rearrangements have been described. The ease of introduction and removal of the trityl group makes it possible to employ it as a protecting group. Trityl protecting groups have found particularly wide application in the synthesis and reactions of glycerides, carbohydrates, nucleosides, nucleotides, and peptides. They have assisted greatly in the development of the chemistry of natural compounds. The lability of the bond between the trityl group and the carbon atom led to the foundation and development of the chemistry of free radicals.

Until recently there have been no reviews dealing with detritylation and transtritylation reactions. The present review deals with data on the detritylation and transtritylation of oxygen, sulphur, nitrogen, carbon, and other tritylated compounds. The bonds between the trityl group and hydrogen and halogen atoms, the reactions of triphenylmethanol, triphenylmethanethiol, and triphenylmethylamine are not considered, since they are best treated as tritylation reactions.

In view of the enormous number of studies on the subject, the formation of triarylmethyl radicals must also be excluded from consideration. These problems may be the subject of separate reviews.

1. THE BOND BETWEEN THE TRITYL GROUP AND THE OXYGEN ATOM

The bond between the trityl group and the oxygen atom in alkyl trityl ethers dissociates when the latter are heated[1-5], acted upon by potassium[6], hydrogen halides[1,7-9], boron trifluoride[10], aluminium chloride[4], phosphorus pentachloride[9] and pentabromide[11], silica gel[12], formic acid, and acetyl chloride[1,13-15], and also when they are hydrolysed with alkali metal hydroxides[1] and inorganic acids[1,8,9,16]. The reaction products are triphenylmethane, triphenylmethanol, triphenylchloromethane, triphenylbromomethane, and triphenylmethylpotassium. When alkyl trityl ethers were allowed to react with magnesium and propyl iodide, the product was tritylmagnesium iodide[17,18], while the reaction with phenylmagnesium bromide yielded tetraphenylmethane[19]. The electrochemical elimination of a trityl protecting group has been demonstrated for *O*-trityl-*N*-palmitoylethanolamine[20].

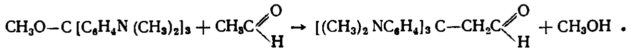
When isopropyl trityl ether is allowed to stand with 0.1% solution of hydrogen chloride in methanol, transtritylation takes place[21]:

$$(CH_3)_2CHO{-}C(C_6H_5)_3 + CH_3OH \rightarrow CH_3O{-}C(C_6H_5)_3 + (CH_3)_2CHOH\ .$$

The reactions of alkyl trityl ethers with allyl alcohol, ethylene glycol, glycerol, and phenol yield respectively allyl trityl ether, the trityl ether of ethylene glycol, the *α*-trityl ether of glycerol, and *p*-hydroxytetraphenylmethane[22]. Methyl and ethyl trityl ethers were used for the tritylation of formamide[23]:

$$RO{-}C(C_6H_5)_3 + HCONH_2 \rightarrow HCONH{-}C(C_6H_5)_3 + ROH$$

Nesmeyanov et al.[24] showed that the reaction of the methyl ether of Crystal Violet with acetaldehyde, propionaldehyde, crotonaldehyde, and nitromethane takes place with formation of a new carbon–carbon bond. For example:



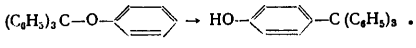
$$CH_3O{-}C[C_6H_4N(CH_3)_2]_3 + CH_3C{\overset{O}{\underset{H}{\lessgtr}}} \rightarrow [(CH_3)_2NC_6H_4]_3C{-}CH_2C{\overset{O}{\underset{H}{\lessgtr}}} + CH_3OH\ .$$

Cycloalkyl trityl ethers are cleaved by sulphuric[25] and acetic[26,27] acids. Benzyl and diphenylmethyl trityl ethers are hydrogenated catalytically on Raney nickel with dissociation of the bond between the trityl group and the oxygen atom[28]:

$$C_6H_5CH_2O{-}C(C_6H_5)_3 \rightarrow C_6H_5CH_2OH + (C_6H_5)_3CH\ .$$

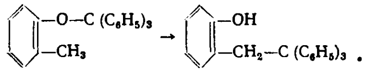
Aryl trityl ethers are cleaved by water[29], alkali metals[6,30-32], hydrogen chloride[33], zinc chloride[34-36], and hydrochloric acid[5,35-37] with formation of the corresponding phenols and triphenylmethane or its derivatives. With acetyl chloride or hydrogen chloride in the presence of calcium chloride, ditrityl ether gives triphenylchloromethane[38,39].

When aryl trityl ethers are heated under different conditions, the corresponding tetraphenylmethane derivatives are obtained[22,30,32,35,40-48]. For example, when phenyl trityl ether is heated in ethylene glycol and glycerol[22,47,48] and also in a mixture of acetic and hydrochloric acids[41], *p*-hydroxytetraphenylmethane forms in 80–100% yield:



Tetraphenylmethane was also isolated in the reaction of phenyl trityl ether with phenylmagnesium bromide[19].

Shorygin[30,49], showed that the reaction of sodium (at 100°C) with *o*-tolyl trityl ether results, apart from the normal decomposition, in a rearrangement which leads to the migration of the trityl group to the side-chain of *o*-cresol:



A similar rearrangement takes place also under the action of zinc chloride[50].

The reaction of the ditrityl ether of catechol with methanol in the presence of hydrogen chloride yields methyl trityl ether[21]. When phenyl trityl ether reacts with monosubstituted benzenes containing *ortho*- and *para*-directing substituents, the initial ether undergoes rearrangement and the benzene derivative is tritylated[51]. For example:

$$C_6H_5O{-}C(C_6H_5)_3 + C_6H_5N(CH_3)_2 \rightarrow p\text{-}HOC_6H_4{-}C(C_6H_5)_3 + p\text{-}(CH_3)_2NC_6H_4{-}C(C_6H_5)_3\ .$$

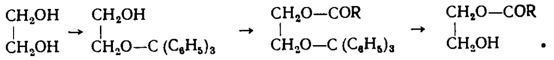
On the basis of the relative amounts of the products, it was concluded that the migration of the trityl group to the *p*-position in both compounds takes place not only by an intermolecular mechanism but partially also by an intramolecular mechanism. The orienting power of the substituents follow the sequence $N(CH_3)_2 > NH_2 > OCH_3$.

Among trityl esters, trityl acetate[15,52-60], trityl benzoate[57,60-63], and others[52,54,60,63-66] have been decomposed. Their pyrolysis yields triphenylmethane[56,62,65]. They are decomposed by water, alcohols, and acetyl chloride with formation of triphenylmethanol, alkyl trityl ethers, and triphenylchloromethane respectively[15,52]. The interaction of trityl acetate with organomagnesium compounds yields, together with detritylation products, the corresponding hydrocarbons[58,59]:

$$CH_3COO{-}C(C_6H_5)_3 + RMgCl \rightarrow (C_6H_5)_3C - R + CH_3COOMgCl\ .$$

Other *O*-trityl compounds have also been decomposed[6,67-75], including peroxides containing one[69] and two[6,70-73] trityl groups and also *O*-trityl organometallic compounds[74].

Trityl protecting groups have been used for the synthesis of monoacyl derivatives of glycol[76]:



$$\begin{array}{l}CH_2OH\\|\\CH_2OH\end{array} \rightarrow \begin{array}{l}CH_2OH\\|\\CH_2O{-}C(C_6H_5)_3\end{array} \rightarrow \begin{array}{l}CH_2O{-}COR\\|\\CH_2O{-}C(C_6H_5)_3\end{array} \rightarrow \begin{array}{l}CH_2O{-}COR\\|\\CH_2OH\end{array}\ .$$

Such protection has also found wide application in the synthesis and investigation of the properties of glycerides[9,21,77-115] including lipoamino-acids[107,109,113-115].

It is interesting to note that the elimination of the trityl group from 1,2-diacyl- and 3-trityl-glycerol results in the migration of the acyl group from the 2-position to the 3-position[98,99,108]. However, detritylation with silicic acid avoids migration of acyl groups[93,106,108,110,111,113]. Optically active diglycerides, which are key intermediates in the synthesis of biologically important phospholipids, have been obtained in this way[104,108,111].

Quite recently in a study of the reaction of ethylene glycol and glycerol with their ditritylation products, the hitherto unknown disproportionation reaction of trityl groups leading to the formation of the corresponding monotritylation products, was observed[116]. For example:

$$HOCH_2CH_2OH + (C_6H_5)_3C{-}OCH_2CH_2O{-}C(C_6H_5)_3 \rightarrow 2\,(C_6H_5)_3C{-}OCH_2CH_2OH\ .$$

The reaction of the ditrityl ether of glycerol with methanol in the presence of hydrogen chloride yields methyl trityl ether[21].

Trityl protecting groups have found wide application in the synthesis of carbohydrates, in the study of the properties and structure of mono-, di-, and poly-saccharides and also their derivatives and analogues[8,9,12,101,102,117-198]. Their great importance in the chemistry of carbohydrates is due not only to the ease of elimination but also to the fact that they normally combine only with a primary hydroxy-group. The rate of tritylation of the primary alcoholic group in D-galactose is 225 times faster than the rate of tritylation of the hydroxy-group at the C_3 atom, evidently owing to the steric factors[168]. Although side reactions sometimes occur in detritylation[118], the trityl group gives ideal protection of the terminal hydroxy-group of the sugar chain in various syntheses.

Catalytic hydrogenation, refluxing with 80% acetic acid, and treatment at room temperature with hydrogen chloride in chloroform or hydrogen bromide in acetic acid are most often used to cleave the trityl ethers of carbohydrates. For example, when trityl ethers of cellulose and starch are shaken with a solution of hydrogen chloride in chloroform, the trityl residues are split off quantitatively as triphenylchloromethane (when aqueous hydrochloric acid is used, the product is triphenylmethanol)[137]. The methylation of the trityl ether of cellulose with dimethyl sulphate results in rapid elimination of the trityl group, while in the methylation with methyl iodide the elimination is slow[120]. It has been observed that the detritylation of tritylation and acylation products with acid reagents is frequently accompanied by the migration of the acyl groups[101,139-143]. The detritylation of (D-β-5′-*O*-trityl-2′,3′-di-*O*-acetylribofuranosyl)indole, yields, in addition to the normal product, also a small amount of the corresponding ribopyranose derivative—the product of the isomerisation of the carbohydrate ring[122].

Trityl[177,199-294] and also mono- and di-*p*-methoxytrityl[227,295-311] protecting groups have found wide application in the synthesis and the investigation of the properties and structure of nucleosides, nucleotides, and oligonucleotides. When triphenylchloromethane is allowed to react with nucleosides, the product is as a rule a 5′-*O*-trityl derivative, although this reagent, while reacting preferentially with a primary hydroxy-group, is nevertheless not entirely specific with respect to the latter[201,217,246,264,265]. In fact uridine forms a ditrityl derivative[217], shown to be 2′,5′-di-*O*-trityluridine[215]. A certain amount of 3′,5′-di-*O*-trityluridine also forms[201].

The differences between the conditions for the formation and cleavage of trityl and benzyl ethers constitute the basis of Todd's synthesis of uridine diphosphate-glucose[312]. Trityl protecting groups have been used in the synthesis and investigation of the properties and structures of the antibiotic nojirimycin[313], coenzyme A,[314,315], vitamin B_2,[316] lipids[317], and steroids[318-320]. It has been found that the detritylation of certain steroid derivatives is accompanied by the migration of the acetyl group[320]; in the absence of a trityl group such rearrangement does not occur.

2. THE BOND BETWEEN THE TRITYL GROUP AND THE SULPHUR ATOM

The bond between the trityl group and the sulphur atom is cleaved when aryl trityl sulphides are heated[321], refluxed in alcohol in the presence of Raney nickel[322], or acted upon by alkali metals[6], bromine[323], iodine[324], iron(II) chloride[325], aluminium bromide[324], silver nitrate[324], potassium permanganate[325], ruthenium tetroxide[326], chromic[325,327], nitric[325], and sulphuric[321] acids, a mixture of hydrochloric and acetic acids[41], and dichloro- and diacetoxy-iodobenzene[328]. The detritylation products are triphenylmethane, triphenylmethanol, triphenylchloromethane, triphenylbromomethane, and ditrityl peroxide. The yields of the peroxide reach 90%.

The interaction of phenyl trityl sulphide with *N*-bromosuccinimide gives a 97% yield of *N*-tritylsuccinimide[328]. The reaction of phenyl trityl sulphide with mercury(II) chloride in methanol takes place by the following mechanism[322]:

$$C_6H_5S{-}C(C_6H_5)_3 + HgCl_2 + CH_3OH \rightarrow CH_3O{-}C(C_6H_5)_3 + C_6H_5SHgCl + HCl\ .$$

The decomposition of ditrityl sulphide[329,330], ditrityl disulphide[329-331], trityl thioacetate[329], and trityl thiobenzoate[329,332] has been described. The dissociation of the bond between the trityl group and the sulphur atom in *p*-tolyl trityl sulphone by water has also been observed[3].

The trityl group has been used to protect the mercapto-group in the synthesis of sulphur-containing acids, amino-acids, peptides, and their derivatives[324,333-355]. These protecting groups have been used, for example, in the synthesis of glutathione[342], oxytocin[333], and cyclic cystine peptides[344,345,351]. Selective detritylation permits the elimination of the *S*-trityl protecting groups with retention of the *N*-trityl[334,342] and other protecting groups attached to the sulphur[354] and nitrogen[334,352,354,355] atoms. Thus in the reaction of the methyl ester of *SN*-ditritylcysteine with silver nitrate in methanol in the presence of pyridine, methanol is tritylated only by the *S*-trityl group[334]. On the other hand, the selective elimination of protecting groups attached to the nitrogen atom with retention of the *S*-trityl protecting group is also possible[353].

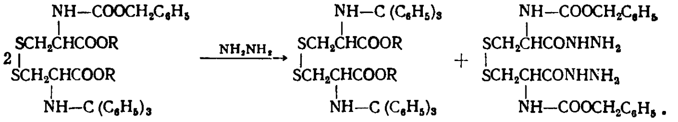
For the synthesis of asymmetric (with respect to the cysteine residues) cystine peptides, the mercapto-groups must be protected in various ways to permit their separate elimination[334,355]. *S*-Tritylcysteine and diphenylmethylcysteine have been proposed for this purpose. *S*-Trityl protecting groups are readily eliminated at room temperature by treatment with heavy metal salts. The *S*-diphenylmethyl group is then unaffected and can be removed separately with trifluoroacetic acid.

3. THE BOND BETWEEN THE TRITYL GROUP AND THE NITROGEN ATOM

As early as 1884, it was known that *N*-trityl groups are readily dissociated in an acid medium[356]. In 1925 trityl derivatives of amino-acids and even of a dipeptide were obtained[8]. However, the effectiveness of trityl protecting groups in the reactions of α-amino-acids and in the synthesis of peptides was not finally recognised until the second half of the present century[333,336,342,344,349-351,354,357-414]. For this reason, the honour and priority in the discovery of trityl protecting groups are attributed not only to Helfferich (1925) but also to Velluse (1955).[415]

N-Trityl protecting groups have been used in the study of the reactions of hydroxy-derivatives[357-359] and mercapto-derivatives[333,334,336,342,344,349-351,354,381,396] of α-amino-acids, diamino-acids[360-362,371,379,401], dicarboxylic[333,342,363-366,370,387,394,395,397-399] and heterocyclic[357,366,370,371,379] α-amino-acids, and also β-amino-acids[411] and cycloserine[369]. They have been also used in the synthesis and the study of the properties of cyclic peptides[344,351,372-378], including gramicidine C and its analogues[375-378]. It has been established that, when trityl protecting groups are employed, the most effective procedure for the synthesis of peptides is the carbodi-imide method.

The principal advantage of the trityl group consists in the ease of its elimination under mild conditions, although steric hindrance of the adjacent carboxy-group sometimes prevents the condensation of tritylamino-acids. With increase of the side chain length in the amino-acid residue, the steric hindrance becomes more pronounced, which is inconvenient from the preparative standpoint. The steric hindrance in $\alpha\omega$-diesters of *N*-trityl derivatives of dicarboxylic amino-acids makes it possible to hydrolyse the ω-ester group with retention of that in the α-position[365,387]. The tritylated acid esters obtained in this way have been successfully used for the synthesis of the peptides of asparagine, glutamine, and isoglutamine[365]. On the hypothesis that the bulky trityl group can suppress the reactivity of the adjacent ester group as a result of steric hindrance, an attempt was made to obtain the corresponding monohydrazide by the reaction of hydrazine with the diester of *N*-benzyloxycarbonyl-*N*-tritylcystine[396]. However, the reaction takes place according to the following mechanism:



$$2\begin{array}{l} \quad NH{-}COOCH_2C_6H_5 \\ \quad | \\ SCH_2CHCOOR \\ | \\ SCH_2CHCOOR \\ \quad | \\ \quad NH{-}C(C_6H_5)_3 \end{array} \xrightarrow{NH_2NH_2} \begin{array}{l} \quad NH{-}C(C_6H_5)_3 \\ \quad | \\ SCH_2CHCOOR \\ | \\ SCH_2CHCOOR \\ \quad | \\ \quad NH{-}C(C_6H_5)_3 \end{array} + \begin{array}{l} \quad NH{-}COOCH_2C_6H_5 \\ \quad | \\ SCH_2CHCONHNH_2 \\ | \\ SCH_2CHCONHNH_2 \\ \quad | \\ \quad NH{-}COOCH_2C_6H_5\ . \end{array}$$

Evidently, under the action of hydrazine there is a disulphide rearrangement involving two molecules of the asymmetric cystine derivative with formation of two symmetrical derivatives.

The high sensitivity of the *N*-trityl group to the action of acids makes possible its elimination under a wide variety of experimental conditions. *N*-Trityl peptides lose their protecting trityl groups when their solutions are refluxed in anhydrous and aqueous acetic acid for several minutes[357,371,379-382,410]. Aqueous trifluoroacetic acid eliminates the *N*-trityl group even at −5 °C.[375-377] It has been stated that the group is eliminated under the influence of lower alcohols[383]. Depending on the reagent used for its elimination, the trityl group is converted into triphenylmethane, triphenylchloromethane, triphenylbromomethane, triphenylmethanol, triphenylmethyl acetate and trifluoroacetate, alkyl trityl ethers, and also mixtures of these compounds[410].

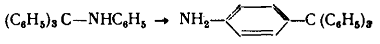
Anhydrous hydrogen chloride in methanol eliminates *N*-trityl substituents from an α-amino group more readily than from an ω-amino group[361,410] and imidazole[366] and also *O*-trityl substituents from phenol[366]. Thus, when trityl groups of these two types are present in the molecule of the same compound, it is possible under certain conditions to eliminate selectively one *N*-trityl substituent attached to an α-amino group with retention of the *S*-trityl substituent[333,334,342,410] or an *N*-substituent attached to an ω-amino-group[360,410]. For example, when the hydrochloride of the methyl ester of *NS*-ditritylcysteine reacts with methanol in the presence of hydrochloric acid, methanol is tritylated by the *N*-trityl protecting group[334]. The selective detritylation of the trityl ester of *N*-tritylglycine allows the selective elimination of the trityl group from the nitrogen atom with retention of the ester group[384]. It is also possible to eliminate selectively the *N*-trityl protecting groups without affecting other protecting groups[375-377,385,386,410]. On the other hand, in catalytic hydrogenation the *N*-trityl group is eliminated more slowly than the *N*-benzyloxycarbonyl or *O*-benzyl groups[366,380].

The condensation of amino-acids having amino-groups protected by *N*-substituents with tritylhydrazine yields the corresponding hydrazides[389,398,399,401]. A particular advantage of protecting groups of this type is that, after the elimination of the trityl group, the resulting derivative may be used directly in peptide synthesis by the azide method.

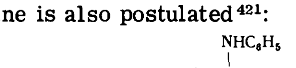
Under the conditions used to prepare certain oximes of *N*-trityl-α-amino-ketones and also on heating the latter in the presence of hydrogen chloride, ethanol is tritylated[416].

The cleavage of alkyl-[1,14,417], dialkyl-[48,417], alkylaryl-[418,419], aryl-[14,417,420-422], and diaryl-[8,423] tritylamines, trityl-[424,425] and ditrityl-[426,427] hydrazines, trityl azide[428,429], *N*-tritylurethanes[430], *N*-tritylacetamide[431], products of the *N*-tritylation of urea and thiourea[8], phenyl-[426,432-439] and benzoyl-[439] azotriphenylmethanes, quaternary ammonium bases containing the trityl group[440], and other *N*-tritylated compounds[441-445] has been described.

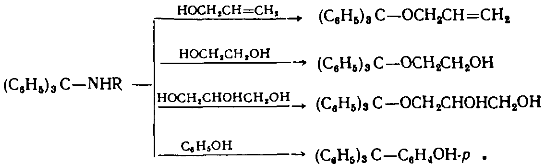
When *N*-tritylaniline[41,422], *N*-(β-cyanoethyl)-*N*-tritylaniline[419], *N*-trityldiphenylamine, and other *N*-tritylarylamines[422,446,447] are heated in an acid medium, in pyridine in the presence of its hydrochloride, or with zinc chloride, *C*-trityl compounds are obtained in yields up to 80%. For example:



The trityl group migrates to the *p*-position when *N*-trityl aniline reacts with monosubstituted benzenes having *ortho*- and *para*-directing substituents[51], as happened in the analogous reaction of phenyl trityl ether. The possibility of the conversion of *N*-trityl aniline into *o*-(phenylamino)-triphenylmethane is also postulated[421]:

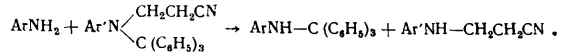


When *N*-tritylalkylamines[47] and *N*-(β-cyanoethyl)-*N*-tritylalkylamines[48] react with allyl alcohol, ethylene glycol, glycerol, and phenol, transtritylation takes place according to the following mechanism:



$$(C_6H_5)_3C{-}NHR \xrightarrow{HOCH_2CH{=}CH_2} (C_6H_5)_3C{-}OCH_2CH{=}CH_2$$
$$(C_6H_5)_3C{-}NHR \xrightarrow{HOCH_2CH_2OH} (C_6H_5)_3C{-}OCH_2CH_2OH$$
$$(C_6H_5)_3C{-}NHR \xrightarrow{HOCH_2CHOHCH_2OH} (C_6H_5)_3C{-}OCH_2CHOHCH_2OH$$
$$(C_6H_5)_3C{-}NHR \xrightarrow{C_6H_5OH} (C_6H_5)_3C{-}C_6H_4OH\text{-}p\ .$$

The reaction of arylamines with *N*-(β-cyanoethyl)-*N*-tritylarylamines involves transtritylation by the mechanism[448]:



$$ArNH_2 + Ar'N\begin{matrix}CH_2CH_2CN\\ C(C_6H_5)_3\end{matrix} \rightarrow ArNH{-}C(C_6H_5)_3 + Ar'NH{-}CH_2CH_2CN\ .$$

1-Tritylimidazole and its 4,5-disubstituted derivatives are readily hydrolysed on refluxing with 10% acetic acid to imidazole and its derivatives and also triphenylmethanol[449]. It is suggested that, when 1-tritylimidazole is heated to its melting point, the trityl group may migrate from the nitrogen atom to a carbon atom[449]. The products of the addition of triphenylchloromethane to pyridine and quinoline are decomposed by water and alcohol to the heterocyclic base and triphenylmethanol or an alkyl trityl ether[3,9].

Together with *O*-trityl protecting groups, *N*-trityl protecting groups have found application in the chemistry of nucleosides and nucleotides[391-395].

4. THE BOND BETWEEN THE TRITYL GROUP AND THE CARBON ATOM

The study of the bond between the trityl group and the carbon atom began with the work of Gomberg[450], who obtained in 1900 a free radical of tervalent carbon (triphenylmethyl) in an attempt to synthesise hexaphenylethane by the action of silver on triphenylbromomethane. This quite unexpected discovery demonstrated for the first time the possibility of the existence of free radicals. The discovery, treated by the majority of chemists with considerable disbelief, was confirmed and developed further in the subsequent studies by Gomberg himself and also by Chichibabin, Markovnikov, Kerman, Flürscheim, Schmidlin, Cone, Walden, Wieland, Ullmann and Borsum, Heintschel, Schlenk, Ziegler, A. E. and B. A. Arbuzov, and others[451-453]. It was established that the crystalline colourless hexaphenylethane dissociates reversibly in solution, particularly at elevated temperatures, forming the yellow triphenylmethyl:

$$(C_6H_5)_3C{-}C(C_6H_5)_3 \rightleftarrows 2\,(C_6H_5)_3C.$$

Gomberg's discovery[450] gave rise to the chemistry of free radicals, which later developed very rapidly. From 1900 up to the present an enormous number of investigations have been carried out in this field. Apart from triphenylmethyl, many free radicals of the triphenylmethane series have been obtained and their properties investigated, including addition, disproportionation, and recombination reactions. These investigations have greatly influenced the development of theoretical concepts in organic chemistry, in particular the study of thermal and photochemical reactions involving chain mechanisms[451-453].

Tetraphenylmethane proved to be a perfectly stable hydrocarbon—its solutions are colourless and the compound itself distils without decomposition at atmospheric pressure at 431°C. However, under the action of a liquid potassium–sodium alloy, it dissociates even at room temperature with formation of triphenylmethane and other products[454]. On distillation[6] or under the action of oxidising agents[3,455] and potassium[6,456], asymmetric tetraphenylethane yields respectively triphenylmethane, triphenylmethanol, and triphenylmethylpotassium.

Chichibabin[457,458] showed that at an elevated temperature pentaphenylethane decomposes, like hexaphenylethane, at the C–C bond of ethane. The pentaphenylethane molecule then breaks down into radicals, which subsequently recombine in a different manner:

$$2\,(C_6H_5)_3C{-}CH(C_6H_5)_2 \rightarrow (C_6H_5)_3C{-}C(C_6H_5)_3 + (C_6H_5)_2CH{-}CH(C_6H_5)_2\ .$$

According to the observations of Cone and Robinson[459], the reaction of phosphorus pentachloride with this compound yields triphenylchloromethane. The instability of the central C–C bond in pentaphenylethane was later studied also by other chemists[6,460-466].

The thermal decomposition of ditritylmethane yields quantitatively a mixture of triphenylmethane and triphenylethylene[467]:

$$(C_6H_5)_3C{-}CH_2{-}C(C_6H_5)_3 \rightarrow (C_6H_5)_3CH + (C_6H_5)_2C{=}CHC_6H_5\ .$$

When two molecules of triphenylmethylsodium react with dichlorodiphenylmethane, the product is octaphenylpropane, which immediately breaks down into triphenylmethyl and pentaphenylethyl[468]:

$$(C_6H_5)_3C{-}C(C_6H_5)_2{-}C(C_6H_5)_3 \rightarrow (C_6H_5)_3C\cdot + (C_6H_5)_3C-(C_6H_5)_2C\cdot$$

The products of the *C*-tritylation of mono-, di-, and tri-hydric phenols, *o*-, *m*-, and *p*-cresols, and also their derivatives undergo slight detritylation on oxidation with chromium trioxide, on distillation with zinc dust and soda lime, and on heating with hydriodic, sulphuric, and acetic acids[6,446,447,469-471]. The dissociation of the carbon–carbon bond is influenced in this case by the position of the trityl group.

A number of studies have been made[466,472–483] on the dissociation of alkyl trityl and aryl trityl ketones. In a study of the possibility of using pyridine as a solvent for the reduction with lithium aluminium hydride of ketones which are sparingly soluble in ether and tetrahydrofuran, Lansbury[475–477] discovered an interesting reaction of phenyl trityl ketone. He found that in pyridine solution phenyl trityl ketone undergoes, with lithium aluminium hydride not normal reduction but reductive dissociation with formation of triphenylmethane and benzaldehyde or benzyl alcohol. Phenyltritylmethanol is an intermediate in this reaction[477]. Methyl trityl ketone is also reduced by the above reductant[476]. When organometallic compounds react with phenyl trityl[466,478] and 1-naphthyl trityl[479] ketones, the bond between the trityl group and the carbon atom is dissociated instead of the expected formation of tertiary alcohols. *C*-Tritylated compounds containing an oxo-group in the ring are known to undergo detritylation[484].

The decomposition of triphenylacetic acid and its derivatives has been extensively investigated[466,485–496]. The pyrolysis of ethyl α-tritylpropionate yields triphenylmethane and ethyl acrylate[497]. Methyl α-methyl-α-tritylpropionate decomposes similarly[497]:

$$(C_6H_5)_3C{-}C(CH_3)_2COOCH_3 \rightarrow (C_6H_5)_3CH + CH_2{=}C(CH_3)COOCH_3 \; .$$

The detritylation process takes place also in the hydrolysis and other reactions of diesters, diamides, and dinitriles of tritylmalonic acid[498–501]. The amide of tritylacetic acid undergoes an interesting transtritylation reaction on heating with sulphuric acid to 200°C:[501]

$$(C_6H_5)_3C{-}CH_2CONH_2 \rightarrow CH_3CONH{-}C(C_6H_5)_3 \; .$$

The self-condensation of methyl trityl ketone[502], the acyloin condensation of ethyl trityl acetate[503], the thermal decomposition of methylazotritylmethane[503], and the hydrolysis of the acid ester obtained from phenyltritylmethanol and phthalic acid[504] are accompanied by detritylation. For example:

$$(C_6H_5)_3C{-}COCH_3 + CH_3CO{-}C(C_6H_5)_3 \rightarrow (C_6H_5)_3C{-}COCH_2COCH_3 + (C_6H_5)_3CH \; .$$

The products of the condensation of triarylmethanols (including triphenylmethanol) with 3-methyl-1-phenyl-5-pyrazolone on dissolution in polar solvents dissociate into ions[505] and their reactions with diazo-compounds yield the corresponding diarylmethanol and an azo-dye[506, 507]. The reaction of carboxylic acids and magnesium bromide with the condensation products of the methyl ether of the base of Crystal Violet with acetaldehyde, propionaldehyde, crotonaldehyde, and nitromethane involves the dissociation of the carbon–carbon bond and the formation of Crystal Violet[24,508,509].

5. THE BOND BETWEEN THE TRITYL GROUP AND OTHER ATOMS

The dissociation of the bond between the trityl group and lithium[466], boron[510,511], magnesium[512], aluminium[511], silicon[513,514], phosphorus[515,516], nickel[517], zinc[518], and germanium[519] atoms has been investigated. For example, the reaction of tritylaluminium compounds with primary and secondary amines takes place as follows[511]:

$$(R)_2Al{-}C(C_6H_5)_3 + (R')_2NH \rightarrow (R)_2Al{-}N(R')_2 + (C_6H_5)_3CH \; .$$

When certain tritylated phosphorus compounds are heated with methanol, methyl trityl ether is formed in 88% yield[516]. Treatment of the trityl derivative of zinc with tributyltin bromide resulted in the isolation of tributyltrityltin[518].

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Radical Degradation and Stabilisation Reactions of Solid Polymers

V.S.Pudov and A.L.Buchachenko

The thermal and oxidative thermal degradation of the majority of polymers occurs by radical mechanisms. Therefore the stabilisation of such polymers consists in the inhibition of the radical degradation processes. The aim of this review is to consider and analyse the kinetics and mechanisms of elementary radical degradation and stabilisation reactions in the solid phase, i.e. to examine the set of reactions which constitute the basis of the degradation and stabilisation processes. Before analysing and interpreting the experimental data, it is necessary, firstly, to note the characteristic features of solid-phase radical reactions which distinguish them from reactions in gases and liquids and, secondly, to consider the general theoretical postulates concerning the kinetics of solid-phase reactions.

The bibliography includes 83 references.

CONTENTS

I. KINETIC CHARACTERISTICS OF SOLID-PHASE RADICAL REACTIONS

The specific physical features of the solid state give rise to the definite kinetic characteristics of solid-phase reactions. The principal features of this type are as follows.

1. For reactions to occur, the reacting species must approach one another; however, in contrast to gas-phase reactions, the duration of contact, i.e. the lifetime of the pair of reacting species, is long, so that a static equilibrium involving all the degrees of freedom is established in the pair. This implies that such pairs must be regarded as kinetically independent species, which has a significant effect on the kinetics and frequently modifies the kinetic equations.

2. Since the pairs are comparatively long-lived, it is also necessary to consider the physical elementary steps involved in the motion of the reacting species (rotation, translation, orientation, etc.). It is then found that the kinetics of chemical reactions are related to the kinetics of molecular motion, i.e. the physical properties and the structure of the polymer.

3. The same chemical elementary steps in the solid phase can occur with a higher activation energy than in the gaseous or liquid phases. Indeed, in a gas or liquid the intrinsic chemical step (for example, the transfer of a hydrogen atom from the molecule to a radical) and steps involving a change in the structure of the reactants (for example, those occurring when the bond hybridisation is altered) take place simultaneously. In the solid phase these steps frequently occur at different times, since the rearrangement of the structure of the reactants after the reaction occurs much more slowly than the chemical reaction itself (during a period of the order of magnitude of the structural relaxation time). This applies to reactants in both the initial and the final states. In practice it implies that the potential surfaces of the elementary reactions in the solid phase may lie higher than for gas-phase or liquid-phase reactions.

The general theory of the kinetics of solid-phase reactions must reflect these features. In the most general case of a reaction between two reaction centres A and B, three kinetic stages may be distinguished: (a) the macrodiffusion stage when the reacting species A (or B) fill the specimen non-uniformly and diffuse as a result of an average concentration gradient; (b) the microdiffusion stage when there is no concentration gradient and the rate of reaction is determined by the frequency with which the species A and B, which are uniformly distributed throughout the specimen, approach one another (the mechanism involved in their mutual approach is unimportant at this stage); this stage results in the formation of the pair (A + B); (c) the intrinsic kinetic stage when the rate of the process is determined by the rate of the chemical interaction in the pair (A + B).

Here A and B may be understood as reaction centres in a group of macromolecules and macroradicals, molecules of reacting gases, low-molecular substances, inhibitors, etc.

We shall consider initially the case where there are only two stages—the microdiffusion and kinetic stages—i.e. where the reaction centres are uniformly distributed in the specimen. For this case, Lebedev proposed a simple cell reaction model and derived formal kinetic rate equations [1]. It is suggested that the chemical interactions of A and B begins only when A and B form a pair, i.e. enter a single "cage" with a volume v^* (of the order of $\frac{4}{3}\pi\lambda^3$, where λ is the effective length of the "monomer" unit). As a result of thermal or any other type of activation from outside, A and B can migrate in the specimen with a migration rate constant k_t and in the vapour phase they can also react with a rate constant k_p. In the steady-state case (with the rates of formation and destruction of the pairs are equal), it is easy to obtain a kinetic rate equation:

$$-\frac{d\,(\mathrm{A})}{dt} = -\frac{d\,(\mathrm{B})}{dt} = k_{\mathrm{eff}}(\mathrm{A})\,(\mathrm{B}), \tag{1}$$

where

$$k_{\mathrm{eff}} = \frac{k_t k_p}{k_t + k_p}\, v^*; \quad (k_t = k_t^{\mathrm{A}} + k_t^{\mathrm{B}}) \tag{2}$$

Thus the law of the additivity of the kinetic resistance in each component stage holds for the effective rate constant for the overall process:

$$1/k_{\mathrm{eff}} = 1/k_t v^* + 1/k_p v^* \tag{3}$$

When $k_t \gg k_p$, the kinetic stage is rate-limiting and $k_{\mathrm{eff}} = k_p v^*$; when $k_t \ll k_p$, the rate is limited by the microdiffusion stage and $k_{\mathrm{eff}} = k_t v^*$.

In the above equations k_t is the rate constant for physical or chemical diffusion of the species and k_p is the unimolecular rate constant for the destruction of the pair, which may be determined either by the frequency of rotation and steric factors for the species in the vapour phase or by the rate of the intrinsic chemical interaction. Since a wide variety of species may be involved in the reactions, the physical significance of k_t and k_p may be various; they can assume any relative values and therefore either of two types of kinetic regimes may be realised.

The cell model for bimolecular solid-phase reactions is confirmed also by non-steady-state kinetics, i.e. kinetics under conditions such that the steady-state concentration of the pairs has not yet been attained (an example is provided by the kinetics of the recombination of the radicals corresponding to the initial sections of the curves relating the rate of degradation of the radicals to time, which were analysed by Lebedev ^{1}).

The rates of bimolecular reactions in the solid phase were calculated by Waite ^{2} even earlier and more rigorously using the macroscopic diffusion equation (for the microdiffusion stage); the results of this calculation are virtually identical with those obtained on the basis of the cell model, but the latter has the advantage of simplicity of the interpretation of the experimental data and clear physical significance of the kinetic constants.

II. KINETICS OF RADICAL DEGRADATION AND STABILISATION REACTIONS OF POLYMERS

We shall now consider the experimental data on the mechanism and kinetics of radical degradation and stabilisation reactions of polymers taking into account the general kinetic considerations described in the preceding section. It will be more convenient to examine the individual reactions of macroradicals and low-molecular-weight radicals, which will henceforth be conventionally referred to as microradicals.

1. Oxidation of Macroradicals

The addition of oxygen to macroradicals is one of the fundamental kinetic chain propagation reactions in the oxidation of polymers. All the experimental data on the kinetics of this reaction were obtained in studies of the conversion of alkyl allyl macroradicals $\dot{R}$ in irradiated polymers into peroxy-macroradicals $\dot{R}O_2$. Such conversion takes place under the action of gaseous oxygen and therefore its rate may be determined by any of the three stages—macrodiffusion, microdiffusion, and kinetic.

The "recognition" of the rate-determining step in a complex multistage process of this kind is difficult. The system of kinetic equations for this case is of the form

$$-\frac{\partial n}{\partial t}=k_{\text{eff}}nc, \tag{4}$$

$$\frac{\partial c}{\partial t}=-k_{\text{eff}}nc+D\nabla^2 c, \tag{5}$$

where n is the concentration of radicals in the polymer (it is postulated that these are stationary) and c the concentration of oxygen. At zero time ($t=0$) we have $n=n_0$ and $c=0$ in the bulk phase and $c=c_0=K_S p$ on the surface of the polymer [K_S is the solubility (Henry's law) constant and p the pressure of oxygen]. The first of these equations corresponds in form to Eqn. (1); the constant k_{eff} is defined by Eqn. (2). Eqn. (5) describes the kinetics of the reaction and of the macrodiffusion of the gas into the polymer.

A rigorous analytical solution of Eqns. (4) and (5) is impossible. A solution was obtained numerically by Lebedev ^{3} using a computer and the results of the rigorous calculation were compared with approximate analytical solutions. Approximate solutions were obtained for limiting cases in which it was possible to neglect certain kinetic stages and to simplify Eqns. (4) and (5). In both cases (exact and approximate) the effective reaction time t_Σ, i.e. the time during which the initial concentration of the radicals $\dot{R}$ diminishes by the factor e, was calculated. Here t_Σ is used instead of $k_\Sigma = I/t_\Sigma$, where k_Σ is the effective rate constant for the overall diffusion-kinetic reaction $\dot{R} \rightarrow \dot{R}O_2$, which is described, as before, by the bimolecular equation $dn/dt = k_\Sigma nc$.

Comparison of the results of the exact and approximate calculations showed that it is possible to formulate several limiting regimes which are realised under various experimental conditions. The principal data are presented in Table 1. The fact that they were obtained for the case where the specimen is in an infinitely long cylinder of radius l does not diminish the generality of the results; for specimens of other shapes (spherical grains, films, etc.), the kinetic expressions remain unchanged except for constant coefficients [only the form of the diffusion term $D\nabla^2c$ in Eqn. (5) depends on the shape of the specimen].

We shall now consider briefly each regime—the conditions under which it occurs and the kinetic parameters. The quasi-steady-state regime is observed when the rate of reaction is high and the solubility of oxygen is low. Table 1 shows that the law of the additivity of the kinetic

Table 1. Kinetic regimes in the diffusion-kinetic process $\dot{R} + O_2 \rightarrow \dot{R}O_2$.

Regime	Experimental conditions	Criteria	Effective duration of reactions t_Σ	Characteristic kinetic features of the regime
Steady-state	high radical concns., low oxygen pressures	$\frac{n_0}{K_p p}>10$	$\frac{1}{k_{\text{эф}}K_p p}+\frac{0.63l^2 n_0}{aDK_p p}$	t_Σ decreases in proportion to p and depends on the dimensions of the specimen and the initial radical concn. n_0
Membrane	large specimen, n_0 large, p small	$\frac{k_{\text{эф}}n_0 l^2}{D}>100$ $n_0/K_p p>10$	$\frac{0,63l^2 n_0}{aDK_p p}$	t_Σ decreases in proportion to p and increases in proportion to n_0 and l^2
Kinetic	small size (l small), n_0 and p small	$\frac{k_{\text{эф}}K_p p l^2}{D}<0,1$ $k_{\text{эф}}n_0 l^2/D<1$	$\frac{1}{k_{\text{эф}}K_p p}$	t_Σ independent of the dimensions of the specimen and the initial radical concentration n_0
Quasi-diffusional	l large, p large, n_0 small	$\frac{k_{\text{эф}}K_p p l^2}{D}>10$ $n_0/K_p p<0,1$	$l\sqrt{\frac{4}{aDK_p p k_{\text{эф}}}}$ $a\simeq 8$	t_Σ independent of n_0, decreases in proportion to p and increases with l

resistances of all three stages holds for k_Σ; the effect of the diffusion constant is then given not by the term aD/l^2 (obtained from the usual Smoluchowski equation $l^2 = aDt$) but by the term $(aD/l^2)(c_0/n_0)$ (as already mentioned, $c_0 = K_s p$).

If the rate of reaction is very high compared with the rate of macrodiffusion, the conditions may be referred to as a membrane regime, since the rate of the process is limited by the rate of leakage of gas through the layer of the specimen (membrane) in which the reaction has already occurred. When the diffusion is rapid, a purely kinetic regime may be realised.

In an experimental study of the variation of t_Σ with oxygen pressure, the concentration of radicals, and the dimensions of the specimen, it is possible, using Table 1, to identify the regime and the rate-determining step of the reaction; by varying the experimental conditions, it is possible to pass from one regime to another.

In the limiting cases it is possible to calculate the following combinations of constants and their temperature variation:

$$\text{kinetic regime} - k_{\text{eff}}K_s = k^0_{\text{eff}}K^0_s\exp\left(-\frac{\epsilon_{\text{eff}} - \Delta H_s}{RT}\right)$$

$$\text{membrane regime} - DK_s = D^0K^0_s\exp\left(-\frac{\epsilon_D - \Delta H_s}{RT}\right)$$

$$\text{quasi-diffusion regime} - k_{\text{eff}}DK_s = k^0_{\text{eff}}D^0K^0_s\exp\left(-\frac{\epsilon_{\text{eff}} + \epsilon_D - \Delta H_s}{RT}\right),$$

and then it is easy to determine the complete set of kinetic constants, the activation energies, and the heats of solution.

On the other hand, if all the constants are already known, it is possible to calculate the rate of the diffusion-kinetic process and to predict the rate-limiting stage. An example of the use of the above theory for the determination of the rate constants for the reaction $\dot{R} + O_2 \rightarrow R\dot{O}_2$ is a study by Lebedev[3]. For alkyl radicals in Teflon,

$$k_{\text{eff}} = 5 \times 10^{-15}\exp(-10000/RT)\ \text{cm}^3\ \text{s}^{-1}$$
$$K_s = 2 \times 10^{12}\exp(10000/RT)\ (\text{cm}^3\ \text{mmHg})^{-1},$$
$$D_{O_2} = 2 \times 10^{-3}\exp(-9000/RT)\ \text{cm}^2\ \text{s}^{-1}.$$

From these relations, it is easy to find that $k_t \gg k_p$, i.e. $k_{\text{eff}} = k_p v^*$. If it is assumed that $v^* = 4 \times 10^{-21}$ cm^3 (for $\lambda = 10$ Å), it is easy to estimate $k^0_p \simeq 10^7\ \text{s}^{-1}$. On the other hand, $k^0_p = f_p \nu$ where ν is the normal pre-exponentional factor for the vapour-phase reaction of $\dot{R}$ and O_2 (of the order of magnitude of the vibration frequency $\nu \simeq 10^{12}\ \text{s}^{-1}$), whence the steric factor for the vapour-phase reaction between $\dot{R}$ and O_2 is $f_p \simeq 10^{-5}$.

Most of the kinetic data on the reactions between $\dot{R}$ and O_2 were obtained in studies on the mechanochemistry of polymers. Although the oxidation conditions (regimes) were not investigated, it may be assumed, since radicals are formed on the surface, that diffusion-dependent stages are absent and the constants determined are equal to $k_p v^*$, as for fluoroalkyl radicals. Table 2 summarises these results.

In the liquid and gaseous phases the reactions $\dot{R} + O_2 \rightarrow R\dot{O}_2$ usually have activation energies close to zero and pre-exponential factors in the range 10^{-11}–10^{-13} cm^3 s^{-1}.

The activation energies for solid-phase reactions are much higher and the pre-exponential factors are much lower. This very interesting feature of solid-phase reactions is probably due to the considerations related to potential surfaces of solid-phase reactions discussed above (see Section I). However, the stage reached in research on quantitative solid-phase reaction kinetics is not yet advanced enough for a serious discussion of any theoretical problems concerning the elementary reaction step.

In concluding our discussion of the kinetics of reactions between $\dot{R}$ and O_2, we may mention that Loy[7] has quoted 6 kcal mole^{-1} as the activation energy for this reaction in irradiated poly(vinyl chloride). However, the rate of reaction depended on the surface area of the powder, i.e. on the dimensions of the polymer grains; this implies that the above activation energy does not refer to the kinetic stage. However, Loy does not quote any other data which would make it possible to identify the regime governing the reaction and find the rate-determining step.

Table 2. Pre-exponential factors and activation energies for the reactions between $\dot{R}$ and O_2 in polymers.

Polymer	$k_p v^*$, cm^3 s^{-1}	ϵ_p, cal mole^{-1}	References
Poly(methyl methacrylate)	$6 \cdot 10^{-15}$	7900	4
Ditto	—	~3800	5
Poly(vinyl acetate)	$1.6 \cdot 10^{-15}$	5900	4
Polystyrene	$4 \cdot 10^{-17}$	5300	4

Although the results presented in Table 1 refer to a particular reaction between gases and stationary radicals in the solid phase, their value is much wider and more fundamental. In particular, in the oxidation of solid polymers (where n should be replaced by the steady-state concentration of radicals, which depends on the rates of their initiation and destruction) these relations permit the determination of the limits of diffusion-dependent kinetics. For example, by studying the rate of sensitised oxidation of polymer film or powder under different experimental conditions (different film thickness, oxygen pressure, rate of initiation, etc.) and using the kinetic results for various regimes, it is possible to determine, in principle, all the constants for the elementary radical oxidation reactions. So far no experimental studies have been carried out on these lines.

The importance of kinetic regimes is not restricted to oxidation reactions. The kinetics of many degradation and stabilisation reactions may be modelled by Eqns. (4) and (5) and the regimes listed in Table 1. Among them, we may include the chain-termination reaction under conditions such that the inhibitor is non-uniformly distributed in the polymer and diffuses to the radical generation centres or reactions where the stabiliser, which inhibits degenerate branching, diffuses in the polymer towards the hydroperoxy-groups responsible for the branching.

2. Reactions with Low-Molecular Substances

The addition of macroradicals $\dot{R}$ to monomeric molecules M was investigated by Butyagin and coworkers in studies of the mechanical dispersion of polymer solutions in various monomers[8,9]. It was found for various combinations $\dot{R}_i + M_j$ that the activation energies (4–6 kcal mole^{-1}) and the pre-exponential factors (10^5–10^7 litre mole^{-1} s^{-1}) are close to the values of ϵ and k^0 in the liquid phase.

The same method was used to determine the rate constants for reactions with low-molecular hydrocarbons: $\dot{R} + rH \rightarrow RH + \dot{r}$. Since the macroradicals formed in the dispersion process are surrounded by solvent molecules, the reaction with them is determined by the true rate constants $k = k_p v^*$; it can be found from the rate of destruction of macroradicals and the rate of accumulation of low-molecular radicals $\dot{r}$ using the equation

$$\frac{(\dot{R})}{(\dot{R})+(\dot{r})} = \frac{1}{k\,(rH)\,t}\{1 - \exp[-k\,(rH)\,t]\}$$

The rate constants for the reactions of polystyrene radicals with toluene, ethylbenzene, and cumene (10^{-14}–10^{-15} $cm^3\,s^{-1}$) determined in this way at 77°K proved to be anomalously high compared with the "liquid phase" constants extrapolated to this temperature; it was suggested that these reactions take place under non-equilibrium conditions in the course of the dispersion of the polymer [8,9].

Activation energies of 38 and 36 kcal $mole^{-1}$ have been quoted [4] for the reaction with cumene of the macroradicals of poly(methyl methacrylate) and poly(vinyl acetate) (obtained mechanochemically) respectively (it should be noted that the maximum activation energy observed for reactions of similar type is only 15 kcal $mole^{-1}$–for the reaction $\dot{C}H_3 + CH_4 \rightarrow CH_4 + \dot{C}H_3$). [10] Since in the study quoted the formation of low-molecular radicals $\dot{r}$ was not observed, the validity of these data and their physical significance remain obscure.

Qualitative evidence for reactions of macroradicals $\dot{R}$ and $R\dot{O}_2$ with aldehydes, phenols, mercaptans, and thiophenols has been quoted in a number of studies [8,11,12], but quantitative data on the kinetics of such reactions are not available.

The above brief analysis shows that there are virtually no quantitative kinetic data for the reactions of macroradicals with low-molecular substances (including inhibitors) although these reactions are important in degradation and stabilisation processes. Firstly, low-molecular substances can serve as transfer-agents for oxidation chains, secondly, they take part in chain-termination reactions, and, thirdly, they function as catalysts for the recombination of macroradicals. In particular, the effectiveness of inhibitors is determined, apart from other conditions, by the relative efficiencies of the inhibitors in chain transfer and chain termination or their ability to catalyse the recombination of the macroradicals. The quantitative kinetic criteria governing such relative efficiencies are essential for practical purposes.

The extensive data on the rate constants for the reaction of radicals $R\dot{O}_2$ with inhibitors in the liquid phase can be hardly used for solid-phase reactions; this follows from general theoretical concepts (see Section I) and is confirmed by the reaction between $\dot{R}$ and O_2 considered above. We may note that, in order to determine the effectiveness of inhibitors in chain termination, it is necessary to know not only the rate constant for the interaction of $R\dot{O}_2$ with the inhibitor (which characterises the kinetic stage) but also the diffusion coefficient of the inhibitor in the polymer (the microdiffusion stage).

3. Reactions of Macroradicals with Macromolecules

These reactions play an important role in the transfer ($\dot{R} + R'H \rightarrow RH + \dot{R}'$) and propagation ($R\dot{O}_2 + RH \rightarrow RO_2H + \dot{R}$) of kinetic chains in polymer degradation. So far there have been no experimental studies designed to determine directly the rate constants for these reactions; here the only source of information is the kinetics of the recombination of alkyl and peroxy-macroradicals in irradiated polymers. Before discussing the kinetics, we shall first consider the recombination mechanism.

The destruction of macroradicals in irradiated polymers follows a bimolecular law. It is reasonable to suppose (as was in fact done in the early studies) that the recombination involves the mutual approach of macroradicals by diffusion. However, later it was found that many important facts are inconsistent with these hypotheses.

Firstly, data on the diffusion mobility of polymeric segments show that the idea of recombination via molecular collision is unsound. Thus even in low-molecular rubbers the diffusion coefficient is $D \simeq 10^{-14}$ $cm^2\,s^{-1}$; it has been estimated [13] that in polystyrene at temperatures close to the glass point $D \simeq 10^{-21}$ $cm^2\,s^{-1}$ and at 20°C $D \simeq 10^{-27}$ $cm^2\,s^{-1}$. This means that the recombination of radicals in such matrices would require an infinitely long period if it involved a diffusion mechanism; in fact the recombination is quite fast even in crystalline polymers, where physical diffusion of macromolecules is altogether without significance.

Secondly, in the same polymers, even in the same specimens, radicals of different chemical structures (alkyl, allyl, and peroxyradicals) recombine at different rates under the same conditions; the temperature ranges in which different radicals recombine are also markedly different. Thus peroxy-radicals usually recombine 10^2–10^3 times faster than alkyl radicals. If the rate of recombination of radicals were determined by the physical diffusion of macromolecules or their segments, the chemical structure of the radicals would have no effect on the rate of recombination.

Table 3. Number of oxygen molecules *n* for each recombined macroradical.

Polymer	T, °C	p_{O_2}, mmHg	n	References
Isotactic polypropylene	60	150	8±1	15.19
	75	150	4.5±1	15
Poly(vinyl chloride)	22	150	6±1	15
	35	150	5±1	15
Polyethylene			3	7
			5	16
Poly(methyl methacrylate)	25	~6; 525	1.5–2	17
Polyepoxyethylene	25		5–10	18

Thirdly, from the standpoint of the diffusion mechanism one cannot explain the finding that in a number of polymers [poly(vinyl chloride), polyformaldehyde] the interaction between oxygen and alkyl radicals does not result in the appearance of peroxy-radicals, although the destruction of alkyl radicals is greatly accelerated; the kinetics of their destruction remain bimolecular as before, and its rate is proportional to the pressure of oxygen [14] (for a more detailed discussion of the kinetics of such catalysis, see below).

Fourthly, the recombination of peroxy-radicals is accompanied by the formation of polymeric hydroperoxide and the absorption of oxygen. Table 3 presents data which show how many oxygen molecules are absorbed for each radical recombined.

Thus, as noted by Loy[7], a peroxy-radical migrating in the polymer leaves behind a trail—a chain of hydroperoxides—until it encounters another radical with which it recombines. It should be noted that the values of *n* in Table 3 are in fact too low, since no account was taken of the amount of oxygen involved in the $R\dot{O}_2$ recombination step; furthermore, during radiolysis radicals are frequently distributed non-uniformly in the specimen, forming groups, and therefore the path traversed by the radicals prior to their recombination is smaller than the path which would be traversed in the case of a uniform distribution. The low value of *n* for poly(methyl methacrylate) is due to the fact that the radicals were obtained by the mechanical degradation of the polymer and are probably localised on the surface.

Table 4. Activation energies and pre-exponential factors for the recombination of the radicals $\dot{R}$ in polymers.

Polymer	Temp., °C	Method of formation of radicals	k^0, $cm^{-3}s^{-1}$	ϵ, kcal $mole^{-1}$	References
Poly(methyl methacrylate	30—55	mechanical degradation	10^{-8}	29	13
	30—60	radiolysis	10^{-8}	28	26
		mechanical degradation	2	26	9
		mechanical degradation	—	37	5
Polyformaldehyde	45—86	radiolysis	10^{-7}	19	14
		destruction in the presence of O_2	10^{-9}	17	14
Poly(vinyl chloride)	70—100	radiolysis	0.7	38	27
		ditto	—	44	28
Acrylate polyesters		radiolysis	$2 \cdot 10^{-8}$	26.5	29
			$2 \cdot 10^{-12}$	12.1	29
			$2 \cdot 10^{-11}$	17.1	29
Polyethylene	40—100	radiolysis	10^{8}	38	24
	—158—123	ditto	$7 \cdot 10^{-17}$	0.7	30
	—103—73	»	$3 \cdot 10^{-5}$	23.1	30
	—53—23	»	$5 \cdot 10^{-8}$	24.8	30
High-pressure polyethylene	40—100	»	1	32	24
Polypropylene	20—80	»	10^{-6}	23	24
	—123—23	»	—	11	31
	—23—25	»	—	48	31
Crystalline Teflon	220—270	»	10^{6}	63	24
Amorphous Teflon	180—220	»	10^{-7}	30	24
Polybutadiene		»	$2 \cdot 10^{-15}$	1.0	20
		»	$3 \cdot 10^{-14}$	4.0	20

All these features of the recombination can be explained by a "chemical" mechanism for the diffusion of radicals, i.e. the migration of free valence (relay mechanism) via the consecutive reactions $\dot{R} + RH \rightarrow RH + \dot{R}$ or $R\dot{O}_2 + RH \rightarrow RO_2H + \dot{R}$. This mechanism probably obtains in the majority of solid polymers; rubbers and amorphous polymers above the glass point probably constitute an exception. Thus in polybutadiene the activation energies for the recombination of allyl radicals are 1–4 kcal $mole^{-1}$,[20] which is close to the values observed for the recombination of radicals in liquids; the recombination rate constants in polybutadiene and amorphous polycapramide diminish markedly with increase in the number of cross-links, i.e. with the increase in the rigidity of the matrix[21,22]. The latter property constitutes a form of criterion for the recombination mechanism.

Eqn. (1) remains valid also for recombination; however, in contrast to the reaction between $\dot{R}$ and O_2 where $k_t \gg k_p$, here the rate-limiting stage is the relay process and not recombination in the vapour phase, i.e. $k_t \ll k_p$. Then $k_{rec} = k_t v^*$. This equation can also be obtained in another way. We introduce the valence diffusion coefficient $D = \frac{1}{6}\lambda^2 k_t$, where k_t is the frequency of "jumps", i.e. the frequency of the elementary steps in physical or chemical diffusion and λ the length of the diffusion path (of the order of dimensions of a monomer unit or the lattice constant). The recombination rate constant $k_{rec} = 8\pi\lambda D$; on substituting *D* in this expression, we have $k_{rec} = \frac{4}{3}\pi\lambda^3 k_t$ or $k_{rec} = k_t v^*$. Thus the recombination kinetics are determined by the kinetics of the valence transfer reactions and the recombination rate constants are the bimolecular rate constants for the relay process. This hypothesis was tested in a recent study[23]; the calculation of k_{rec} for the radicals $\dot{R}$ in polyethylene using the above equation for *D* and k_t for the reaction between $\dot{C}_2H_5$ and heptane in the liquid phase gave good agreement between the calculated and experimental values of k_{rec}. Tables 4 and 5 list the experimental results on the kinetics of the recombination of $\dot{R}$ and $R\dot{O}_2$ radicals in solid polymers.

Table 5. Activation energies and pre-exponential factors for the recombination of the radicals $R\dot{O}_2$ in polymers.

Polymer	Temp °C	Method of formation of radicals	k^0 $cm^{-3}s^{-1}$	ϵ, kcal $mole^{-1}$,	Refs.
Poly(methyl methacrylate)	5-37	mechanical degradation	$5 \cdot 10^{-9}$	17	32
		ditto	$1 \cdot 10^{-9}$	18	13*
Crystalline Teflon		radiolysis	10^{-10}	26	24
Amorphous Teflon		ditto	10^{-16}	10	24
Poly(vinyl acetate)	-17-(+37)	mechanical degradation	10^{-8}	18	13*
Ditto		ditto	—	14.5	4
Polystyrene	-25-(+40)	»	10^{-7}	18	13*
		»	—	12	4.33

*Recalculated by Butyagin[17].

It is striking that the activation energies for recombination reach enormous values; in most cases the pre-exponential factors are anomalously high and are without physical significance; furthermore, there is a linear relation between the logarithm of the pre-exponential factor and the activation energy—the compensation effect (CEF)[24] (the nature of the compensation effect in these reactions is discussed below).

Clearly these results give no information about the kinetics of the valence transfer reactions. The reason for this is probable that the kinetics of reactions in polymers are related to the kinetics of molecular motion and in this sense the measured constants are not elementary. One can only suppose that the activation energies are about 13–17 kcal $mole^{-1}$ for reactions between $\dot{R}$ and RH and 10–15 kcal $mole^{-1}$ for reactions between $R\dot{O}_2$ and RH. In particular, the activation energy of the reaction between $R\dot{O}_2$ and RH in poly(methyl methacrylate), determined by a chemiluminescence method, is 11 kcal $mole^{-1}$.[17]

In certain polymers [polyformaldehyde, poly(vinyl chloride), polyamides] alkyl radicals are not fully converted into peroxy-radicals under the action of oxygen, as is usually the case, but the rate of their destruction is greatly increased. The rate of such catalytic recombination was calculated by Lebedev[25], who showed that catalysis is possible under conditions such that the diffusion of oxygen is hindered and the relay process $R\dot{O}_2 + RH \rightarrow RO_2H + \dot{R}$ is much faster than the reaction between $\dot{R}$ and RH. The rate of recombination is then $w_{rec} = k_{rec}(\dot{R})^2(O_2)$, where k_{rec}^{-1} may be calculated as the sum of the kinetic resistances in all the stages: macrodiffusion, microdiffusion, and kinetic; a linear relation between

w_{rec} and oxygen pressure has been observed experimentally[14].

The above analysis shows that at present there are no reliable data for the chain-propagation constants in solid polymers. Even the few studies available on the solid-phase oxidation of polymers, carried out in recent years, are open to a number of serious objections.

Recently an interesting study was carried out on the oxidation of polypropylene (degree of crystallinity 50%) at 110-140°C.[34]. The steady-state concentrations of the hydroperoxide and peroxy-radicals and the rate of absorption of oxygen were measured; these data are insufficient for the calculation of all the elementary constants. It was shown that the oxidation mechanism is almost the same as the mechanism of the oxidation of liquid hydrocarbons: the initiation takes place on decomposition of the hydroperoxide and the rate of reaction is proportional to $(ROOH)^{1/2}$, i.e. the chain termination is quadratic (recombination of $R\dot{O}_2$).

The chain propagation constant for reaction between $R\dot{O}_2$ and RH is of the form

$$k_{prop} = 5 \times 10^{-16} \exp(-9000/RT)\ cm^3\ s^{-1}.$$

The chain termination constant is $k_{ter} = 7.5 \times 10^{-15}$ cm^3 s^{-1} and the activation energy for chain termination is zero. From the standpoint of the above hypotheses concerning the migration of free valence by a relay mechanism, ϵ_{form} should be close to ϵ_{prop}. Even if one assumes that chain termination takes place via the physical diffusion of segments, the high chain termination rate constant and the zero activation energy are still quite incomprehensible (k_{ter} is higher almost by a power of ten than k_{ter} for 2,4,6-trimethylheptane, which may be regarded as a model of polypropylene[35]).

The results obtained by Chien and Boss[34] can be understood and can be seen to have physical significance if it is assumed that chain termination is effected by a product which readily reacts with the macroradicals $\dot{R}$ (with an activation energy close to zero) and readily diffuses in the polymer (also with an almost zero activation energy); this product then plays the role of a catalyst for the recombination reaction. This hypothesis has not of course been proved (although a method for experimental tests may be suggested), but, if found to be valid, it may be of fundamental importance. One cannot exclude the possibility that in the oxidation of solid polymers this mechanism of the termination of kinetic chains plays a leading role.

Denisov et al.[83] found for the sensitised oxidation of solid polyethylene (temperature range 13 deg)

$$k_{prop}/\sqrt{k_{ter}} = 7 \times 10^7 \exp(-21250/RT)\ mole^{-1/2}\ kg^{1/2}\ s^{-1/2}.$$

4. Decomposition of Hydroperoxides and Degenerate Branching in Polymers

Hydroperoxides are responsible for the degenerate branching in oxidative thermal degradation of polymers. Degenerate branching constitutes the principal stage in the oxidation process. Therefore the study of the kinetics of the decomposition of the hydroperoxides of polymers and of the probability of forming free radicals in the decomposition process constitutes a serious and important problem.

We shall consider initially the results obtained for the mechanism and kinetics of the decomposition of hydroperoxides in polymers and then the data on the formation of radicals and the probability of degenerate branching in polymers.

Decomposition of hydroperoxides. The following principal mechanisms for the decomposition of hydroperoxides (HP) have been considered in the literature;

$$ROOH \rightarrow R\dot{O} + \dot{O}H \qquad (I)$$

$$ROOH + RH \rightarrow R\dot{O} + H_2O + \dot{R} \qquad (II)$$

$$ROOH + ROOH \rightarrow R\dot{O} + H_2O + R\dot{O}_2 \qquad (III)$$

The unimolecular decomposition [reaction (I)] takes place with a high activation energy of about 35–40 kcal mole^{-1}.[36] It occurs only at low hydroperoxide concentrations in solvents without weakly bound hydrogen atoms. Reactions (III) and (II) are more probable; the heat of reaction (III) is approximately 9 kcal and that of reaction (II) varies within wide limits, depending on the R–H bond energy[37]. Reaction (III) predominates at high hydroperoxide concentrations, while at low concentrations and for enthalpy changes comparable with the heat of reaction (III) reaction (II) predominates. In solid polymers reaction (III), in the form in which it occurs in liquids, is even less probable. However, one cannot exclude another kinetic variant of this reaction, which is described by a first-order equation, while the stoichiometry of the reaction corresponds to Eqn. (III). The point is that, as already mentioned, hydroperoxides are obtained in the oxidation of polymers as a result of a sequence of two elementary reactions $R + O_2 \rightarrow R\dot{O}_2$ and $R\dot{O}_2 + RH \rightarrow RO_2H + \dot{R}$. Owing to the relay mechanism of the oxidation process, hydroperoxides are distributed in chains, each of which is in contact only with the nearest adjacent hydroperoxy-groups and the interaction with other peroxy-groups is unlikely. Then the decomposition of the hydroperoxide can occur in pairs and the decomposition kinetics are described by a first-order kinetic law.

In polymers containing weakly bound hydrogen atoms mechanism (II) will predominate; since usually $[ROOH] \ll [RH]$, it will also be described by a first-order kinetic equation. The only polymer for which the decomposition of hydroperoxides was studied in detail is polypropylene. However, even in this case there are contradictory views. A number of investigators[38,39] believe that the decomposition of the hydroperoxide is described by a second-order kinetic equation, in accordance with mechanism (III). This conclusion is based on the finding that the time variation of the concentration of the hydroperoxide derived from polypropylene is satisfactorily described by the equation

$$\frac{1}{[ROOH]} - \frac{1}{[ROOH]_0} = kt\ . \qquad (6)$$

The activation energy (27 kcal mole^{-1}) obtained by these investigators, which is typical for a process of this type, is also consistent with mechanism (II).

However, this is inconsistent with another observation by Dudorov et al.[38], who established that the degree of conversion of the initial peroxide is independent of the initial concentration of the hydroperoxide. Such a relation is typical for a first-order reaction. As a result, the rate constant for the decomposition of the hydroperoxide calculated from Eqn. (6) does not remain invariant when the initial hydroperoxide concentration is changed. Evidently the decomposition of hydroperoxides in atactic polypropylene cannot be described by mechanism (III). In fact recalculation of the results of Dudorov et al.[38] in terms of kinetic equations which are first-order in to the hydroperoxide concentration shows that, over a wide concentration range (7.4×10^{-3}–0.5 mole kg^{-1}), the constant remains satisfactorily invariant.

The above example confirms yet again the rule that, in order to determine the true order of the reaction, it is insufficient to investigate time dependences alone; a comprehensive kinetic study of the reaction is necessary. This is even more valid for polymers, since the hydroperoxide cannot be isolated from the latter in a pure form. For this reason the reaction is studied in a medium consisting of the oxidised polymer where the peroxide ROOH is present in addition to the hydroperoxide (incidentally, one usually obtains a set of different hydroperoxides, which may decompose at different rates); the peroxides are as a rule more stable than the hydroperoxides. When the mixture contains peroxides which decompose at different rates, the variation with time of their overall concentration is described by an equation which has nothing in common with the true reaction mechanism. Fig. 1 shows as an example the calculation of the time variation of the overall concentration of hydroperoxides in a 4 : 1 mixture assuming that the rate constants for their monomolecular breakdown are 4.6×10^{-2} min^{-1} and 4.6×10^{-3} min^{-1}.

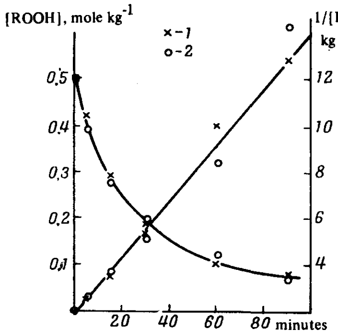


Figure 1. Decomposition of polypropylene hydroperoxide: 1) calculated points; 2) experimental values taken from Dudorov et al.[38]

Fig. 1 shows that the change in overall concentration up to 90% conversion is satisfactorily described by a second-order kinetic equation even though the hydroperoxides decompose [by a known unimolecular mechanism].

In a study[40] dealing with the decomposition of the hydroperoxides derived from isotactic polypropylene it was shown that the time variation of the concentration of the hydroperoxide is satisfactorily described by a second-order equation and the calculated rate constant remains invariant as the initial concentration of the hydroperoxide is varied.

However, the activation energies obtained[38-40] (25 to 27 kcal mole^{-1}) are inconsistent with the hypothesis of a purely unimolecular decomposition of the hydroperoxide (I). Furthermore, it has been established that the rate constant for the decomposition of hydroperoxides from isotactic polypropylene increases on introduction into the polymer of substances with labile hydrogen atoms[40] and diminishes when the polymer is diluted with substances in which all the hydrogen atoms are strongly bound[41]. Fig. 2 presents the decrease of the first-order rate constant when polypropylene is diluted with naphthalene or cetane. On the basis of these data, it is suggested[40,41] that the decomposition of hydroperoxides from isotactic polypropylene takes place according to mechanism (II). The hydrogen atoms attached to the tertiary carbon atoms evidently participate in the reaction. The experimental yield of water[41] amounts to 85% of theoretical.

The above mechanism is confirmed by the results obtained in a study of the kinetics of the absorption of oxygen and the assimilation of hydroperoxides in the oxidation of isotactic polypropylene[43]. On the basis of the mechanism proposed for the process, the authors calculated from these data the rate constant for the decomposition of the hydroperoxides by two independent procedures. The calculated constant agreed satisfactorily with the value obtained in the study of the thermal decomposition of polypropylene hydroperoxides.

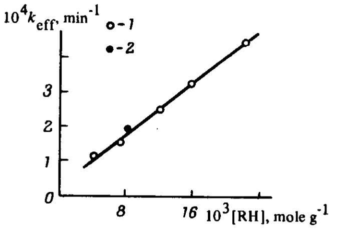
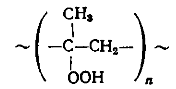


Figure 2. Variation of the effective rate constant for the decomposition of polypropylene hydroperoxide with polymer concentration: 1) dilution with naphthalene; 2) dilution with cetane.

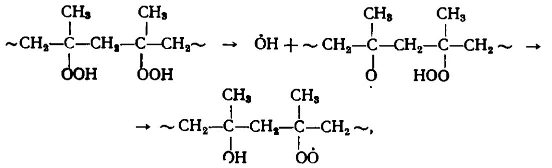
The study of the decomposition of the polypropylene hydroperoxides obtained in the sensitised oxidation of the polymer in a dilute solution is of considerable interest[43]. In this procedure hydroperoxy-groups distributed along the macromolecule at adjacent tertiary carbon atoms should form:



$$\sim\left(-\underset{\mathrm{OOH}}{\overset{\mathrm{CH_3}}{\mathrm{C}}}-\mathrm{CH_2}-\right)_n\sim$$

The authors demonstrated[44] that their hydroperoxides have precisely this structure; furthermore, they obtained the distribution of groups with respect to n, as shown in Fig. 3. It was found that 50% of the hydroperoxides are present in the form of pairs and only 7–9% in the form of single molecules.

The authors describe the breakdown of such hydroperoxides by the sum of two first-order kinetic equations with rate constants of 16×10^{-4} and 8×10^{-5} s^{-1} at 120°C. They suggest that the rapid reaction ($k = 16 \times 10^{-4}$ s^{-1}) is the chain decomposition of adjacent hydroperoxy-groups:



$$\sim\mathrm{CH_2}-\underset{\mathrm{OOH}}{\overset{\mathrm{CH_3}}{\mathrm{C}}}-\mathrm{CH_2}-\underset{\mathrm{OOH}}{\overset{\mathrm{CH_3}}{\mathrm{C}}}-\mathrm{CH_2}\sim \;\rightarrow\; \dot{\mathrm{O}}\mathrm{H} + \sim\mathrm{CH_2}-\underset{\dot{\mathrm{O}}}{\overset{\mathrm{CH_3}}{\mathrm{C}}}-\mathrm{CH_2}-\underset{\mathrm{HOO}}{\overset{\mathrm{CH_3}}{\mathrm{C}}}-\mathrm{CH_2}\sim \;\rightarrow$$

$$\rightarrow \sim\mathrm{CH_2}-\underset{\mathrm{OH}}{\overset{\mathrm{CH_3}}{\mathrm{C}}}-\mathrm{CH_2}-\underset{\mathrm{O\dot{O}}}{\overset{\mathrm{CH_3}}{\mathrm{C}}}-\mathrm{CH_2}\sim, \qquad \text{(IV)}$$

and the slow reaction is the chain decomposition of isolated groups:

$$\mathrm{ROOH} + \mathrm{R\dot{O}}\ (\dot{\mathrm{O}}\mathrm{H},\ \mathrm{R\dot{O}_2}) \rightarrow \mathrm{R\dot{O}_2}. \qquad \text{(V)}$$

The authors believe that this mechanism is confirmed by the fact that the contribution of the slow reaction is

10–15%, i.e. is close to the fraction of isolated hydroperoxy-groups and that the introduction of large amounts of an inhibitor (ionol) diminishes the contribution of the fast reaction and lowers the rate of the slow reaction to a limiting value, which can also be obtained by reducing the initial concentration of the hydroperoxide.

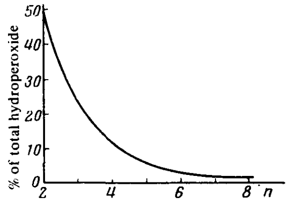


Figure 3. Distribution of adjacent hydroperoxy-groups with respect to *n* in polypropylene according to the data of Chien et al.[44]

However, the above study involves significant contradictions. In the first place the chain decomposition of the hydroperoxide cannot follow a first-order kinetic law. This is also shown by the variation of the rate constant for the slow reaction with the initial concentration of the hydroperoxide found by the authors themselves[43]. Furthermore, the contribution of the "slow" reaction must be much greater (30–40%). Indeed in the decomposition of two adjacent hydroperoxy-groups by mechanism (IV) two radicals, $\dot{O}H$ and $R\dot{O}_2$, are formed. Probably there is a high probability of the conversion of $R\dot{O}_2$ into the hydroperoxide, which will be formed as a separate molecule. Thus one half of the binary and one third of the ternary hydroperoxide sequences must ultimately decompose at the rate of the "slow" reaction.

Furthermore, in the chain decomposition of the hydroperoxide the yield of radicals per decomposition step should be much less than two, while Chien and Jabloner[43] found it to be 1.8. These findings show that the mechanism proposed[43] for the decomposition of the hydroperoxide derived from polypropylene is open to serious objections. It is difficult at present to interpret these results unambiguously.

In the decomposition of hydroperoxides in other polymers (other than polypropylene) the situation is even less satisfactory; data for such processes are virtually lacking. The results of Chien and coworkers[45] and Denisov and coworkers[46] for the decomposition of the hydroperoxides derived from polyethylene constitute an exception. However, the two sets of data show considerable discrepancies.

While Denisov and coworkers concluded that in polyethylene the hydroperoxides undergo a chain decomposition (an inhibitor retards the reaction), Chien and coworkers suggest that there is no chain decomposition in the breakdown of the polyethylene hydroperoxides, since inhibitors do not affect the decomposition process. According to these authors' findings[45], two unimolecular reactions take place in polyethylene: fast and slow reactions with activation energies of 25 and 27 kcal mole^{-1} respectively. According to Denisov[46], the activation energy for the inhibited decomposition of the hydroperoxides is 35 kcal mole^{-1}; it is suggested that the decomposition process is unimolecular and has mechanism (I). The authors of both investigations found that the rates of decompositions of the polyethylene hydroperoxides are the same in solution and in the solid phase.

Probability of radical formation in the decomposition of hydroperoxides. The available literature data on the probability of radical formation in the decomposition of hydroperoxides derived from polymers can be divided into two groups. The first group includes results obtained for the decomposition of the hydroperoxides in a vacuum or in an inert atmosphere[47] and the second group includes data obtained in an atmosphere of oxygen[42,43,45,46].

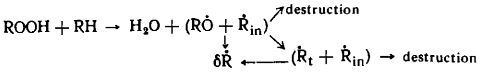
The inhibitor method in one form or another is used for the quantitative determination of the number of radicals formed in the breakdown of the hydroperoxide. The following difficulties must be overcome. As a rule, it is possible to obtain hydroperoxides derived from the polymers at concentrations of 10^{-5}–10^{-4} mole g^{-1}. In order to ensure the complete removal of the radicals by the inhibitor, the concentration of the latter in the polymer must be about 10^{-4} mole g^{-1}. When the probability of the formation of radicals is 10^{-2}–10^{-3}, about 1% of the inhibitor is consumed. Such a change in concentration is outside the error limits of the measurements.

In order to calculate the number of radicals formed in the decomposition of polypropylene hydroperoxides in a vacuum[47,48], a new version of the inhibitor method was developed. Phenoxy-radicals with t-butyl group in the *ortho*-positions can split off isobutene[49]. The amount of isobutene serves as a measure of the number of phenoxy-radicals formed in the interaction between phenol and radicals.

The mechanism of the radical processes can be represented by the following series of reactions:

$$ROOH \rightarrow \delta\dot{R} \xrightarrow{PhOH} \delta\,Ph\dot{O} \rightarrow \sigma\gamma\ (\text{iso-}C_4H_8)\ .$$

In order to find δ, it is necessary to determine, in addition to the amount of isobutene, also γ—the yield of isobutene in the decomposition of a phenoxy-radical. It was found that at 130°C in polypropylene 10% of phenoxy-radicals derived from ionol broke down with formation of isobutene, i.e. $\gamma = 10 \times 10^{-2}$.[47] The calculations showed that 17 radicals are formed for each thousand polypropylene hydroperoxide molecules decomposed in a vacuum. Such a low yield of radicals in the absence of a chain process can be explained either by postulating that the main bulk of the hydroperoxides break down without the formation of radicals or that most of the radicals formed are destroyed by recombination within the cage:



$$\begin{tikzcd} ROOH + RH \arrow[r] & H_2O + (R\dot{O} + \dot{R}_{in}) \arrow[d] \arrow[r] \arrow[rd] & \text{destruction} \\ & \delta\dot{R} & (\dot{R}_t + \dot{R}_{in}) \arrow[l] \arrow[r] & \text{destruction} \end{tikzcd}$$

A number of facts suggest that the latter explanation is correct. Thus, in a study dealing with the oxidation of isotactic polypropylene[42], it was shown, by comparing the rates of absorption of oxygen and of the decomposition of the hydroperoxide, that in the presence of O_2 the yield of radicals is much higher and approaches 2.

Table 6 shows the variation of δ with the pressure of O_2. The fact that in the presence of oxygen the mechanism of the decomposition of the hydroperoxide does not change is confirmed by the constancy of the rate of its decomposition both in a vacuum and in the presence of O_2.

Analogous calculation based on the data of Chien and Boss yields $\delta = 1.2$ for solid polypropylene at $p_{O_2} =$ 760 mmHg and 120°C.[34,43] For comparison, it should be noted that, using the inhibitor method, Chien obtained $\delta = 1.8$ for the decomposition of polypropylene hydroperoxides in solution at an O_2 pressure of 760 mmHg [43] and $\delta = 0.2$ for polyethylene hydroperoxides under the same conditions [45]. Denisov and coworkers [46] showed that the probability of the formation of radicals in the decomposition of polyethylene hydroperoxides is the same in solution and in the solid phase and is lower than the probability reported by Chien and coworkers [45] by a factor of 100. It is difficult to account for such a discrepancy between the results.

Table 6. Dependence of the yield of radicals δ in the decomposition of polypropylene hydroperoxide on the pressure of O_2 ($T = 130°C$).

p_{O_2}, mmHg	δ
0	$17 \cdot 10^{-3}$
50	0.25
100	0.5
200	0.8
400	1.2
600	1.5

The data for the variation of δ with oxygen pressure can probably be explained only on the basis of the cage effect hypothesis. The decomposition of hydroperoxides derived from polymers entails the formation of a pair of radicals which, in the absence of powerful radical acceptors, recombine with a high degree of probability. By adding to the radicals, oxygen can participate in the cage reactions and can alter the value of δ. However, it must be admitted that the mechanism of such participation remains obscure.

The participation of oxygen in the cage reactions makes it possible to estimate the lifetime of the cage τ. Evidently the order of magnitude of this time must not be less than that of the time during which the oxygen molecule migrates over the distance separating two nearest oxygen molecules (or half this distance). Using the available data on the solubility and diffusion of O_2 in polypropylene [50], we obtain τ for the amorphous polymer at 130°C of the order of 10^{-6}–10^{-8} s; in the crystalline polymer this quantity is probably somewhat larger. The value of τ obtained here agrees well with τ estimated from the probability of the breakdown of $R\dot{O}$ radicals (see below).

Shlyapnikova and Yasina [51] secured direct evidence that the yield of radicals in the breakdown of the hydroperoxides derived from solid propylene increases under the influence of oxygen; δ then varies linearly with oxygen pressure: $\delta = \delta_0 + \delta_i p_{O_2}$, where $\delta_i/\delta_0 \simeq 2 \times 10^{-3}\ \text{mmHg}^{-1}$ for the liberation of methane from the cage and $\delta_i/\delta_0 \simeq 1.3 \times 10^{-2}\ \text{mmHg}^{-1}$ for the liberation of propene.

From the standpoint of the stabilisation of polymers, it is significant that the yield of radicals in the decomposition of polymer hydroperoxides can also be increased by certain inhibitors. Thus in a study of the effect of ionol on the yield of hydrocarbons in the breakdown of polypropylene hydroperoxide [48], the results presented in Fig. 4 were obtained. Volatile hydrocarbons (methane, ethane, propane, propene, and isobutene) are produced in the breakdown of alkyl macroradicals generated from the hydroperoxide and isobutene is formed in addition also from phenoxy-radicals—the product of the interaction of ionol with macroradicals. Fig. 4 shows that the yields of all the hydrocarbons, with the exception of isobutene, decrease with increase in the concentration of the inhibitor; however, the decrease is not to zero but only to a limiting value. At the same time the amount of isobutene increases continuously. These results can be readily explained if it is supposed that the inhibitor can participate in an additional radical generation process. Then, starting with a certain inhibitor concentration, the concentration of radicals in the polymer becomes constant and independent of the concentration of the inhibitor, because the rates of formation and destruction of radicals are both proportional to the latter. This is why the rate of formation of hydrocarbons and consequently their yield cease to depend on the inhibitor concentration. At the same time the total amount of radicals and hence also the yield of isobutene increase continuously with increasing ionol concentration. Thus the inhibitor participates both in the destruction of radicals and in their formation.

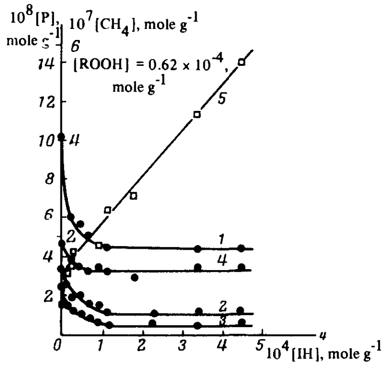


Figure 4. Dependence of the yield of polypropylene hydroperoxide decomposition products on the concentration of ionol: 1) methane; 2) ethane; 3) propane; 4) propene; 5) isobutene.

A kinetic analysis of the role of the inhibitor in the production of radicals and quantitative estimates of this participation have been made [48]. For example, in the breakdown of the polypropylene hydroperoxides in a vacuum at 130°C the yield of radicals in the presence of 5×10^{-4} M ionol increases by a factor of 5.

In principle, one can consider two mechanisms for the involvement of the inhibitor in radical generation. Firstly, the inhibitor may "enter" the cage ($R\dot{O} + \dot{R}_{in}$) destroying one of the radicals; the second radical is then capable of chain propagation. Secondly, the inhibitor can react with the polymer hydroperoxide; such a reaction is an additional source of radicals.

The branching function of the inhibitor can be shown only when the primary yield of radicals in the breakdown of the hydroperoxide (without the participation of the inhibitor) is very low.

In fact the inhibitor can successfully compete with the cage recombination of radicals only if the rate constant for its interaction with the radicals is not less than the rate constant for their recombination and the concentration of the inhibitor is also fairly high. At the usually employed inhibitor concentration (0.01–0.01 mole kg^{-1}) the probability of the interaction of the inhibitor with the cage is low (10^{-2}–10^{-4}). For this reason, such interaction can be important only when the spontaneous liberation of radicals from the cage is also low. In the direct interaction of the inhibitor with the hydroperoxide the following factors are evident. If the probability of the formation of radicals in the breakdown of the hydroperoxide is low, then even a slight interaction between the inhibitor and the hydroperoxide can have a significant effect on the yield of radicals. Otherwise even a high rate of interaction of the inhibitor with the peroxide cannot affect appreciably the efficiency of radical formation.

The above analysis of the data shows that no unambiguous results are yet available on the yield of radicals in the breakdown of polymer hydroperoxides in the presence of oxygen. In some studies the yield of radicals in the presence of oxygen has been determined as about 10^{-2} to 10^{-3}, while in others it is of the order of unity.

Nevertheless this finding is fairly important. The point is that the idea of the involvement of the inhibitor in degenerate branching in the oxidation of polymers and the associated theory of the effect of inhibitors (critical concentrations, classification of inhibitors into "strong" and "weak", etc.) are based on the hypothesis of a low value of δ; these hypotheses were put forward by Shlyapnikov and Neiman[52,53] and confirmed in studies of the high-temperature (180–220°C) inhibited oxidation of polypropylene.

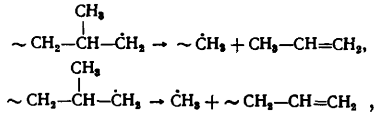
Thus there exists a definite contradiction concerning the value of δ. Possibly in solid polymers (at 100–130°C) δ is close to unity, while in melts at temperatures in the range 180–220°C δ is small (although from the physical point of view the opposite relation would be expected). Evidently the unambiguous solution to the problem of the probability of degenerate branching in the breakdown of hydroperoxides in polymers is very important for the theory of polymer stabilisation.

5. Decomposition of Macroradicals (Degradation of the Polymer Chain)

The kinetics of the decomposition of macroradicals of different types are of exceptional interest for the theory of degradation processes. Unfortunately there are virtually no quantitative data for the rates of decomposition in the solid phase. For this reason, only the qualitative aspects of this problem will be considered here.

In various forms of polymer degradation the following types of radicals play a leading role: alkyl macroradicals and peroxy- and alkoxy-macroradicals.

Decomposition of alkyl macroradicals. These reactions are usually investigated in thermal degradation processes of polymers at temperatures in excess of 300°C; this is because the rate of their decomposition is low. Thus it is known from the kinetics of gas-phase reactions[54] that low-molecular alkyl radicals break down with an activation energy exceeding 30 kcal mole^{-1}. Probably the activation energy for the decomposition of high-molecular radicals does not differ appreciably from this value. The breakdown of alkyl macroradicals leads to the rupture of the polymer chain and the formation of radicals with a free valence at the end of the macrochain (terminal macroradicals). These radicals give rise to volatile degradation products and in many cases alkyl macroradicals may isomerise, which leads to a wide range of degradation products. For example, in the thermal degradation of polypropylene the following reactions are postulated[55,56]:



$$\sim CH_2\text{—}\underset{}{\overset{CH_3}{\overset{|}{C}}}H\text{—}\dot{C}H_2 \rightarrow \sim\dot{C}H_2 + CH_3\text{—}CH\text{=}CH_2,$$

$$\sim CH_2\text{—}\overset{CH_3}{\overset{|}{C}}H\text{—}\dot{C}H_2 \rightarrow \dot{C}H_3 + \sim CH_2\text{—}CH\text{=}CH_2\ ,$$

etc.

Decomposition reactions of alkyl macroradicals have been observed in the inhibited oxidation of polypropylene at 200°C,[57] in the mechanical degradation of a number of polymers[58], and also in the breakdown of polypropylene hydroperoxide at 130°C.[59] In the last case a detailed study was made of the kinetics of the formation of volatile hydrocarbons—the degradation products of the terminal macroradicals. The yield was found to be extremely low. In the breakdown of 1.26×10^{-4} mole of hydroperoxide, at a concentration of 1.26×10^{-4} mole g^{-1} in the polymer, the amounts of products were 16.7×10^{-7} mole of methane, 0.85×10^{-7} mole of ethane, 0.89×10^{-7} mole of propane, 1.4×10^{-7} mole of propene, and 0.19×10^{-7} mole of isobutene. These data make it possible to estimate the probability of the decomposition of alkyl macroradicals at 130°C. In the same study it was shown that the terminal macroradicals are obtained mainly in the breakdown of alkoxy- and not alkyl radicals. For this reason, only half of the radicals liberated from the "cage" ($R\dot{O}$ + $\dot{R}_{in}$) are terminal. Since the yield of radicals is in this case 1.7×10^{-2},[47] it follows that 1.26×10^{-4} mole of hydroperoxide gives 10.7×10^{-7} mole of $\dot{R}_t$. Consequently only 8% of the $\dot{R}_t$ radicals decompose with formation of propene while the remaining 92% are converted into "inner" macroradicals by the reaction

$$\dot{R}_t + RH \rightarrow R_tH + \dot{R}_{in}$$

or isomerise and yield other hydrocarbons (propane, ethane, isobutene, etc.). Thus the rate of the chain-transfer reactions exceeds at least by a factor of ten the rate of decomposition of the terminal macroradicals.

In those cases where the activity of the alkyl macroradicals is low, the yield of the monomer is much higher; for example, in the degradation of poly(methyl methacrylate) (PMMA) almost pure monomer is found among the products. The rate constants for the depolymerisation of the terminal macroradicals have been measured in such processes: the rate constant for the breakdown of macroradicals in the photo-degradation of PMMA was measured by Cowley and Melville using the sector method at 167°C[60] and was found to be 5.8×10^{-2} s^{-1}. According to the same authors' estimate, the activation energy is 18.5 kcal mole^{-1}. These values agree well with data obtained in the measurements of the rate of decomposition of the radicals $\sim\dot{C}(CH_3)(COOCH_3)$ in PMMA at 20°C.[32] It was found that at a radical concentration of 10^{18} spins g^{-1} the rate of formation of methyl methacrylate is 0.56×10^{15} particles per cm^3 per second; hence the rate constant for the decomposition is 0.56×10^{-3} s^{-1}. According to the data of Cowley and Melville, it should be about 10^{-3} s^{-1} at 20°C. Thus depolymerisation in the solid phase takes place at the same rate as in the liquid phase[9].

Alkoxy-macroradicals. The activation energy for the decomposition of alkoxy-radicals in the gaseous and liquid phases does not exceed 10–12 kcal mole^{-1},[61] i.e. they are much more stable than alkyl radicals.

In the mechanism of the thermal oxidative degradation it is thought that alkoxy-radicals play a leading role in the dissociation of polymer chains. Thus Tobolsky, who studied the sensitised oxidation of polypropylene (in the absence of branching) at 80°C, established[62] that under these conditions at least one rupture of polymer chain occurs on the average for each oxidation chain. Hence it was concluded that the polymer chain ruptures in the recombination process of peroxy-radicals:

$$R\dot{O}_2 + R\dot{O}_2 \rightarrow 2R\dot{O} + O_2 \, .$$

The $R\dot{O}$ radicals formed break down with rupture of the polymer chain. Thus the probability of the decomposition of $R\dot{O}$ radicals is close to unity.

In oxidation processes with degenerate branching the principal source of $R\dot{O}$ radicals is the breakdown of hydroperoxide:

$$ROOH + RH \rightarrow (R\dot{O} + \dot{R}_c) + H_2O \, .$$

A quantitative study of the decomposition products of polypropylene hydroperoxides made it possible to estimate the probability of the breakdown of alkoxy-radicals[59]. It was established that in the decomposition of polypropylene hydroperoxide the amount of oxygen-containing products formed (formaldehyde, acetone, acetaldehyde, etc.), which may be obtained only from terminal hydroperoxides, is about 10–15% of the total amount hydroperoxides decomposed. Hence the yield of oxygen-containing products is equal to $\alpha\beta$, where α is the probability of the decomposition of $R\dot{O}$ radicals and β is the fraction of terminal hydroperoxides relative to the total amount of hydroperoxides; β may be determined as follows.

If it is assumed that in the breakdown of the hydroperoxide $\alpha\dot{R}_t$ and $(1 - \alpha)\,\dot{R}_{in}$ were formed, then these radicals would initiate new oxidation chains of length ν. Each chain, begun by the radical $\dot{R}_t$, contains one R_tOOH molecule and $(\nu - 1)R_{in}OOH$ molecules and the chain begun by $\dot{R}_{in}$ consists entirely of $R_{in}OOH$. Hence $\beta = \alpha/2\nu$ or $\alpha^2/2\nu = 0.10\text{–}0.15$. According to Pudov[63], ν at 130°C varies in the range 5–1.5; hence $0.5 \leqslant \alpha \leqslant 1$.

Thus the rate of dissociation of the polymer chain in the oxidation of polypropylene must not be less than the rate of decomposition of the hydroperoxides.

Bearing in mind that the probability of the breakdown of the radicals $R\dot{O}$ is high (about 1.0) and the yield of radicals liberated from the cage is low (about 1.7×10^{-2}), one must conclude that the decomposition of these radicals takes place during the lifetime of the cage. If 11 kcal mole^{-1} is adopted for the activation energy for the breakdown of $R\dot{O}$ radicals in polypropylene and about 10^{13} s^{-1} for the pre-exponential factor, it is possible to estimate the lower limit of the lifetime of the cage ($R\dot{O} + \dot{R}_{in}$); it proves to be 10^{-6}–10^{-7} s^{-1}.

A high probability of the dissociation of the chain in the breakdown of the peroxide was observed in the oxidation of polyoxymethylene copolymers at 160°C.[64] In the oxidative thermal degradation of rubbers it was also shown by a kinetic procedure that the probability of the breakdown of alkoxy-radicals is unity[65], i.e. even in rubbers the breakdown of $R\dot{O}$ at 100–130°C is much faster than the recombination in the vapour phase ($RO + \dot{R}_{in}$).

Thus alkoxy-radicals appear to be the principal species responsible for both the formation of volatile degradation products and the dissociation of polymer chains.

The kinetics of the decomposition of peroxy-radicals in Teflon according to the reaction

$$R\dot{O}_2 \rightarrow \dot{R} + O_2$$

were investigated by Voevodskii and coworkers[24]. The rate constant is $k = 10^8 \exp(-20\,000/RT)$ s^{-1}. The energy of the $R\text{–}O\dot{O}$ bond in this radical is about 10 kcal mole^{-1}.

We shall now consider the contribution of $R\dot{O}_2$ radicals to chain degradation. In 1959 Neiman and coworkers[66] compared the rates of decomposition of the hydroperoxide in the polymer and the rate of isomerisation of peroxy-radicals and concluded that they are of the same order of magnitude. Recently published data confirm this finding. Chien and Boss[34] showed that in the oxidation of polypropylene at 130°C the steady-state concentrations of the hydroperoxide and peroxy-radicals are 0.30×10^{-6} and 10.2×10^{-6} mole litre^{-1} respectively and the rate constant for the breakdown of the hydroperoxide is 16.5×10^{-4} s^{-1}. If it is assumed that the activation energy for the isomerisation of peroxy-radicals is about 20 kcal mole^{-1}†,[67] it is found that the rates of isomerisation of peroxy-radicals and of the decomposition of the hydroperoxide are comparable. This conclusion is confirmed by the data of Denisov and coworkers[68], according to which the contribution of the isomerisation of $R\dot{O}_2$ to the degradation of polymer chains is about 10%.

6. Cage Effects and Radical Pairs in Solid Polymers

Numerous studies on cage effects in the decomposition of initiators in the liquid phase showed that the probability of the liberation of radicals from the cage or from a radical pair is 0.3–0.7, i.e. 30–70% of the radicals avoid recombination in the cage. The principal mechanism of the liberation of radicals involves diffusion; this is confirmed by the finding that the yield of radicals depends on the viscosity, obeying the Debye–Stokes diffusion equation[69].

The data on the yields of radicals in highly viscous media (including polymers) are somewhat contradictory. In a number of studies yields of radicals close to those observed in the liquid phase are quoted. Haas[70] found that in the decomposition of benzoyl peroxide in polystyrene and poly(vinyl chloride) the probability of the liberation of radicals from the cell is 0.5–0.6. These data agree with the results of Denisov and coworkers[71], according to which about 70% of the radicals recombine in the cage in the breakdown of lauroyl peroxide in solid polystyrene (at 80°C) and about 95–96% in the breakdown of bisazoisobutyronitrile.

It may be expected that the yield of radicals liberated by the diffusion mechanism will be sharply reduced in solid polymers; this is clearly illustrated by the data in Table 7.

Evidently, the fraction of the products of recombination in the cage (t-butyl peroxide) increases with the viscosity of the medium and there is a parallel decrease of the fraction of the products derived from the radicals liberated from the cage (t-butyl alcohol).

In very viscous media relay mechanisms, including the interaction between an active species and the wall of the cage, play a significant role[70,73] supplementing to the diffusion mechanism of the liberation of radicals from the cage. It is useful to estimate the relative contributions of the mechanisms whereby radicals are released from the cage. The migration of low-molecular species by diffusion in polymers is characterised by diffusion coefficients in the range 10^{-7}–10^{-10} cm^2 s^{-1}. The liberation of radicals from the cage via interaction with the cage walls (for example, the abstraction of a hydrogen atom) can also be

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†This value is fairly accurate. In fact for $R\dot{O}_2$ we have $\epsilon_{isomer} - \epsilon_{prod} \simeq 8.5$ kcal mole^{-1};[67] when $\epsilon_{prod} \simeq$ 12 kcal/mole^{-1}, $\epsilon_{isomer} \simeq 20$ kcal mole^{-1}.

characterised by a "chemical" diffusion constant, which is related to the rate constant for the abstraction of a hydrogen atom by the expression $D = \frac{1}{6}\lambda^2 k'$, where λ is a quantity of the order of magnitude of the intermolecular distance and k' is the frequency of the step involving the abstraction of a hydrogen atom, equal to the product of the rate constant for this reaction k and the polymer concentration (RH).

Table 7. Products of the decomposition of di-t-butyl peroxyoxalate at 35°C.[72]

Medium	Viscosity, cP	Yield of products as t-butoxy-radicals, %		
		t-butyl-peroxide	t-butyl alcohol	acetone
n-Pentane	0.22	4	95	1
Liquid silicone	74	46	46	0.5
Liquid paraffin	80	78	16	0
Polychlorotrifluoroethylene	560	88	2	7
Polyisobutylene	>1000	93	4.6	0

On substituting in this equation the usual values $\lambda \simeq 5$ Å and (RH) $\simeq 10^{22}$ cm^{-3}, we obtain $D \simeq 4 \times 10^{-6}\, k$. Thus, for the liberation of radicals from the cage by the relay mechanism to be comparable with the liberation by the diffusion mechanism, k must be of the order of 2.5×10^{-14}–10^{-17} cm^3 s^{-1}. Hence it is clear that for mobile species ($D \geqslant 10^{-7}$ cm^2 s^{-1}) the diffusion mechanism predominates; only in the case of the most reactive radicals can interaction with the cage wall play an appreciable role.

The liberation from the cage of less mobile species probably takes place by both mechanisms, their relative contributions being determined by the reactivity and mobility of the species. This is illustrated by the data of Smirnov et al.[74], who measured the effectiveness of various initiators in liquid and solid acrylate oligo-esters. The effectiveness of bisazoisobutyronitrile diminishes from 0.5 to 0.035 on transition from the liquid to the solid acrylate oligo-ester, while the decrease of the effectiveness of acyl peroxides is only from 0.5 to 0.3. The authors suggest that, for the relatively unreactive radicals $(CH_3)_2\dot{C}CN$, the extent of liberation from the cage is wholly determined by the diffusion of the radical and therefore depends markedly on the viscosity of the medium. On the other hand, for the radicals $RC\dot{O}O$ a relay mechanism plays an important role in the separation of the radical pair and the effectiveness of the initiation depends much less on the viscosity of the medium. It is possible to account for the results of Haas[70] quoted above and other data in a similar manner.

It has recently been shown that radical pairs in the cages can be detected by ESR. In such pairs dipole and exchange interactions take place between the unpaired electrons of the radicals and are reflected in the ESR spectra. The ESR spectra have been reviewed in relation to the theory of biradical systems (including radical pairs)[75]. In radical pairs trapped in crystals the distances between the radicals are rigidly fixed and therefore the energy of the dipole interaction between unpaired electrons is rigorously determined; this dipole splitting is a characteristic feature of the ESR spectra of radical pairs. The average distance between the unpaired electrons is found from the magnitude of the splitting.

In most cases the distance is 4–6 Å.[76] The kinetics of the reaction in pairs of azobutyronitrile radicals were investigated by Lebedev[77]. The probability of the liberation of radicals from the pair at 77°K in azobutyronitrile is about 2×10^{-3}. The rate constant for the "quenching" of the pair, i.e. for the recombination of the radicals in the pair, is given by an expression of the form[76]

$$k = 10^8 \exp(-3500/RT)\ \mathrm{s}^{-1}.$$

Thus in the solid phase even recombination in the pair requires an activation energy, i.e. the lifetime of the radical pair may be fairly long.

In glasses and polymers a fairly wide distribution of separations between radicals in each pair is to be expected. The ESR spectra in such cases are fairly broad and in general it is impossible to detect pairs in the region of the usual ESR transitions ($\Delta M_S = 1$). However, recently radical pairs have been detected in irradiated polymers (polyethylene, polyformaldehyde, polypropylene, etc.) by recording the "forbidden" $\Delta M_S = 2$ signal[78] (this signal corresponds to the simultaneous reorientation of both electron spins in the pair).

It is difficult to determine the concentrations of the pairs from such signals and to investigate the kinetics of their reactions, but the very fact of their detection in polymers is remarkable. The search for the broad signals due to radical pairs corresponding to $\Delta M_S = 1$ is more promising and these have also been observed[78,79].

III. RELATIONS BETWEEN THE KINETICS OF RADICAL REACTIONS AND THE KINETICS OF MOLECULAR MOTION IN POLYMERS

In the previous section convincing evidence was presented showing that in the majority of solid polymers radical recombination occurs by a relay mechanism. At first sight it would appear to follow from this that the kinetics of such reactions must be determined only by the chemical reactivity of the radicals and should not be sensitive to the physical state and the physical properties of the polymer matrix. However, a number of facts are inconsistent with this conclusion. Thus it is known that the temperature ranges in which molecular motion is "unfrozen" (for example, as measured by NMR) are the same as the temperature ranges in which radicals are destroyed. The kinetics of radical recombination in acrylate polyester glasses are qualitatively related to the rigidity of the matrix[29]. The rate of destruction of alkyl radicals in oriented polystyrene is much lower than in the non-oriented polymer[13]. The rate of recombination of PMMA peroxy-radicals in the stressed polymer is much higher than in the polymer subjected to preliminary annealing[5].

The relation between the reaction kinetics and the kinetics of molecular motion is not only qualitative but also quantitative. Thus in PMMA the effective activation energy for the destruction of alkyl radicals is 28 kcal mole^{-1},[26] while the activation energy for segmental motion, measured by NMR, is 27 ± 10 kcal mole^{-1}.[80] In polypropylene the destruction of the radicals in the low-temperature region takes place with an activation energy of 11 kcal mole^{-1}; the activation energy for molecular motion in the same temperature range is (100–250°K) is 13 kcal mole^{-1}. In the high-temperature region (> 250°K) the activation energies are respectively 48 and 58 kcal mole^{-1}.[30] The same behaviour is observed in polyethylene[31]. In the high-temperature region radicals with stereochemical conformations corresponding to a regular spiral are destroyed, while radicals with a distorted structure, markedly differing from the spiral structure, recombine at low temperatures (they are apparently localised in amorphous regions or structural defects).

Frequently such quantitative correspondance is regarded as proof of a diffusion mechanism for the recombination of radicals and the high activation energies for recombination are usually explained by the co-operative nature of the diffusion, requiring the simultaneous rearrangement of the structure and of the packing of a large number of segments and units of the polymer chains.

However, it should be noted that in the vast majority of such cases pre-exponential factors for the rate constant are anomalously high and are without physical significance. Furthermore, there is a linear relation between the logarithm of the pre-exponential factor (or the entropy of activation) and the energy (enthalpy) of activation, i.e. the compensation effect. Therefore it is clear that the above purely qualitative explanation of the correspondence between the reaction kinetics and the kinetics of molecular motion is inadequate.

Lebedev et al. were the first to draw attention to the compensation effect in the radical recombination reactions in polymers[24]. They proposed an explanation for this effect on the hypothesis that, over the temperature range of the recombination reactions, the activation energy decreases with increasing temperature as a result of changes in the structure of the polymer. The effective activation energy and the pre-exponential factor are then given by the following expressions:

$$\varepsilon_{\text{eff}} = \varepsilon(T) - T\,\partial\varepsilon/\partial T\ , \tag{7}$$

$$k^0_{\text{eff}} = k^0 \exp\left(-\frac{1}{R}\frac{\partial\varepsilon}{\partial T}\right) \tag{8}$$

and are linked by the reciprocal relation $\lg k^0_{\text{eff}} = A + B\epsilon_{\text{eff}}$.

However, this explanation of the compensation effect and the kinetic characteristics of the recombination is valid only within the framework of the hypothesis of a diffusion mechanism for the recombination process. In fact it is necessary to seek kinetic models which would yield the compensation effect within the framework of the relay recombination mechanism, i.e. the compensation effect associated with the rate constants k_t for the relay processes (see Tables 5 and 6).

The following model is the most natural. The reaction of $\dot{R}$ and RH (or $R\dot{O}_2$ and RH) requires that a definite orientation of the reactants—be achieved before the activated complex. Such a "preparatory" state i_p is attained via a series of thermodynamic equilibrium states $i_1, i_2, \ldots, i_{p-1}$, corresponding to different orientations of the reactants. The kinetic mechanism of the reaction can be represented as follows:

$$\dot{R} + RH \overset{K_1}{\rightleftarrows} i_1 \overset{K_2}{\rightleftarrows} \ldots \overset{K_p}{\rightleftarrows} i_p \xrightarrow{k_0} RH + \dot{R}\ , \tag{9}$$

where K_i are the constants governing the equilibria between the various states and k_0 is the rate constant for the reaction in the "preparatory" state.

It is easy to show that the measured effective rate constant is then $k_{\text{eff}} = k_0 \prod_p K_p$, where $\prod_p$ is the symbol representing the product of the constant K_p for all p states.

In the simplest case one may assume that all the states are of equal importance, i.e. for all the equilibrium constants one may write

$$K_p = e^{\Delta S_p/R} e^{-\Delta H_p/RT}.$$

Then

$$k_{\text{eff}} = k^0_0 \exp(p\,\Delta S_p/R) \exp\left(-\frac{\varepsilon + p\,\Delta H_p}{RT}\right) \tag{10}$$

where k^0_0 and ϵ are the pre-exponential factor and the activation energy for the reaction in state i_p.

Evidently the compensation effect is implied in this equation; furthermore, since the number of states p may depend upon temperature, this equation involves an additional cause of the compensation effect—by the mechanism of Lebedev et al.[24] It is noteworthy that an equation similar to Eqn. (10) can be obtained on the hypothesis that the "pre-start" state is attained by the "simultaneous" rearrangement of a large co-operative group, but within the framework of the model considered above this hypothesis is not essential.

Eqn. (10) also implies a relation between the reaction kinetics and the kinetics of molecular motion. In fact mechanism (9) is applicable to the motion of the polymer segment or a certain probe-species in the polymer matrix (for example a paramagnetic probe[81]) and all the considerations associated with this mechanism are valid. Then for the frequency of motion of the segment (or the probe), we have the equation $\nu_{\text{eff}} = \nu_0 \prod_p K_p$ or

$$\nu_{\text{eff}} = \nu^0_0 \exp(p\,\Delta S/R) \exp\left(-\frac{\varepsilon_r + p\,\Delta H_p}{RT}\right)$$

This equation is analogous to Eqn. (10); here ν^0_0 and ϵ_r are the true pre-exponential factor and the activation energy for the intrinsic motion of the segment or the probe. In particular, if it is found that ϵ and $\epsilon_r \ll p\Delta H_p$, then the effective activation energies for the reaction and molecular motion will be equal; examples of such agreement were quoted at the beginning of this section.

Thus the kinetic model represented by mechanism (9) gives a qualitatively satisfactory description of both the compensation effect and the relation linking the reaction kinetics to the structure of the polymer and the kinetics of molecular motion. It may be supposed that these considerations are in principle applicable to all radical reactions in solid polymers, including reactions in radical pairs.

Finally, the problem of the relation between the reaction kinetics and the structure, properties, and the molecular mobility of the polymers remains one of the most important and fundamental; in this respect hardly anything has been done and almost nothing is known apart from certain general hypotheses. A similar situation is typical also for liquid-phase radical reactions[82]; in both cases the solution of the general kinetic problem is necessary.

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The above review has dealt with almost all the most important radical degradation and stabilisation reactions of polymers, their role in the overall process has been assessed, and their quantitative kinetic characteristics have been described. It is noteworthy that the level achieved in the quantitative kinetics of radical degradation and stabilisation reactions of polymers is fairly low. For the majority of elementary reactions, there are no quantitative data and one must be satisfied with only approximate estimates of the activation energies and rate constants. For many reactions, the available data are very contradictory; this frequently applies not only to the kinetic constants but even to the mechanisms. The most contradictory data concern the chain propagation and termination reactions, degenerate branching reactions, and the participation of inhibitors in these processes, despite the fact that these reactions are in fact the most important in oxidative thermal degradation.

However, the principal differences between the mechanism of degradation and stabilisation of solid polymers and the mechanism of liquid-phase oxidation are already clear; a kinetic theory for solid-phase reactions has been developed to a degree quite sufficient for the solution of problems associated with the degradation and stabilisation of solid polymers; the physical significance of the solid-phase rate constants and its difference from the physical significance of the "liquid-phase" and "gas-phase" constants are largely clear. Experimental difficulties in the study of elementary radical reactions in solid polymers are also not of fundamental importance in most cases.

Essentially, first steps have now been taken in this field and the principal kinetic problems associated with the specific features of the solid phase have been formulated. The solution of these problems constitutes an important component in the creation of a scientific basis for the stabilisation of polymers.

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Institute of Chemical Physics,
USSR Academy of Sciences,
Moscow

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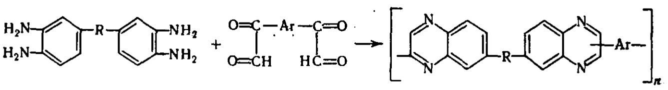
Polyquinoxalines

A.M.Berlin

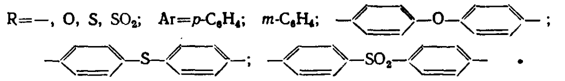
The present Review reports the most recent work on the synthesis, properties, and structure of a further class of thermostable heterocyclic polymers containing six-membered heterocyclic rings—the polyquinoxalines. A list of 24 references is given.

A considerable amount of research has been undertaken during recent years, both abroad and in the Soviet Union, on the production of thermostable polymeric materials. The fairly extensive class of macromolecular substances containing heterocyclic rings in the main chain is of undoubted interest, because several heterocycles, e.g. 1,3,5-triazine, oxadiazole, pyrazole, benzimidazole, benzoxazole, benzothiazole, etc., possess excellent stability to the action of heat, light, and oxidising agents, and are resistant to acids, bases, and various chemical reagents. The main investigations of the chemistry of macromolecular compounds containing five-membered heterocycles have been discussed in a number of reviews[1-4].

In view of the great thermal stability of the quinoxaline ring and its resistance to chemical reagents, several workers have synthesised polymers with chains containing these rings. They used the polycondensation of aromatic tetra-amines with bis-α-diketones:



where

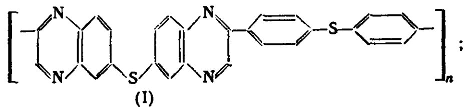


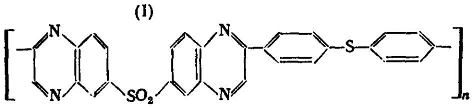
Two methods are at present used for the synthesis of polyquinoxalines: (1) stoichiometric quantities of the monomers are heated at 225–250°C for several hours[5], and the resulting polymer has an intermediate molecular weight which is then increased by further heating in a vacuum to 375°C; (2) the monomers first react in a solvent such as dioxan[5,6] or hexamethylphosphoramide (HMPA),[7] and the resulting solids of low molecular weight are again heated in a vacuum at 375°C. The polyquinoxaline obtained from *p*-phenylenediglyoxal and 3,3′-diaminobenzidine[5], which contains completely conjugated aromatic chains, possesses very high thermal stability when heated either in air or in nitrogen, its decomposition temperature being 500°C and above. It is insoluble in the usual organic solvents, and sparingly soluble in hexamethylphosphoramide; films obtained even from a polymer of high molecular weight are extremely brittle.

The introduction of an oxygen bridge into the polymer chain[8] increased the solubility of the polymers. Films cast from their solutions in hexamethylphosphoramide were also brittle initially, and showed various colours from pale yellow to red. After they had been heated in a vacuum in an atmosphere of nitrogen at 350–400°C, however, they were converted into tough, flexible, transparent films. Unfortunately, no information is given on the stability of these films. It is interesting that their infrared spectra have the same characteristic absorption bands before and after heating, which suggests the absence of cross-links in the polymer. On this basis the diminution in the solubility of the polymers after prolonged heating was explained by further increase in their molecular weight. This observation is common to all synthetic linear polyquinoxalines.

The presence of an oxygen bridge had no effect on the thermal stability of the polymers, the introduction of various sulphur-containing groups[9] produced only a slight decrease (the limit of thermal stability remained above 400°C even in air), and up to a considerable molecular weight these polymers retained their solubility not only in sulphuric acid but also in hexamethylphosphoramide (Table 1).

Polyquinoxalines[9] having the structures


(I)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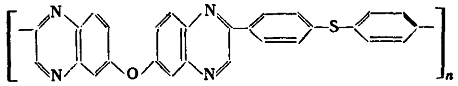
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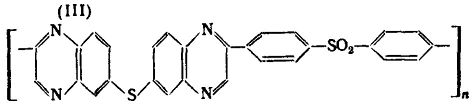
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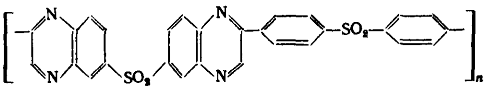
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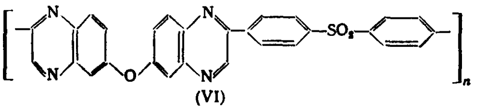
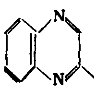
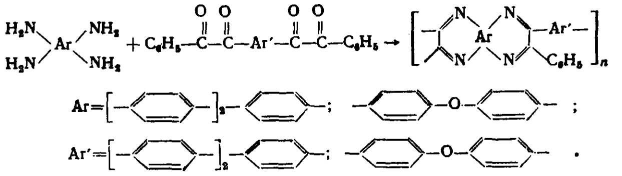

(VI)

have been obtained.

It had been shown previously that the pyrazine hydrogen in the quinoxaline ring



undergoes oxidation first[10]. An attempt was therefore made[10] to increase the stability of polyquinoxalines to oxidation by replacing the pyrazine hydrogen by a phenyl group. Four phenylated polyquinoxalines were obtained by the scheme



These polymers were synthesised in the melt and in solution.

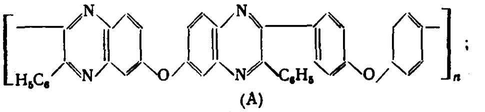
Condensation in the melt was performed at 180°, 200°, and 280°C and then at 380–400°C for 1 h. The resulting polymers exhibited extraordinarily good adhesion to glass. Various solvents—dimethylformamide, dimethylacetamide, *m*-cresol—were used for polycondensation in solution, between the temperature limits of −10° and 202°C. The initially formed polymer of intermediate molecular weight (η = 0.6–1.0) was then heated at 400°C until the final polymer (η = 1.5–2.2) was formed. Solutions of the polymers in *m*-cresol showed perfect stability for 30 days. Films from 10% *m*-cresol solutions of these polymers possessed a high tensile strength and excellent flexibility after being heated to 300°C.[10]

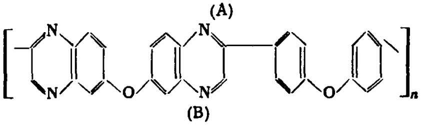
Table 1.

Polymer	Stage	Colour	Solubility, % in		[η]*	Wt. lost at, °C
			HMPA	H_2SO_4		
(I)	1st	brown	100	100	0.35	—
	2nd	black	70	100	2.40	500
(II)	1st	yellow	75	100	0.45	—
	2nd	brown	55	90	0.80	440
(III)	1st	yellow	100	100	0.35	—
	2nd	black	19	70	1.07	460
(IV)	1st	brown	100	100	0.41	—
	2nd	black	50	80	1.12	460
(V)	1st	brown	100	100	0.33	—
	2nd	brown	21	80	1.22	420
(VI)	1st	yellow	100	100	0.26	—
	2nd	black	14	60	1.11	420

*[η] = logarithmic viscosity in hexamethylphosphoramide, concentration 0.25 g/100 ml.

Phenylated polyquinoxalines, as expected, exhibited outstanding thermal stability and resistance to oxidation. The authors showed this by making a thermogravimetric analysis (Fig. 1), and also by the isothermal aging (Fig. 2) in air and in helium of two polyquinoxalines differing only in the presence of phenyl groups in one of them.


(A)


(B)

In helium the difference between the temperatures at which decomposition begins in phenylated and ordinary linear polyquinoxalines is about 40 deg, and in air it is still larger. Furthermore, the phenylated polyquinoxalines have considerably higher glass points, the value for the polymer (A) being 437°C. It is interesting that both polymers (A) and (B) are stable in air at 316°C (600°F), and 92–95% of the original weight remains after heating for 200 h. However, after 100 h at 371°C (700°F) the polymer (A) retains 93% of the original weight, and polymer (B) only 63%; the latter breaks down completely after being heated for 160 h, whereas polymer (A) retains 50% of its weight after heating for 200 h (Fig. 2).

Phenylated polyquinoxalines are stable to the action of 40% alkali. After boiling in 40% caustic potash for 6 h, polymer (A) was regained in quantitative yield, its viscosity, analysis, and infrared spectra being unchanged.

The characteristics of several polyquinoxalines are given in Table 2.

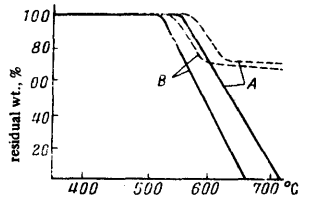
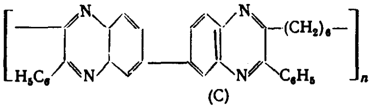
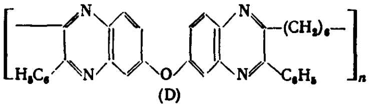


Figure 1. Thermogravimetric analysis of polyquinoxalines (A) and (B): full line in air; broken line in helium.

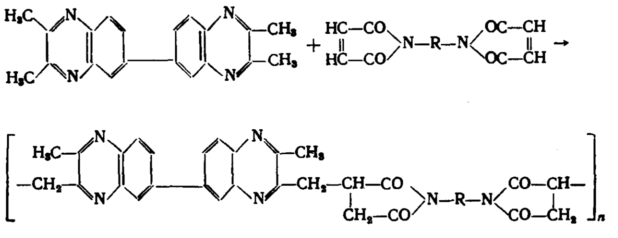
Aliphatic polyphenylquinoxalines have been obtained[11] by analogous methods to the above, by the reaction of 1,10-diphenyldecane-1,2,9,10-tetraone with 3,3′-diaminobenzidine or bis-3,4-diaminophenyl ether. As expected, the resulting polymers


(C)


(D)

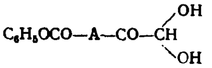
had a lower thermal stability than the aromatic polyphenylquinoxalines, their decomposition temperatures in air and in helium being about 450°C. The reduced viscosity (0.5% H_2SO_4 solution at 25°C) of such polymers was 1.16 and 1.04 for (C) and (D) respectively; they both possessed excellent adhesion to glass.

Quinoxalinimide polymers have been obtained[12] by the reaction of 2,2′,3,3′-tetramethylbiquinoxalinyl with *o*- and *m*-phenylenebismaleimides:



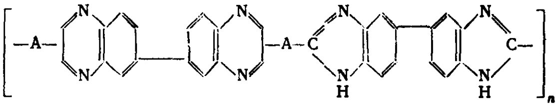
The reaction was conducted in anhydrous toluene, in xylene, or in dimethylformamide. The polymers are soluble in dimethylformamide, hexamethylphosphoramide, and sulphuric acid, do not melt, and lose 8% in weight when heated in air at 200°C for 2 h. No information is given on the molecular weight of the polymers.

New mixed polymers, polybenzimidazoquinoxalines, have been obtained[13] by the reaction of previously unreported phenoxycarbonylphenylglyoxals having the general formula



$$C_6H_5OCO{-}A{-}CO{-}CH(OH)_2$$

(where A represents *m*- or *p*-phenylene) with aromatic tetra-amines. In the opinion of the authors[13] quinoxaline rings are formed initially, and the structure of the resulting polymers corresponds to the formula



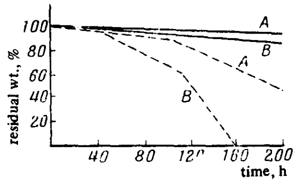
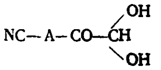


Figure 2. Kinetic curves for the loss in weight of polyquinoxalines (A) and (B) under isothermal conditions in air: full line at 316°C (600°F); broken line at 371°C (700°F).

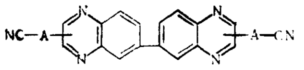
The reduced viscosity of the polymers varied between 0.28 and 0.42.

Nitriles of glyoxals with the general formula



$$NC{-}A{-}CO{-}CH(OH)_2$$

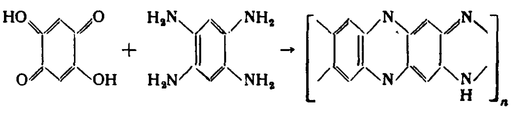
react with 3,3′-diaminobenzidine to give biscyanoarylbiquinoxalinyls



which in turn, on treatment with tetra-amine hydrochlorides in polyphosphoric acid, also formed polybenzimidazoquinoxalines.

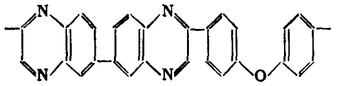
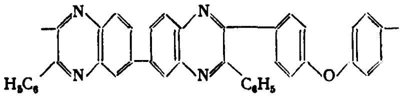
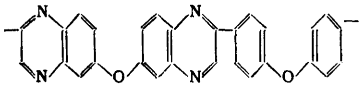
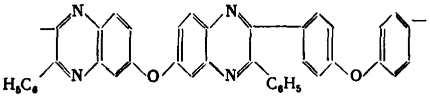
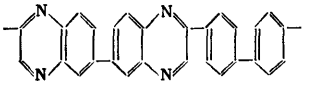
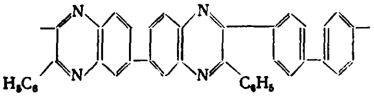
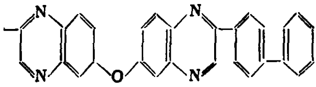
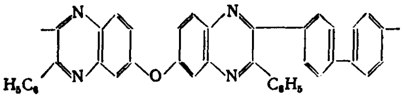
Published information indicates that work on the polyquinoxalines is developing in two main directions—(1) the synthesis of linear polyquinoxalines discussed above, and (2) the synthesis of ladderlike polyquinoxalines—the second line of research being further divided into two subgroups as it were—(*a*) substances such as tetra-amines and tetracarbonyl compounds are used for the synthesis, and (*b*) compounds already containing a quinoxaline ring are used.

The interaction of stoichiometric quantities of 2,5-dihydroxy-*p*-benzoquinone with the tetrahydrochloride of benzene-1,2,4,5-tetra-amine in dimethylacetamide, hexamethylphosphoramide, or polyphosphoric acid leads to the formation of a polymer having a ladderlike structure[14]:



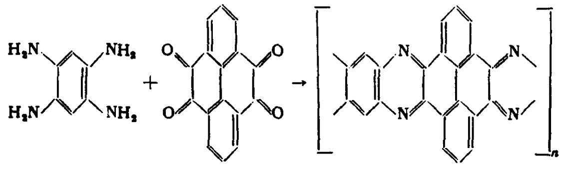
Polymers obtained in dimethylacetamide and hexamethylphosphoramide can be redissolved in these solvents after precipitation, and only after being heated at a low pressure do they lose their solubility. The occurrence of solubility in ladderlike polymers may be due to the formation of stable aggregates of polymer and solvent molecules, especially as ~ 20% of dimethylacetamide is removed from the polymer only by prolonged heating in a vacuum.

Table 2. Properties of polyquinoxalines[10].

[Chain unit]	η_{red}*, dl g^{-1}	Decomp. temp., °C, in air	Decomp. temp., °C, in He	Glass point	Residual wt. after heating in air at 371°C**, %, for 100 h	Residual wt. after heating in air at 371°C**, %, for 200 h
	2.06	510	530	388	60	0
	2.05	520	550	420	80	40
	1.61	510	540	382	70	0
	2.16	550	560	437	93	50
	1.42	530	540	386	70	0
	1.50	530	550	404	90	45
	1.75	520	540	390	64	0
	1.71	530	550	410	78	35

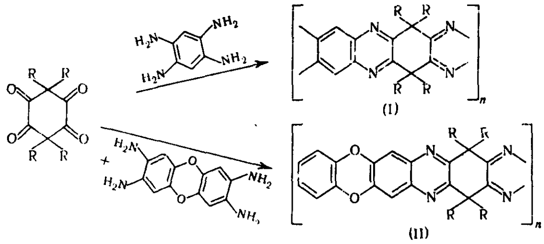
*0.5% solution in H_2SO_4 at 25°C.
**Particle size 140–240 mesh.

The thermal stability of these polymers in air was the same as that of the usual linear polyquinoxalines under similar conditions, probably owing to the presence in them of linear sections as well as the ladderlike structure. To test this hypothesis and obtain a completely aromatic ladderlike polyquinoxaline, pyrene-4,5,9,10-tetraone was used as the initial tetracarbonyl compound[15]:



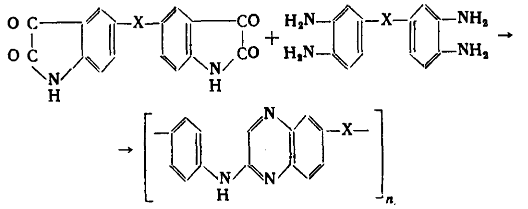
These polymers dissolved in hexamethylphosphoramide and in hexafluoropropan-2-ol, which was rather unexpected for ladderlike polymers. They began to decompose in air at 460°C, and in nitrogen at 683°C, the losses in weight by the onset of decomposition being less than 4% in both cases. Thus it can be accepted that in this case the authors were able to obtain a completely aromatic ladderlike polyquinoxaline, which in an inert atmosphere surpassed in thermal stability the known linear aromatic polyquinoxalines.

As was to be expected, ladderlike polyquinoxalines (η_{red} = 0.2–1.06) obtained from aliphatic tetracarbonyl monomers, e.g. 3,3,6,6-tetramethylcyclohexane-1,2,4,5-tetraone[16], are of no interest. Thermogravimetric analysis indicated that these polymers were considerably less stable than aromatic ladderlike polyquinoxalines: thus polymer (I) decomposes rapidly in air at 390°C, and (II) at 200°C.



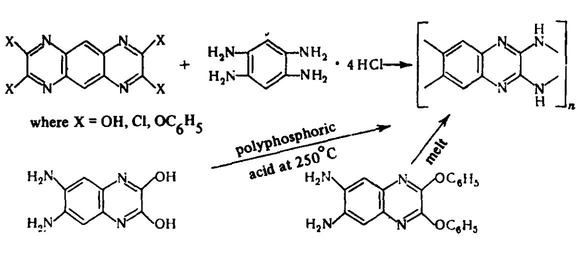
Both polymers begin to decompose slowly when heated in nitrogen at about 400°C.

Bulgarian scientists are investigating[17] the possibility of obtaining partly ladderlike polymers containing 6*H*-indolo[2,3-*b*]quinoxaline (indophenazine) as the main chain unit. Such polymers are prepared from the condensation of bisisatins with tetra-amines by heating in polyphosphoric acid:



They are powders, soluble in hexamethylphosphoramide, dimethylacetamide, dimethyl sulphoxide, and sulphuric acid. No data are given on their molecular weight or their thermal stability.

A ladderlike polymer has been obtained by condensing benzene-1,2,4,5-tetra-amine with a 2,3,6,7-tetrasubstituted 1,4,5,8-tetra-aza-anthracene[18,19] and by the self-condensation of 6,7-diamino-2,3-dihydroxy(or diphenoxy)quinoxaline:



Polycondensation was conducted in solution, in a melt, and in polyphosphoric acid; the reduced viscosity in methanesulphonic acid reached 2.5. Analogous polymers have been synthesised[19] also with 3,3′-diaminobenzidine. These polymers begin to lose weight when heated in air at about 350°C, and in nitrogen at 550°C, which is also explained by an imperfect ladderlike structure. This is evidently supplemented by too high a content of piperazine hydrogen atoms in the polymers, these being the first[10] to undergo thermo-oxidative degradation.

Thermally stable "ladderlike" or partly "ladderlike" polymers have recently been described which contain alternating quinoxaline and thiazine[20] or oxazine[21] units. They are obtained by condensing two diaminoarenedithiols—4,6-diaminobenzene-1,3-dithiol and 3,3′-dimercaptobenzidine—with three tetrachloro-derivatives of quinoxaline—2,3,6,7-tetrachloro-1,4,5,8-tetra-aza-anthracene, 2,2′,3,3′-tetrachloro-6,6′-biquinoxalinyl, and bis-2,3-dichloroquinoxalin-6-yl ether—in various combinations or by condensing diaminoarenediols, e.g. 2,5-diaminoquinol and 3,3′-dihydroxybenzidine, also with tetrasubstituted derivatives of quinoxaline. The solvents used for the reaction of aminoarenethiols are dimethylacetamide, hexamethylphosphoramide, and polyphosphoric acid. The resulting polymers are coloured powders, insoluble in the usual organic solvents and sparingly soluble in sulphuric and methanesulphonic acids. The reduced viscosity of a 0.2% solution of the polymers in methanesulphonic acid at 30°C varied from 0.22 to 1.55. A given polymer had a higher viscosity when dimethylacetamide was used as solvent in its preparation; polymers obtained in polyphosphoric acid had the lowest viscosities. No quinoxalinobenzoxazine was formed in dimethylacetamide; pyridine, naphthalene, and polyphosphoric acid were used as solvents to obtain the corresponding polymers.

Thermogravimetric analysis of polymers containing quinoxaline and thiazine units in the chain showed that in most cases they began to lose weight at about 500°C in nitrogen and at about 400°C in air. Data on thermal stability for the corresponding polymers containing oxazine rings are given only in an inert atmosphere, where they begin to lose weight at about 450°C.

The structure of polymers containing quinoxaline rings—both linear and "ladderlike"—was in all cases proved by a comparative study of the polymers and of model compounds, which included their ultraviolet spectra.

It is seen from the above survey that polyquinoxalines constitute an extremely promising class of thermostable polymers. Unfortunately, very little information is yet available on their practical application. It has been reported[22] that a plastic, which withstands heating to 480°C (900°F), has been developed on the basis of a polyquinoxaline of unstated composition. This material was tested at 590°C in an inert atmosphere, approaching the conditions of outer space. It is light, resembling graphite in structure, inelastic, and electrically non-conducting.

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While this paper was being printed, further papers were published on the synthesis of ladderlike[23] and phenylated[24] polyquinoxalines.

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Institute of Organoelementary
Compounds, USSR Academy of
Sciences, Moscow

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Physicochemical and Spectroscopic Characteristics of Associated Compounds and Their Solutions

A.G.Kovaleva

In order to make the method of liquid-liquid extraction usable, it is necessary to have the complete characteristics of the liquid systems to be separated. The study and comparison of a range of physicochemical and spectroscopic properties of such systems makes it possible to discover factors affecting the miscibility of the liquids and to establish the presence of specific interactions between the components.

The study of specific interactions with the aim of determining their nature is complicated and requires in each case specific models which include the individual features of the interacting species. When such investigations are combined with the study of solutions by physicochemical techniques, the nature of the solutions and the mechanisms of the processes occurring in them are gradually elucidated.

The present review deals with solubility and the most important physicochemical methods for the investigation of the hydrogen bond in solutions. Certain problems in infrared spectra associated with the effects of general and specific intermolecular interactions and the effect of hydrogen bonds of the type OH...O=C in systems with ketones and aliphatic acids are discussed. The bibliography includes 146 references.

CONTENTS

1. INTRODUCTION

The technique involving the extraction of substances from their solutions by other solvents depends on a knowledge of the miscibilities of the components. A number of publications deal with miscibility in liquid systems. In some of these the results of experimental measurements of miscibilities are reported, while in others the variation of the binodal curve with temperature is discussed or the partition coefficients are quoted. However, experimental data on the effects of hydrogen bonds and of the molecular structures of the components on the miscibility are presented in only a few papers.

Physicochemical methods of analysis provide information about the nature of the processes occurring in these systems. On the other hand molecular spectroscopy is a direct method whereby it is possible to determine the interacting groups and the structure of the compounds formed. Indirect methods frequently fail to yield unambiguous information concerning this problem.

The elucidation of the mechanism of the interaction between the components of liquid systems requires the investigation and the comparison of a range of physicochemical and spectroscopic characteristics of the solutions.

2. SOLUBILITY AND CERTAIN PHYSICOCHEMICAL PROPERTIES

Solubility constitutes one of the most distinctive effects of intermolecular forces. Mendeleev believes that solutions are the best subjects for the investigation of the general phenomena of chemical interactions. He regarded dissolution as a chemical process leading to the formation of definite and indefinite compounds without a sharp boundary between them and the solutions as "liquid dissociation systems consisting of species of the solvent, the solute, and definite unstable but exothermic compounds formed by them, one or several, depending on the nature of the constituent elements"[1].

In solutions there is a very wide variety of chemical interactions leading to the formation of compounds of different stabilities and therefore solutions may play a significant role in the solution of the general problem of the nature of a chemical compound. Mendeleev wrote that "in the solution there must be association between species of different kinds, interacting chemically, combining, breaking down, or forming systems". This involves the operation of forces of different intensities which lead to the formation of compounds of different stabilities. According to Mendeleev[2], "it is futile to seek simplicities ranging over the entire scale of dissolution [phenomena]. It is futile to seek a function expressing the sum total of the observations". And further[3]: "...the formation of solutions may be regarded from two aspects: physical and chemical and in solutions it is more evident than elsewhere how close to one another are these two aspects of natural science". Mendeleev in fact chose solutions for the investigation of the problem of chemical compounds.

The aim of the modern studies on the problem of solubility is to establish special relations governing the dissolution of individual groups of substances in solvents of the same chemical type. Up to the present time, there has been no quantitative theoretical calculation of the solubility in the majority of cases. Theoretical advances are restricted mainly to the derivation of qualitative and semiquantitative relations. On the other hand, the creation of a quantitative theory of solubility would extend greatly the possibilities for the discovery of laws governing the intermolecular forces in concentrated solutions and for the investigation of the internal structure of solutions.

Attempts to set up a theory of solubility and to establish a physical and chemical standpoint concerning solutions were undertaken by Shreder[4], Semenchenko[7-9], who interpreted the solubility data in Seidel's handbook[10], and Shakhparonov[11-14].

The complex problem of intermolecular interactions has been solved only for rarefied gases, i.e. for the case where the intermolecular distances greatly exceed molecular dimensions. On the other hand, in the study of the liquid state we encounter distances close to equilibrium and the familiar expressions for orientation, polarisation, and dispersion forces cease to be valid; this makes it difficult to give a satisfactory description of intermolecular interactions in the liquid phase.

Furthermore, the liquid state of matter is characterised by a wide variety of types of interactions between the molecules. These include both different types of classical van der Waals interactions (orientation, inductive, and dispersion interactions) and physicochemical interactions of a wide variety of types (complex formation and hydrogen bonding).

Interactions of the first type (general intermolecular interactions) result, after averaging with respect to configuration and volume, in the effect of the solvent as a physical dielectric medium (volume dielectric effect).

Interactions of the second type, a characteristic feature of which is that they are directional, are physicochemical in nature and in fact lead to the formation of a fairly strong bond between molecules, the energy of which is nevertheless significantly lower than the energy of the chemical bond. Evidently this type of interaction is determined to a greater degree than the first by the individual properties and the nature of the solute and solvent molecules (specific intermolecular interactions).

The types of interaction discussed above are not of equal importance. Systems may exist in which specific interactions of one type or another are absent while van der Waals interactions are observed in all cases. The study of the specific interactions with the aim of elucidating their nature is undoubtedly very complex and requires definite models for each case which take into account the individual features of the interacting species.

The physical and chemical properties of water, alcohols, acids, proteins, and many other practically important substances depend significantly on the interaction of two functional groups of one or different molecules.

The formation of hydrogen bonds is a principal factor which determines the nature of the changes in the majority of physical and certain chemical properties in solution or in the pure substance. This is quite reasonable, since the formation of a hydrogen bond can alter not only the mass, dimensions, and the shape of the species and the distribution of individual atoms but also the electronic structures of the functional groups.

Hydrogen bonds were discovered for the first time by Il'inskii[15] in a study of solubility and were then found also by other classical methods in the study of vapour pressure and density, molecular weight, dielectric constant, distribution between different phases, molar volume, refractive index, electrical conductivity, and thermal conductivity.

Depending on molecular structure, intermolecular hydrogen bonds can lead to different types of association, complexes, structures with a multiplicity of bonds, chains, rings, and three-dimensional networks.

The differences in the types of association complexes formed via hydrogen bonding is one of the principal causes of the differences between the physicochemical properties of these substances in the liquid and solid states. As emphasised by Hildebrand[5], not all deviations should be attributed to one factor only. At the same time there is no doubt that in many cases a significant proportion of the deviations in the physicochemical properties of liquids and solutions are in fact determined by hydrogen bonds.

The capacity of various classes of organic compounds for the formation of hydrogen bonds was thoroughly investigated by Ewell et al.[16], who developed a simple classification, according to which different liquids were divided into five groups.

One must emphasise not only the quantitative but also the qualitative differences between three-dimensional association complexes (networks) and cyclic dimers and also between chain association complexes and cyclic dimers. Therefore Ewell is not quite correct in combining into a single class alcohols, acids, and amines. Acids, which form almost exclusively cyclic dimers, should constitute an entirely separate class. The system proposed provides a basis for qualitative predictions when only the dissociation or formation of hydrogen bonds takes place. In those cases where dissolution disturbs an existing equilibrium or sets up a new one, the classification is of less value.

The different amounts of molecules combined into association complexes and their continuous time variation make it difficult to apply the familiar thermodynamic postulates in the calculation of the dynamic equilibrium between such complexes. There is a complicated relation between the strength of a hydrogen bond of a given type, the average "lifetime" of association complexes with different numbers of molecules, and the capacity of molecules of different structures to form several hydrogen bonds simultaneously. All these problems become even more complicated when solvates are formed from different component molecules.

As pointed out by Landsberg[17], Malyshev[18], and Batuev[19-21], the solubility of water, methanol, and formic acid in acetone and dioxan is due to the dissociation of the hydrogen bonds of the pure substance and the formation of new bonds between solvent and solute molecules.

It has been established[22] that, in addition to hydrogen bonds of the type OH...O and N−H...O observed in water, alcohols, phenols, carboxylic acids, and ammonia, hydrogen bonds of the type C−H...O or C−H...N are formed on dissolution of chloroform, bromoform, or hydrogen chloride in solvents containing oxygen and nitrogen. This was confirmed by measurements of the viscosities[23], dielectric constants[24], and freezing points of these solutions[25].

The most important methods for the investigation of hydrogen bonds in solutions, are, apart from spectroscopic procedures, those based on the determination of dielectric properties of the liquids, the measurement of the vapour pressure, cryoscopy, and the study of solubility, partition between phases, viscosity, and density.

The theory of the dielectric constant may be regarded as a supplement to the modern theory of the liquid state. Dielectric properties arise as a statistical average result of many microprocesses. Hypotheses concerning the relation between dielectric properties and structure have been put forward by Girard[26]. He believes that monohydric alcohols can form two types of association complexes—polar and non-polar, the former predominating in primary and secondary alcohols and the latter in tertiary alcohols by virtue of the characteristics of their structure. Accordingly in the first case there is an anomalous increase in polarisation and in the second a decrease. The temperature variation of polarisation confirms that the breakdown of association complexes of the first type should make the decrease of the dielectric constant with temperature more rapid and the breakdown of association complexes of the second type should not only reduce the temperature-induced decrease of polarisation predicted by theory but should in fact result in an increase of the dielectric constant. This has been confirmed experimentally for certain isomers of higher alcohols[27] and also pyridine[28] and carboxylic acids[29,30]. The dielectric properties of acetic, propionic, butyric, and valeric acids are characterised by an increase of the dielectric constant with temperature[30-35]. The dielectric constants of caproic, oenanthic, and caprylic acids are almost invariant in the temperature range investigated[36]. These phenomena are usually explained by the formation of non-polar dimers in the liquid state.

The views on the mechanism of the effect of temperature on the dielectric constant are extremely varied. The most reasonable is the hypothesis that the formation of hydrogen bonds in the dimer may entail a significant change in the dipole moment of the molecule not only as a result of dipoles induced by long- and short-range forces but also in consequence of the super-position under these conditions of the electron clouds and the redistribution of electron density in the dimer. With increase of temperature, the hydrogen bonds in the dimer are deformed and their length changes, which leads to a change in the vibration frequencies of the molecule and the paramagnetic resonance signals[37-39]. Kerr's molecular constants calculated from measurements of the dielectric constants of dilute acetic acid solutions in benzene suggested[40] that a centrosymmetric planar conformation is most likely for carboxylic acid dimers. On the other hand, calculation of the same quantities for the dioxan–acetic acid complex showed that the latter has a non-planar structure and the angle φ between the molecular planes of the acid and dioxan is approximately 80°. Thus in the general case the effect of the hydrogen bond on the dielectric properties must be considered in two ways—as a factor responsible for the correlation between the relative orientations of molecules and as a factor leading to an additional change in the molecular dipole moment.

The cryoscopic method has been widely used for studies on the hydrogen bond, mainly for a qualitative assessment of the possible existence and type of association complexes and also for the determination of the equilibrium constant K_n in the association processes investigated. Cherkashin[41,42] determined cryoscopically the degree of association and the molecular composition of a number of organic substances dissolved in benzene, in particular[43,44] propionic and acetic acids. The average association constants K_n for acetic and propionic acids proved to be 0.5×10^5 and 1.5×10^3 respectively. According to Cherkashin's data, the straight line for the ideal dimer ($K_n = \infty$) and the calculated curve for acetic and propionic acids differ very appreciably from the experimental curves, which the author explains by an intermolecular field interaction and a weak chemical interaction with formation of readily dissociable association complexes. The author confirmed that acetic acid in benzene solution has the molecular composition $(CH_3COOH)_2$. The marked deviation from the ideal dimer curve in the case of formic acid is explained by chain association and a sharp change in the composition of the molecules as a function of the concentration of the acid.

Lutskii's studies[45,46] showed that density and viscosity data for solutions may be used to establish qualitatively the presence and nature of the association of the solute. The author showed that, when alcohol and benzene are used as solvents, the variation of the density and viscosity is the same despite the postulated difference in the nature of association in these different solvents, the variation being the same not only qualitatively but also quantitatively. The author explains this by postulating that in the comparatively concentrated solutions investigated, the species involved in association with the molecules of the solvent (alcohol, benzene) are not single molecules of the test substance but groups. The latter evidently do not break down on dissociation. It is interesting that the relations found for the densities and viscosities of aromatic acids in benzene and alcohol are similar to those observed for the pure substances in the liquid state; the author believes this makes it possible to draw inferences concerning the presence and nature of association of the solute based on the densities of the solutions.

The properties of aqueous acid solutions have been investigated by a number of workers. The viscosities, densities, and critical temperatures of the systems acetic acid–water and butyric acid–water have been studied by Solomko[47]. The viscosity and density isotherms for these systems have maxima, occurring at the same composition in the acetic acid–water system. For the system butyric acid–water, the density maximum is displaced towards higher water contents.

Golik et al.[48] investigated the kinematic viscosities of acetic and butyric acids in water at 30–90°C and established that the viscosity isotherms of aqueous acid solutions have maxima, which are more pronounced the higher the critical point of the acid and the greater the difference between the viscosities of the components. With increase of temperature, the maximum is somewhat reduced. The complex concentration variation of the viscosity is explained by the formation of structural entities due to the interaction between the carboxy-groups of the acids and the hydroxy-groups of water. Glagoleva studied the equilibrium in the system formic acid–water[49] and the viscosities and specific gravities[50,51] of the systems formic acid–water and acetic acid–water. These data established the formation of the compounds $HCOOH.H_2O$, $HCOOH.2H_2O$, $CH_3COOH.H_2O$, and $CH_3COOH.2H_2O$. In a study of the heats and integral heats of dilution of formic acid solutions, Glagoleva[52] established that these quantities are a maximum when the solution contains 1–2 moles of water per mole of acid. She assumes that, for aqueous solutions containing two moles of water for each two moles of acetic acid, a hydrate with a chain structure and a dimer with the composition $2CH_3COOH.2H_2O$ are formed, while in the presence of two moles of water per mole of acid the species produced is a hydrate with the composition $CH_3COOH.2H_2O$. These hypotheses were subsequently confirmed by Glagoleva herself[53] and other investigators[54-57] using Raman spectroscopy.

Spectroscopic investigations are particularly important in the study of the structure of liquids and solutions. The study of the molecular spectra of solutions reveals more clearly the role of individual groups of atoms in the molecule in the formation of intermolecular bonds.

3. INFRARED SPECTROSCOPIC EFFECTS OF UNIVERSAL AND SPECIFIC INTERMOLECULAR INTERACTIONS

Real systems can be adequately described only by taking into account the collective and individual effects of the molecules in the surrounding medium on the spectrum of the molecule in solution. However, at the present time there is no rigorous and logical theory of the effect of intermolecular interactions on the infrared spectra of solute molecules. Therefore the subdivision of interactions into general (collective) and specific (individual), which entails the introduction of model hypotheses in the study of specific interactions taking into account the individual features of the interacting species, is justified although it is in fact extremely arbitrary, and in real systems there is a continuous gradation from pair interactions to the overall effect of the surrounding species on the solute molecule[58].

The conditions under which the test molecule in solution interacts with a light wave differ from those for an isolated molecule. This is the reason why it is necessary to introduce generalised parameters such as the dielectric constant and the refractive index, which take into account the effect on the test molecule of the sum total of the surrounding species treated as a physical medium. The concept of a reactive field, introduced by Onsager[60], acting on the molecule from the direction of the adjacent species surrounding it, which it has polarised, proved to be extremely fruitful in this respect. Kirkwood[61] and Bauer and Magat[62] showed on the basis of the Onsager model that, when the infrared vibration is regarded as that of a simple oscillating dipole, then its frequencies in the vapour phase (ν_V) and in solution (ν_S) are related by the expression $(\nu_V - \nu_S)/\nu_V = C(\epsilon - 1)/(2\epsilon + 1)$. In this relation ϵ is the dielectric constant of the solvent and C is a constant. It holds best for solvents of low polarity in which the interaction between the solute and solvent molecules is slight. These theories are difficult to test quantitatively because of the impossibility of determining the coefficient C, which depends on assumptions about the dimensions and form of the overall orientation of solvent molecules around the solute molecules and cannot be found experimentally.

Plots of $(\epsilon - 1)/(2\epsilon + 1)$ against $(\nu_V - \nu_S)/\nu_V$ are straight lines for non-polar solvents, while for solvents with proton-donor or proton-acceptor properties the points deviate appreciably from linearity. Probably in those cases the effect of polarisation interactions which occur in non-polar solvents is supplemented by an effect due to the orientation of the solvent molecules or an effect caused by the formation of a molecular complex[63]. A dielectric theory of the effect of the solvent on the infrared spectra of molecules has been developed by Pullin[64,65]. He suggested that the frequency shift depends in the general case both on the dielectric constant ϵ and the refractive index n_0 of the solvent as well as on the molar volumes V of the solvent and the solute which is included implicitly in the expression for the radius of the Onsager cavity. Pullin proposed the following function $f(x, V) = (1/V)(x - 1)/(2x + 1)$, where $x = \epsilon$ or n_0^2 and V is a characteristic of the dimensions of the Onsager cavity. Buckingham[66,67] explained the effect of the solvent on the infrared spectra of molecules from the standpoint of both general and specific interactions. Bellamy and coworkers[68,69] showed that the problem of the effect of the solvent on the infrared frequencies of solid molecules cannot be solved taking into account the general effect only. Not only dielectric effects but also specific interactions, expressed in the formation of association complexes of the solute and solvent molecules, play a dominant role, while the association complexes may have various natures. Thus, when polar media (alcohol, water) are used, association complexes are formed as a result of hydrogen bonding and, according to Bellamy's postulates[70], the higher the polarity of the bond the greater the relative frequency shift.

Thus the possibility of treating the effect of the solvent on the intensities and positions of the infrared bands is very limited. In the general case specific interactions are always observed against the background of the general effect of the medium.

The spectroscopic method for the investigation of molecular association due to hydrogen bonding is fundamental; it is the only procedure which makes it possible to elucidate the distribution of atoms in the vicinity of donor and acceptor groups and the mechanism of the formation of the hydrogen bond.

The forces responsible for the formation of the hydrogen bond differ in magnitude from those which give rise to the ordinary chemical bond. In the general case the energy of the hydrogen bond consists of the electrostatic energy E_{el}, donor–acceptor interaction (with participation of the s orbital of the hydrogen atom) and π-electron interaction arising by virtue of the participation of the π orbital E_π of the hydrogen atom[71]. The role of the individual components in different types of hydrogen bonds may not be the same.

The spectra of compounds forming hydrogen bonds have been investigated in particular detail by Landsberg and coworkers[72-74], Chulanovskii and coworkers[75-80], Batuev[19-21], Stepanov[81-83], Vol'kenshtein[84], and Sokolov[85-87]. They developed a theory of hydrogen bonds on the basis of experimental studies of the spectroscopic effects of hydrogen bonds in many of the most important substances (alcohols, organic acids, etc.). The causes of the formation of the hydrogen bond were examined systematically by Sokolov[88,89]. The conditions necessary for its formation reduce to the asymmetry of the interacting groups. In order to elucidate finally the distribution of electron density in the hydrogen bridge, experimental data must be resorted to. Infrared spectra do not provide information about changes in electron density near the hydrogen atom. On the other hand, proton magnetic resonance spectra, where the displacement of the signal is very sensitive to the formation of a hydrogen bond, are more suitable for this purpose. According to Aleksandrov and Sokolov[90], the change in the screening of the proton on formation of the complex RA–H...BR′ probably depends (1) on the change in the polarity of the A–H bond (a shift of the centre of gravity of the electron cloud of this bond towards the atom A), (2) on the extension of the A–H bond, (3) on the formation of the donor–acceptor bond H...B, which leads to a shift of the centre of gravity of the cloud of the unshared pair of electrons of B towards the atom H, (4) on the effect of the electric field of the dipole of the BR′ molecule, and (5) on the effect of the unshared pair of p electrons of the atom B (or the B–R′ π bond). The increase in the proton magnetic screening constant σ due to the increase of polarity on formation of the donor–acceptor H...B bond probably plays a dominant role. Thus Sokolov[85-87,91] concentrates attention on the change in the infrared absorption spectrum of the ν_S stretching vibrations and on proton transfer processes.

When a substance dissolves, various absorption bands may show perturbation of different magnitudes and types. Two types of such perturbation have been established[76,77]—bulk-phase and local. In the bulk-phase interaction the state of the molecule is determined by a large number of surrounding molecules, and in a gradual change of the composition of the solvent the characteristics of the absorption band also gradually alter.

Local interactions are extremely varied and are of different types even in the case of a thoroughly investigated type of intermolecular interaction such as hydrogen bonding. The state of the active group of the absorbing molecule is determined by several adjacent molecules and the changes in the spectroscopic characteristics of the bands are discrete. The effect of the local intermolecular field on the infrared absorption frequency associated with the C=O stretching vibrations in ketones has been investigated by Gadzhiev[92] over a wide range of temperatures (from +80° to −180°C). The observed shifts of the C=O stretching vibration bands of ketones on lowering the temperature are accounted for by an increase in intermolecular interaction due to a decrease of the distance between the molecules and an increase in the residence time of the molecule in the state of equilibrium. The temperature variation of the shift in the infrared absorption band of the C=O group of ketones is linear.

On transition from one type of local bond to another, i.e. on breakdown of one and formation of another association complex, observed on dissolution, the following changes may occur in the vibration spectrum: (1) the stretching-vibration bands are displaced towards lower frequencies (compared with the absorption band for an isolated molecule) and the position of the maximum of the band depends on temperature—the lower the temperature the greater is the displacement of the maximum towards lower frequencies; however, exceptions are also known[77,93], when the formation of local bonds does not cause a bathochromic shift of the stretching vibration bands; (2) there is an appreciable change in absorption intensity, which is sometimes very large for the fundamental bands of the stretching vibrations involved in the formation of the molecular bond; here the discrete structure is more complex than in cases where a shift does occur; (3) the absorption band due to these bonds becomes appreciably broader.

When association complexes break down in a pure liquid or in a solution, converse changes occur in the characteristics of the stretching vibration band. The most typical difference between the molecular bonds of the newly formed association complexes on the one hand and the chemical bond in molecules on the other consists in the ready reversibility of the association process under normal conditions due to the thermal motion of molecules, a wide variety of possible interactions between molecules, and an insufficiently defined nature of the association complexes produced.

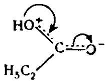
All these factors complicate our understanding of the molecular state in solutions. Furthermore, in contrast to the solid state, in liquids there is a possibility of the coexistence, with different probabilities, of various types of intermolecular hydrogen bonds, including those which do not correspond to the absolute potential energy minimum[78].

Structural changes in solutions can be investigated in greater detail by spectroscopic procedures than by physicochemical methods. In the structural analysis of the solutions the elucidation of the structural elements of molecules responsible for the intermolecular bond and its type and also the nature and strength of intermolecular association are of interest.

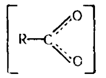
4. SPECTROSCOPIC EFFECTS OF HYDROGEN BONDS OF THE TYPE OH...O=C

Spectroscopic effects of hydrogen bonds of the type OH...O=C have been usually investigated on the basis of data for the O–H stretching vibrations, which made it possible to assess the state of the hydrogen atom alone[94]. A more detailed study of this bond indicates the necessity of elucidating the role of at least three atoms (A, H, and B) in the schematic structure of the hydrogen bond RA–H...BR′. For this, it is necessary to investigate not only the A–H spectrum but also the spectra of the R–A and B–R′ groups. On the other hand, the formation of the bond OH...O=C entails a change in the stretching vibration frequencies of both O–H and C=O groups. Although the shift is in this case smaller, the overlapping by other bands (C–H, O–H) is also less pronounced in the study of equilibria involving associated substances such as, for example, water and alcohols.

According to infrared spectroscopic data, the carboxy-groups of aliphatic acids have an asymmetric structure: the proton is located within the electron cloud of one of the oxygen atoms[95]. The properties of acids and quantum-chemical considerations[96] make it possible to attribute the following formula to propionic acid for example:



The frequency of the carbonyl group is very sensitive to interaction with other bonds[97]. Depending on the nature of the substituent in the organic group, the position of carbonyl bands can be somewhat displaced[98-100]. When an aliphatic group is replaced by an aromatic group, the band is displaced towards longer wavelengths (1690 cm^{-1} in the spectrum of benzoic acid). The presence of electrophilic substituents in the organic group gives rise to a hypsochromic shift: 1735 cm^{-1} in the spectrum of monochloroacetic acid[98] and 1730 cm^{-1} in that of α-chloropropionic acid[101]. This phenomenon can be explained directly by the mutual effects of the bonds: the partial shift of the electron to the C=O bond or, conversely, a shift of the C=O electron to an electron-acceptor group. When an electron is transferred to the C=O bond, the force constant of the latter k_{C-O} and hence the frequency are reduced, while in the opposite case they are increased. On the other hand, spectra of the ions derived from the acids do not contain such frequencies but they do include characteristic bands in the region 1510–1650 cm^{-1} (antisymmetric vibration of the COO$^-$ group) and at about 1400 cm^{-1}, corresponding to the symmetrical vibrations of this group[96,102,103]. The spectrum changes in this way because both oxygen atoms in the ion, linked to a carbon atom, become equivalent:



The carboxylate ion has a symmetrical structure in aqueous solutions of acid, where it is formed as a result of acid dissociation, and also in salts where the metal atom is equally associated with both oxygen atoms[96]. It must be noted that the stretching-vibration frequency of the carbonyl group at about 1700 cm^{-1} is due to C=O groups hydrogen bonded into dimers and is most intense in the infrared. However, this band may not always be observed or can be observed very weakly in the Raman spectrum. If the dimer formed by the association of acids has a centre of symmetry, only antisymmetric vibrations will be active in the infrared spectrum, while in the Raman spectrum symmetrical vibrations will be active[104], where the corresponding carbonyl frequency is 1660 cm^{-1}. The appearance of a frequency in the range 1660–1670 cm^{-1} in the infrared spectrum is associated with the breakdown of ring symmetry in the liquid phase as a result of the interaction between the dimers.

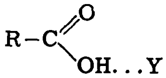
In a number of studies the effect of hydrogen bonding and association of liquid acids on the frequency and intensity of the C=O characteristic vibrations was considered[55-57,104-106]. Gillette and Daniels[106] observed a change in the structure of the C=O band over a wide temperature range in the vapour phase. The authors interpreted the structural changes of the bands as due to the simultaneous presence of monomeric and dimeric acetic acid species.

Batuev[55-57] compared the Raman spectra of liquid formic, acetic, isobutyric, and isovaleric acids at room temperature and concluded that the carbonyl group is extremely sensitive to the formation of a hydrogen bond and under its influence the C=O frequency undergoes a considerable shift, spreading into broad diffuse bands. Depending on the number and positions of the C=O absorption bands, Batuev divided acids into three groups: formic acid with frequencies at 1670 and 1724 cm^{-1}, acetic acid with frequencies of 1665, 1713, and 1740 cm^{-1}, and the remaining acids characterised by a single frequency in the form of a narrow line in the range 1660–1670 cm^{-1}. He believes that association in formic and acetic acids is largely of a polymeric type, in contrast to heavier acids, which may be regarded as dimeric. However, Smolianskii[107] observed in the infrared spectrum of liquid isobutyric acid a second component (on the high-frequency side) of absorption band due to the hydrogen-bonded C=O group. The doublet structure of the band is explained by the presence of open-chain dimers in the acid, which is confirmed by an increase in the intensity of the high-frequency component at 1720 cm^{-1} as temperature is increased.

Feneant-Emard[108] confirmed Batuev's observation in the study of the Raman spectra of acids and at the same time discovered a higher frequency, at 1760 instead of 1740 cm^{-1}. He noted that both these bands can probably be attributed to an open-chain dimer, since the adoption of the hypothesis of polymeric chain association would probably entail a very low concentration of non-hydrogen-bonded groups at the end of the chain, which could not be detected in the Raman spectrum.

Constant[109] showed by ultrasonic spectroscopy that not only acetic acid polymers but also polymers of aliphatic acids with longer chains exist. He believes that the percentage polymerisation increases with the length of the carbon chain of the acid.

Lascombe et al.[110] found from the position of the C=O band in the infrared spectra of liquid propionic, butyric, and caproic acids that the carbonyl group gives rise to a band at a lower frequency than for the free C=O group in inert solvents, in addition to the band associated with the dimer. The relative intensity of the second component in the spectra of these acids is reduced with increasing carbon chain length. These workers believe that the appearance in the infrared spectrum of the band at 1748–1755 cm^{-1}, like that of the band at 1740–1760 cm^{-1} in the Raman spectrum, is associated with the formation of polymers in which only the OH component of the carboxy-group is involved in hydrogen bonding, in agreement with Constant's data[109]. On the other hand, the intensity of the high-frequency component of the dimeric band is directly related, as noted by Feneant-Emard, to the molecular weight of the polymer. However, Lascombe et al. believe that the presence of this band cannot be accounted for solely by the existence of open-chain dimers because in this region there is also a band which is observed in the spectra of solutions when the solvent is a proton acceptor and the structure



$R-C(=O)-OH\ldots Y$

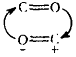
is attributed to the complex formed.

Shubin[111,112] investigated the hydroxyl band in the infrared spectra of formic, acetic, propionic, butyric, isobutyric, and isovaleric acids in the gas and liquid phases. He showed that the position and shape of the absorption bands, which characterise the bond involving the hydroxy-group and also the extinction coefficient, scarcely change on transition from the gas to the liquid phase. Formic acid was an exception. For formic acid, the band in the spectrum of the liquid phase is somewhat broader than for the gas phase, which can be accounted for by the partial chain association of the acid in the liquid phase. This suggested that the type of association of the acid in the liquid phase is the same as in the gas phase, for which dimeric association has been established by Pauling and Brockway using electron diffraction[113]. The temperature variation of the absorption maximum in the band due to the dimer makes it possible to determine the heats of dissociation of formic, acetic, propionic, butyric, isobutyric, and isovaleric acids in the gas phase. The energy of the OH...O=C bond proved to be the same for all the acids investigated (except formic) and approximately equal to 8.3 kcal $mole^{-1}$.

The relations governing the effect of adjacent atoms on the intensity and frequency of the stretching vibrations of the carbonyl group in carboxylic acids are similar to the relations characteristic of ketones. Since there have been only a few infrared spectroscopic studies of the carbonyl group in monocarboxylic acids using solvents of different types, we shall employ studies on the carbonyl group of ketones in the comparison.

Bottreau et al.[114] studied the effect of non-polar solvents (hexane) on the stretching vibration frequency of the carbonyl group of ketones. A detailed study led to the conclusion that the observed spectroscopic changes are a result of two simultaneous effects.

1. *Effect of the breakdown of ketone association complexes.* When two associated adjacent molecules



, each of which is in the electric field of the other are considered, the direction of the field displaces the electrons of the double bonds towards the oxygen atom. Dissolution in hexane leads to the separation of the dipoles and enables the displaced electrons to return to the C=O bond; this is accompanied by a progressive increase in the carbonyl vibration frequency.

2. *The Kirkwood effect.* Dissolution of ketones in the test solvent (carbon tetrachloride, hexane, cyclohexane) decreases the dielectric constant of the medium (reflected in an increase of the vibration frequency of the carbonyl group). Wishing to elucidate the contributions of the two effects, the authors eliminated the effect due to bond dissociation by hydrogen bonding the ketone molecule to phenol molecules before dilution with the solvent. This made it possible to observe the influence of the Kirkwood effect on the carbonyl frequency alone. It is easily seen that, whereas inert solvents increase the carbonyl frequency in ketones, in proton-donor solvents such as chloroform, bromoform, and butanol the C=O frequency falls as a result of the formation of a complex of the type C=O...H–C or C=O...H–O. Thus the C=O stretching vibration frequency is 1715 cm^{-1} in pure acetone, 1722 in hexane solution, 1721 in cyclohexane, 1717.5 in carbon tetrachloride, 1709.5 in chloroform, 1707 in bromoform, and 1709 in butanol. The carbonyl group in carboxylic acid monomers behave similarly.

The change in the antisymmetric C=O frequency of the acid dimer and of the C=O frequency of the monomer is different in solvents of different types. The C=O stretching vibrational band due to the acid dimers depends on the polarisability of the solvent. In solutions with a high concentration of the acid, polarisation diminishes due to the dimerisation of the acid molecules. Conversely polarisation increases in inert solvents (heptane, carbon tetrachloride) on dilution. This is caused by the presence in certain such solvents of a mixture of highly polar single acid molecules and weakly polar or non-polar dimers. These changes in the polarisation of the solution have an effect on the C=O vibration frequencies of the acid dimers, altering the ring symmetry and the frequency of the dimer carbonyl group. Solutions of acids in solvents capable of forming hydrogen-bonded complexes have been investigated to a much lesser extent and the interpretation of the results is much more complicated.

In Denisov's systematic studies[115,116] problems of the effect of the hydrogen bond of the type O–H...O=C on the stretching-vibration band of the carbonyl group in ketones were considered. Denisov showed that in liquid systems containing a strong acid (acetic, mono-, di-, and trichloroacetic, trifluoroacetic) and a ketone the formation of a mixed complex predominates over the dimerisation of acids. The absorption spectra of cyclohexanone (0.39 M) and trichloroacetic acid (0.016 M) in carbon tetrachloride contain bands due to cyclohexanone (1717 cm^{-1}), acid dimers (1751 cm^{-1}), and acid monomers (1787 cm^{-1}). On the other hand, these bands are absent from the spectrum of a mixture of cyclohexanone and trichloroacetic acid and are replaced by bands corresponding to interaction products.

Denisov assigned the 1764 cm^{-1} band to the carbonyl vibrations of the acid, the hydroxy-group of which is involved in hydrogen bonding with the ketone. The 1691 cm^{-1} band is interpreted as due to the C=O frequency of the ketone participating in hydrogen bonding with acid molecules. By investigating the dependence of the parameters of the C=O band on the properties of the components of the complex, the author showed that the spectroscopic characteristics of the C=O band of the ketone involved in hydrogen bonds of the type C=O...HO depend not only on the properties of the C=O group but also on those of the OH group. The same may be said of systems containing a strong acid and an ether[117], nitrile, ester, or another molecule with sufficiently strong electron-donating capacity.

The formation of an acid–ketone complex was observed also by Reeves[118] in a study of hydrogen bonding by proton resonance. He showed that, in a solvent with pronounced electron-donor properties such as acetone and acetonitrile, dimeric acid molecules are involved in the equilibrium between the hydrogen-bonded complex and the monomer of the type

$$[RCOOH]_2 + 2D \rightleftarrows 2RCOOH \cdot D,$$

where D is a powerful electron donor.

We may note that in the spectra of solutions of acids in solvents which are powerful proton acceptors (ethers, esters, ketones, acetonitrile, dioxan) one band is always observed[98] in the region of the stretching vibrations of the carbonyl group. Only at a concentration equal to or exceeding 10^{-1} M does a band characteristic of the dimer appear at low frequencies. One may predict that, by analogy with the behaviour of ketones in proton-donor solvents, complexes of the type C=O...H–O will form with acids, as a result of which the intensity of the acid monomer band increases relative to the dimer band and is somewhat displaced towards lower frequencies. It becomes clear that even more complex interactions will be observed in solutions where the solvent behaves both as a proton donor and acceptor.

Water molecules possess both proton-donor and proton-acceptor properties. Both these properties in water as a solvent are weak, because the majority of the hydrogen and oxygen atoms are involved in the formation of the intermolecular hydrogen bonds of water itself. The solubility of carboxylic acids in water has been investigated because of their importance in biology and chemistry. However, few acids other than formic and acetic have been investigated (spectroscopically) and only over a narrow range of concentrations. Table 1 presents spectroscopic data for two-component monocarboxylic acid–hydroxylated solvent systems. The Table shows that a band due to the C=O group in acids is sensitive to association and the formation of a hydrogen bond. Furthermore, in the study of the carbonyl stretching vibration band it appears possible to obtain data concerning the immediate environment of the COOH group, which is particularly important in the investigation of the properties of solutions in the acid extraction process. We shall consider some of these studies.

Table 1. Raman frequencies of two-component systems monocarboxylic acid–hydroxylated solvent.

Solvent	Acid	Concn. of acid	Frequency, cm^{-1}	References
H_2O	HCOOH	10–15%	1660 w.., 1710	19–21, 55–57
H_2O	HCOOH	40%	1708	119
H_2O	HCOOH	1 : 2	1712	120
H_2O	CH_3COOH	10%	1710	19–21 55–57
H_2O	CH_3COOH	dilute aqueous soln.	1710	120[a]
H_2O	CH_3COOH	conc. soln. with a small amount of water	1730, 1660, 1766 w..	120
H_2O	CH_3COOH	10 mole %	1710	121
CH_3OH	CH_3COOH	10 mole %	1707	121
C_2H_5OH	CH_3COOH	10 mole %	1707	121
C_4H_9OH	CH_3COOH	20–40 mole %	1706, 1736	121
C_4H_9OH	CH_3COOH	60–80–90 mole %	1660, 1703, 1745	121
H_2O	CH_3COOH	83.5 wt.%	1697, 1665, 1745	122
H_2O	CH_3COOH	78.8 wt.%	1690, 1667, 1745	122
H_2O	CH_3COOH	76.9 wt.%	1700, 1687	122
H_2O	CH_3COOH	65.1 wt.%	1700, 1680, 1760	122
H_2O	CH_3COOH	21.9 wt.%	1700, 1695	122
H_2O	CH_3COOH	1.3 wt.%	1695, 1705	122
H_2O	CH_3COOH	87 %	1715, 1670 w.	91[b]
H_2O	CH_3COOH	equimolar soln.	1715, 1670 w.	91
H_2O	CH_3COOH	63 %	1715, 1760 w.	91
C_4H_9OH	CH_3COOH	10^{-2} M	1710, 1754[c]	110
C_4H_9OH	CH_3COOH	1.0 M	1710, 1754[c]	110
H_2O	C_2H_5COOH	equimolar soln.	1720, 1708, w. , 1750 w.[c]	123
C_4H_9OH	C_2H_5COOH	10^{-2} M	1715, 1740[c]	110
C_4H_9OH	C_2H_5COOH	1 M	1715, 1740[c]	110
C_4H_9OH	C_3H_7COOH	10^{-2} M	1709, 1737[c]	110
C_4H_9OH	C_6H_5COOH	10^{-2} M	1708, 1737[c]	110

[a] Frequencies of 1660, 1712, and 1745 cm^{-1} were observed in the spectrum of pure acetic acid.

[b] Frequencies of 1670, 1715, and 1760 cm^{-1} were observed in the spectrum of pure acetic acid.

[c] Frequencies in the infrared spectrum are quoted.

Lascombe et al.[110] observed that acetic, propionic, valeric, hexanoic, and benzoic acids in butanol exhibit two frequencies (in particular the 1710 and 1754 cm^{-1} frequencies of acetic acid), which can be attributed to two types of complexes, the formation of which entails hydrogen bonding involving the carbonyl group (1710 cm^{-1}) and the hydroxy-group of the acids (1754 cm^{-1}), a change in the concentration from 10^{-2} M to 1 M being without effect on the observed bands. Izmailov and Kutsyna[121] observed the following changes in the Raman spectra of the same solutions (acetic acid in butanol) as the acid concentration was varied: at a concentration of 10 mole % they observed a single band at 1706 cm^{-1} which they assumed to correspond to addition products with the composition AB_2; at 20–40 mole % two frequencies were found at 1706 and 1736 cm^{-1}, the first being more intense than the second; in the spectrum of the solution at a concentration of 60 mole % three bands were observed at 1660, 1703, and 1745 cm^{-1}. The same frequencies also persist in the solution at a concentration of 80–90 mole % of the acid, the intensity of the line due to the dimer increasing continuously, which is evidence for the presence of dimeric acid molecules together with molecules linked to the solvent species. The authors assumed that in solutions of acetic, monochloroacetic, and trichloroacetic acids at low concentrations in water, methanol, or butanol the same addition products are formed since the same frequencies are observed in all these solutions: 1706 and 1710 cm^{-1} for acetic acid in alcohols and water and correspondingly at 1736 and 1728 cm^{-1} for monochloroacetic acid and 1760 and 1748 cm^{-1} for trichloroacetic acid.

Glagoleva and Ferkhlin[122] made a very thorough investigation over limited ranges of aqueous solutions of acetic acid at low concentrations. Their data demonstrate that in the presence of 33 wt. % of acid the carbonyl band is very pronounced and has a maximum at 1700 cm^{-1}. Bands are also observed at 1710 and 1680 cm^{-1}. At high dilutions, the band remains in the same position up to a concentration of 8.3 wt. % and then the maximum at 1700 cm^{-1} disappears, but the bands at 1690 and 1710 cm^{-1} persist down to an acid concentration of 1.3 wt. %. The appearance of a band at 1690 cm^{-1} is explained by the formation of hydrates. This may be evidence that the hydrogen bond between water molecules and the carbonyl group of the acid persist for a fairly long time despite the fact that at a concentration of 6.0 wt. % dissociation of the acid begins. These data suggest that solvates of several types exist in dilute solutions.

It is no less interesting to compare the data of Glagoleva and Ferkhlin[122] with those of Feneant[124] for high concentrations of the acid in the same system (both studies were based on Raman spectroscopy). According to Glagoleva and Ferkhlin[122], the band with the highest intensity is at 1700 cm^{-1} in the concentration range 87.0–63.0 wt. %, while at a concentration of 78.8 wt. % a new band appears at 1690 cm^{-1}; Glagoleva and also Izmailov and Kutsyna demonstrated the formation of monohydrates in the same concentration range. According to these authors, further dilution did not change the form of the band, but at concentrations of 62.8 and 65.0 wt. % of the acid the 1700 cm^{-1} band becomes sharper and narrower. The authors conclude that dihydrates are formed in this concentration range. However, according to Feneant[124], in the spectra of solutions at a concentration of 65 wt. % the band at 1715 cm^{-1} has the highest intensity and can be assigned to the dimeric monohydrate; on further dilution (63 wt. %) the same frequency remains the most intense and is interpreted by the authors as due to the dihydrate. According to the observations of the authors of both investigations, the band associated with the dimer disappears at these concentrations. The changes occurring in the solution are attributed to the formation of association complexes of several types.

The change in the contour of the stretching vibration band due to the C=O group in carboxylic acids on formation of an intermolecular hydrogen bond[104,107] is of considerable interest. Since the relations concerning the effect of adjacent atoms on the intensity and frequency of the C=O stretching vibrations in carboxylic acids are similar to those characteristic of ketones, the observed frequencies were assigned[123] by analogy with the C=O frequencies of ketones, in accordance with a number of investigations[114-116,125] and also in accordance with data on the stretching vibrations of the carbonyl group of acids in solvents of different types[19-21,55-57,100,106-117,110,121,122,124,126]. The spectrum of an equimolar mixture of propionic acid and water[123] (Table 1) has a characteristic band at 1723 cm^{-1} and a shoulder at about 1708 cm^{-1} on its long-wavelength slope.

The presence of a single intense band suggests that a 1 : 1 addition product with the same composition is mainly formed in the solution. Very small amounts of acid dimers and solvates of the composition A_2B and AB persist in the solution, as shown by the weak band at 1750 cm^{-1}. The carbonyl group of the acid remains free in such complexes (A is the acid and B is water).

The study of the infrared spectra of homogeneous saturated water–monocarboxylic acid (propionic, valeric, oenanthic)–heptane systems[123] over a wide range of concentrations and analysis of the results led to the following postulates and conclusions. In solutions with a high molar content of the inert solvent (heptane) (5.70–4.20 M) acid concentrations in the range 0.7–0.9 M, and water concentrations in the range 0.04–0.10 M, similar C=O frequencies (1720–1725 cm^{-1}) are observed for all the systems. Probably open-chain acid dimers, undergoing O–H...O–H and O–H...O=C interactions with water molecules, are present in such solutions and the nature of the hydrogen bond in the addition products and the structure of the association complexes differ little.

In the spectra of solutions with high contents of acids (1.00–5.00 M) and water (0.5–3.0 M) absorption bands due to the C=O group appear at 1740–1745 cm^{-1}, which indicates the presence of addition products A_2B and AB containing free carbonyl groups.

In solutions with high acid (8.0–5.0 M) and water (0.6–7.0 M) concentrations differences are observed in the structure of the hydrates of the systems investigated[123]. Hydrates with the composition AB_2 (band at about 1690 cm^{-1}) are formed mainly in solutions with propionic acid and are present in insignificant concentrations in solutions of valeric and oenanthic acids. In highly concentrated solutions of the latter bands due to acid dimers and possibly free water molecules (1715 cm^{-1}) appear. Bands of this kind are absent from the spectra of propionic acid solutions. The spectra of the postulated complexes may be formulated more precisely by studying the spectra of solutions of the deuterated derivatives[126].

The changes in the intensity of the carbonyl band were investigated by Venograd and Spurr[127] and by Huggins and Pimentel[128]. The ratios of the integral absorption coefficients of the carbonyl bands of the acid dimers and monomers measured by Venograd and Spurr are 1.15 for acetic acid, 1.36 for propionic acid, 1.22 for benzoic acid, and 1.32 for toluic acid. When complex aggregates of associated molecules are formed, the interpretation of the intensities and the widths of the band becomes much more complicated. To account for the spectra of such complexes, it is necessary to take into consideration angular deformation vibrations. Huggins and Pimentel arrived at a similar conclusion[128] and separated hydrogen-bonded systems into two classes: in the first they included systems with hydrogen-bonded complexes and in the second systems with hydrogen-bonded polymers.

A simple relation was observed between the frequency shift and the intensity of absorption by hydrogen-bonded complexes. There is a linear hydrogen bond in the complexes. When bonds of this kind are formed, an increase in the intensity of the stretching vibration bands accompanies their frequency shift. The same workers showed that the intensity does not alter on formation of a non-linear hydrogen bond. The decrease of the integral intensity of the C=O band with increasing concentrations of acid and water in the systems can probably be accounted for by the formation of a non-linear hydrogen bond in acid–water association complexes[123]. Such data lead to the conclusion that, when the system A–H...B deviates from linearity, the intensity of the bands associated with the stretching vibrations involved in the formation of hydrogen bonds does not increase.

Sokolov[86] showed that the spectroscopic effect of the hydrogen bond may be related to the proton transfer process and consequently to a change in acidity. The reason for the decrease of acidity in the homologous series of acids is a positive inductive effect[129]. A characteristic feature of the inductive effect is its rapid decay along the chain of single bonds, which is evident from the acid dissociation constants: 17.6×10^{-5} for formic acid, 1.76×10^{-5} for acetic acid, 1.34×10^{-5} for propionic acid, 1.50×10^{-5} for valeric acid, and 1.38×10^{-5} for heptanoic acid. On the other hand, the first ionisation potential of aliphatic acids[130] increases in the sequence $H < CH_3 < C_2H_5 < C_3H_7$: 11.33 eV for formic acid, 10.66 eV for acetic acid, 10.47 eV for propionic acid, and 10.22 eV for butyric acid.

The energy of the hydrogen bond formed by monocarboxylic acids depends on both factors and its constancy in the homologous series of acids ($\Delta H = 7.5-8.0$ kcal mole^{-1}) implies that the increase of the electron-donor capacity of the C=O group is compensated by a decrease of the proton-donor capacity of the O–H group.

The systematic study of the spectroscopic effects of hydrogen bonds began with the work of Gordy and Stanford[131,132] and also Searles[133] and Tamres[134]. They established that the low-frequency shift of the A–H stretching vibration band on formation of a hydrogen bond increases linearly with the basicity of the solvent.

In their study of hydroxylated substances and proton-acceptor substances (acetone, acetophenone, cyclohexanone), Singul and Ignat'eva[135] drew attention to the frequency change observed in the vibration spectra of proton acceptors. They established an inverse correlation between the shift of the C=O band and the pK_a of the hydroxylated substances. The hydroxylated solvents used were the initial members of the homologous series of saturated monohydric alcohols ranging from methanol to butanol and water and phenol, the greatest C=O frequency shift being observed when the ketone interacts with phenol. Since a linear relation was obtained for each ketone, this also characterises the different basicities of the ketones investigated.

A direct correlation was established[135] between the change in the frequency of the C=O group of acetic acid and its substituted derivatives and also substituted benzoic acids on the one hand and the acid strength in alcohol solutions on the other. A similar relation was found[123] between the frequency of the carbonyl group in carboxylic acids, participating in the formation of an acid–water complex, and their acid strength in the aqueous solution.

The linear relation between the C=O frequency shift and the pK can be explained by the relations linking the acid strength and the frequency of the carbonyl group to its polarisation and therefore any intermolecular interaction which alters the bond polarisation leads to a change in both acid strength and the carbonyl frequency.

In many cases a correlation has been observed between the spectroscopic characteristics of the C=O group and the parameters of free molecules[93,115,116]. Denisov's studies[115] showed that for the systems ketone–acid there is a correlation between the shift of the carbonyl band of the ketone and its first ionisation potential. The latter can probably serve as a measure of the relative electron-donor capacity of the ketone. As in the ketone series, the variation of the relative shift of the carbonyl band with the first ionisation potential was observed in the series of esters[137]. However, in the case of the ester carbonyl band a larger carbonyl shift occurs over a smaller range of ionisation potentials, although esters are poorer proton acceptors[138] than ketones. Probably the C=O frequency shift can serve as a measure of electron-donor capacity only within an individual class of compounds.

A number of determinations of the dimerisation energy of carboxylic acids in the gas phase as the principal characteristic of the hydrogen bond have been made[112,139]. The energy of the hydrogen bond in dimerised monocarboxylic acids does not change in the gas phase either when the molecular weight increases or when the structure of the non-carboxy-residue is altered[111,140].

The energies of the hydrogen bonds of certain acids in carbon tetrachloride solutions have been determined in a number of investigations[141-144]. However, very few data characterising the strength of the hydrogen bond of carboxylic acids in different solvents have been published[107]. The energies of the hydrogen bond in carboxylic acids per O–H...O=C bond are listed in Table 2.

Table 2. Energies of formation of O–H...O=C hydrogen bonds according to spectroscopic data.

Acid	Medium	Energy, kcal mole^{-1}	References
From acetic to valeric	gas phase	2 (8—8.5)	112
Acetic	CCl_4	2 (5.38)	141
Acetic	CCl_4	2 (5.38)	139
Isobutyric	CCl_4	2 (5.5)	107
Benzoic	CCl_4	2 (5.25)	144
Benzoic*	CCl_4	2 (8.2)*; 2 (4.2)*	145, 146
Benzoic*	$CHCl_3$	2 (6.35)	145
Isobutyric	$CHCl_3$	2 (4.2)	107

*Data on the energy of the hydrogen bond obtained by Klages and Möhler[145].

**Data of Wall and Banes[146].

Comparison of the effects of various solvents on the energy of the hydrogen bond shows that, on transition from the gas phase to the solution, even in an inert solvent such as carbon tetrachloride, there is a considerable decrease of the hydrogen bond energy. The energy of the O–H...O=C bond for solutions of acids in chloroform is even lower. Probably a change in the solvent may alter the type of equilibrium (dimer $\rightleftharpoons$ open chain dimer $\rightleftharpoons$ monomer) and the relative content of the monomer. The presence of open-chain dimers of carboxylic acids can explain the discrepancy between the bond energies for gases and solutions in carbon tetrachloride. To account for the decreased hydrogen bonding in acids dissolved in chloroform compared with the solutions in carbon tetrachloride, it is suggested[107] that the complexes are formed via $RC{=}O...HCCl_3$ hydrogen bonds and the acid monomers interact with chloroform more strongly than with carbon tetrachloride.

In solutions in hydroxylated solvents it is possible to determine only the formation constant of the complex which yields information about the average energy of the hydrogen bond in the compound, while adequate data on the energy of the individual C=O. . .H–O bond cannot be obtained. Therefore it is impossible to compare the frequency of the C=O group bound in the complex with the energy of the corresponding hydrogen bond.

The dependence of the relative shift $\Delta\nu/\nu$ of the absorption bands due to the C=O groups in acid dimers and monomers on the universal interaction function $(n^2-1)(2n^2+1)$ makes it possible to assess the strength of the interaction between the components in solution[110,123]. The effect of solvents on the frequency of the C=O group of acid dimers differs appreciably from their effect on the C=O frequency of monomers. Regardless of the nature of the solvent, plots based on the Kirkwood–Bauer–Magat formula show that all the points corresponding to the C=O frequency of the dimers are distributed near a straight line, while those corresponding to the C=O frequencies of the monomers lie to the right of the theoretical straight line. The effect of the solvent on the dimer is smaller, since the dimer is a symmetrical complex with a dipole moment close to zero because its active polar groups C=O and O–H are hydrogen-bonded. On the other hand, the effect of the medium, which leads to a decrease of the potential energy, may be regarded as a consequence of the interaction of the acid molecules with one or several of the surrounding solvent molecules.

Thus we have examined the results of many investigations[55–57,106–108,110,115–117,123,126] devoted to the effect of the hydrogen bond on the absorption bands of proton-acceptor groups in the infrared and Raman spectra. These data show that the band due to the stretching vibrations of the C=O group in ketones and monocarboxylic acids is sensitive to association and the formation of a hydrogen bond, while the change in the contour of the band due to the C=O group in carboxylic acids on formation of an intermolecular bond yields data on the immediate environment of the carboxy-group.

The increase in the number of observed bands in the region of the C=O stretching vibrations of carboxylic acids is evidence of the formation of different types of association complexes (dimer, open-chain dimer, compounds with the composition AB, A_2B, AB_2). The presence of different types of association complexes has been established on the basis of the temperature[104,107] or concentration[55–57,107,110,115–117,120–123,126] variation of the band positions. In many cases it is possible to determine the type of the association complexes in the systems by simultaneous application of infrared and Raman spectroscopic methods together with physicochemical methods[34,36,40–53,121–123].

Studies of the effect of the hydrogen bond on the infrared absorption spectra due to the stretching vibrations of proton-acceptor groups have been made only in recent years; the general form of the relation governing the force constants of such systems has not yet been elucidated. Its elucidation will provide new information about the structure of the complexes formed in the systems.

Summarising, it is noteworthy that the study of the physicochemical and spectroscopic characteristics of associated compounds and their solutions indicates a wide variety of intermolecular interactions in solutions. Comprehensive studies of the properties of a definite group of substances and the discovery of special relations will in future contribute to a general and unique solution theory.

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Catalytic Electron Transfer

S.N.Zelenin and M.L.Khidekel'

The possibilities of obtaining catalysts and catalytic systems for redox hydrogen-transfer reactions are discussed. Use is made of the method of analogy with enzymatic catalysis and modern ideas on electron-transfer reactions. The general requirements to be satisfied by an "optimal" catalyst for hydrogen transfer, the conditions for rapid electron transfer, and some characteristic features of electron transfer in a biochemical oxidation chain are examined. The promising possibilities revealed by this approach for the selection of catalysts and catalytic systems for various reductions are demonstrated. The bibliography contains 206 references.

CONTENTS

I. INTRODUCTION

One possible approach to the development of a scientific basis for the preparation of catalysts and catalytic systems is to use the method of analogy with enzymes. Results obtained in enzymology make it possible to explain many features of the structure and mechanism of action of coenzymes and enzymes on the basis of the ideas of organic and coordination chemistry. This makes it possible to reach definite conclusions regarding the chemical characteristics of the components of the active centres of enzymes, the principles of their activation and the activation of substrates, and the organisation of the individual components into more complex structures. On this basis it is possible, with a sufficient degree of reliability, to formulate some of the general principles determining the structure and catalytic properties of enzymes. It appears to us that it is now possible to realise these principles and to prepare corresponding analogues and analogue systems of various levels of organisation.

It may be assumed that the development of this approach will open up extensive possibilities for the preparation of new effective catalysts and catalytic systems for various reactions.

In the present review we have considered, for the example of redox reactions, some problems of the preparation of catalysts and catalytic systems using the method of analogy with enzymes.

We shall first analyse the general requirements to be satisfied by catalysts for redox reactions. The simplest catalytic hydrogen-transfer cycle consists of a reaction between a hydrogen donor (AH_2) and a catalyst (Q) (stage 1) and the reactions of the reduced forms of the catalyst with an acceptor (B) (stage 2):

$$AH_2 + Q \xrightarrow{k_1} QH_2 + A, \qquad (1)$$

$$QH_2 + B \xrightarrow{k_2} Q + BH_2. \qquad (2)$$

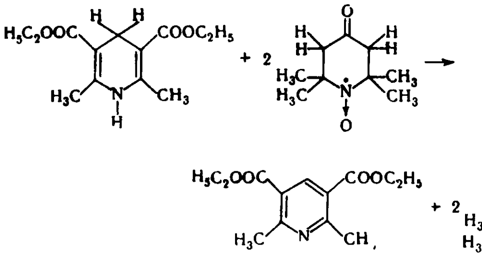
The best catalyst for the catalytic cycle corresponds to the maximal value of the rate of catalytic transfer (w).

The rate w is related to the constants k_1 and k_2 by the equation

$$w = \frac{k_1 k_2 [\mathrm{AH_2}][\mathrm{B}][\mathrm{Q}]_0}{k_1[\mathrm{AH_2}] + k_2[\mathrm{B}]} \quad . \tag{3}$$

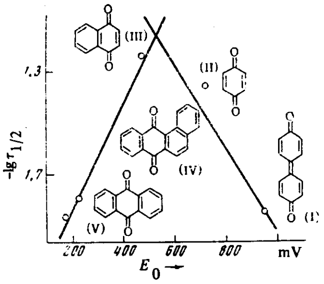
The value of w is determined by the absolute values of the constants, and also by the ratio between them. It follows from an analysis of Eqn. (3) that if $k_1 \gg k_2$ (or $k_2 \gg k_1$), we have $w = k_2[\mathrm{B}][\mathrm{Q}]_0$ (or $w = k_1[\mathrm{AH_2}][\mathrm{Q}]_0$), that is the rate of the catalytic transfer of hydrogen in the limiting cases is proportional to one of the constants k_1 or k_2, and in the intermediate range of values of the constants, a maximum is observed in the range where k_1 and k_2 are approximately equal. For the same redox substrate pair, characterised by a definite decrease in free energy ΔF^0, the constants k_1 and k_2 are not independent, but are related to one another by the expression $\Delta F^0 = \Delta F_1^0 + \Delta F_2^0$, where ΔF_1^0 and ΔF_2^0 are the free energy changes in reactions (1) and (2). Although in general there is no simple relationship between thermodynamic and kinetic constants, it follows from the last relationship that with improvement of the acceptor properties of the catalyst (in the thermodynamic sense) there is a simultaneous deterioration in its ability to act as a donor. Thus for the given catalytic cycle there exists an "optimum" catalyst, exhibiting strong donor and acceptor properties with respect to the substrates.

The literature contains examples illustrating the existence of an optimal dependence of the overall rate of catalytic reactions on the values of the individual constants for stages (1) and (2). Thus for the catalytic transfer of hydrogen in the reaction


(4)

the most effective catalysts correspond to a limited range of catalyst redox potentials 0.4–0.6 V.[1,2] The Figure demonstrates the dependence of the rate of the catalytic transfer of hydrogen in reaction (4) for a series of para-quinones on the redox potential of the quinone. When quinones are used as catalyst-transfer agents in hydrogenation, derivatives of 9,10-anthraquinone are more active than derivatives of 1,4-naphthaquinone and 1,4-benzoquinone[3]. A similar relationship with a catalytic efficiency maximum is also found for enzyme systems[4]. Moreover, the greater the redox potential of the quinone, the greater the rate at which it is reduced, and the lower the rate of oxidation of the corresponding hydroquinone. Analogous relationships were observed[5] in the catalytic decomposition of hydrogen peroxide by metal complexes.

It may be concluded that in general the realisation of a catalytic cycle involving two (or more) successive stages with comparable rates always leads to the existence of an optimal dependence of the overall rate of catalysis on the values of the rates of the separate stages, or, in the final analysis, on the thermodynamic characteristics of the catalysts. This principle of redox catalysis has an analogy in other types of catalysis, in particular heterogeneous catalysis[6]. For example, from the principle of energetic correspondence of Balandin's multiplet theory it follows that "if a process involving a catalyst is represented as taking place in a number of stages, the most favourable path will be that in which the energetic effects of the stages are equal".[7] Note that to obtain the "optimum" catalyst it is also necessary to satisfy the condition of a minimum value for the energetic effects of the stages.



Dependence of the rate of transfer of hydrogen in reaction (4) on the redox potential of the para-quinones used as catalysts for the reaction.

As a result, there are two requirements to be satisfied by catalysts for greatest activity in any specific reaction: firstly, it is necessary to select a catalyst which will satisfy the optimum condition for a given catalytic cycle, and secondly, the structure of the catalyst should be such that the rate constants k_1 and k_2 have the maximum possible values. For example, catalysts for reaction (4) include *o*-naphthaquinone (redox potential $E_0 = 0.58$ V) and Methylene Blue ($E_0 = 0.534$ V), which satisfy the optimum condition for the reaction. The constants k_1 and k_2 have the values 30 litre mole^{-1} min^{-1} and 30 litre mole^{-1} min^{-1} respectively for *o*-naphthaquinone and 2.6×10^3 litre mole^{-1} min^{-1} and 4.1×10^3 litre mole^{-1} min^{-1} respectively for Methylene Blue (at 30°).[8]

One possible way of predicting the values of the rates of reactions (1) and (2) is by using linear relationships between the thermodynamic and kinetic parameters of these reactions.

The large amount of data on the rate constants of redox reactions enables examples of a linear relationship between the free energy change in the redox act and the free energy of activation to be found[9-16].

Proportionality between the kinetic parameters is observed, for example, for electron-transfer reactions with similar mechanisms, when the transmission coefficient (of activated complex theory) is approximately constant in the series of reactions being compared and when the contribution of electrostatic interactions to the free energy of activation differs little on going from one reaction to another[12-17].

The reactions of a given reagent with a series of structurally similar compounds obviously satisfies these requirements. It is for such series of reactions that correlations have been observed between the free energy of activation and the change in free energy for the process.

Relationships of this kind have been found, for example, for reactions of electron transfer between Fe^{2+} and various complexes of Fe^{3+} (and other ions),[17] the reactions of the HO_2^- ion with various metal ions[5], the reaction of the Fe^{3+}

ion with various hydroquinones[5,12-16], the transfer of hydride ion between xanthone and a series of triarylmethyl cations[18], the reduction of quinones by derivatives of 1,4-dihydropyridine[19], the transfer of hydrogen to quinones from hydrazo-compounds and 1,4-dihydronaphthalene[20,21], and the reduction of various flavins by dihydrolipoic acid and dihydronicotinamide adenine dinucleotide[22]. Other examples can be found in the literature[11,23,24].

The optimum condition limits the choice of catalysts for a given reaction to a definite range of catalyst redox potentials. In this connection, important significance for redox catalysis is acquired, on the one hand, by factors favouring rapid electron transfer in reactions characterised by relatively small changes in free energy, and, on the other hand, by the principles of the functioning and organisation of the catalyst systems, since it must apparently be assumed that high rates of electron transfer in each elementary act with the above limitations can be observed only for a definite range of donors and acceptors.

The transfer of electrons in inorganic systems usually takes place at rates of $10^{-2}-10^{2}$ litre mole^{-1} s^{-1}, with activation energies of 15–21 kcal mole^{-1}.[25,26]. Rates of electron transfer equal to $10^{7}-10^{8}$ litre mole^{-1} s^{-1} and even greater than 10^{9} litre mole^{-1} s^{-1} are observed only in individual instances for simple systems.

On the other hand, for enzyme systems the rates of electron transfer are generally extremely high. For example, the oxidation of a number of metabolites in mitochondria takes place in the presence of catalyst–enzyme systems at rates of ~ $10^{7}-10^{8}$ litre mole^{-1} s^{-1}, with activation energies of 7–8 kcal mole^{-1}.[31]

Enzyme systems are distinguished by the fact that a high rate of electron flow is maintained along a chain of several catalyst–transfer agents. The decrease in the free energy of the reaction in each elementary act of electron transfer along the enzymatic chain is relatively small compared with ordinary redox systems[32].

It is natural to assume that enzymes effectively satisfy the requirements made of them as redox catalysts, and that the structure of the coenzymes and the functional groups forming part of the active centres of the enzymes are extremely well adapted to the functions of rapid electron transfer. This makes it possible to select and prepare catalysts for redox reactions by making use of data on the structure, mechanism of action, and methods of organisation of enzymes.

First of all let us consider briefly the conditions for the rapid transfer of electrons. The basic theoretical principles of the mechanism of electron-transfer reactions have been considered by Libby[33], Eyring and coworkers[25], Weiss[34], Laidler[35], Marcus[12], Halpern and Orgel[36], Levich and Dogonadze[37,38], and others[39-41]. Excellent reviews of experimental results and theoretical conclusions have been published[42-45].

II. CONDITIONS OF RAPID ELECTRON TRANSFER

1. Thermodynamic Criterion of Transfer

According to this criterion, the greater the decrease in the free energy of a reaction, the greater the probability of a high reaction rate. The possibility of using this criterion in redox catalysis is limited, as can be seen from the foregoing discussion.

It may also be noted that the rate of a redox reaction may vary considerably, depending on the detailed mechanism of the process. Thus despite favourable thermodynamic relationships at room temperature, electron transfer does not take place without catalysts in the systems $Sn^{II}-Fe^{III}$, $Tl^{I}-Ce^{IV}$, dihydronicotinamide adenine dinucleotide (and its simple analogues)—molecular oxygen, sodium hydridoborate—nitroso-compounds, etc.[46-49]

2. Principle of Equivalent Exchange by Electrons[50-52]

According to this principle, first put forward by Shaffer, a reaction is rapid if in the course of the reaction the molecules of the oxidising agent and reducing agent respectively take up and give up the same number of electrons. If these numbers differ, the reaction is slow. This criterion is of considerable importance for the qualitative prediction of the rates of redox reactions. It leads to an extremely important consequence, directly related to redox catalysis: reactions in which there is equivalent exchange by electrons and which take place at a low rate will be accelerated by compounds capable of acting simultaneously as one-electron and two-electron oxidising agents and reducing agents.

In enzymatic catalysis, extensive use is made of structures capable of undergoing reversible one-electron and two-electron oxidation and reduction (flavones, quinones, cobalamines).[53-55]

Until recently, only isolated examples of catalytic reactions in which the principle of equivalent exchange is observed had been published[50-52,56-58].

This principle has been applied most fully and extensively in work on the development of new catalysts and catalytic systems for various redox reactions[1,2,59-63].

For example, it has been shown that the rate of the reaction between dihydropyridine compounds (hydride reducing agents) and molecular oxygen or the stable radical of 2,2,6,6-tetramethylpiperidone-4 (a one-electron oxidising agent) is increased considerably in the presence of flavins, quinones, and similar compounds[1,2,59]. The selection of a catalyst may be made on the basis of the values of the redox potentials[1,2]. It has been found that this type of catalysis may extend to other reducing agents: metal hydrides and molecular hydrogen activated by hydrogenation catalysts[3,59,62-66]. In the presence of these catalysts it is also possible, by means of hydride reducing agents, to reduce aromatic nitroso- and nitro-compounds, compounds with positive halogen, and complex compounds of metals with variable valency[60-62,66].

When Shaffer's principle is used, it is necessary to make allowance for the fact that the types of reacting compounds, ligands, and medium influence the ability of, for example, the donor to act as a hydride or one-electron reducing agent. Thus a change in the medium, influencing the stability of the intermediate states of oxidation of the catalyst or substrate, and complex formation, leading to stabilisation of intermediate states of oxidation, may alter both the mechanism and the rate of a redox reaction.

The catalytic oxidation of the dianions of organic compounds in common media was studied by Russell and coworkers[67]. The increase in the rate of the catalytic transfer of hydrogen as a result of the possible formation of a complex of the donor with a π-acceptor and a complex of an intermediate state of the catalyst with a metal ion has been studied[68,69].

3. Energy of Coulombic Interaction and Energy of Franck–Condon Rearrangement

The energy of the Coulombic interaction between the donor and the acceptor and the energy of the Franck–Condon rearrangement, that is the energy required for rearrangement of the ligand and solvate environment of the donor and acceptor in the change to the activated complex, appear in the free energy of activation of the redox reaction and determine it completely[12-16,42]. A decrease in the sum of these two terms leads to an increase in the rate of electron transfer.

As a rule, the rates of electron transfer between oppositely charged ions or between an ion and a neutral molecule are much greater than those between ions of the same sign. For example, the rate of the reaction of Fe^{2+} with $IrCl_6^{2-}$ is greater by an order of magnitude than the rate of the reaction of Fe^{2+} with the 1,10-phenanthroline complex of Fe^{3+}, which has the same ΔE^0 value[17]. The activation energies of these reactions are comparable (1.9 kcal $mole^{-1}$ and 0.8 kcal $mole^{-1}$), but the entropy of activation is much smaller for $IrCl_6^{2-}$ than for the phenanthroline complex of Fe^{III}.

Very high values (~ 10^9 litre $mole^{-1}$ s^{-1}) are observed for the rates of exchange by electrons in both the forward and back directions in the tris-(4,7-dimethyl-1,10-phenanthroline) Fe^{II}–$IrCl_6^{2-}$ system[27]. The reactions of Fe^{3+} with the anions of hydroquinones is more rapid than the same reactions in acid media[12-16]. The rate constants for the disproportionation of neutral benzosemiquinones and the anions of benzosemiquinones are 10^9 litre $mole^{-1}$ s^{-1} and 5×10^6 litre $mole^{-1}$ s^{-1} respectively[70].

A fact of importance for redox catalysis is that the rate of electron transfer between ions of identical sign is usually increased if the bridging group in the activated complex (that is the group joining the donor and the acceptor) is a ligand with the opposite sign (Cl^-, Br^-, I^-, OH^-, etc.).[42,71,72] The dimensions of the bridging group influence the forces of electrostatic repulsion between ions of the same sign[42,43,72].

Let us now consider the factors which decrease the energy of the Franck–Condon rearrangement. Firstly, if the reagents have similar structures and show little change in the solvate sheath, the rate of electron transfer in these systems will be maximal[34]. This explains the rapid electron transfer between the MnO_4^{2-} and MnO_4^- ions, which have identical structures, and the slow exchange between AsO_4^{3-} and AsO_3^{3-}, which have different structures. Secondly, since the greatest contribution to the energy of the Franck–Condon rearrangement is made by the energy used in the rearrangement of the inner and outer coordination spheres of the reagents, the introduction of, for example, the iron ion into the rigid structure of the porphyrin in cytochromes increases its ability to undergo redox reactions, compared with hydrated iron[34]. High rates of electron transfer (10^8–10^9 litre $mole^{-1}$ s^{-1}) are observed between ions containing bulky ligands with extensive π-electron systems[17,27]. The activation energies of these reactions are very low and coincide with the activation energies of reactions whose rates are limited by diffusion. Thirdly, strong electronic interaction between the reagents and a bridging group, in Sutin's opinion[44], can stabilise the activated complex and decrease the total free energy required for rearrangement of the inner and outer coordination spheres of the reagents on electron transfer.

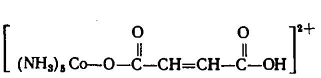
Finally, according to Libby[33], the rate of electron exchange is increased if it is possible to produce an activated complex whose geometry remains symmetrical to within the vibrational amplitudes involved in zero point motion ("symmetry principle").

4. Degree of Electronic Coupling Between the Reagents (Linearity of the Trajectory of the Electrons)[73]

The existence of an activated complex and low values for the Coulombic repulsion and the energy of the Franck–Condon rearrangement do not guarantee high rates of electron transfer—the possibility of sufficient electronic interaction between the reagents in the activated complex is necessary. In this connection it is important to emphasise the significance of bridging groups for the electronic coupling of reagents. Bridging groups provide orbitals of suitable symmetry, in which the electrons of the reducing agent may be delocalised and then transferred to the oxidising agent. If an electron moves from a t_{2g} orbital of the reducing agent to a t_{2g} orbital of the oxidising agent, we should expect easy transfer through bridging groups containing π-electrons, since these orbitals effectively overlap the π-orbitals of the bridging group. If the transfer involves e_g orbitals, the limitations of symmetry greatly reduce the efficiency of the process. Thus for redox catalysis it is important that the catalyst be a compound–bridging group with a structure ensuring the necessary electronic coupling between the reagents through the electronic system of the catalyst and the formation of various complexes (chelates, π-complexes, etc.).

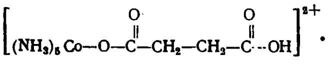
Published data show that the existence, in the bridging group, of positions for the additional binding of reagents in the activated complex favours electron transfer[74,75]. For Co^{III} complexes containing bridging groups capable of forming chelate structures with the Cr^{II} cation–reducing agent, the observed rates of transfer are higher than those for Co^{III} complexes whose bridging groups do not have positions for binding Cr^{II}.[74,75]

As a rule, bridging groups containing π-systems favour electron transfer to a greater extent than bridging groups containing σ-systems[71,76]. The classical example illustrating this conclusion was described by Taube[71]: the rate of reduction of the complex



$$\left[(NH_3)_5Co{-}O{-}\overset{\overset{O}{\|}}{C}{-}CH{=}CH{-}\overset{\overset{O}{\|}}{C}{-}OH\right]^{2+}$$

by the Cr^{II} ion is greater by two orders of magnitude than the rate of reduction of the complex



$$\left[(NH_3)_5Co{-}O{-}\overset{\overset{O}{\|}}{C}{-}CH_2{-}CH_2{-}\overset{\overset{O}{\|}}{C}{-}OH\right]^{2+}.$$

A high rate of electron exchange was observed in the reduction of the Fe^{3+} ion by the complex $(Fe-N_3)^{2+}$ in aqueous medium[77]. The bridging group provides its unshared pairs for bonding with the metal ion. The rate of electron transfer in the $Co(phen)_3^{2+}$–$Co(phen)_3^{3+}$ system is greater by six orders of magnitude than that in the corresponding ammines[71] (phen represents 1,10-phenanthroline).

A higher rate of electron transfer is observed in the case of the hexakis(phenyl isonitrile) complexes of Mn^+ and Mn^{2+}, compared with the ethyl and t-butyl isonitrile complexes[78]. It is assumed[78] that the activated complex has a structure in which there is overlap of the π-system

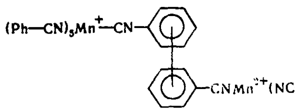
Rate constants for electron transfer in various reactions of organic compounds with the corresponding radical-anions.

Compound	Solvent	k, litre mole^{-1} s^{-1}	E_{act}, kcal mole^{-1}	Temp., °C	References
Benzene	THF : DMF = 2 : 1	$7.7 \cdot 10^7$	$2,8 \pm 0.6$	18	80
Naphthalene	DME	$1.6 \cdot 10^9$ $(\sim 10^9)$	5	23	79, 81
Ditto	THF	$2 \cdot 10^9$ $(8 \cdot 10^7)$	5	23	79, 81
Naphthalene[a]	THF	$3 \cdot 10^7$ $(1.8 \cdot 10^7)$ $(5.7 \cdot 10^7)$		23	79, 81, 90
Naphthalene[b]	THF	$6 \cdot 10^7$ $(5.7 \cdot 10^7)$		23	79, 81
Ditto	DME	$1 \cdot 10^8$		23	81
Anthracene		$1.2 \cdot 10^9$	3.0		80
1,4-Benzoquinone	DMF	$3.8 \cdot 10^8$			28, 85
Duroquinone	DMF	$6,2 \cdot 10^7$			28, 85
Vitamin B	DMF	$1.6 \cdot 10^7$			85
1,4-Naphthaquinone	DMF	$4.2 \cdot 10^8$			85
Vitamin K_3	DMF	$4 \cdot 10^8$			85
Vitamin $K_{1(20)}$	DMF	$1.3 \cdot 10^8$			85
Tetracyanoethylene	THF	$2.1 \cdot 10^8$			82
Anthracene	DMF	$4.8 \cdot 10^8$			82
Nitrobenzene	DMF	$3 \cdot 10^7$			28
Ditto	DMF + 10% H_2O	$3.2 \cdot 10^5$			28
p-Dinitrobenzene	DMF	$6 \cdot 10^8$			28
m-Dinitrobenzene	DMF	$5.2 \cdot 10^8$			28
p-Chloronitrobenzene	DMF	$7.9 \cdot 10^7$			28
m-Chloronitrobenzene	DMF	$8.8 \cdot 10^7$			28
3,5-Dichloronitrobenzene	DMF	$1.6 \cdot 10^8$			28
Radical-anion of cyclo-octatetraene[c]	THF	10^9			87
Cyclo-octatetraene	THF	$\sim 10^4$			87
Tri-*p*-nitrophenylmethane	(Na^+)DME	$4.35 \cdot 10^9$	2.04	25	83
Ditto	(K^+)	$5.99 \cdot 10^9$	1.99	25	83
"	THF(Na^+)	$4.56 \cdot 10^9$	0.86—2.63	25	83
"	THF(K^+)	$4.7 \cdot 10^9$	2.25	25	83
"	Pyridine(Na^+)	$6.79 \cdot 10^9$	2.03	25	83
"	Pyridine(K^+)	$8.7 \cdot 10^9$	1.95	25	83
"	Acetonitrile(Na^+)	$16.3 \cdot 10^9$	1.04	25	83
"	(K^+)	$13.8 \cdot 10^9$	1.12	25	63
p-Xylene	DME	$\sim 2.8 \cdot 10^7$ $10^{12} \exp(-6200/RT)$	6.2	25	88
Xanthone[d]	DMF	$4.56 \cdot 10^8$	5.1	37	84
	THF	$4.48 \cdot 10^8$	4.3	25	
	THP	$4.68 \cdot 10^8$		7	
	Me-THF	$4.32 \cdot 10^8$		0	
Xanthone[e]	DME	$2.5 \cdot 10^8$		25	84
Benzophenone[f]	DMF	$1.10 \cdot 10^8$	6.3	25	84
	THF	$1.14 \cdot 10^8$	6.0	12	
Benzophenone[g]	DME	$1.56 \cdot 10^8$		25	84
Benzophenone[h]	THF	$\sim 2.5 \cdot 10^8$		25	84
Xanthone	CH_3Cl	$\sim 10^9$		25	84
Benzophenone[i]	DME Me-THF Dioxan	$< 10^8$		25	84
1-(α-Naphthyl)-1-phenylethane	DMF	$6.8 \cdot 10^7$	1.6	25	89
	THF	$1.9 \cdot 10^7$	2.3		
Tri-t-butylphenol	CCl_4	$6.6 \cdot 10^2$		27	91
Tetrabutylindophenol	CCl_4	$1.4 \cdot 10^3$		27	91
	Cyclohexane	$2.2 \cdot 10^3$			
Diphenylhydroxylamine	CCl_4	$> 10^7$		27	91
Di-t-butylhydroxylamine	CCl_4	$3.2 \cdot 10^2$		27	91
	Chlorobenzene	$2.4 \cdot 10^2$			
t-Butyl-2,6-dimethoxyphenylhydroxylamine	Chlorobenzene	$5.2 \cdot 10^2$		27	91
	Chloroform	< 20			
	CH_2Cl_2, acetone				
Hexahelicene	THF	$k_{dd} = 1.2 \cdot 10^{10}$ $k_{dl} = 3 \cdot 10^9$		23	92
Fluoranil[j]	90% THF + 10% acetonitrile	$\sim 10^8$		—75	86

[a] Reaction with naphthalenide (Na^+). [b] Reaction with naphthalenide (K^+). [c] Reaction with the di-anion of cyclo-octatetraene. [d] Reaction with the xanthone radical-anion (Na^+). [e] Reaction with the xanthone radical-anion (Rb^+). [f] Reaction with the benzophenone radical-anion (Na^+). [g] Reaction with the benzophenone radical-anion (Rb^+). [h] Reaction with the benzophenone radical-anion (K^+). [i] Reaction with the complex of the benzophenone radical-anion, the metal ion, and the neutral benzophenone molecule. [j] Reaction with the fluoroanil anion.

THF—tetrahydrofuran, DME—dimethoxyethane, DMF—dimethylformamide, THP—tetrahydropyran, and Me-THF—methyltetrahydrofuran.

of the benzene rings and which cannot be achieved in the case of alkyl isonitrile ligands

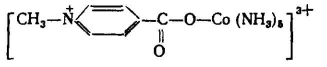


An unusually high rate of electron transfer is observed between tris-(4,7-dimethyl-1,10-phenanthroline)-Fe^{II} and hexachloroiridate(IV).[27] The rate constants for transfer in the forward and back directions are 10^9 litre mole^{-1} s^{-1} and 4×10^9 litre mole^{-1} s^{-1} respectively. The most probable mechanism of transfer involves delocalisation of the electron over all three phenanthroline ligands and overlap of the appropriate orbitals of the chloride ions with the π-system of the phenanthroline ligands. The high rate of electron transfer suggests that the overlap is sufficient to make possible the ready transfer of an electron, accompanied by rearrangement of the ligands in the solvate sheaths. High rates of electron exchange are observed between neutral organic molecules and their ions[28,79-92].

All the organic systems of this type which have been studied up to the present have extensive electronic systems, the ready overlap of which ensures high rates of transfer. The values of various rate constants for electron transfer between radical-ions and neutral molecules are given in the Table.

The above discussion leads to the following qualitative conclusion—the more extensive the conjugated system in the organic compound, the greater the rate of transfer. The rate constants for the reaction increase in the order: benzene < naphthalene ~ anthracene. An important feature is that in the reactions given in the Table, the change in free energy is equal to zero.

The transfer of electrons through bridging groups may be accompanied by oxidation or reduction of these groups[93-96]. Sometimes the lifetime of these states is greater than the half-reaction time for the individual electronic reactions, and sometimes it is so great that chemical changes in the bridging group are possible, for example cis–trans isomerisation in the reduction of the pentamminemalato-complex of Co^{III} by Cr^{II} ions[92,94]. The rapid reduction, by Cr^{II} ions, of the complex



takes place with the intermediate formation of the radical-cation, stabilised by conjugation[95,96]. The easier the reduction and oxidation of the bridging group, the greater the observed rate of electron transfer[74,93-96]. The ligands which are readily reduced and oxidised are generally extensive conjugated systems.

5. Spin Preservation Rule

Spin preservation is an important factor influencing the rate of redox reactions: systems for which changes in spin are expected are characterised by low rates of electron transfer. Preservation of spin on electron transfer to the activated complex requires the use of high-lying excited electron orbitals, so that high rates are impossible. The difference in the rates of reactions involving molecules with more than one unpaired electron can apparently be explained on the basis of this forbidden case[97].

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The above conditions for rapid electron transfer can be used in the selection of catalysts for the catalytic cycle described above [reactions (1) and (2)]. Since its characteristic feature is that the most effective catalysts have redox potentials lying in a definite range, an important significance for the estimation of the rate constants k_1 and k_2 is acquired by an equation obtained by Marcus[12-16], relating the rate constant of the forward reaction k_{12} between a donor A^- and an acceptor B

$$A^- + B \underset{k_{21}}{\overset{k_{12}}{\rightleftarrows}} A + B^-$$

to the equilibrium constant K_{12} (it also defines the redox potential) and the rate constants of the one-electron exchange reactions k_{11} and k_{22}

$$A^- + A \overset{k_{11}}{\rightleftarrows} A + A^-$$

$$B^- + B \overset{k_{22}}{\rightleftarrows} B + B^-$$

The constants k_{11} and k_{22} may either be measured by physical methods (EPR, NMR) or predicted on the basis of the conditions for rapid transfer.

Following Marcus, we can write

$$K_{12} = (k_{11}k_{22}k_{12}\cdot f)^{1/2} \qquad (5)$$

where

$$\ln f = \frac{(\ln K_{12})^2}{4\ln(k_{11}\cdot k_{22}/z^2)},$$

z is the frequency of bimolecular collisions in the solution ($z \sim 10^{11}$ litre mole^{-1} s^{-1} and f is often close to unity).

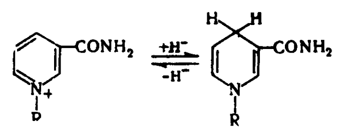
Although the theoretical calculations were carried out by Marcus for a definite model of the reaction, in which rupture or formation of chemical bonds does not take place (electron transfer by the so-called outer-sphere activated complex mechanism) it must be assumed that its conclusions can be extended to many systems. This conclusion is confirmed by experimental results[17,42,85,98]. For example, Eqn. (5) has been used to estimate the relative rate constants for redox reactions of biologically important quinones—vitamins *K* and *E*—compared with 1,4-naphthaquinone and duroquinone. The relationship between these constants and the length of the side chain of vitamins *K* and *E*, and the possibility that they take part in the biochemical respiration chain as electron transfer catalysts has been discussed on this basis[85]. In simpler systems, quinones in fact act as effective catalysts for the transfer of an electron from various reducing agents to a large number of acceptors[1,3,59,61,63,66,99-101].

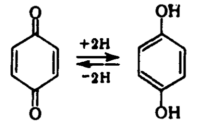
In concluding this section, we may point out that despite the large number of redox reactions studied, there are extremely few examples of catalytic reactions in which criteria of rapid electron transfer have been used. At the same time, enzymatic redox catalysis is a process which is organised in a definite fashion and in which conditions for rapid electron transfer are realised and use is made of structural elements which are well adapted for carrying out the functions of catalysts for redox reactions. Consequently, it is of interest to examine the general principles of the construction and functioning of enzymes of redox reactions, with the aim of producing new catalysts and catalytic systems on this basis.

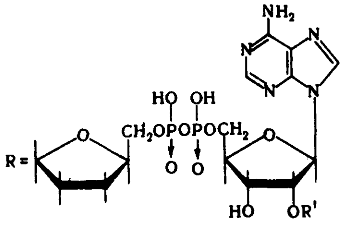
III. SOME CHARACTERISTIC FEATURES OF ENZYMATIC TRANSFER OF ELECTRONS (HYDROGEN)

1. Structure of Groups in the Active Centre of Enzymes (Coenzymes)

Of the coenzymes used in enzymatic redox catalysis, of which there is a limited number[102], mention may be made of nicotinamide adenine dinucleotide (NAD), nicotinamide adenine dinucleotide phosphate (NADP), flavin mononucleotide (FMN), flavin adenine dinucleotide (FAD), metal–porphyrin complexes, ascorbic acid, lipoic acid, coenzyme Q (ubiquinone), vitamin K, and vitamin B_{12}, the structures and reactions of which are given below:

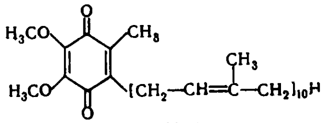




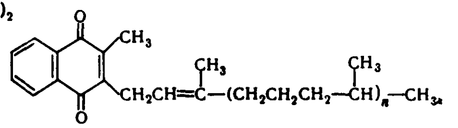


NAD : R' = H

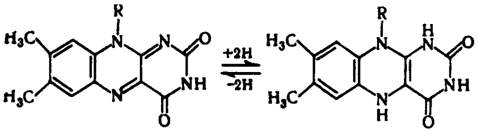
NADP : R' = —P(OH)₂ → O

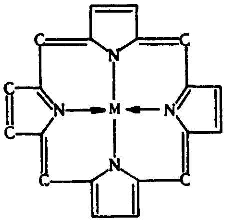


ubiquinone



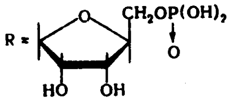
Vitamin K_n



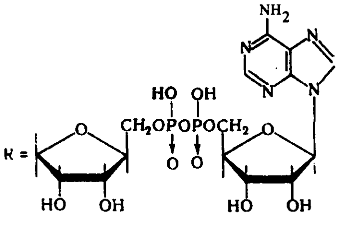


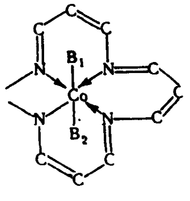
metalloporphyrin

FMN



FAD





Vitamin B_{12}

The coenzymes show the following characteristic structural features.

The highly universal action of coenzymes[103] is due to the fact that in these coenzymes, the properties of various classes of compound are combined. All the coenzymes are (or contain) conjugated heterocyclic systems with acid–base centres and various groups adapted for reversible bond and complex formation. As a result, they may be effective bridging groups (catalysts) or contain such groups.

The presence in the coenzymes of extensive π-electron systems is directly related to their catalytic functions. In Bersuker's opinion[104], redox enzymes can be regarded as characteristic electronic systems of high capacity, since they can readily take up and give up electrons without significant change in energy. For example, the iron–porphyrin complex can act as a powerful acceptor and also as a no less powerful donor, taking effective part in electron transfer. On the other hand, conjugated systems can increase the rates of electron transfer as a result of conduction through the system of π-bonds.

The ready conversion of one systems of conjugated bonds into another is responsible, for example, for the functioning of the coenzymes NAD, NADP, FMN, FAD, and also coenzymes with quinone structures. Here, an apparently general principle is the principle of minimal breakdown of the π-system of the coenzyme with the introduction of the entire conjugated system into the reaction. Calculations[105-107] show that the oxidised form of the coenzyme is a very effective electron acceptor, and the reduced form an effective electron donor. The formation of various complexes with the coenzyme alters its donor–acceptor properties considerably (see, for example, the review of the flavins[108]).

The possibility of maintaining a steady-state concentration of catalytically active forms (semiquinones – QH) through the equilibrium between the completely oxidised (Q) and reduced (QH_2) forms of the coenzyme (flavins and quinones) $QH_2 + Q \rightleftharpoons 2QH$, in which the rates of electron exchange between the various oxidised forms of the coenzyme are extremely high[85], is an important property of enzyme–transfer agents.

In the case of vitamin B_{12}, the highly reactive state of Co^{II}, with one or several unpaired electrons, exists[55] as a result of the equilibrium $Co^{II} + Co^{I} \rightleftharpoons 2Co^{II}$.

The various possibilities for stabilisation of the catalytically active forms of coenzymes by delocalisation of the unpaired electrons over the conjugated systems, and the formation of complexes with metal ions or π-acceptors, are also related to the characteristic features of the structure of coenzymes[108-116].

2. Role of π-Complexes in Enzymatic Catalysis[117-122]

The formation of π-complexes leads firstly to an increase in the extent of the conjugated system and hence to the possibility of electron transfer over considerable distances, and secondly to stabilisation of the catalytically active forms of the coenzymes.

Most of the available published data on this subject relates to the detection and identification of the π-complexes of dihydronicotinamide adenine dinucleotides, flavins, quinones, and other coenzymes with conjugated systems. The biological role of coenzymes is undoubtedly due to their ability to form various π-complexes.

Thus it is assumed[123-125] that the transfer of electrons in mitochondria and chloroplasts is brought about by π-complexes of the metalloporphyrin–quinone or chlorophyll–quinone types respectively. The values of the measured formation constants for the formation of π-complexes between vitamin K_3 and biologically important electron donors—Co-mesoporphyrin-IX-dimethyl ether and chlorophyll—show that these complexes are quite capable of existing under the conditions of enzymatic reactions and of influencing electron transfer.

The formation of π-complexes between NAD-H_2 and flavins has been studied[110,125]; identical π-complexes may also be obtained in the reaction of reduced flavin with NAD.

Molecular complexes of NAD and its simple analogues with various electron donors, I^-, indole, tryptophan, and serotine† have been studied[126].

Of considerable importance for an understanding of the role of π-bonding in enzymatic catalysis are various facts[127-129] which indicate electronic interaction of the "charge transfer" type between the adenine and nicotinamide (or isoalloxazine) rings within the enzyme itself.

Study of the complexes of indole with the pyridinium ion showed that the absorption spectra of these systems are similar to the spectra of the enzyme glyceral-3-phosphate dehydrogenase. It is suggested[130] that the bond between NAD and the protein in the enzyme is produced as a result of the formation of a π-complex. Similarly, the bond between flavin and a protein may be produced through a π-complex with tyrosine[131,132]. A large number of π-complexes are formed by the isoalloxazine ring, which can often be regarded not only as an electron acceptor (complexes with purines, HI, dihydropyridines, hydroquinones, phenols, and other compounds) but also as a π-electron donor (complexes with tetracyanoethylene or 2,3-dichloro-5,6-dimethyl-1,4-benzoquinone). Dimethylalloxazine, for example, behaves in this way, and the ability of this compound to act as donor or acceptor shows a correlation with the energies of the higher occupied and lower vacant orbitals[183]. Isoalloxazines and related dyes are known to form molecular complexes with purines, pyrimidines, indoles, phenols, and other compounds of biological interest[110,134-137].

Finally, molecular complexes of quinones are widely known[121,138-140]. The complexes of quinones with flavins and cytochromes are of greatest interest, since they are active groups of enzyme–transfer agents, which come into direct contact in electron transfer processes.

Although it can definitely be stated that the π-complexes of many redox coenzymes take part in biochemical reactions as intermediate structures, there is almost no direct proof of this. Some of the difficulty is due to the fact that even in those instances where the accumulation of reaction products takes place in the same sense as the change in the concentration of the intermediate π-complex[140], it cannot be guaranteed that the chief reaction path is that involving the formation of the π-complex, and does not by-pass it.

$$A + B \xrightarrow{(\pi\text{-complex})} \text{products}$$

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† It is not clear whether seroten or serotonin is intended here (Ed. of Translation).

It can be said that the factors corresponding to the formation of π-complexes favour electron transfer from the donor to the acceptor.

It may be noted that the existence of π-bonding between the substrate and the enzyme tyrosinase under anaerobic conditions[120] shows that this complex is apparently an intermediate in the oxidation of substrates by molecular oxygen. The examples of the participation of NAD and FAD in intramolecular complexes, in π-complexes with aromatic aminoacids, and in complexes with one another may indicate not only the nature of the bonding between the coenzyme and the apoenzyme, but also the existence of intermediate catalytically active states involving reducing agents, for example NAD-H_2 (source of hydrogen) and the hydrogen acceptor FMN, FAD, or quinone.

3. Role of Semi-quinones in Enzymatic Catalysis

As indicated above, a characteristic feature of enzymatic catalysis is the existence of a steady-state concentration of catalytically active intermediate forms (semi-quinones, Co^{II}, etc.) through the equilibrium between the completely oxidised and reduced forms of the coenzyme. The maintenance of a steady-state concentration of catalytically active forms is due to the structural characteristics of the coenzymes. In this connection, a factor of considerable importance in redox catalysis by enzymes undoubtedly is the possibility of additional stabilisation of intermediate radical and highly active biradical states of the coenzymes, and also reactive low-valency and other states of metal ions, as a result of the inclusion of the corresponding π- or d-electrons in conjugated systems of sufficient extent.

At an early date, Michaelis[141] suggested the existence of radical–enzyme complexes as a necessary condition for the essential one-electron transfer in enzymatic redox reactions.

Current data indicate that there is stabilisation of the radicals as a result of the formation of π-complexes under conditions of both non-enzymatic[108-116] and enzymatic[111-113,115,116] reactions. Stable complexes of flavin radicals with iodine and phenol were recently obtained[114].

It may be assumed that in many instances the detection of radicals under the conditions of enzymatic reactions is related to additional delocalisation of the unpaired electron either on a suitable conjugated system of the protein or on suitable orbitals of the metal ion.

The chief theories on the role of free radicals are associated with the name of Michaelis, who considered that all biological redox reactions must have a stage involving one-electron transfer, the intermediate compounds being free radicals[141].

At the present time, the role of radical intermediate forms in enzymatic catalysis remains the subject of a large amount of discussion[112,113,115,116,141,142], since even with modern methods of study it is not always possible to relate the facts of the detection, identification, and behaviour of radicals under various conditions to the actual mechanism of enzymatic catalysis. The problem is also complicated by the variety of ways in which free radicals can be stabilised and destabilised, for example by π-bonding, complex formation with metal ions, concurrent chemical reactions which do not affect the free valency, etc.

As already indicated, a characteristic feature of the reversible flavin–dihydroflavin reaction and the analogous quinone–hydroquinone reactions is the ready formation of free radicals as intermediate compounds. The mechanism of formation of radicals in these systems is based on the equilibria

$$QH_2 + Q \underset{k_{21}}{\overset{k_{12}}{\rightleftarrows}} [QH_2 \cdot Q] \underset{k_{32}}{\overset{k_{23}}{\rightleftarrows}} 2\,QH,$$

where QH_2, QH, Q, and $[QH_2.Q]$ represent the reduced, the semi-quinone, and the oxidised forms of the flavin or quinone, and the intermediate complex, which is usually a π-complex.

Depending on the medium, these equilibria are superimposed on the reversible reactions of addition and removal of a proton from the various forms of flavin or quinone[112,115,116,144,145]. In aqueous and aqueous-alcoholic media, hydroxide ions may act as possible reducing agents to semi-quinones[146-149].

The temperature-jump method has been used to study the reaction between FMN and FMN-H_2 at pH = 4.7 and a temperature of 298°K.[150] The values of the constants k_{12}, k_{21}, k_{23}, and k_{32}, equal to $> 10^9$ litre $mole^{-1}\ s^{-1}$, $> 10^6\ s^{-1}$, $5 \times 10^3\ s^{-1}$, and $6 \times 10^6\ mole^{-1}\ s^{-1}$ respectively, show that the rates of electron transfer in the two directions approximately coincide. The data on the isotope effect evidently indicate that transfer of an electron to the intermediate complex is less probable than transfer of a hydrogen atom.

It is of particular interest to compare the rates of one-electron exchange and transfer of hydride ion in quinone–hydroquinone systems. The constants k_{21} and k_{23} can apparently be regarded as proportional to the rates of hydride ion transfer and one-electron exchange, since in the intermediate complex the hydrogen atoms which undergo exchange are equivalent with respect to the two flavone (or quinone) rings, present in the complex.

If this is so, the rate of transfer of two electrons in the FMN–FMN-H_2 system is much greater than the rate of exchange by an electron in the same system. It may be assumed that the rates of electron transfer are markedly dependent both on the structure of the flavin or quinone and on the nature and degree of the binding of the coenzymes in reactions of enzymatic catalysis.

Unfortunately, in other systems these rate constants for electron transfer are unknown, although the rates of one-electron transfer in the forward and back directions have been measured[70,151-155]:

$$QH_2 + Q \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} 2\,QH\ .$$

The values of the constants k_1 and k_{-1} are fairly high (10^7–10^{10} $mole^{-1}\ s^{-1}$).

Usually, as expected, the $QH^\cdot$ radical disproportionates much more rapidly than its deprotonated form $Q^\cdot$.[70,155]

The complexity of the study of electron transfer in the Q + QH_2 system is also due to the need to make allowance for redox reactions of exchange by electrons

$$Q + QH \rightleftarrows QH + Q$$
$$QH + QH_2 \rightleftarrows QH_2 + QH\ .$$

This reaction takes place at a high rate (values of the constants up to 10^{10} litre $mole^{-1}\ s^{-1}$) (see Table on page 107 and Refs. 28 and 85).

The oxidised, semi-quinone, and reduced forms of the flavins or quinones readily form various complexes: π-complexes with one another and various π-acceptors and π-donors, and complexes with metal ions and other complex-forming species[108,110-114,120,121,124-141,157-159].

As a result of complex formation, there is an increase in the effective concentration of intermediate radical forms.

For example, the maximal concentration of flavosemiquinones is observed in acidic and alkaline media[115,116] and does not exceed several percent of the total concentration of flavin, whereas the maximum concentration of flavosemiquinones in the presence of various metal ions is observed in neutral media and may amount to almost 100% of the flavin concentration[113].

The oxidised form of flavin reacts specifically with a metal ion, whereas the reduced form is inert[113]. Thus flavin forms very stable chelates only with Ag^+ and Cu^+ ions, and in the complex of flavin with Cu^+, reversible electron transfer takes place between the partners. The spectra of the complexes $[Fl^-.Cu^+] \Longleftrightarrow [Fl^{2\circ}.Cu^{2+}]$ and $[Fl^-.Ag^+]$ correspond to the isoelectronic spectrum of the protonated flavosemiquinone $[Fl^{\cdot}.H_2^+]$.[160,161]

Fe^{2+} and MoO^{3+} ions react equally strongly with flavin, but in contrast to the situation with the Ag^+ and Cu^+ compounds, the flavin in the complexes with Fe^{2+} and MoC^{3+} is completely reduced to the semiquinone[113,162].

It should be emphasised that the semiquinones of flavins are able to form complexes with, as a rule, many more metal ions than the oxidised or reduced forms[163,164]. With diamagnetic metal ions (Zn^{2+}, Cd^{2+}) the flavosemiquinone gives an EPR spectrum with a hyperfine structure which is quite different from that of free flavosemiquinone, although the absorption spectra in the visible range are approximately identical[159,163,165]: this indicates a marked change in the electron density in the flavosemiquinone on complex formation with metal ions.

It has been suggested that the role of metal ions in enzymatic catalysis possibly involves the stabilisation of the flavin semiquinone[163].

Bray and coworkers[166], in a study of reactions catalysed by xanthine oxidase (a flavin enzyme containing Fe and Mo), showed by the EPR method that in the anaerobic reduction of xanthine oxidase and the aerobic oxidation of xanthin, the flavosemiquinone and Mo^V are formed as intermediate products. The results indicate that this radical is joined to the protein or the metal[166].

In view of the marked ability of semiquinones to form various complexes, proofs of direct electron transfer in systems containing flavins and quinones must be approached with some caution.

Study of the EPR spectrum of the π-complex [NAD-H_2.FMN] [167] showed the presence of free radicals, associated only with the flavin part of the complex. This was explained on the basis of the following reaction scheme

$$\text{NAD-H}_2 + \text{FMN} \rightleftharpoons [\text{NAD-H}_2^{\dot{+}}.\text{FMN}^{\dot{-}}] \rightleftharpoons \text{NAD-H}_2^{\dot{+}} + \text{FMN}^{\dot{-}}$$
$$2\text{NAD-H}_2^{\dot{+}} \rightleftharpoons \text{NAD-H}^+ + \text{NAD-H}_2 + \text{H}^+$$
$$\text{FMN}^{\dot{-}} + \text{H}^+ \rightleftharpoons \text{FMN-H}^{\cdot}.$$

The intermediate free radical NAD-$H_2^{\dot{+}}$ immediately undergoes disproportionation, to form the completely reduced and oxidised pyridine nucleotides. Thus the result of the overall reaction is the reduction of FMN at the expense of the NAD-H_2, to the semiquinone, without the formation of free radicals of NAD-H_2.

On the other hand, there exists the possibility of complete reduction of the flavin in the π-complex, the formation of semiquinones through the equilibirium between the oxidised and reduced forms of the flavin, and stabilisation of the resulting flavosemiquinone by its inclusion in a π-complex with the oxidised form of nicotinamide adenine dinucleotide.

This mechanism of stabilisation of semiquinones may also be realised in reactions of N-benzyldihydronicotinamide with quinones, where semiquinones have been detected[168]. The authors cited consider that this proves one-electron transfer, since the semiquinones were not detected by the EPR method under the same conditions in the quinone–hydroquinone system. Allowance must be made, however, for the fact that the reaction between dihydropyridine and 1,4-benzoquinone is fairly slow[169], whereas the attainment of equilibrium in the quinone–hydroquinone system is a very rapid process[70,134-137,151-156]

Because of complex formation, it is not always possible to observe correlations between the appearance of an EPR signal and the absorption bands assigned to the semiquinone[112]. It was found, for example, that the absorption spectra of the enzyme lipoyl dehydrogenase are the same for the reduction by dithionite and by the substrate, but an EPR signal is not observed, because of the formation of a complex between the flavosemiquinone and a sulphur-containing radical, formed in the enzyme. This complex plays a central role in processes catalysed by the enzyme lipoyl dehydrogenase; it is a catalytically active intermediate complex. The completely reduced enzyme is catalytically inert, at least in reactions with physiological substrates.

In a study of the mechanism of action of the oxidase of D-aminoacids it was found that the catalytically active intermediate product is a complex between the semiquinone form of the flavin and a radical of the aminoacid; in agreement with this, the concentration of the flavosemiquinone increased with increase in the concentration of the aminoacid[112].

Although many conclusions are still controversial, it may be taken that the formation of complexes by radicals increases the effective concentration of the radicals—this may have a significant influence on the overall rate of electron transfer[170].

On the other hand, complex formation by radicals may alter considerably the electron distribution in the radicals[113,159,170] and this in turn influences the rate and specificity of the process.

Ehrenberg[115,116] detected free radicals by means of the EPR method in the reaction between "old yellow" enzyme and NAD-H_2. He showed that the radicals are combined with a slowly vibrating protein molecule. The unpaired electron is localised chiefly in that part of the isoalloxazine molecule which is not combined with the protein. This electron density distribution is extremely sensitive to the smallest changes in the structure of the environment of the radical.

The action of the enzyme on the free radicals formed in a number of instances from the substrates is of interest[171]. Nakamura[172] established that in the oxidation of hydroquinone by the copper-containing enzyme laccase, a semiquinone is formed as the primary reaction product. The formation of free radicals in the oxidation of hydroquinone, pyrogallol, pyrocatechol, and other compounds was observed by a number of authors in processes involving peroxidase[173] and phenol oxidase[174].

Work illustrating the specific behaviour of semiquinones compared with other redox forms is of particular interest.

The important role of semiquinones is emphasised by Yamasaki and Ohnishi[153], who showed that the rate of the reduction of cytochrome C by hydroquinone is greatly increased in the presence of quinone. This increase was attributed to the formation of para-benzosemiquinone. The reduction of cytochrome C by the semiquinone is rapid and plays an important role in the redox equilibrium between the ferro-ferricytochrome C and quinone–hydroquinone systems. A kinetic study by the EPR method showed the following reaction mechanism:

$$QH_2 + Q \rightleftarrows 2QH$$

QH + ferricytochrome C ⇌ quinone + ferrocytochrome C.

The same result was previously obtained in a study of simpler systems[175].

The rapid reduction of cytochrome C in reactions of oxidases (peroxidase, ascorbic acid oxidase), which catalyse the two-stage oxidation of hydrogen donors, is also associated with the formation of semiquinone free radicals from the donor molecule[176].

The autocatalysis of the oxidation of reduced flavin by molecular oxygen may indicate a high rate of reaction of the flavosemiquinone with oxygen, compared with the reduced flavin[177]. The addition of the oxidised flavin to the FMN-H_2–O_2 system increases the rate of oxidation[177].

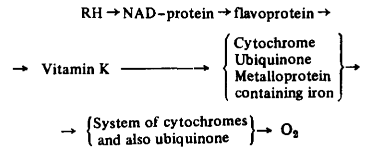
This was proved experimentally with other systems. An interesting feature is the behaviour of the semiquinone of thionine (a dye structurally similar to the flavins) in the reduction of the Fe^{3+} ion. The rate constants[151] for the oxidation of thionine semiquinone and its reduced form by Fe^{3+} ions are 7.9×10^4 litre mole^{-1} s^{-1} and 2.6×10^2 litre mole^{-1} s^{-1} respectively.

The reactivity of the semiquinone is determined by many factors. Thus it has been established that the flavin semiquinone produced by the action of various flavoproteins is oxidised by hexacyanoferrate(III) with great difficulty in the presence of a substrate; is however the substrate is absent, the oxidation is instantaneous[162,170,178].

Various flavosemiquinones are so strongly stabilised by a protein or a metal ion that they undergo extremely slow oxidation by molecular oxygen, and reduction by $S_2O_4^{2-}$ ions[112,113].

4. Catalytic Electron Transfer Chains

A characteristic feature of enzyme catalysis is the use of so-called catalytic chains, that is systems consisting of several enzymes[31,179,180]. For example, the oxidation of a number of metabolites in mitochondria takes place in the presence of a system of catalysts consisting of nicotinamide adenine nucleotide enzymes, flavoproteins, quinones, cytochromes, and metalloproteins. The chief sections of this chain are shown in the following scheme:



At different ends of the respiratory hydrogen transfer chain, there is preliminary activation of the substrates: the hydrogen donor RH and the hydrogen acceptor molecular oxygen, and electron transfer along the chain takes place at a very high rate (10^7–10^8 mole^{-1} s^{-1}, activation energy 7–8 kcal mole^{-1} [31]) and is highly specific. The term activation is understood to mean the formation of enzyme–substrate complexes in which the necessary rearrangement of the electronic structure of the hydrogen donor or acceptor and an orientation of the reagents convenient for the reaction take place. The formation of enzyme–substrate complexes leads to an increase in the rate and specificity of the enzymatic reaction. In particular cases a coenzyme may act as substrate.

It should first of all be emphasised that the key sections of the respiratory chain are those in which interaction of pyridine nucleotide and flavin enzymes with hydrogen donors and acceptors (particularly molecular oxygen), and also reaction of these enzymes with one another, take place. It is the study of these sections which may show why redox systems use not one universal catalyst but a chain of catalysts. This problem of course applies to other biochemical systems. It is natural to assume that the chief advantages of the catalytic chain lie in the fact that these chains are best able to satisfy the specific conditions of the reaction—the rates of electron transfer along the chain are high, and the reagents are activated and separated in space. This makes it possible to overcome the limitations imposed by the diffusion of reacting species to the active centre and also to generate reaction products in definite positions, so that their possible influence on the course of the reaction may be reduced to a minimum[179].

We may note the characteristic features of the biochemical respiratory chain given above. In the initial section of the chain, the substrate is oxidised by the direct transfer of hydrogen to the nicotinamide coenzyme. Most of the data on the mechanism of oxidation under the conditions of both model and enzymatic reactions indicates that hydrogen is transferred to nicotinamide coenzymes in the form of hydride ion[181], but no specific theories regarding the details of the mechanism of this reaction exist[102].

The final substrate of the electron transfer chain is molecular oxygen in aerobic organisms and nitrates and nitrites in anaerobic organisms. The mechanism of the reduction of these acceptors is apparently a one-electron mechanism (see Ref. 182 for oxygen).

Most of the available data[180] indicate that systems involving cytochromes function as one-electron transfer agents, although other possibilities can be pictured. For example, it was recently shown that the ferrogem–ferrigem electrode reaction is a two-electron process[186]. [This reference does not mention the stated reaction. (Ed. of Translation)].

Flavin and quinone-containing enzymes, on the other hand, take part in both one-electron and two-electron reactions. Under ordinary conditions, for example, flavins are apparently reduced by a hydride-ion mechanism under the influence of NAD-H_2,[22,53,54,181,184,185] and dihydrolipoic acid[22]. The dependence of the hydride-ion and hydrogen-atom mechanisms for the reduction of quinones on the reaction conditions has been discussed[186].

From the reduced nicotinamide coenzymes NAD-H_2 and NADP-H_2, hydrogen is transferred chiefly by a hydride-ion mechanism to many substrates, including flavins and quinones[53,54,181,187].

This fact is of importance in the explanation of the high rates of electron transfer in redox chains involving dihydropyridine and flavin enzymes. It may be assumed that in the catalytic chains the process is separated into stages differing in their chemical mechanisms—at one end of the chain, hydride ion is transferred from the substrate to the nicotinamide coenzyme, and at the other end, one-electron reduction of the acceptor takes place. Between the two ends of the chain there are systems containing flavin and quinone coenzymes capable of being reduced by a hydride-ion mechanism and oxidised with transfer of a hydrogen atom or an electron[53,54].

The separation of the process into stages with different chemical mechanisms not only leads to an increase in the rate of electron transfer as a result of observation of the principle of equivalent exchange by charges, but also ensures specificity of the reduction process relative to substrates which tend to undergo definite types of interaction.

IV. CATALYTIC ASPECTS OF ELECTRON TRANSFER

The conclusions reached in the previous sections are extremely useful in the search for catalysts for electron transfer reactions. We shall illustrate this for the examples already mentioned in the present review.

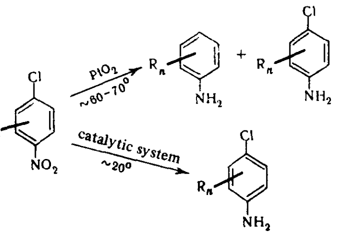
The rates of reactions of hydrogen transfer from reducing agents chiefly of the hydride type to probable one-electron acceptors, according to Shaffer's principle, should be increased by compounds capable of acting as one- and two-electron oxidising agents and reducing agents. In enzymatic catalysis, coenzymes with quinone and isoalloxazine structures, and also vitamin B_{12}, are compounds of this type.

For example, if dihydropyridine compounds, which are predominantly hydride ion donors[19,187-201] and whose reducing power is no less than that of molecular hydrogen[202], are used, the range of compounds reduced by NAD-H_2 and its models is greatly extended, and the rates of hydrogen transfer are increased in the presence of flavins, quinones, and similar dyes as catalysts[1,2,59-61]. Molecular oxygen[59], the stable radical of 2,2,6,6-tetramethylpiperidone-4 N-oxide[1,2], nitro- and nitroso-compounds[60,61], nitramine[61], N-bromosuccinimide[61], the acetylacetonato-compounds of Co^{III}, Fe^{III}, MoVI, and V^{V}, and also cyclopentadienyltitanium dichloride and cyclopentadienylvanadium dichloride[61]. The results obtained made it possible to apply the same principles of searching for organic catalysts with the isoalloxazine and quinone structures to the reaction of transfer of hydrogen from metal hydrides[59,61,63], organoelemental hydrides[203], formamidinesulphinic acid[62], dianions (organic and inorganic),[62] etc.

The next step in the use of the analogies with enzymes in catalysis is the development of catalytic systems which are more effective than the individual components[3,61,64-66,68,69]. Thus by taking account of the ability of the dihydropyridine ring to form π-complexes with various π-acceptors, it has been possible to find catalytic systems including π-acceptors and catalyst–transfer agents and having a higher efficiency in reaction (4) than the individual components of the system[69]. Published work[69] indicates that the mechanism of action of these catalytic systems apparently involves the formation of a π-complex between the reducing agent (1,4-dihydropyridine or cyclohexa-1,4-diene) and a π-acceptor (tetracyanoethylene, tetracyanoquinodimethane, 1,3,5-trinitrobenzene, etc.), in which there is a change in the ability of the reducing agent to act as a hydride ion and hydrogen atom (electron) donor.

Other effective catalytic systems for reaction (4), consisting of a catalyst–transfer agent and a metal ion, increase the rate of reduction of 2,2,6,6-tetramethylpiperidone-4 N-oxide and oxygen, possibly as a result of the ability of the semiquinones to form complexes with metal ions[68].

Catalytic hydrogenation systems, in the presence of which there is a marked change in both the rate and the specificity of hydrogenation[9,64-66,203,204], are of considerable interest. Catalytic systems of the first type consist of ordinary hydrogenation catalysts (heterogeneous or homogeneous) and catalyst–transfer agents, which can include quinones[3,66] and dimethylglyoximato-complexes of cobalt[64,65] and rhodium[203]. These catalytic systems are many times more effective in the hydrogenation of nitro-, nitroso-, azo-, azoxy, and hydrazo-compounds, compared with ordinary catalysts. In the hydrogenation of various halogenonitrobenzenes in the presence of, for example, the PtO_2 – sodium anthraquinone-2-sulphonate catalytic system, the rate of reduction of the nitro-group increases, and the dehalogenation is completely suppressed, since the hydrogenation takes place at room temperature, and in the presence of a transfer agent there is a decrease in the duration of contact between the substrate and the heterogeneous catalyst[205]:



Other catalytic hydrogenation systems, instead of catalyst–transfer agents, contain activating substrates as a result of the formation of various complexes[204,206]. On this basis, selective catalytic systems have been developed for the hydrogenation of unsaturated ketones, acrolein, and cinnamaldehyde.

These results lead to the following conclusions.

1. In a number of instances it is possible to obtain effective catalysts for various reactions on the basis of an analysis of the characteristic features of the structure and mechanism of action of enzymes.
2. For the rational selection of catalysts for a given process, it is necessary to take account of the thermodynamic characteristics of the catalyst and the structural correspondence between the reagents and the components of the catalytic systems in the limiting stage of the process.
3. The use of catalyst–transfer agents in redox reactions is extremely promising for carrying out various chemical processes at a high rate with high specificity under mild conditions.

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Institute of Chemical Physics,
Academy of Sciences of the USSR

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Reactions of Aziridines with Ring Expansion

F.N.Gladysheva, A.P.Sineokov, and V.S.Etlis

The review gives a systematic account of the literature on the reactions of aziridines with the expansion of the three-membered ring by intramolecular and intermolecular cyclisation mechanisms. The intermolecular interaction of aziridines with aldehydes and ketones, CO_2, COS, and CS_2, and with isocyanates and isothiocyanates with formation of five-membered heterocyclic compounds (oxazolidines, thiazolidinones, thiazolidinethiones, imidazolidinones, and others) is discussed. The isomerisation of *N*-vinyl and *N*-acyl derivatives to the corresponding pyrrolines, oxazolines, and other five-membered heterocyclic compounds as well as dimerisation reactions of aziridines and their interaction with epoxy ethylene and nitrones are discussed.
The bibliography includes 88 references.

CONTENTS

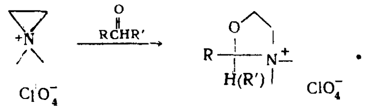
I. INTRODUCTION

The simplest nitrogen-containing three-membered heterocyclic compounds (aziridines) are extremely reactive[1-3]. They readily undergo addition reactions both with retention and opening of the aziridine ring. Under the action of acids, anhydrides, alcohols, amines, mercaptans, and other compounds, the three-membered ring opens and various *N*-substituted compounds are formed. In contrast to epoxy- and thioepoxy-alkanes, aziridines can react as amino-compounds with participation of the free electron pair of the nitrogen atom and the retention of the ring. They form aziridinium salts, add to the C=C double bond of keten, to activated double bonds of acrylic esters, and to conjugated double bonds of diene hydrocarbons, are acylated by acid anhydrides and chlorides to *N*-acylaziridines, cause ring opening of epoxyethane and ethylene sulphide, are dimerised to *N*-aminoethylaziridines, etc. A systematic account of the above reactions is given in the monograph of Gembitskii et al.[3], which contains the most complete description of the structure, properties, and methods of synthesis of aziridines and their reactions. Among the wide variety of the reactions of aziridines, a special place is occupied by reactions involving the expansion of the three-membered ring, which may be regarded as intermolecular and intramolecular interactions. The present review gives a systematic account of the literature on this problem up to 1968 inclusive.

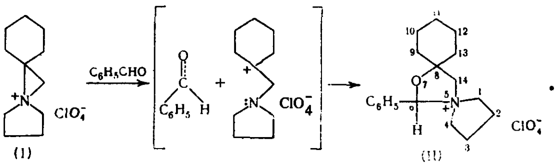
II. INTERMOLECULAR CYCLISATION

1. Reactions of Aziridines with Aldehydes and Ketones

The expansion of the aziridine ring in reactions with aldehydes and ketones was observed for the first time with aziridinium salts. Aziridinium salts were obtained by the nucleophilic attack of diazomethane on iminium compounds[4,5]. The proposed mechanism of the reaction of aziridinium salts with aldehydes[6] postulates the conversion of the three-membered cyclic ion to a five-membered ion with participation of the carbonyl group of the aldehyde or ketone:

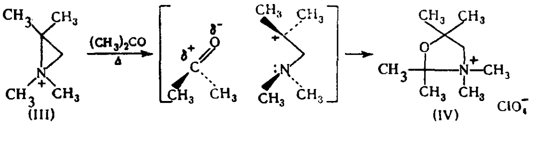


The mechanism consists of the opening of the aziridine ring to give a more stable positively charged tertiary β-aminocarbonium ion, which reacts with the polarised carbonyl group forming five-membered heterocyclic compounds—oxazolidinium salts. Thus, on heating, 5-azoniadispiro[4, 0, 5, 1]dodecane perchlorate (I) in an excess of benzaldehyde at 60°C for 48 h, a new compound was isolated—6-phenyl-5-azonia-7-oxaspiro[4, 2, 5, 1]tetradecane perchlorate (II):



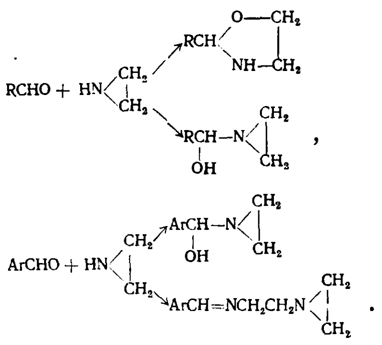
The infrared spectra of the compound isolated did not show absorptions characteristic of ^+N-H or C=O bonds, which is evidence that the C=O bond breaks with formation of a five-membered heterocycle.

The above reaction is general, this being confirmed by the reaction of benzaldehyde with analogues of compound (I). Aziridinium perchlorate reacts with a number of aliphatic cyclic and aromatic ketones[7]. Thus the reaction of 1,1,2,2-tetramethylaziridinium perchlorate (III) on heating in an excess of acetone has been investigated. Analysis and NMR spectra indicate that the final reaction product is 2,2,3,3,5,5-hexamethyloxazolidinium perchlorate (IV):

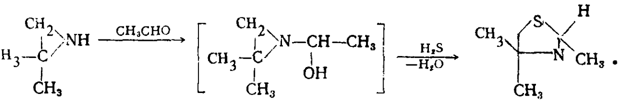


The reaction of the perchlorate (III) was carried out with cyclopentanone, cyclohexanone, methyl phenyl ketone, and other (cyclic and aromatic) ketones with heating to 65°C for 12–24 h. In each case stable oxazolidine derivatives were isolated and characterised. The interaction of aziridines unsubstituted at the nitrogen atom (in the form of free bases) with aldehydes does not lead to oxazolidines, as suggested by Doughty[8].

A number of investigations[9–15] have clearly demonstrated that under these conditions there is a possibility of the formation of *N*-aziridinemethanols or in certain cases *N*-(arylidene-β-aminoethyl)aziridines:



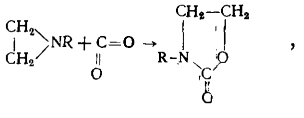
The formation of 2,4,4-trimethylthiazolidine[16] was observed in the reaction of acetaldehyde with 2,2-dimethylaziridine followed by saturation with hydrogen sulphide. One of the two possible mechanisms of reactions of this type postulates the formation of 2-alkyl-*N*-hydroxyaziridines, which yield thiazolidines under the action of hydrogen sulphide. In the second mechanism aziridine is converted into an amino-thiol, which is then converted into thiazolidine under the action of the carbonyl compound. The first mechanism is to be preferred in the case of the highly reactive acetaldehyde:



2. Interaction of Aziridines with Carbon Dioxide, Carbon Oxysulphide, and Carbon Disulphide

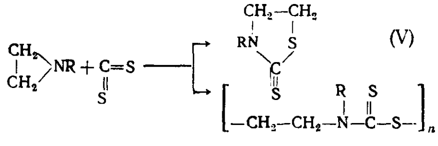
Oxirans and thi-irans react with carbon dioxide and its sulphur analogues with expansion of the three-membered rings[17]. In the reaction with carbon dioxide at room temperature, unsubstituted aziridine polymerises vigorously[18] and in the reaction with carbon monoxide, carbon oxysulphide, and carbon disulphide, it gives rise to thermoplastic resins[3].

Carbon dioxide does not react with aziridines in the absence of a catalyst. On heating with carbon dioxide in the presence of tetraethylammonium bromide (TEAB), equimolar amounts of *N*-arylaziridines give high yields of *N*-aryloxazolidinones[19,20]:

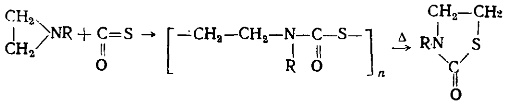


where R = C_6H_5, p-$CH_3C_6H_4$, o-$CH_3OC_6H_4$, or p-$CH_3OC_6H_4$. In the reaction of *o*- and *p*-methoxyphenylaziridines the corresponding *NN'*-diarylpiperazines were isolated as side products in yields up to 40%. In the reaction of *o*-tolylaziridine with carbon dioxide the formation of an oxazolidinone was not observed, the aziridine being dimerised due to the catalytic effect of TEAB.[21] Unsubstituted aziridine and its *C*-derivatives react with carbon disulphide forming thiothiazolidinones[22].

The reaction of carbon disulphide with *N*-arylaziridines under the conditions described for the reaction with carbon dioxide[19,20] leads to the expansion of the aziridine ring to that of *N*-arylthiazolidinethiones (V) (8–15%):



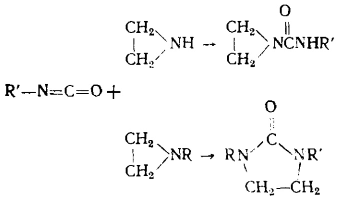
The main reaction products are characteristic copolymers of *N*-arylaziridines and carbon disulphide in molar proportions of 1 : 1. These copolymers are thermally unstable and on heating to 200–250°C dissociate with formation of the corresponding *N*-arylthiazolidinethiones (V) in a yield of 40–50%. The reaction of *N*-arylaziridines with carbon oxysulphide leads to the formation of ring expansion products only via the stage involving the copolymerisation of the reactant under the reaction conditions:



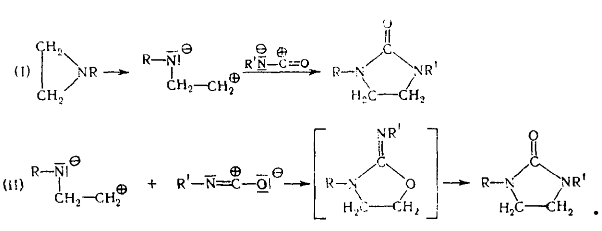
The thermal dissociation of the copolymers at 250°C leads to the formation of *N*-arylthiazolidinones (VI).

3. Interaction with Isocyanates and Isothiocyanates

The isocyanate molecule with the bond system N=C=O can react with aziridines with dissociation of the C=N or C=O bond. Aziridines unsubstituted at the nitrogen atom add to the C=N bond with formation of *NN'*-ethyleneureas[23–25]. In the reactions of *N*-substituted aziridines with isocyanates[26] the expansion of the aziridine rings to that of imidazolidinones was observed:

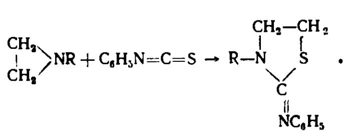


The reaction was carried out in the presence of a catalyst (lithium halides) at a temperature in excess of 100°C in an inert solvent. The interaction of *N*-acyl- and *N*-alkyl-aziridines with *N*-aryl, *N*-cyclohexyl, *N*-acyl, and *N*-sulphonyl isocyanates was investigated. For certain *N*-aryl and *N*-alkyl isocyanates, a competitive trimerisation reaction catalysed by tertiary amines was observed. The following two reaction mechanisms were proposed:



In the first mechanism the cleavage of a C–N bond of aziridine followed by the addition of the ion formed to the polarised N=C bond of the isocyanate with subsequent formation of an imidazolidinone is postulated. According to the second mechanism, an intermediate 2-imino-oxazolidine is formed and converted into a 1,3-disubstituted imidazolidin-2-one. The second mechanism is comparable with the mechanisms of the analogous reactions of epoxyethane[27].

Unsubstituted aziridines with an active hydrogen atom react with isothiocyanates with formation of *NN*-ethylenethioureas[28,29]. *N*-Aryl-substituted aziridines dissociate the C=S bond of the isothiocyanate in the presence of tetraethylammonium bromide, and are converted into the corresponding 3-aryl-2-phenyliminothiazolidines[21]:



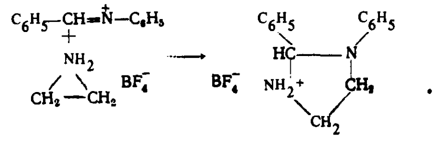
where R = C_6H_5, *o*-$CH_3C_6H_4$, *p*-$CH_3C_6H_4$, *o*-$CH_3OC_6H_4$, or *p*-$CH_3OC_6H_4$.

The infrared spectra of the compounds isolated show an intense absorption band in the region of 1632 cm^{-1}, which has been assigned to the vibration of the C=N bond.

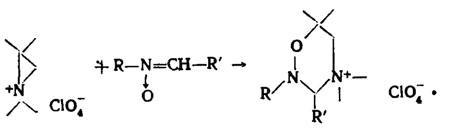
The reaction of *N*-phenylaziridine with methyl isothiocyanate under analogous conditions led to the isolation, together with 2-methylimino-3-phenylthiazolidine, of trimethyltrithioisocyanurate—the product of the trimerisation of the isothiocyanate. A similar reaction takes place with epoxyalkanes[30].

4. Interaction with Schiff Bases and Nitrones

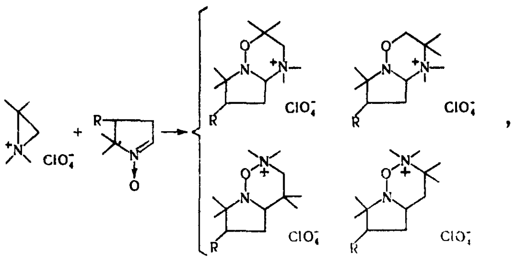
The possibility of the reaction of aziridine with the C=N bond of isocyanate is confirmed by the reaction of its derivatives with Schiff bases. Aziridinium salts readily add to the C=N bond of *N*-benzylideneaniline[31] with formation of 1,2-diphenylimidazolinium fluoroborate:



Nitrones, the structure of which includes the group C=$\overset{\overset{O}{\uparrow}}{N}$, add to aziridine derivatives with formation of six-membered adducts in proportions of 1 : 1.[32]

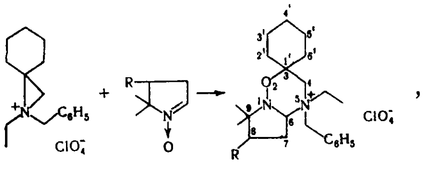


1,3-Dipolar addition to olefinic or acetylenic bonds with formation of isoxazolidine derivatives is characteristic of nitrones. Their interaction with aziridines can be explained similarly. Thus, the reaction of 1,1,2,2-tetramethylaziridinium perchlorate with 5,5-dimethyl- and 4,5,5-trimethyl-Δ^1-pyrroline-1-oxides at room temperature over a period of five days leads to the formation of one of a number of 1 : 1 adducts, since, depending on the course of the reaction, the C–N⁺ bond of aziridine can disssociate in different ways:



where R = H or CH_3.

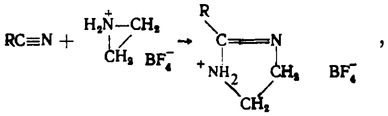
Under analogous conditions, 1-benzyl-1-ethyl-1-azoniaspiro[2,5]octane perchlorate gives rise to even more complex 1 : 1 adducts. Their analysis and infrared spectra confirm the formation of 5-benzyl-5-ethyl-8,9,9-trimethyl-1-aza-5-azonia-2-oxabicyclo[4,3,0]nonane-3-spiro-1′-cyclohexane perchlorate:



where R = H or CH_3.

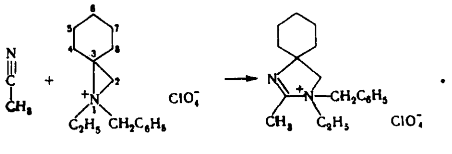
5. Interaction with Nitriles

The expansion of the aziridine ring is observed in the interaction with the C≡N bond of nitriles. Thus in the reaction between aziridinium tetrafluoroborate and various nitriles[31] the corresponding imidazolidinium salts were isolated:



where R = CH_3, C_6H_5, or $C_6H_5CH_2$.

After heating 1-benzyl-1-ethyl-1-azoniaspiro[2,5]octane perchlorate with acetonitrile[33], a new compound was isolated—3-benzyl-3-ethyl-2-methyl-1-aza-3-azoniaspiro[4,5]dec-1-ene perchlorate, the infrared spectrum of which contains the absorption band $\nu_{C=N}$ = 1715 cm^{-1}. The structure of the compound was also demonstrated by NMR spectroscopy.

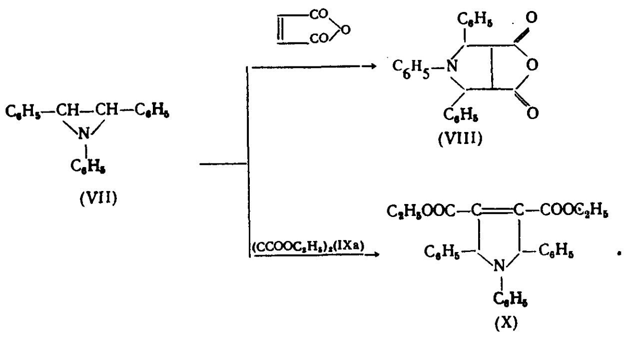


6. Interaction of Aziridines with Alkenes and Alkynes

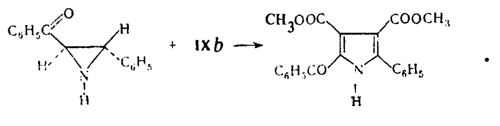
Aziridine ring expansion reactions are most often preceded by the rupture of the ring at carbon–nitrogen bonds. However, the carbon–carbon bond of the aziridine ring can also break with subsequent ring expansion. Such reaction takes place with reactive alkenes and alkynes[34–39].

The interaction of 1,2,3-triphenylaziridine (VII) with maleic anhydride takes place with formation of an expansion product of the three-membered ring in 94% yield, formed as a result of the dissociation of the C–C bond of aziridine and addition to the C=C bond of maleic anhydride[34]. The structure of the adduct (VIII) isolated was demonstrated by analysis and infrared spectroscopy.

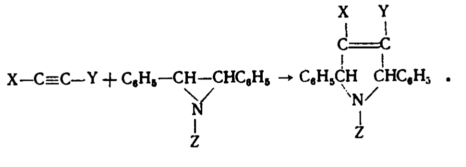
An example of the dissociation of the C–C bond in compound (VII) is provided by its reaction with diethyl acetylenedicarboxylate (IXa), which led to the isolation of a 98% yield of the pyrroline (X):



When *trans*-3-benzoyl-2-phenylaziridine was heated with dimethyl acetylenedicarboxylate (IXb) in xylene for 18 h, 2-benzyl-5-benzoyl-3,4-dimethoxycarbonylpyrrole was obtained in 80% yield[35]:



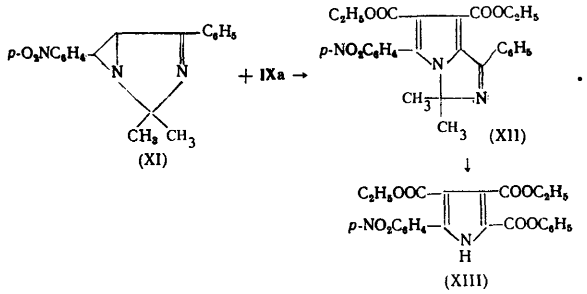
The interaction of triarylaziridines with various alkynes has been investigated[38]. When the reactions are carried out in toluene solution at room temperature (5 to 15 h), the corresponding Δ^3-pyrrolines are obtained in high yields:



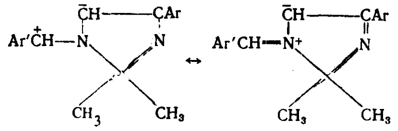
where X, Y = $COOC_2H_5$ and Z = C_6H_5; X = $COOC_2H_5$, Y = H, and Z = C_6H_5; X, Y = C_6H_5CO and Z = C_6H_5; X, Y = CF_3 and Z = C_6H_5; X, Y = $COOC_2H_5$ and Z = p-BrC_6H_4; X, Y = C_6H_5CO and Z = p-BrC_6H_4.

The reaction of aziridine with di(trifluoromethyl)acetylene was carried out in a sealed tube at 200°C for 12 h. The structures of the compounds isolated were confirmed by analysis of the infrared spectra. Their further chemical reactions were also studied.

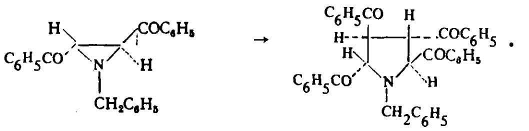
Similar interactions of aziridines with alkenes and alkynes, leading to the dissociation of the C–C bonds, were observed also in more complex heterocyclic systems[40]. When 1,3-diazabicyclo[3,1,0]hex-3-ene (XI) was heated in xylene with compound (IX), the diethyl ester of 3,3-dimethyl-5-(*p*-nitrophenyl)-1-phenyl-3*H*-pyrrolo[1,2-*c*]imidazole-6,7-dicarboxylic acid (XII) was obtained in a quantitative yield[38]:



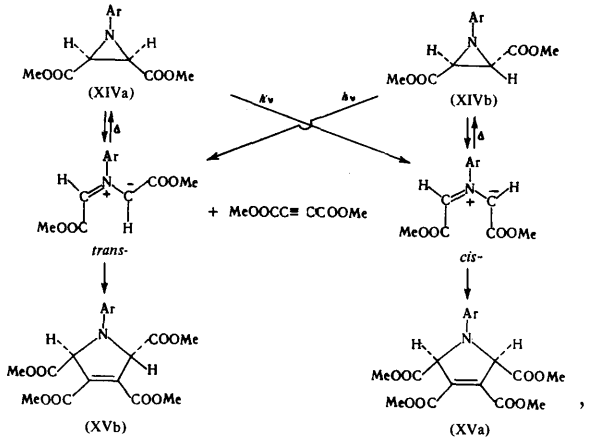
The structure of compound (XII) was demonstrated by acid hydrolysis to the diethyl ester of 2-benzoyl-5-*p*-nitrophenylpyrroledicarboxylic acid (XIII) and acetone. The authors also synthesised and characterised the adducts (XI) with diethyl fumarate, diethyl azodicarboxylic ester, *N*-phenylmaleimide, and also *cis*- and *trans*-dibenzoylethylene. It was postulated that this interaction is preceded by the rearrangement of compound (XI), to a 1,3-dipolar compound which then reacts in this form:



Attempts were also made earlier to account for the mechanism of this type of interaction by the 1,3-cycloaddition of the reactants to the aziridine derivatives[36]. 1-Benzyl-2,3-*trans*-dibenzoylaziridine is converted into *trans*-dibenzoylethylene (34% yield) and a certain amount of a ring expansion product—1-benzyl-1,2,3,4-(all-*trans*)-tetrabenzoylpyrrolidine:



The formation of the five-membered planar ring of the aziridine ring-expansion products gives rise to *cis*- and *trans*-isomerism. When dimethyl esters of 1-(4-methoxyphenyl)aziridine-2,3-dicarboxylic acid (XIVa, b) are heated in an excess of a "dipolarophile" ($CH_3OOCC{\equiv}CCOOCH_3$), a mixture of *cis*- and *trans*-isomers of the tetraesters (XVa, b)[39] is obtained, the proportions depending on the reaction conditions. The equilibrium between the *cis*- and *trans*-isomers has been investigated by NMR spectroscopy



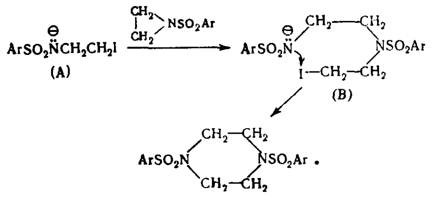
where Ar = $C_6H_4OCH_3$.

The thermal interaction of aziridines with a "dipolarophile" without solvent at 100–120°C takes place with the inversion of the configuration of the aziridine, while in the photochemical reaction the configuration is preserved. Thus, when 1 mole of compound (XIVa) and 10 moles of (IXb) were heated at 100°C for 14 h, compound (XVb) was isolated in 88% yield; under analogous conditions, compound (XIVb) is converted into compound (XVa) in 71% yield. Under the conditions of the photochemical reaction, compound (XIVb) is converted into compound (XVb) in 69% yield.

7. Dimerisation of Aziridine Derivatives and Interaction with Epoxyethane

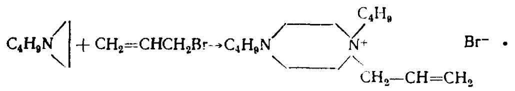
Oxygen- and sulphur-containing three-membered heterocyclic compounds dimerise under certain conditions to the corresponding dioxans[2] and dithians[41]. Aziridines also dimerise. The conversion of 1-methylaziridine into 1,4-dimethylpiperazine has been described[42]. The formation of piperazine derivatives in reactions of β-chloroethylamines has been observed. Kinetic studies of such reactions led to the conclusion[43,44] that chloroethylamines initially cyclise to aziridinium salts as intermediates, which then react further to give salts derived from piperazine. Piperazine derivatives were isolated after rearrangement of aziridines under the action of acids[45,46] and as side products in the isomerisation of aziridine derivatives[47].

1-Aroyl-2-alkylaziridines, 1-arylsulphonylaziridines, and 1-arylaziridines dimersie under the catalytic action of iodine. It is suggested that the first stage in the formation of piperazines[47] is a bimolecular substitution reaction of aziridine to give an ion derived from 2-iodoethylamine. Thus 1-arylsulphonylaziridines give rise to an ion (A) derived from *N*-(2-iodoethyl)arylsulphonimide, which attacks the methylene carbon of a second molecule of 1-arylsulphonylaziridine with formation of an intermediate ion (B):

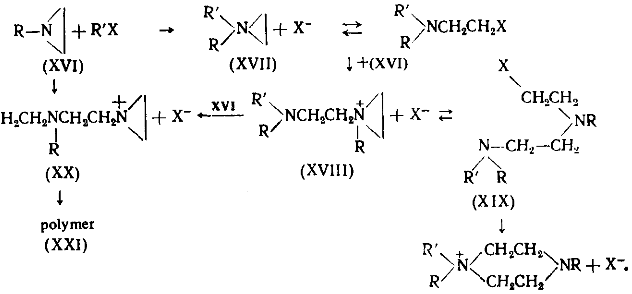


Piperazine is formed when an iodide ion is split off from the ion (B). The dimerisation of aziridine-1-carboxanilide to *NN*-di(phenylcarbamoyl) piperazine takes place similarly.

Dick[48] investigated the effect of alkylating agents on aziridine and succeeded in isolating piperazine derivatives. When allyl bromide is heated with 9 moles of *N*-butylaziridine in dry acetone, 1-allyl-1,4-di-*N*-butylpiperazinium bromide is formed in 96% yield:



Other alkylating agents have also been used: methyl iodide, methyl *p*-toluenesulphonate, ethyl *p*-toluenesulphonate, and ethyl bromide. The results of the experiments clearly show that in their reaction with aziridines alkylating agents favour the formation of piperazines. The mechanism of the opening of the ring of 1-alkylaziridines is known to involve catalysis by alkyl halides, including S_N2 attack by the nucleophilic agent on the aziridine ring. The following mechanism is proposed for the formation of piperazines:



Aziridine (XVII) forms a dimer (XVIII) by an S_N2 reaction. Then, if X^- is a powerful nucleophilic agent, compound (XVIII) reacts with it to form compound (XIX), which cyclises. However, if X^- is a weak nucleophilic agent, for example the toluenesulphonate ion, compound (XVII) is not converted into compound (XIX) but causes ring opening in the next aziridine molecule, forming the trimer (XX) and then polymeric compounds (XXI). It is known that under certain conditions the reactions of acids or alkylating agents with aziridine derivatives yield polyaziridines. The reaction of aziridines with alkylating agents is significantly influenced by the solvent. For example, acetone favours the formation of piperazine, while more polar solvents favour the polymerisation (XVIII) → (XX) → (XXI).

The formation of 1,1-dialkylaziridinium salts of type (XVII) when aziridine interacts with alkylating agents was demonstrated also in earlier studies[49,50].

The dimerisation of *N*-aryl derivatives of aziridines was observed when the latter were heated in the presence of a catalytic amount of tetraethylammonium bromide. The coupling of two three-membered heterocycles—*N*-arylaziridine and epoxyethane[51]—has been reported. Since the dimerisation of aziridine may compete with this type of interaction, the reaction was carried out in a large excess of epoxyethane:

$$\mathrm{Ar{-}N}\left\langle\begin{matrix}\mathrm{CH_2}\\ |\\ \mathrm{CH_2}\end{matrix}\right. + \left.\begin{matrix}\mathrm{CH_2}\\ |\\ \mathrm{CH_2}\end{matrix}\right\rangle\mathrm{O} \xrightarrow{\text{TEAB}} \mathrm{ArN}\left\langle\begin{matrix}\mathrm{CH_2{-}CH_2}\\ \mathrm{CH_2{-}CH_2}\end{matrix}\right\rangle\mathrm{O},$$

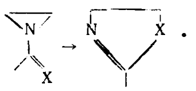
where Ar = C_6H_5, *o*-$CH_3C_6H_4$, *p*-$CH_3C_6H_4$, *o*-$CH_3OC_6H_4$, or *p*-$CH_3OC_6H_4$.

In the reactions of *N*-(*o*-methylphenyl)- and *N*-(*o*-methoxyphenyl)aziridines, *NN'*-diarylpiperazines were isolated in 30% yield together with morpholines. Ethylene sulphide does not take part in this reaction, undergoing quantitative polymerisation.

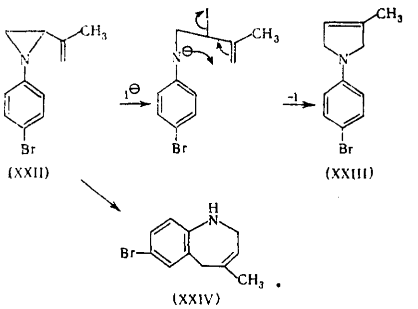
III. INTRAMOLECULAR CYCLISATION

1. Rearrangement of *N*-Vinyl Derivatives of Aziridines

Substituted aziridines undergo reactions typical for their hydrocarbon analogues—cyclopropanes. Under the action of nucleophiles and acids on heating, vinylcyclopropane isomerises to cyclopentene[52]. Similar processes have been observed for vinylaziridines:



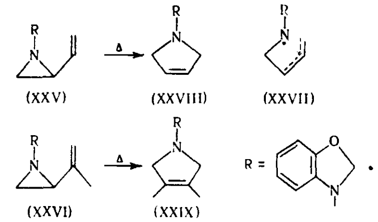
When *N*-methylvinyl(*p*-bromophenyl)aziridine (XXII) was heated with sodium iodide in dry acetone, 1-(*p*-bromophenyl)-3-methyl-3-pyrroline (XXIII) was isolated[53]:



(XXII) (XXIII) (XXIV)

The authors suggest that the mechanism of this reaction involves nucleophilic attack on aziridine by I⁻ with opening of the aziridine ring and subsequent displacement of iodine and formation of compound (XXIII). However, when *N*-vinylaziridine (XXII) is heated in xylene without a catalyst, the isomeric compound (XXIV), which is not a product of the expansion of the aziridine ring, is formed in a high yield. The structure of compound (XXIV) was demonstrated by the presence in its infrared spectrum of an absorption band characteristic of the NH group and also by the formation of the corresponding derivatives of phenylthiourea on heating with phenyl isothiocyanate.

Certain *N*-substituted 2-vinylaziridines [(XXV) and (XXVI)] undergo pyrolytic isomerisation in decalin solution at 180°C:[54]



(XXV) (XXVIII) (XXVII)

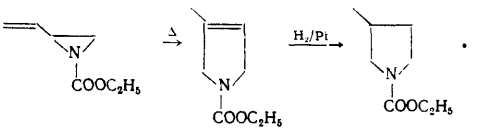
(XXVI) (XXIX)

The products of the expansion of the aziridine ring (Δ^3-pyrrolines) are formed in 80% yield. The mechanism of their formation can be accounted for by postulating the opening of the aziridine ring with dissociation of the C–N bond. The reaction proceeds via the intermediate formation of the aza-allyl biradical (XXVII), the stability of which is higher than that of the alkylallyl biradical formed in the rearrangement of vinylcyclopropanes to cyclopentenes[52].

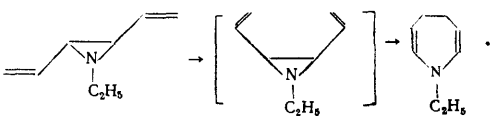
Comparison of the rates of conversion of the aziridines (XXV) and (XXVI) by heating in decalin at 150°C for 1 h shows that compound (XXVI) isomerises to compound (XXIX) to an extent of 100%, while the isomerisation of compound (XXV) to compound (XXVIII) takes place to the extent of 60% only. This can be explained by the greater stability of the tertiary allyl radical compared with the secondary radical.

The above aziridines (XXV) and (XXVI) are converted into Δ^3-pyrrolines under the action of a nucleophilic agent (sodium iodide) in boiling acetone with a yield of only 2% over a period of 24 h. In this case ring opening is not facilitated by the negative charge on the nitrogen atom. The conversion of three-membered rings into five-membered rings is possible only when the three-membered system is activated[55].

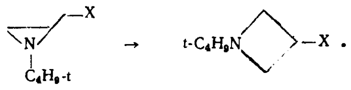
N-Ethoxycarbonyl-2-methyl-2-vinylaziridine isomerises in a gas-chromatographic column at 100°C or above with formation of *N*-ethoxycarbonyl-3-methyl-Δ^3-pyrroline[56]:



The presence of two vinyl substituents at the carbon atoms of aziridines leads to an unusual reaction involving the expansion of the three-membered ring to a seven-membered ring[57]: 2,3-divinylaziridine is converted into *N*-ethyldihydroazepine:



According to the latest literature data[58], certain aziridines rearrange to azetidine derivatives as a result of solvating ionisation:

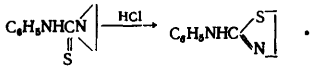


where X = OTs, OH, OC_2H_5, or Br.

2. Isomerisation of Aziridine Derivatives

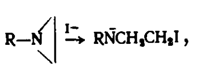
The isomerisation of aziridine derivatives, which is an example of intramolecular cyclisation, constitutes the most thoroughly investigated type of rearrangements of aziridines. The rearrangement of *N*-acyl derivatives of aziridines, *NN'*-ethyleneureas, and thioureas, obtained by the interaction of aziridines unsubstituted at the nitrogen atom with isocyanic acid esters, benzoyl and thiobenzoyl chlorides, chlorocarbonic acid esters, and other compounds, led to the synthesis of many five-membered heterocyclic derivatives—oxazolines, oxazolidinones, thiazolidinones, imidazolidinones, and others.

In 1895 Gabriel[28] observed for the first time the conversion of aziridine-1-thiocarboxanilide into 2-anilino-Δ^2-thiazoline under the action of concentrated hydrochloric acid:

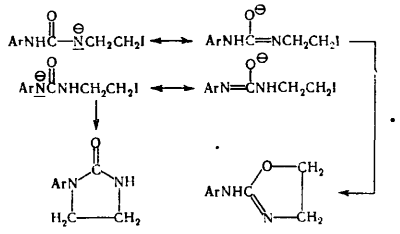


Later it was established that this type of reaction takes place readily in the presence of various nucleophilic agents which facilitate the dissociation of the C–N bond of the three-membered ring of aziridine.

Heine[59] proposed a mechanism for the nucleophilic catalytic isomerisation of aziridine derivatives, in which the formation of an anion derived from 2-iodoethylamine in the reaction in the presence of sodium iodide is postulated:



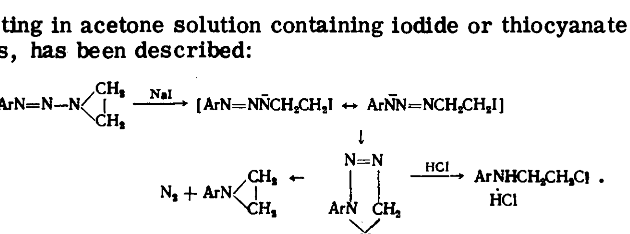
where R = ArCO, ArC=NR′, $\mathrm{Ar_2N\underset{\|\atop O}{C}}$–, or ArN=N–. The subsequent reaction of the anions formed can take place in different ways[47]; cyclisation may precede the tautomeric conversion of anions when there is a hydrogen atom at the nitrogen atom of *NN'*-ethyleneiminoureas:



(XXX) (XXXI)

For example, in the isomerisation of aziridine-1-carboxanilide in acetone solution in the presence of sodium iodide a mixture of products was isolated. The use of a small amount of acetone and an excess of sodium iodide leads to the formation of 1-phenylimidazolidin-2-one (XXX) in 85% yield. In an excess of acetone with a small amount of sodium iodide compound (XXX), the aziridine dimer, and a small amount of 2-anilino-Δ^2-oxazoline (XXXI) are formed.

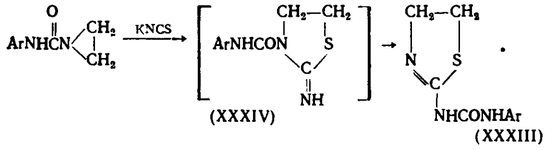
The synthesis of certain 1-arylazoaziridines[60], which are converted into 1-aryl-Δ^2-1,2,3-triazolines (XXXII) on heating in acetone solution containing iodide or thiocyanate ions, has been described:



(XXXII)

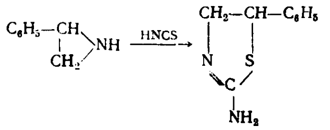
The products of the rearrangement of compound (XXXII) in turn serve as starting materials for the synthesis of a wide variety of *N*-arylaziridines which are difficult to obtain in other ways.

It should be noted that, apart from its catalytic effect, the thiocyanate ion can interact with aziridines, also yielding ring-expansion products. Thus, aziridine-1-carboxylic acid arylamides kept for 30 h in acetone with potassium thiocyanate are converted into 2-(3-arylureido)-Δ^2-thiazolines (XXXIII)[24], which are formed via the intermediate 2-imino-3-arylcarbamoyl-thiozilidines (XXXIV):

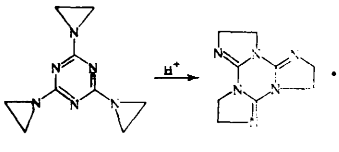


(XXXIV) (XXXIII)

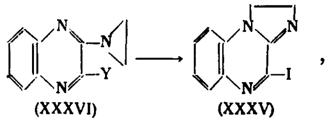
The mechanism of this interaction is consistent with the data of Gabriel[61], who described the effect of thiocyanic acid on 2-phenylaziridine:



The isomerisation of 2-alkyl-1-aroylaziridines, aziridine-1-thiocarboxanilides, and 1-arylsulphonylaziridines under the action of sodium iodide and thiocyanate ions in acetone[47] leads to the corresponding oxazolines and thiazolines—products of intramolecular cyclisation. 2,4,6-Tri-(1′-aziridino)-*s*-triazine isomerises on refluxing in acetonitrile solution in the presence of triethylammonium chloride to 2,3,6,7,10,11-hexahydrotrisimidazo-*s*-triazine:



New heterocyclic systems—1,2-dihydroimidazo[1,2-*a*]-quinoxamines (XXXVa, b)—have been obtained by the isomerisation of (1′-aziridino)quinoxamines (XXXVIa, b):[62]

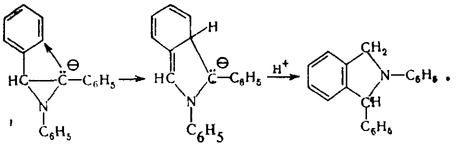


(XXXVI) (XXXV)

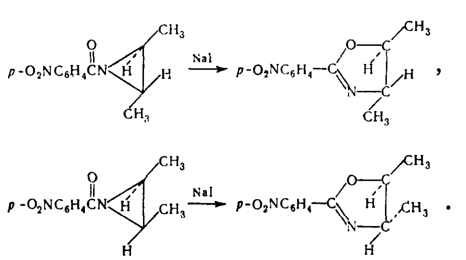
where (a) Y = Cl and (b) Y = CH_3O.

The conversion of compound (XXXVIa) into (XXXVa) takes place readily in acetone containing sodium iodide, while compound (XXXVIb), is converted into compound (XXXVb) in acetone solution containing sodium methoxide. The analogous isomerisation of 1-(*N*-arylbenzimidazolyl)-aziridine can be used to synthesise Δ^2-imidazolines[63].

The isomerisation of 1,2,3-triphenylaziridine is one of the first examples of carbanionic rearrangement involving the aziridine ring[64]. When 1,2,3-triphenylaziridine was heated in toluene in the presence of potassium t-butoxide in a sealed tube at 180°C, 1,2-diphenylisoindoline was isolated. The reaction may take place via the formation of the carbanion (XXXVII), which, after attack on the benzene ring, can be converted into the intermediate complex (XXXVIII); this undergoes a tautomeric conversion into 1,2-diphenylisoindoline:

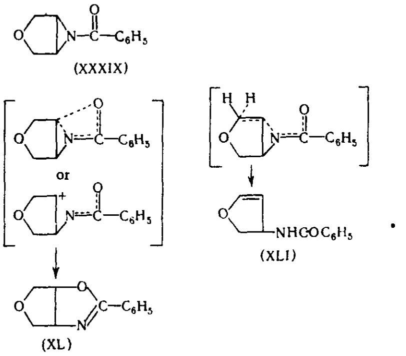

(XXXVII) (XXXVIII)

The isomerisation of certain 2,3-substituted *cis*- and *trans*-1-(*p*-nitrobenzoyl)aziridines, which are converted into the corresponding oxazolines under the action of iodide ions[65], is striking. The stereochemistry of this reaction has been investigated. In acetone solution containing iodide ions *trans*-2,3-dimethyl-1-(*p*-nitrobenzoyl)-aziridine isomerised to *trans*-4,5-dimethyl-2-(*p*-nitrophenyl)-Δ^2-oxazoline in 96% yield, while the *cis*-derivative of aziridine was converted into the corresponding *cis*-derivative of oxazoline:



The acid-catalysed isomerisation of 2,2-dimethyl-1-(*p*-nitrobenzoyl)aziridine[66] can take place via the intermediate formation of the tertiary carbonium ion $[ArCoNHCH_2\overset{+}{C}(CH_3)_2]$.

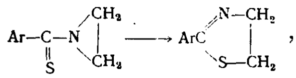
The isomerisation has been observed also for more complex bicyclic aziridines (XXXIX), which also yield ring-opening products on heating in the presence of sodium iodide. The high probability of the rearrangement of aziridines into the corresponding oxazolines via the formation of amides has been demonstrated[67]:


(XXXIX) (XLI) (XL)

When the aziridine derivative 6-aza-3-oxabicyclo[3,1,0]-hexane (XXXIX) and also its 6-methyl and 6-benzyl derivatives are heated, the oxazolines (XL) are formed but not the amides (XLI). The amide formed could be easily isolated under the experimental conditions, since it was shown that the amides are higher-melting less soluble products, which are more readily crystallised than oxazolines; the NMR spectra of compound (XL) differ from those of the isomeric amide (XLI). The hypothesis that the initially formed amide (XLI) cyclises under the reaction conditions is also unlikely, since it has been established that amides of this kind are stable on heating and cyclise to oxazolines only in concentrated sulphuric acid at room temperature[68].

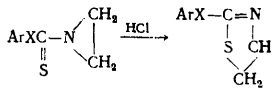
The oxazolines (XL) were also isolated after heating the benzoyl derivative of compound (XXXIX) with sodium iodide in acetone or acetonitrile. The mechanism of their formation is of the type of the isomerisation, described above, with formation of an ion derived from an iodoalkylamine[9].

Further studies[69] confirmed these findings in more complex heterocyclic systems. Conditions were found for the synthesis of 2,2-dimethyl-1-(*p*-nitrobenzoyl)-1-aza-spiro[2,5]octane and 1-azaspiro[2,4-]heptane, which yield the corresponding *N*-nitrobenzoyl derivatives. The isomeric *N*-cycloalkenylmethyl-*p*-nitrobenzamides readily isomerise to spiro-oxazolines. Picric and *p*-toluenesulphonic acids have also been used as nucleophilic agents for the isomerisation; in their presence 1-thioaroylaziridines were converted into 2-arylthiazolidines in benzene solution[70]:



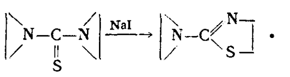
where Ar = p-ClC_6H_4, p-$CH_3C_6H_4$, or p-$CH_3OC_6H_4$.

1-(Aryloxythiocarbonyl)- and 1-(aryldithiocarbonyl)-aziridines readily polymerise on standing at room temperature and are converted into 2-aryloxythiazolines and 2-arylthiothiazolines by treatment with hydrochloric acid at 20°C:

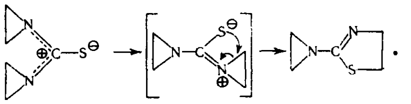


where X = O or S.

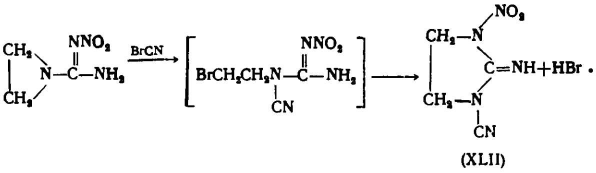
The extremely reactive 1,1′-(thiocarbonyl)bisaziridines readily isomerise in the presence of sodium iodide to a product formed as a result of the expansion of one of the aziridine rings[71,72]:



The reaction takes place quantitatively in 30 min at room temperature. The high reactivity of the bisaziridine can be explained by the high polarisation of the thiocarbonyl group in which the charge is delocalised between both aziridine nitrogen atoms:

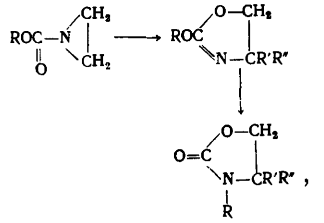


1-Nitroamidinoaziridines, obtained by the reaction of 2-methyl-1-nitro-2-thiopseudourea with aziridine and its 2-methyl derivative are examples of aziridines capable of isomerisation reactions[73]. In an acid medium the compounds isolated were converted into alkylnitroguanidines, while their cyanobromination leads to the formation of five-membered heterocycles—3-cyano-2-imino-1-nitro-imidazolidine (XLII) and 2-amino-1-nitroimidazolidinium bromide (XLIII)—in high yields. The cyanobromination of 1-nitroamidinoaziridine evidently takes place via the intermediate formation of *N*-(2-bromoethyl)-*N*-cyanonitroguanidine, which cyclises by an S_N2 mechanism with formation of compound (XLII) in 43% yield. The hydrogen bromide evolved reacts with aziridine to form 2-bromoethyl-3-nitroguanidine, which readily cyclises to compound (XLIII) in 41% yield.



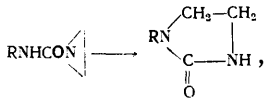
(XLII)

The aziridine derivatives of formic acid isomerise to oxazoline and oxazolidinone derivatives[74]. In this case the catalyst is sodium iodide in an aprotic solvent; an increase in the relative amount of sodium iodide in the initial mixture of reactants in excess of 0.1 mole leads to a decrease of the yield of the isomerisation products:

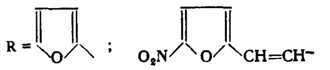


where R′ = R″ = H or R, R′, and R″ are hydrocarbons with more than 8 carbon atoms.

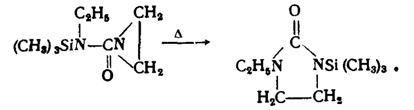
Japanese investigators[75] observed the isomerisation of *N*-[*β*-(5-nitro-2-furyl)vinyl]- and *N*-(2-furyl)-ethyleneureas at room temperature in acetone or acetonitrile solution in the presence of sodium iodide. The structure of the imidazolidin-2-ones formed in 85–90% yield was demonstrated by analyses, infrared spectroscopy, and syntheses. The mechanism of the rearrangement is consistent with that described previously:



where

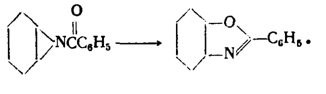


The aziridine ring-expansion reaction has been observed for ethyleneureas containing silicon atoms together with the aziridine ring[76]. *N*-Silylaziridines were obtained by the reaction of aziridine and trimethylchlorosilane. Their subsequent reaction with isocyanates leads to the formation of *N*-silylethyleneureas, which form imidazolidine derivatives of silicon on heat treatment:

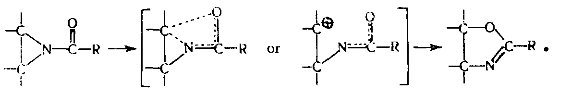


The structure of the imidazolidinones isolated was demonstrated by NMR spectroscopy, solvolysis of the product at the Si–N bond, and infrared spectroscopy of the decomposition products.

Many compounds, which readily isomerise under the influence of nucleophilic catalysts, undergo pyrolytic isomerisation to the corresponding ring-expansion products. Thus Gabriel[28] noted that redistilled 1-benzoylaziridine is converted on heating in a sealed tube to 240°C into 2-phenyl-Δ^2-oxazoline. The pyrolysis of *N*-benzoyl-*cis*-cyclohexeneimine leads to *trans*-4,5-tetramethylene-2-phenyl-Δ^2-oxazoline in 20% yield[59]:

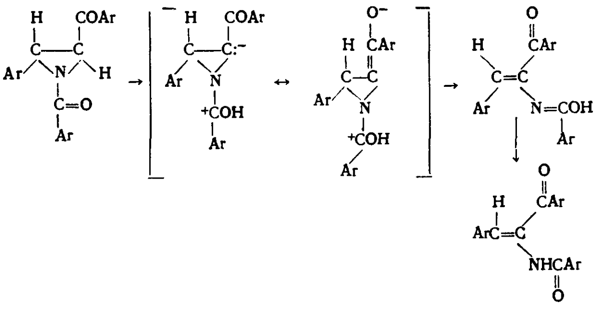


The thermolysis of the corresponding *cis*- and *trans*-1-(*p*-nitrobenzoyl)-2,3-diphenylaziridines leads to the *cis*- and *trans*-derivatives of oxazoline[66]. The mechanism of the pyrolytic isomerisations to oxazolines probably includes a four-centre displacement[59] or the intermediate contraction of the ion pair[67]:



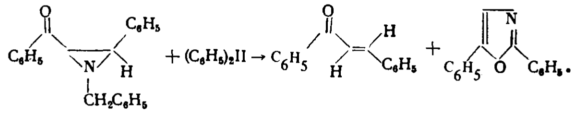
The study of the pyrolytic isomerisation of 1-acylaziridines taking into account stereochemical and kinetic data[66,77] led to the hypothesis that this intramolecular rearrangement consists of *cis*-elimination, including the displacement of the proton from the alkyl group to the amide oxygen. This displacement is impossible in the absence of an alkyl group at an aziridine carbon atom in 1-aroylaziridines or in the presence of steric factors preventing the formation of a bond between the amide oxygen and a proton.

On heating in boiling xylene, 1,3-diaroyl-2,3-arylaziridines[66] are converted into *α*-benzamidobenzoylacetophenone. In this case oxazolines are not formed, since there is a possibility of the displacement of the acid aziridine hydrogen atom to the amide oxygen atom and a reaction involving the dissociation of the carbon–nitrogen bond of the ring:

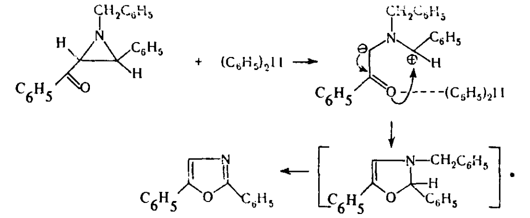


The isomerisation of aziridine derivatives involving the dissociation of the C–C bond of aziridine is known[78-81]. *trans*-3-Benzoyl-1-benzyl-2-phenylaziridine is converted into *trans*-benzylideneacetophenone (73% yield) and

2,5-diphenyloxazole (7% yield) on heating with diphenyliodonium iodide:



The following mechanism has been proposed for the isomerisation of aziridines to ring-expansion products[79]:

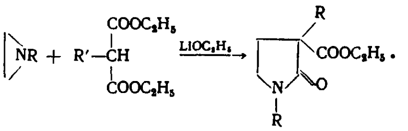


Diphenyliodonium iodide behaves as a Lewis acid and interacts with the C=O group, protonating the aziridine ring. The reaction of diphenyliodonium iodide with 2-benzoylaziridine yielded 2,5-diaryloxazoles and *αβ*-substituted ketones[80]. The aziridine ring-expansion product was not isolated when the reaction was carried out in anhydrous acetone and therefore the possibility of the formation of 2,3-dihydro-oxazoles cannot be explained, like the isomerisation of *N*-aroylaziridines, by the Heine mechanism. One of the possible mechanisms involves the interaction of diphenyliodonium iodide with the carbonyl group of the aziridine substituent and the dissociation of the aziridine C–C bond.

3. Interaction of Aziridines with Malonic Ester

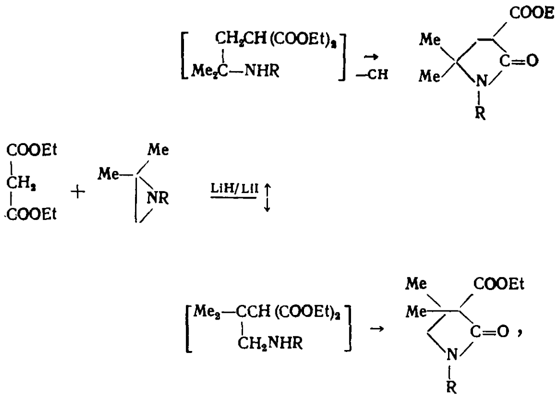
The reaction of aziridines with malonic ester leads to the formation of ring-expansion products—substituted pyrrolidinones. The first step in this reaction is aminoethylation, the subsequent intramolecular cyclisation with elimination of alcohol leading to the formation of pyrrolidinone derivatives.

In the reaction of *N*-phenylaziridine with malonic ester in the presence of lithium ethoxide, 3-ethoxycarbonyl-1-phenylpyrrolidin-2-one is formed[82,83]:



The reaction of 1-(*β*-phenylethyl)aziridine was carried out similarly[85]. In the presence of an excess of malonic ester aziridine is protonated. Under the influence of the enolate of malonic ester, the occurrence of competing processes is possible: *N*-alkylation (dimerisation of aziridine) and *C*-alkylation—formation of 3-ethoxycarbonyl-1-phenylethyl-pyrrolidin-2-one in 30% yield.

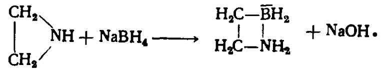
When malonic ester was heated with 2,2-dimethyl-1-(*β*-phenylethyl)aziridine in benzene[85] in the presence of LiH and LiI, 2-ethoxycarbonyl-5,5-dimethyl-1-(*β*-phenylethyl)pyrrolidin-2-one was isolated and then converted by alkaline hydrolysis into 5,5-dimethyl-1-(*β*-phenylethyl)-pyrrolidin-2-one:



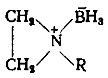
where R = $C_6H_5CH_2CH_2$.

Analysis and the NMR spectra led to the conclusion that the interaction of asymmetric aziridines with malonic ester involves an unsubstituted carbon atom with subsequent cyclisation to pyrrolidinone derivatives.

Earlier it was reported that unsubstituted aziridine reacts with sodium borohydride to forma four-membered heterocycle[86]:



Later investigations of this reaction confirmed the formation of aziridine salts (aminoboranes) in this process[87]:



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Whilst the present review was in the press, a paper dealing with the isomerisation of 1-(*p*-nitrobenzoyl)-2-vinylaziridine to a seven-membered derivative was published[88].

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Acyl Isocyanates

K.A.Nuridzhanyan

The methods of preparation and the reactions of acyl isocyanates are considered. The bibliography includes 197 references.

CONTENTS

I. INTRODUCTION

The advances in the chemistry of organic isocyanates have been reviewed fairly regularly[1-5] but these reviews dealt only with aryl and alkyl isocyanates. Recently new classes of compounds in which the isocyanate group is linked to silicon[6,7], phosphorus[6,8-13], difluorophosphoryl, fluorocarbonyl[14] and thioacyl[15-20], sulphonyl[21], etc. groups have been discovered and their properties investigated. The chemistry of each of these classes of isocyanates is fairly specific and requires a separate review. A recent review dealing with the chemistry of acyl and sulphonyl isocyanates, isothiocyanates, and isoselenocyanates[22] emphasises the similarity of the properties and not the specific features of the individual classes of isocyanates. Consequently reviews of such general type and those on specific branches of the chemistry of isocyanates are not mutually exclusive, supplementing one another. The inevitable repititions can be justified in each case by a new approach to the analysis of the literature data and new conclusions.

Such a special review on the chemistry of sulphonyl isocyanate was published recently[21] but the advances in the chemistry of acyl isocyanates have not as yet been reviewed.

Acyl isocyanates were obtained for the first time in 1862 by Schützenberger[23,24], i.e. 13 years after Würtz's discovery of organic isocyanates[24]; however, convenient methods for their synthesis became available only recently[26], which stimulated more extensive studies on these compounds.

Acyl isocyanates are chemically more reactive than the widely known[2,3] isocyanic acid esters. The presence of the additional acyl carbonyl group R–CONCO not only increases the reactivity but is also responsible for the ability of these compounds to undergo various reactions involving the formation of heterocycles.

In view of the above considerations, the author assumed that the present review, which deals with the syntheses, properties, and applications of acyl isocyanate and covers the literature up to January 1st, 1968, will be of interest and will stimulate further development of the chemistry of this interesting class of organic compounds.

II. METHODS OF SYNTHESIS OF ACYL ISOCYANATES

The available methods for the preparation of acyl isocyanates can be divided into two types: syntheses where the NCO group is already present in the starting materials and syntheses where it is produced in the course of the reaction.

1. Synthesis by the Reaction of Carboxylic Acid Chlorides with Cyanate Salts

Acetyl isocyanate, together with acetonitrile, was obtained by the reaction of silver cyanate[23,24] or mercury fulminate[27] with acetyl chloride. Under the same conditions, the reaction of silver cyanate and benzoyl chloride yields only benzonitrile[23]. The reaction of mercury fulminate with benzoyl chloride[28,29] or of silver fulminate with benzoyl bromide[30] followed by treatment of the reaction products with water led to the isolation of dibenzoylurea and a product melting at 107°C[28,29], which eventually proved to be (not until 1954) 3, 5-diphenyl-1, 2, 4-oxadiazole[31].

Acetyl and benzoyl isocyanates were obtained in a pure form for the first time in 1903 by slow addition of silver cyanate to an excess of the chloride of the corresponding acid with rapid distillation of the isocyanate produced[32,33].

Billeter's method[32,33] was subsequently improved by Hill and Degnan[34-36] and then by Areus and Prydol[37,38] and until 1962 remained virtually the only method for the synthesis of acyl isocyanates[31,39-42]. In 1963 Steyermark proposed a more convenient method for the preparation of acyl isocyanates by the reaction of carboxylic acid halides with cyanic acid in the presence of organic bases. The yield of acyl cyanates reaches 90%, but in a number of cases the process is complicated by the formation of polymeric products[43,44].

2. The Reaction of Phosgene and Phosgene-Forming Compounds With Acid Amides

The first attempts to prepare acyl isocyanate from carboxylic acid amides were unsuccessful[45-47]. Later, Waltmann and Wolf[48-51] shows that in an autoclave at 150°C a mixture of the amide and phosgene or trichloromethyl formate and other phosgene-forming compounds (among which oxalyl chloride may also be included[52]) in the presence of pyridine forms acylcarbamoyl chloride, which on heating in benzene with calcium oxide yields acyl isocyanate. However, this method did not become as important in the synthesis of isocyanates as the reaction of amines with phosgene[2,3].

The reaction of acid amides with oxalyl chloride proved to be more promising for the synthesis of acyl isocyanates[26,47,53-70]:

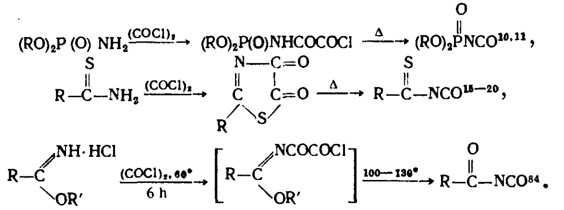
$$RCONH_2 + (COCl)_2 \xrightarrow{-2HCl, -CO} RCONCO.$$

The effect of oxalyl chloride on amides was investigated even earlier[71]: with a 1:2 reactant ratio, diacylurea was obtained[47,71,72], the thermal decomposition of which resulted in the formation of an amide, diacetamide, a nitrile, cyanuric acid, and carbon dioxide[73], while with a 1 : 1 reactant ratio the products were 2-alkylideneoxazolidine-4, 5-dione[47,74–78] and others.

Speziale and Smith[26,47,55] showed that, when the products of the reaction of oxalyl chloride with amides are subjected to thermal decomposition in a vacuum at fairly low temperatures with simultaneous distillation of the decomposition products, aroyl isocyanates are obtained in high yields. The yield of aliphatic acyl isocyanates is usually lower, and in the case of propionyl isocyanate it amounted to only 0.8%[55].

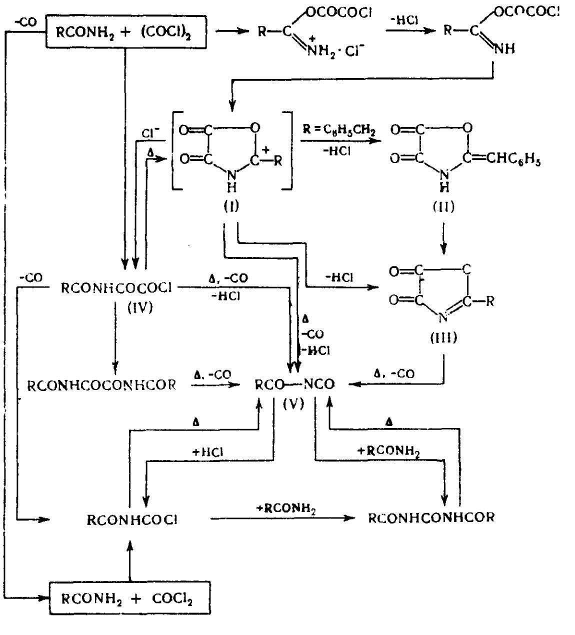
The above method of preparation of aroyl isocyanates was improved by Neidlein[70]. After these investigations, there was a considerable increase of interest also in the chemistry of oxalyl chloride[79–82], which was successfully used in the synthesis of other classes of acyl isocyanates:

$$RSO_2NH_2 \xrightarrow{(COCl)_2} RSO_2NHCOCOCl \xrightarrow{\Delta} RSO_2NCO^{83},$$



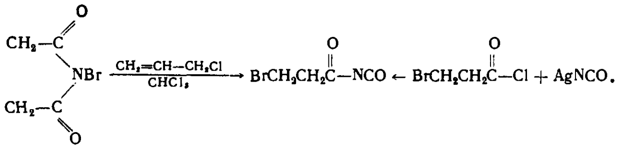
In the reaction of oxalyl chloride with carboxylic acid amides an *O*-aclyation product is probably formed initially and is then converted, with elimination of HCl and CO, either via the intermediate formation of compounds (II), (III), or (IV) or directly, into the acyl isocyanate (V). The low yield of alkanoyl isocyanates compared with that of aroyl isocyanates can probably be accounted for by the different stabilities of compounds (I). By analogy with 2-alkylideneoxazolidine-4, 5-dione[76], aryl-containing compounds (I) are more resistant to attack by the chloride ion than their alkyl analogues (Scheme 1)[68].

Scheme 1



For this reason the aryl compound decomposes only on heating in a vacuum and compound (V) is formed in a high yield. The alkyl derivative of compound (I) decomposes already under the reaction conditions with formation of compound (IV), which then enters into a number of side processes (Scheme 1)[66].

The method of preparation of β-bromopropionyl isocyanate by the rearrangement of *N*-bromosuccinimide is in a class by itself[85–88]:



The reaction takes place only in the presence of chloroform or bromoform and certain halogeno-olefins (allyl chloride and bromide, methylallyl chloride, 2, 3-dibromopropene, 3-bromo-2-t-butylpropene) in the presence of benzoyl peroxide. In the presence of crotyl bromide, 1-bromopropene, $\alpha\alpha\alpha$-trichlorotoluene, and a number of other olefins the reaction does not occur. The maximum yield of β-bromopropionyl isocyanate (70%) is attained on refluxing in chloroform for 4 h equimolar amounts of *N*-bromosuccinimide, allyl chloride, and a catalytic amount of benzoyl peroxide[88]. The product was also isolated in 16% yield in the photochemical bromination of 1, 4-*endo*-oxocyclohexane with *N*-bromosuccinimide in carbon tetrachloride. The reaction is of a radical type; this type of rearrangement does not occur with either chloro- or iodo-succinimides[86].

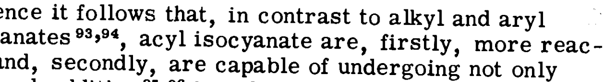
III. PROPERTIES OF ACYL ISOCYANATES

1. Physical Properties

Acyl isocyanates are colourless or yellowish liquids or low-melting solids which can be distilled in a vacuum. They have a sharp odour, and are readily hydrolysed by atmospheric moisture; they dissolve in the majority of organic solvents. Their infrared spectra[89,90] contain absorption bands at 2244 ± 1 cm^{-1} (asymmetric vibrations of the O=C=N group) and 1430 cm^{-1} (symmetrical vibrations of the O=C=N group); the bands at 1740 and 1050 cm^{-1} correspond to the vibrations of the C=O and C−N bonds in the group R−C(O)−N=; the bands due to the deformation vibrations of O=C=N and NC=O groups are located respectively at 632 and 570 cm^{-1}.

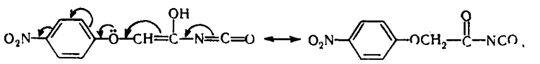
2. Chemical Properties

The characteristic features of the chemical properties of acyl isocyanates are a result of the charge and electron density distribution in the group CONCO, which may be described by the resonance of the following valence structures[91,92]:



$$R-\overset{\overset{O}{\|}}{C}-N=\overset{+}{C}-\bar{O} \leftrightarrow R-\overset{\overset{O^-}{|}}{C}=N-\overset{+}{C}=O \leftrightarrow R-\overset{\overset{O}{\|}}{C}-N=C=O \leftrightarrow R-\overset{\overset{O}{\|}}{C}-\bar{N}-\overset{+}{C}=O.$$

Hence it follows that, in contrast to alkyl and aryl isocyanates[93,94], acyl isocyanate are, firstly, more reactive and, secondly, are capable of undergoing not only 1, 2-cycloaddition[95,96] but also 1, 4-cycloaddition[91,92,97–99] reactions. In some cases the presence of the acyl group may be the cause of other more special properties of acyl isocyanates. Thus the surprisingly effective transmission of the influence of substituents on the reactivity of aryloxyacetyl isocyanates may be accounted for by the possibility of their tautomerism[68]:

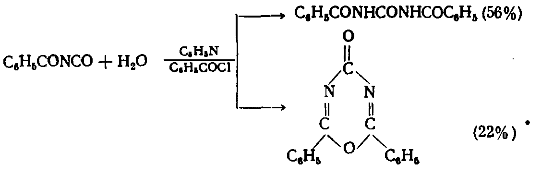


which evidently cannot occur in the case of aryloxyethyl isocyanates.

A. Reactions at Oxygen–Hydrogen and Sulphur–Hydrogen Bonds

The reaction with water of acetyl isocyanate[27], β-bromopropionyl isocyanate, etc.[85,86] yields the corresponding amides and carbon dioxide, the conversion of benzoyl isocyanate being to the extent of 75% into the amide and to the extent of 25% into dibenzoylurea[32].

In 1*N* sodium hydroxide solution benzoyl isocyanate forms only benzamide[37], while in a mixture with aqueous pyridine and benzoyl chloride it gives 56% of dibenzoylurea and 22% of 4-oxo-2,6-diphenyl-1,3,5-oxadiazine[31]. The last product is formed also under anhydrous conditions when the reaction is catalysed by an *N*-substituted pyridinium salt[92,100].



Acids react with acyl isocyanates with much greater difficulty. Thus the reaction with dialkyl phosphites takes place only in the presence of sodium ethoxide or catalytic amounts of triethylamine at 80–90°C over a period of 4 h.[101] The reaction of hydrogen chloride with acyl isocyanates gives the corresponding acylcarbamoyl chlorides[27,48-51].

The reaction of alcohols with acyl isocyanates has been most thoroughly investigated. It has been shown that they react more vigorously than phenols[66], giving good yields of acyl carbamates[26,27,32,38,55-57,60,64,66,68,85,88,101-104].

Polyhydric alcohols form with acyl isocyanates products corresponding to different degrees of addition—monoacyl, diacyl, etc. carbamates[88,102,105,106].

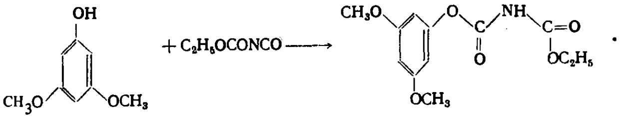
It has been erroneously assumed that the reaction of acetyl isocyanate with glycol gives a bis-addition product, while benzoyl isocyanate forms only the monoaddition product even when present in an excess. Later it was shown[106] that, regardless of their structure, acyl (and aroyl) isocyanates react with polyhydric alcohols to form as a rule polyaddition products, while with phenols monoaddition products are obtained. Thus, regardless of their structure, the reactant ratio, and the presence or absence of water in the reaction medium, the reaction of acyl (and aroyl) isocyanates with glycerol yields only products of addition to all three hydroxy-groups. Monoaddition could be achieved only by the action of 2,4-dichlorophenoxyacetyl isocyanate on isopropylidene-glycerol with subsequent ethanolysis of the product[106].

The presence in the alcohols of other functional groups—halogen atoms[55,57,66,88,102,105,107] and nitrile[88,102], carbonyl[88], carboxy-[102], dimethylamino-[57], xanthogenyl and dithiocarbamoyl groups[107,108], or unsaturated carbon–carbon bonds[55,57,66,88,102]—does not usually alter the normal course of their addition to acyl isocyanates.

However, if the alcohol molecule contains another functional group where the electron density at the constituent atom is higher than at the oxygen atom, for example NH_2, then the acyl isocyanate reacts preferentially with this group rather than with the hydroxy-group. The reaction with ethanolamine takes place stepwise in this way[39,105,106]:

$$HOCH_2CH_2NH_2 \xrightarrow{RCONCO} RCONHCONHCH_2CH_2OH \xrightarrow{RCONCO} RCONHCONHCH_2CH_2OCONHCOR\,.$$

Alkoxycarbonyl isocyanates react with 3,5-disubstituted phenols in two ways, depending on the electron-donor properties of the substituents: if the substituents are powerful donors (R_2N), then the isocyanate adds to a carbon atom of the aromatic ring (see Russ. p. 133), but if their electron-donor properties are less pronounced (OCH_3), then normal addition to the OH group takes place[109]:



Oximes, which are more basic than phenol[110], react with acyl isocyanates just as vigorously as alcohols and at room temperature form as a rule stable crystalline acyl carbamoyloxyoximes[111-113]:

$$\rangle C{=}N{-}OH + RCONCO \xrightarrow{20^\circ} RCONHCOON{=}C\langle\ .$$

However, the corresponding derivatives of acetaldoxime can be obtained only at 0°C, since at 20°C they readily decompose[111].

The reactivity of oximes depends to a considerable degree on the steric configuration of the substituent in the *cis*-position relative to the hydroxy-group and to a lesser extent on the bulk of the *trans*-substituent and the electronic effects of the substituents. For this reason, ketoximes are less reactive than aldoximes and among the latter the *syn*-isomer is the more reactive[112].

The reaction of acyl isocyanates with *syn*- and *anti*-benzaldoximes yields only *syn*-acylcarbamoylbenzaldoxime[111].

Mercaptans react with acyl isocyanates less vigorously than their oxygen analogues, forming the corresponding thiolocarbamates[26,56,58,66]:

$$R{-}SH + R'CONCO \xrightarrow{20^\circ} R'CONHCOSR\,.$$

The reaction of terephthaloyl di-isocyanate with thiophenol yields terephthaloyl bis(phenylthiolocarbamate)[98].

B. Reactions at Nitrogen–Hydrogen Bonds.

Ammonia and primary and secondary amines react vigorously with acyl isocyanates at room temperature with formation of the ureides of the corresponding acids[26,32,38,39,42,57,68,84,85,88,101,103]. With increase of the basicity of the amines, their reactivity also rises[67,68].

By virtue of the exceptional ease and completeness of this reaction, it is frequently used to identify new acyl isocyanates[27,43,47,56,59]. Bis-acyl isocyanates also react readily with amines[98].

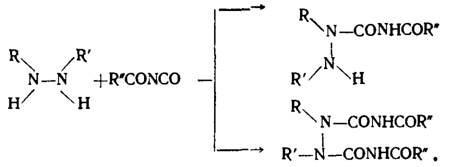
Polyfunctional compounds containing, apart from the amino-group, multiple bonds[68] and HO,[39,105,114] NO_2,[67,114] Me_2N,[67] COOEt, COOH,[114] and other groups form primarily ureides. When the molecule contains two amino-groups or an amino-group and a hydroxy-group, initially one NH_2 group reacts completely[39,106], and then, in the presence of an excess of acyl isocyanate, addition to the second NH_2 or OH group takes place[105,106,114].

Hydroxylamine and its derivatives react with acyl isocyanates in the same way as other amino-alcohols with formation of hydroxy- or alkoxy-ureas[40,62,69,114]:

$$RO{-}NH_2 + R'CONCO \rightarrow RONHCONHCOR'.$$

The reaction takes place readily not only with the free bases[62,69,114] but also with hydroxylammonium salts in the presence of pyridine[40].

Like other diamines[32,105,114], *hydrazine and its derivatives* can react with acyl isocyanates to form two series of compounds[32,38,61,115,116]:



However, the mode of reaction depends little on the reactant ratio; the decisive factors here are the nature of the acyl isocyanate and the substituents and the nitrogen atoms of the hydrazine. Hydrazine hydrate contains two equivalent (as regards nucleophilic properties) nitrogen atoms and therefore its reaction with benzoyl isocyanate yields only 1, 6-dibenzoylurea[38].

The basicities of the two nitrogen atoms in arylhydrazines are not the same and therefore the nitrogen atom furthest removed from the aryl group enters into the reaction[38].

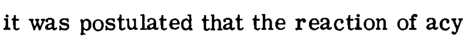
The structure of 4-benzoyl-1-phenylsemicarbazide obtained for the first time in this way by Billeter[32] was subsequently demonstrated by Arcus and Prydal[38], who showed at the same time that 4-nitro- and 2, 4-dinitrophenylhydrazines also react. The reaction with terephthaloyl di-isocyanate takes place similarly but involves two isocyanate groups[98].

Thus aroyl isocyanates[32,38,98] form with hydrazine monoaddition products. In contrast to them, acyl isocyanates tend to form diadducts[32,61,69,115,116].

However, α-halogenoacyl isocyanates react with phenyl- and 4-nitrophenyl-hydrazines to form both di- and monoaddition products, the yield of which varies with the reaction ratio[115].

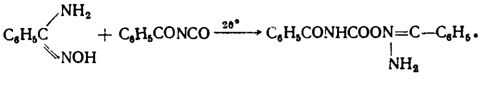
The more reactive aryloxyacetyl isocyanates readily form in high yields (similarly to aroyl isocyanates) predominantly monoadducts with phenyl- and 4-nitrophenylhydrazines[61,69]. In contrast to the latter, the reactions with 2, 4-dinitrophenylhydrazine of all acyl isocyanates, regardless of their structure, result only in monoaddition products[115].

The reaction of aldehyde and ketone hydrazones with acyl isocyanates in molar proportions of 1 : 1 results in ready formation of the corresponding 4-acylsemicarbazones[117,118] and the reaction in proportions of 2 : 1 yields of diadducts, which probably have the structure of 3-alkylideneamino-1, 5-diacylbiuret[119]:



$$R_2C{=}NNH_2 + 2R'CONCO \rightarrow R'CONHCO\underset{\displaystyle N{=}CR_2}{N}CONHCOR'.$$

Initially it was postulated that the reaction of acyl isocyanates with *amidoximes* results in the formation of *N*-(acylcarbamoyl)amidoximes[120], but NMR and infrared spectroscopic measurements showed that the addition is exclusively to the oxygen atom:



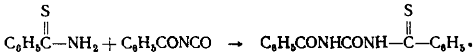
$$C_6H_5C\begin{matrix}\nearrow NH_2\\ \searrow NOH\end{matrix} + C_6H_5CONCO \xrightarrow{20^\circ} C_6H_5CONHCOON{=}\underset{\displaystyle NH_2}{C}{-}C_6H_5.$$

Acyl isocyanates react with *acid amides* with greater difficulty than with the compounds examined above, containing N–H, O–H, or S–H bonds. The reaction takes place on heating and leads to the formation of the corresponding diacylureas[27,28,30,32,45,71,121-123].

Sulphonamides form with acyl isocyanates *N*-sulphonyl-*N′*-acylureas[32,124]:

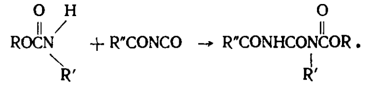
$$R{-}SO_2NH_2 + R'CONCO \rightarrow R'CONHCONHSO_2R.$$

The reaction of *thiobenzamide* and benzoyl isocyanate on refluxing in benzene yields *N*-benzoyl-*N′*-thiobenzoylurea[125]:



$$C_6H_5\overset{\displaystyle S}{\overset{\|}{C}}{-}NH_2 + C_6H_5CONCO \rightarrow C_6H_5CONHCONH{-}\overset{\displaystyle S}{\overset{\|}{C}}{-}C_6H_5.$$

Carbamates react with acyl isocyanates more readily than carboxylic acid amides, forming in all cases, in contrast to aryl isocyanates[126-128], the corresponding acyl allophanates[61,69,114,129]:



$$RO\overset{\displaystyle O}{\overset{\|}{C}}N\begin{matrix}\nearrow H\\ \searrow R'\end{matrix} + R''CONCO \rightarrow R''CONHCO\underset{\displaystyle R'}{N}\overset{\displaystyle O}{\overset{\|}{C}}OR.$$

Ureas[35] *and thioureas*[36] react with acyl isocyanate, forming respectively acylbiurets and acylthiobiurets[33-36,39].

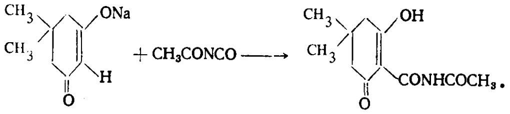
Hydrazoic acid reacts vigorously with acyl isocyanates giving high yields of acylcarbamoyl azides which are stable at room temperature[130,131]:

$$N{\equiv}N{=}N{-}H + RCONCO \rightarrow RCONHCON_3.$$

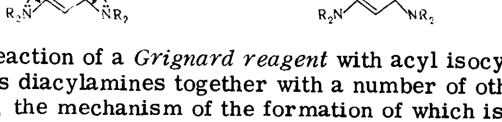
The reaction with terephthaloyl di-isocyanate takes place similarly[98].

C. Reactions at Carbon–Hydrogen Bonds and with Grignard Reagents

The carbon–hydrogen bond can be readily involved in the reaction with acyl isocyanates if the electron density at the carbon atom is sufficiently high. This reaction usually gives acylamides[109,132]. Thus in the synthesis of tetracycline an acetylcarbamoyl substituent was introduced into dimedone with the aid of acetyl isocyanate[132]:



Ethoxycarbonyl isocyanate enters into a similar reaction with somewhat greater difficulty[132]. Thus the reaction with 3, 5-di(dialkylamino)phenol yields 2, 4-dialkylamino-6-hydroxybenzoyl carbamates[109]:



The reaction of a *Grignard reagent* with acyl isocyanates also gives diacylamines together with a number of other products, the mechanism of the formation of which is still obscure[133]:

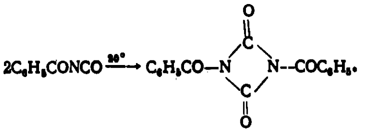
$$\begin{aligned}RMgX + C_6H_5CONCO \xrightarrow{20^\circ} C_6H_5CONHCOR + C_6H_5COR + C_6H_5CONHCONHCOC_6H_5 +\\ + C_6H_5CONHCONH_2 + C_6H_5CONH_2 + C_6H_5CONHCOC_6H_5.\end{aligned}$$

The composition of the reaction products depends on the ratio and order of addition of the starting materials and the nature of the organic group and the halogen in the organomagnesium compound.

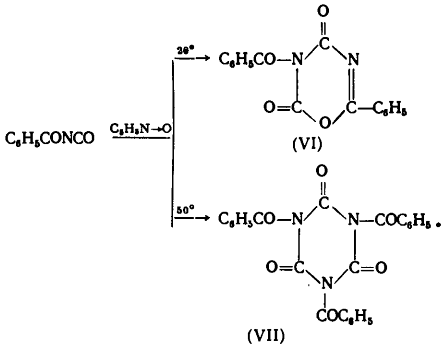
D. 1,2- and 1,4-Cycloaddition Reactions

a. Dimerisation and trimerisation of acyl isocyanates. Both 1,2- and 1,4- cycloaddition reactions are characteristic of acyl isocyanates[99] and therefore in the presence of the usual catalysts for the polymerisation of isocyanates (pyridine[134], triethylamine[135], and others) two series of dimers and the corresponding trimers are formed[92,98,100].

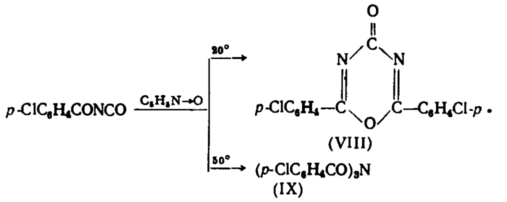
By treating benzoyl isocyanate with pyridine, Neidlein[98] obtained 82% yield of the benzoyl isocyanate dimer (1,3-dibenzoyluretidine-2,4-dione):



By the action of pyridine 1-oxide on benzoyl isocyanate at 20° and 50°C, Tsuge and Mizuguchi[92,100] obtained respectively the isomeric dimer [5-benzoyl-4,6-dioxo-2-phenyl-1,3,5-oxadiazine (VI)] and trimer [tribenzoyl isocyanurate (VII) (m.p. 162°C)]:


(VI)
(VII)

The polymerisation reaction is influenced not only by temperature but also by the nature of the catalyst and the substituent in the benzene ring[92,100]. Thus when p-chlorobenzoyl isocyanate is treated with pyridine 1-oxide at 20°C, the product is 2,6-di-(p-chlorophenyl)-4-oxo-1,3,5-oxadiazine (VIII), while at 50°C tri-(p-chlorobenzoyl)amine (IX) is formed:


(VIII)
(IX)

Similarly at 50°C p-nitrobenzoyl isocyanate yields tri-(p-nitrobenzoyl)amine together with a small amount of 2,6-di-(p-nitrophenyl)-4-oxo-1,3,5-oxadiazine.

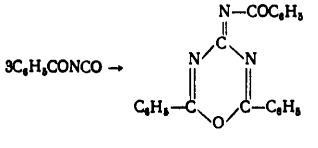
In the presence of tin tetrachloride benzoyl and p-methoxybenzoyl isocyanate are converted into the corresponding trimers.

Triethylamine converts benzoyl isocyanate at 50°C into the dimer (VI); at 80°C 2,4-diphenyl-6-oxo-1,3,5-oxadiazine is formed together with a small amount of tribenzoylamine and triphenyl-*s*-triazine.

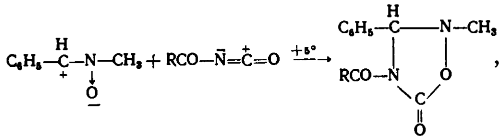
Under these conditions, p-methoxybenzoyl isocyanate forms a trimer and p-chloro- and p-nitro-benzoyl isocyanates are converted into the corresponding 6-oxo-1,3,5-oxadiazines.

Regardless of the nature of the substituent in the acyl isocyanate, N-substituted pyridinium salts in all cases lead to the formation of the same products—2,6-diaryl-4-oxo-1,3,5-oxadiazines[92,100].

Phospholen oxides convert benzoyl isocyanate into 4-benzamido-2,6-diphenyl-1,3,5-oxadiazine[136]:

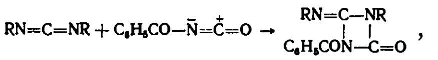


b. 1,2-Cycloaddition reactions. The reaction of *N-methyl benzaldoxime* with acyl isocyanates yields 1,2-cycloaddition products—4-acyl-2-methyl-3-phenyl-1,2,4-oxadiazolidin-5-one[95,99]:



where R = C_6H_5 or CH_2Cl.

Carbodi-imides add to benzoyl isocyanate with formation of 1-benzoyl-4-phenylimino-1,3-uretidin-2-one[95,99]:



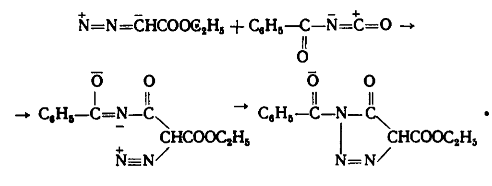
$$RN{=}C{=}NR + C_6H_5CO{-}\bar{N}{=}\overset{+}{C}{=}O \rightarrow \begin{array}{l} RN{=}C{-}NR \\ C_6H_5CON{-}C{=}O \end{array},$$

where R = C_6H_5 or C_6H_{11}.

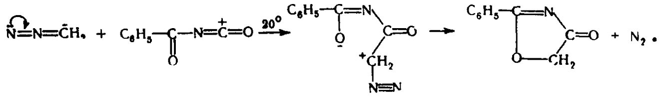
1,3-Dienes (butadiene, isoprene, 2,3-dimethylbutadiene, cyclopentadiene, etc.) react with acyl isocyanates similarly to carbodi-imides, forming the corresponding β-lactams[96]:

$$CH_2{=}CH{-}CH{=}CH_2 + C_6H_5CONCO \xrightarrow{0-40^\circ} \begin{array}{l} CH_2{=}CH{-}CH{-}CH_2 \\ C_6H_5CON{-}C{=}O \end{array}.$$

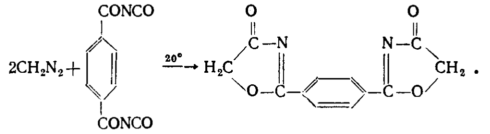
Diazoacetic ester, which may be regarded as a 1,3-dipole, forms with benzoyl isocyanate the ethyl ester of 1-benzoyl-5-oxotriazole-4-carboxylic acid. Probably the reaction takes place in two stages: initially an adduct is formed, which then undergoes intramolecular cyclisation[91]:



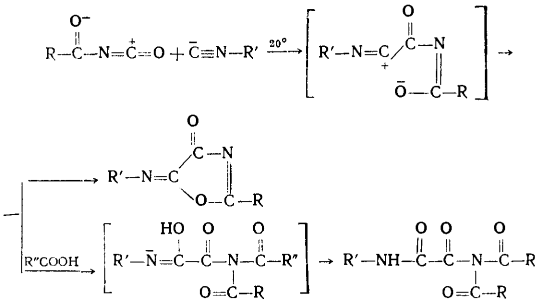
c. 1,4-Cycloaddition reactions. In contrast to diazoacetic ester, *diazomethane* reacts with benzoyl isocyanate as a 1,1-dipole[91], which results in the formation of 2-phenyl-4-oxazolone. Here too the initially formed adduct undergoes subsequently intramolecular cyclisation[97-99]:



Similarly the reaction of terephthaloyl di-isocyanate with diazomethane readily yields 1,4-di-(4-oxo-Δ^3-oxazolin-2-yl)benzene[98]:



Isonitriles, which are also 1,2-dipoles[91,99,137], react with acyl isocyanates to give 2-aryl(alkyl)-5-aryl(alkyl)-imino-oxazolin-4-ones. The reaction evidently takes place as in the preceding cases, via an intermediate adduct, which, in the absence of other reactants, undergoes subsequent intramolecular cyclisation[91]. However, when the reaction mixture contains an acid, the latter probably prevents the cyclisation of the intermediate, forming a second intermediate which is subsequently converted into a linear mixed amide[138]:

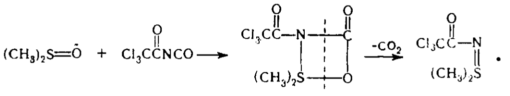


where R = R′ = R″ = C_6H_5 or C_6H_{11}.

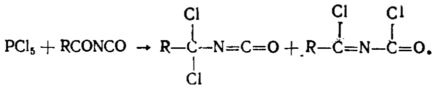
Di-isonitriles react similarly. 1,4-Di-isocyanobenzene and 1,4- and 1,3-di-isocyanocyclohexanes readily react with benzoyl isocyanate to form a mixture of the *cis*- and *trans*- isomers respectively of 5,5′-(*p*-phenylenedinitrilo)bis(2-phenyl-2-oxazolin-4-one and 5,5′-[1,3(or 1,4)-cyclohexylenedinitrilo)bis(2-phenyl-2-oxazolin-4-one[137].

E. Substitution Reactions

a. Reactions with elimination of CO from the isocyanate group. The reaction of *dimethyl sulphoxide* with dichloroacetyl isocyanate at 20°C in ether and with trichloroacetyl isocyanate (mixture refluxed in acetonitrile) gives high yields of the corresponding *N*-acylsulphimines[139]. By analogy with sulphonyl isocyanates[140], the reaction of acyl isocyanates probably takes place via 1,2-cycloaddition with subsequent elimination of carbon dioxide:

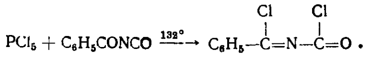


b. Reactions with elimination of an oxygen atom. *Phosphorus pentachloride chlorinates* acyl isocyanates in different ways depending on the nature of the acyl group, but this always involves only the elimination of one oxygen atom from the acyl carbonyl[141,142]. On prolonged heating with phosphorus pentachloride, mono-, di-, and tri-chloro acetyl isocyanates form a mixture of αα-dichloroalkyl isocyanate and α-chloroalkylidenecarbamoyl chloride:



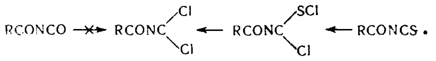
$$PCl_5 + RCONCO \rightarrow RCCl_2-N{=}C{=}O + R-CCl{=}N-CCl{=}O.$$

Under these conditions, benzoyl isocyanate yields only α-chlorobenzylidenecarbamoyl chloride[141,142]:



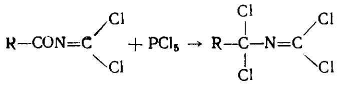
$$PCl_5 + C_6H_5CONCO \xrightarrow{132^\circ} C_6H_5-CCl{=}N-CCl{=}O.$$

More extensive chlorination of benzoyl isocyanate could not be achieved[141]. The dichlorides of *N*-acylisonitriles have been obtained by the chlorination of acyl isothiocyanates[141-146]:



$$RCONCO \not\rightarrow RCONCCl_2 \leftarrow RCONC(SCl)Cl \leftarrow RCONCS.$$

On heating with phosphorus pentachloride, the dichlorides yield products corresponding to more extensive chlorination of acyl isocyanates[141,142]:



$$R-CON{=}CCl_2 + PCl_5 \rightarrow R-CCl_2-N{=}CCl_2.$$

IV. APPLICATIONS OF ACYL ISOCYANATES

Higher (stearyl, palmityl, etc.) acyl isocyanates have been patented as agents for imparting water-repellent properties to textiles[48-51]. The possibility of using acyl isocyanates for the synthesis of polymers[147] and for the identification of alcohols[88] is being investigated. Acyl isocyanates are used in preparative organic chemistry for the synthesis of a wide variety of different classes of compounds: ureides[42,56,57,59,104,114,121-124,148], acyl carbamates[60,102,104,108,115,149-156], acyl thiolcarbamates[58,157], acylbiurets[34-36], acyl alkoxyureas[40,158], acyl allophanates[68,129], acylsemicarbazides[61,69,115], acylcarbamoyliminophosphoranes[130], *N*-alkylidene-1-aminohydantoins[117], 1,5-diaryl-3-hydroxy-1,2,4-triazoles[38], benzoxazines[109], and other heterocyclic compounds[108,159,160] with biological activity[148,150-156,161,162-179]. Halogenoacyl carbamates obtained in this way have been patented as stabilisers for photographic emulsions[104].

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During the period when this review was being dealt with by the editors, the following papers were published.

1. *On the methods of preparation*: from oxalyl chloride and imino-esters[180,181] or chloroimino-esters[182] of carboxylic acids or the amides of chrysanthemic acid[183] and from trifluoroacetic anhydride and isocyanic acid[184].

2. *On chemical reactions*: with hydrazines[185,186], alcohols, mercaptans and amines[187-189], enamines[190], ethyleneimine[191], 2-aminothiazoles[192], *N*-(trimethylsilyl)-dialkylamines[193], hydroperoxides[194], substituted ketens[195], perchloric acid[196], and dienes[197].

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All-Union Research Institute for Chemical Plant Protection Agents, Moscow

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Polymerisation of Allyl Compounds

V.I.Volodina, A.I.Tarasov, and S.S.Spasskii

The review deals with the advances in the theory of the formation of allyl polymers and their practical applications. Until recently there was only limited interest in allyl polymers because with the usual free-radical initiation allyl compounds polymerise with difficulty and yield polymers with a low molecular weight. The principal cause of the formation of low-molecular-weight polymers is degradative chain transfer to the monomer, as a result of which the kinetic chain is terminated. A property of the degradative chain transfer is the constancy of *dM/dP*, i.e. a linear relation between the amount of peroxide decomposed and the amount of monomer polymerised. In addition to degradative chain transfer, a characteristic feature of allyl monomers is effective chain transfer, which depends on the structure of the monomer.

The polymerisation of diallyl compounds has a cyclolinear mechanism, which leads to the formation of macromolecules with alternating cyclic and linear units.

The behaviour of allyl monomers in copolymerisation reactions is determined by their low reactivity compared with that of the majority of vinyl monomers. The chemical structure of allyl monomers does not as a rule have a significant influence on their reactivity.

In recent years polymers based on allyl monomers have found many applications in engineering. Copolymerisation with other monomers and polymers yielded materials with high mechanical strength, thermal and chemical stability, and good insulating and adhesive properties. They are used as fibres, films, coatings, optical glasses, binders for reinforced plastics, etc.

The bibliography includes 386 references.

CONTENTS

I. INTRODUCTION

Allyl polymers are obtained by the polymerisation and copolymerisation of allyl compounds, which are characterised by the presence of the allyl group $CH_2=CH-CH_2$. The name of these compounds arises from the fact that they are the principal component of the essential oil of garlic–diallyl sulphide.

In recent years there has been increased interest in allyl resins because of their exceptional physical and electrical properties. They have found extensive application in electronic and electrical engineering industries (insulators, connecting sleeves, gas-tight seals, etc.)[1]. The diallyl phthalate and diallyl isophthalate pre-polymers are thermosetting resins with thermal and chemical stability and exceptional insulating properties; articles made from them are characterised by their dimensional stability[2].

Reinforced materials based on these resins exhibit stability of mechanical strength in prolonged use over a wide range of temperatures and humidities[3].

There is a considerable promise of development for phosphorus-containing allyl polymers, which are used as fire-resistant materials[4].

Allyl monomers are used in coatings and copolymers based on them are used to improve the thermal stability and the resistance to wear of certain materials.

The above wide range of the applications of allyl polymers accounts for the interest in them. However, the extensive data and practical experience accumulated in recent years have not been reflected in Soviet reviews or monographs. Abroad there have also been very few such publications[1,5,6].

II. ALLYL POLYMERISATION

All known methods of initiation are used in the polymerisation of allyl compounds. However, the effectiveness of the initiating agents is not the same. In the presence of free-radical initiators, allyl compounds polymerise with difficulty and give polymers in low yields and with low molecular weights[7]. This applies to a lesser extent to diallyl compounds, which form three-dimensional structures even at relatively low conversions.

Ionic catalysts are more effective. In their presence certain allyl compounds form polymers with very high molecular weights.

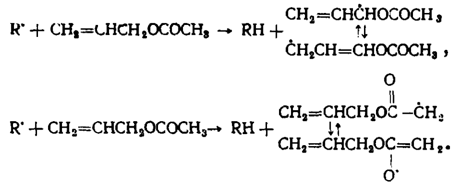
The use of γ-radiation also makes it possible to obtain allyl polymers with high molecular weights. For certain allyl monomers, this is the only method of polymerisation.

1. Radical Polymerisation

The same elementary steps are characteristic of the free-radical polymerisation of allyl and vinyl monomers, but for the former the chain transfer from the growing radical to the monomer leads not only to the termination of the growing radical but also to the cessation of the chain reaction. Bartlett, Gaylord, Eirich, Walling, and others[4,8-28] have investigated the mechanism and kinetics of the radical polymerisation of allyl compounds.

In the radical polymerisation of allyl monomers, benzoyl peroxide is most often used as an initiator. Gaylord, Nozaki, and others[23-25] showed that the decomposition of benzoyl peroxide in allyl alcohol, allyl bromide, and allyl esters is a first-order reaction, the rate constant of which increases with the initial concentration of the peroxide. The rate of decomposition of benzoyl peroxide in allyl esters is not the same, decreasing in the sequence allyl trimethylacetate > allyl propionate > allyl acetate > allyl ethyl carbonate.

In the initiation of the polymerisation of allyl acetate with benzoyl peroxide there is a possibility of the formation of two types of radicals, which are incapable of chain propagation because they are stabilised by conjugation[13]:



$$R^{\cdot} + CH_2{=}CHCH_2OCOCH_3 \rightarrow RH + \begin{matrix} CH_2{=}CH\dot{C}HOCOCH_3 \\ \uparrow\downarrow \\ \dot{C}H_2CH{=}CHOCOCH_3 \end{matrix},$$

$$R^{\cdot} + CH_2{=}CHCH_2OCOCH_3 \rightarrow RH + \begin{matrix} CH_2{=}CHCH_2O\overset{\overset{O}{\|}}{C}-\dot{C}H_2 \\ \downarrow\uparrow \\ CH_2{=}CHCH_2O\underset{\underset{O^{\cdot}}{|}}{C}{=}CH_2 \end{matrix}.$$

On this basis, Bartlett and Altschul[13] proposed a mechanism for the radical polymerisation of allyl monomers and found that the ratio of the amount of monomer consumed to the amount of benzoyl peroxide decomposed is constant. This discovery constituted an important milestone in the development of the theory of the radical polymerisation of allyl compounds. Later Gaylord and Eirich[25] gave a more complete polymerisation mechanism, for example with allyl acetate:

$$(C_6H_5COO)_2 \xrightarrow{k_1} 2C_6H_5COO^{\cdot}, \quad (1)$$

$$C_6H_5COO^{\cdot} + CH_2{=}CHCH_2OCOCH_3 \xrightarrow{k_a} C_6H_5COOCH_2\dot{C}HCH_2OCOCH_3, \quad (2)$$

$$C_6H_5COO^{\cdot} + CH_2{=}CHCH_2OCOCH_3 \xrightarrow{k_b} C_6H_5CH_2\dot{C}HCH_2OCOCH_3 + CO_2, \quad (3)$$

$$C_6H_5COO^{\cdot} + CH_2{=}CHCH_2OCOCH_3 \xrightarrow{k_c} C_6H_5COOH + CH_2{=}CH\dot{C}HOCOCH_3\ (r), \quad (4)$$

$$C_6H_5COO^{\cdot} + CH_2{=}CHCH_2OCOCH_3 \xrightarrow{k_d} C_6H_5COOH + CH_2{=}CHCH_2OCO\dot{C}H_2\ (\gamma), \quad (5)$$

$$R_n + CH_2{=}CHCH_2OCOCH_3 \xrightarrow{k_2} R_nCH_2\dot{C}HCH_2OCOCH_3, \quad (6)$$

$$R + CH_2{=}CHCH_2OCOCH_3 \xrightarrow{k_3} RH + CH_2{=}CH\dot{C}HOCOCH_3\ (r), \quad (7)$$

$$R + CH_2{=}CHCH_2OCOCH_3 \xrightarrow{k_4} RH + CH_2{=}CHCH_2OCO\dot{C}H_2, \quad (8)$$

$$r + r \xrightarrow{k_5} r - r, \quad (9)$$

$$\gamma + \gamma \xrightarrow{k_6} \gamma - \gamma, \quad (10)$$

$$r + \gamma \xrightarrow{k_7} r - \gamma. \quad (11)$$

Kinetic analysis of this mechanism led to an expression, which essentially confirms the finding of Bartlett and Altschul:

$$\frac{dM}{dP} = 2\left[1 + \frac{(k_2 + k_3 + k_4)(k_a + k_b)}{k^0 (k_3 + k_4)}\right] = \text{const},$$

where $k^0 = k_a + k_b + k_c + k_d$.

In the study of the polymerisation of allyl trimethylacetate the authors of this mechanism observed, and other investigators confirmed[11,14,26,28], that the kinetics of the polymerisation of certain allyl monomers are significantly affected by radical substitution reactions. Therefore, Gaylord and Eirich[25] modified the kinetic mechanism, replacing reactions (5), (8), (10), and (11) by others corresponding to a radical-substitution mechanism:

$$C_6H_5COO^{\cdot} + CH_2{=}CHCH_2OCOC(CH_3)_3 \xrightarrow{k_d'} CH_2{=}CHCH_2OCOC_6H_5 + (CH_3)_3CCOO^{\cdot}, \quad (12)$$

$$R + CH_2{=}CHCH_2OCOC(CH_3)_3 \xrightarrow{k_4'} CH_2{=}CHCH_2R + (CH_3)_3CCOO^{\cdot}, \quad (13)$$

$$(CH_3)_3CCOO^{\cdot} + CH_2{=}CHCH_2OCOC(CH_3)_3 \xrightarrow{k_{4a}} (CH_3)_3CH + CH_2{=}CH\dot{C}HOCOC(CH_3)_3\ (r), \quad (14)$$

$$(CH_3)_3CCOO^{\cdot} + CH_2{=}CHCH_2OCOC(CH_3)_3 \xrightarrow{k_{4b}} CH_3{=}CHCH_2C(CH_3)_3 + CO_2 + (CH_3)_3CCOO^{\cdot}. \quad (15)$$

In the steady state

$$\frac{dM}{dP} = \frac{2}{k^0}\left[(k_a + k_b + k_c) + \frac{(k_2 + k_3)(k_a + k_b)}{k_3 + k_4'} + k^{*}\right] = \text{const},$$

where

$$k^{*} = k_d' + \frac{k_4'(k_a + k_b)}{k_3 + k_4'}.$$

Probably both mechanisms of allyl polymerisation can occur independently, since they show significant differences.

The main conclusion which follows from the mechanisms is the constancy of *dM/dP*, i.e. a linear relation between the amount of benzoyl peroxide consumed and the amount of monomer polymerised. This implies that in the polymerisation of allyl monomers the rates of chain propagation and termination are similar. Such a rate of chain termination can be explained by chain transfer to the monomer, which results in the formation of radicals stabilised by conjugation and incapable of chain propagation. This type of chain transfer is called degradative and the constancy of *dM/dP* is its characteristic property.

The occurrence of degradative chain transfer was demonstrated experimentally by Bartlett and Tate[19] in the polymerisation of deuterium-substituted allyl acetate $CH_2{=}CHCD_2OCOCH_3$.

When ordinary hydrogen is replaced by deuterium in allyl acetate, the rate of polymerisation increases by a factor between 1.93 and 2.89.

The molecular weight of the deuteriated polymer increases by a factor of 2.38. On the other hand, it is known that the rate of dissociation of hydrogen in a radical substitution reaction is approximately three times higher than for deuterium. On this basis, one may assert that chain termination occurs as a result of the interaction of the growing polymeric radical with the monomer.

Characteristic allyl polymerisation is observed even when the α-methyl group is located in the side-chain of the monomer. Thus isopropenyl acetate polymerised in the presence of benzoyl peroxide gives a polymer with a low molecular weight[22].

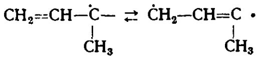
As well as degradative chain transfer, the polymerisation of allyl monomers exhibits effective chain transfer where allyl radicals can combine with monomers and thus propagate the chain reaction[10,11,14,15,25,26]. Sakurada and Takahashi[15] proposed a kinetic mechanism taking into account the effective chain transfer and derived an equation for the quantitative determination of the degradative chain transfer allowing for the effective transfer:

$$\frac{k_D}{k_D + k_T} = \frac{2\overline{DP}}{\left[\frac{dM}{dP}\right]_0 + 2},$$

where k_D and k_T are the rate constants for the degradative and effective chain transfer of the growing polymer radical to the allyl monomer and $\overline{DP}$ is the average degree of polymerisation.

The quantity $k_D/(k_D + k_T)$ for allyl esters and ethers decreases in the sequence allyl ethyl ether > allyl carbonate > allyl acetate > allyl propionate > allyl trimethylacetate > allyl laurate > allyl benzoate > allyl chloroacetate.

In the polymerisation of the first three allyl esters about 50% of the chain transfer reactions are effective. The more effective chain transfer in allyl chloride and allyl chloroacetate (65–86%) results from the formation of halogen-containing reactive radicals: $CH_2{=}CH\dot{C}HCl$ and $CH_2{=}CHCH_2OCO\dot{C}HCl$. Gaylord[11] observed that the contribution of effective chain transfer reactions in the polymerisation of allyl acetate is only 24%. The explanation is that, of the two resonance structures of the allyl radicals $CH_2{=}CH\dot{C}H \rightleftharpoons \dot{C}H_2{-}CH{=}CH_2$ in allyl acetate, the secondary (left-hand) radical is more stable, while in methylallyl acetate the primary (right-hand) radical of the pair



$$CH_2{=}CH-\underset{\displaystyle CH_3}{\underset{|}{\dot{C}}}- \rightleftarrows \dot{C}H_2-CH{=}\underset{\displaystyle CH_3}{\underset{|}{C}}\ \cdot$$

is more stable by virtue of the effect of the electron-donating methyl group. Since the primary radical is more reactive than the secondary radical, it participates more in the effective chain transfer, which in this case reaches 86%.

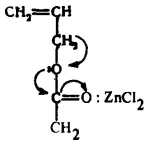
Walling and coworkers[17,18] showed that the degradative chain transfer can be significantly suppressed by the polymerisation of allyl monomers under pressure. When the pressure is changed from 1 to 8 atm, the overall rate of polymerisation increases by a factor of 5. The average degree of polymerisation also rises and the rate of chain termination falls.

This is evidence that the kinetic chain lengthens and chain transfer to the monomer becomes less degradative.

2. Complex–Radical Polymerisation

In a number of studies[29-31] attention has been drawn to the acceleration of the radical polymerisation of certain vinyl compounds in the presence of co-ordination-unsaturated metal halides such as LiCl, $ZnCl_2$, etc.

It has been suggested that this type of polymerisation be referred to as complex–radical polymerisation[32]. A similar acceleration is observed in the polymerisation and copolymerisation of allyl monomers[32-34]. It follows from the experimental data obtained in these studies that metal halides form complexes with the functional groups of the monomers. In the allyl acetate–$ZnCl_2$ complex the bond is formed largely via the group C=O, which leads to the shift of electron density over the entire group $-CH_2-O-\overset{\displaystyle O}{\overset{\|}{C}}-$. The structure of the allyl acetate–$ZnCl_2$ complex can be represented thus:



On the basis of this mechanism, it is difficult to explain the change in the activity of the double bond of the monomer or the activity of the chain propagation radicals under the influence of $ZnCl_2$. Furthermore, the increased rate of chain propagation when other conditions are identical should result in an increase of chain length, which is not observed experimentally. The increased rate of polymerisation may be due to the decreased probability of the degradative chain transfer of the monomer molecules in the complex. Another possible explanation of the increased rate is activation of the allyl radical in the complex, as a result of which it becomes capable of dissociating the double bonds of the monomer molecules, i.e. degradative chain transfer is transformed into effective chain transfer.

The conditions for chain propagation can be established because short-range order arises in the systems monomer–$ZnCl_2$ particularly at high concentrations of the complex-forming agent, as in labile polymerisation seeding agents[32]. One cannot exclude the possibility that the characteristic features of the polymerisation of allyl monomers can be accounted for by the simultaneous operation of all these factors. Thus, under the influence of the complex-forming agent, a significant change in the type of allyl polymerisation is observed. This provides a wide scope for the regulation of polymerisation processes initiated by radical agents.

3. Radiation-induced Polymerisation

Radiation-induced polymerisation is one of the most promising methods for the preparation of allyl polymers with high molecular weights. Dolmatov and Polak[35-38] investigated the mechanism and kinetics of such polymerisation. Radiation-induced allyl polymerisation can be largely described by a radical mechanism[39-44].

The kinetic mechanism takes into account the chain initiation by radicals produced by the radiolysis of the monomer, polymer, and the solvent. Chain propagation takes place via the monomer and polymer and its termination is mainly the result of degradative chain transfer to the monomer—with formation of an allyl radical incapable of chain propagation.

In the analysis of this mechanism Dolmatov[38] introduces the following simplifying assumptions.

1. The reactivity of radicals formed in the radiolysis of the monomer, polymer, and solvent is the same.
2. The overall rate of radiolysis consists of the sum of the rates of radiolysis of the monomer, polymer, and the solvent.

Polymerisation mechanism (M is the monomer, P the polymer, S the solvent, and I the inhibitor):

$$A_1{=}CH_2{=}CH-\dot{C}H_2,\quad A_2{=}CH_2{=}CH\dot{C}H-OH\,.$$

Initiation $$M \xrightarrow{k_d^m} R^{\cdot} + A_1$$

$$P \xrightarrow{k_d^p} R^{\cdot}$$

$$S \overset{k_d^s}{-} R^{\cdot}$$

Chain propagation $$R^{\cdot} + M \xrightarrow{k_i} RM^{\cdot}$$

$$RM^{\cdot} + M \xrightarrow{k_p} R\dot{M}_n$$

$$R\dot{M}_n + P \overset{k_p'}{-} R\dot{M}_n$$

Chain termination $$R\dot{M}_n + M \xrightarrow{kt} P + A_2 \quad \text{(by monomer)},$$

$$R^{\cdot} + I \xrightarrow{k_n} RI \quad \text{(by inhibitor)}.$$

The radiolysis of allyl alcohol in the solid phase[39] and in aqueous solution[40] and also the radiolysis of other allyl derivatives takes place predominantly at the All–X bond with formation of an allyl radical having the structure $CH_2{=}CH-\dot{C}H_2$, which is denoted by A_1. With allyl alcohol, the polymerisation is initiated by the $\dot{O}H$ radical, since it adds to the double bond of allyl alcohol more effectively than it removes the labile hydrogen atom from the α-methyl group[41]. In the chain termination the allyl radical $CH_2{=}CH\dot{C}HOH$, denoted by A_2, is formed.

The recombination of the allyl radicals A_1 and A_2 results in the formation of a certain number of molecules of allyl dimers, the participation of which in chain propagation leads to the formation of a reactive polymer containing a reactive allyl double bond. The concentration of such diallyl molecules is directly related to the length of the kinetic chain.

The kinetic mechanism of polymerisation in the solid phase is elucidated by the transition state method taking into account the change in the volume of the system as a result of contraction. The rate of conversion in the solid phase is determined from the usual set of equations supplemented by the contraction equation:

$$\frac{dW}{dt} = 100\,\%\,\frac{k_p}{k_t}J\cdot\frac{k_d^m n + k_d^p p}{n_0}\ ,$$

where J is the radiation dose rate, n_0 and n are the numbers of moles of the monomer before irradiation and at time t, and p is the number of moles of the polymer in monomer units.

The variation of the yield of the monomer with the duration of irradiation is linear[35], the initial rate of conversion is therefore equal to the rate of conversion at any other stage. This is possible when $k_p^m = k_d^p$.

The equality of the rate constants for the radiolysis of the monomer and the polymer implies the equality of the radiochemical yields of the corresponding radicals. Thus the rate of conversion can be written in the form

$$\frac{dW}{dt} = 100\,\%\,\frac{k_d^m k_p}{k_i}\,J\,,$$

i.e. the rate of conversion is constant, independent of the yield of the polymer, and directly proportional to the radiation dose rate.

The degree of polymerisation of allyl monomers increases with the yield of the polymer. If the initiating effect is due solely to the hydroxy-radical, then in the initial stage the degree of polymerisation should be equal to the degree of polymerisation of allyl alcohol initiated by hydrogen peroxide (about 5–10). Indeed at 52.5°C k_p/k_t = 10.2 and it is evident from the work of Dolmatov and Polak[36] that the limiting viscosity number hardly changes up to 80% conversion. At this conversion a polymer with an average degree of polymerisation in excess of 340 begins to form. The participation of the oligomer in polymerisation leads to a branched polymer, which is reflected in a low value of the limiting viscosity number and a higher Huggins constant[36].

4. Ionic Polymerisation

Friedel–Krafts and Ziegler–Natta catalysts are used for the ionic polymerisation of allyl compounds[45–61]. The rate of polymerisation by catalysts of this type depends to a considerable degree on the structure of the allyl compound. However, a distinct correlation has not yet been established between the structure and the capacity of allyl polymers for polymerisation.

In the polymerisation of allylbenzene and allylcyclohexane[48] on chromium oxide catalysts it was found that the rate of polymerisation increases when the benzene ring is replaced by the alicyclic cyclohexane ring. The explanation is that the allyl group in allylcyclohexane is adsorbed on the surface of the catalyst with the major plane of the cyclohexane ring oriented parallel to the surface, while in the case of allylbenzene the allyl group is displaced from the surface of the catalyst.

The degree of adsorption of allylbenzene exceeds by a factor of approximately 3 that of allylcyclohexane. Therefore it is possible that the stable adsorption of the benzene ring with displacement of the allyl group from the surface hinders the interaction between the electrons of the double bond of the monomer and the electron orbitals of the catalyst. This may be the cause of the inertness of the chromium oxide catalyst. The polymerisation of allylcyclohexane can be accounted for by the planar disposition of the molecules on the surface of the chromium oxide catalyst.

The polymerisation of allyl ethers of allyl-substituted phenols on Friedel–Krafts catalysts[59–61] involves only the allyl ether group, while the allyl side groups are not polymerised. Therefore initially thermoplastic resins are produced, which are then converted into thermoreactive resins in the presence of benzoyl peroxide as a result of cross-linking via the allyl side groups. Ziegler–Natta catalysts were used in the polymerisation of allyl acrylate, allyl methacrylate, allyl chloride, and allylbenzene[46,47,49,51,52,54].

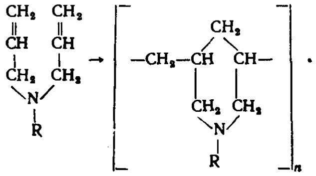
According to D'Alelio et al.[46], the amount of the cationic component $TiCl_4$ in the mixture plays a decisive role in the polymerisation of allylbenzene on these catalysts. The optimum ratio tri-isobutylaluminium : titanium tetrachloride is 1 : 1. With increase of this ratio, the isomerisation of allylbenzene to propenylbenzene predominates. Apart from the ratio $AlR_3 : TiCl_4$, the polarity and the polarisability of the monomer, steric factors, etc. play a significant role in polymerisation on Ziegler–Natta catalysts.

The polymerisation of diallyldimethylsilane and diallylmethylphenylsilane[55] on Ziegler–Natta catalysts in n-heptane yielded solid rubberlike products soluble in benzene at room temperature. The residual degree of unsaturation of these polymers was 12–40%. Polymers obtained with $Al(C_2H_5)_3 : TiCl_4 > 1$ had the lowest degree of unsaturation.

5. Cyclopolymerisation

A characteristic feature of the polymerisation of allyl monomers is a cyclic polymerisation mechanism, investigated for the first time by Butler[62]. Cyclopolymerisation (alternating intra- and inter-molecular polymerisation) occurs with a wide range of monomers when the familiar catalytic systems are used under particular conditions[42,62–79]. Cyclolinear polymers are obtained mainly in the polymerisation of diallyl compounds. This is consistent with Butler's assertion[78] that the main type of chain propagation in the polymerisation of symmetrical 1,6-dienes involves cyclisation, which leads to the formation of a small number of cross links and also residual double bonds. Symmetrical 1,5-dienes polymerise analogously[80]. Butler[63] explains the tendency towards cyclopolymerisation by the fact that the process takes place with a smaller energy expenditure than the intermolecular chain propagation. The lower energy pathway may arise as a result of the electronic interaction between the double bonds of the 1,6-diene or between the reaction centres formed in the interaction between the initiator and the intramolecular double bond.

Matsoyan et al.[66] investigated the capacity of N-substituted tertiary diallylamines and diallylamides for cyclic polymerisation as a function of the nature of the substituent. When polar substituents with electronegative groups are attached to the nitrogen atom of diallylamine, the products are capable of polymerisation in the presence of free-radical initiators with formation of piperidine rings in the main chain:

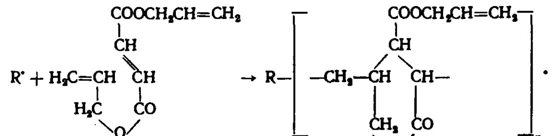


This is associated with the polarisability of allyl groups caused by the displacement of π-electron density of the double bond under the influence of the electron-acceptor substituent.

It is interesting to note that the only substituted diallylamines capable of polarisation are those where the electron-acceptor substituents C=O, C≡N, and SO_2 are linked directly to the nitrogen atom. An increase of the electron-acceptor effect of the substituent favours polymerisation. For example, the effect of substituents in *NN*-diallylamides can be arranged in the following sequence:

$$ClCH_2CO > CH_3CO > CH_3CH_2CO.$$

The studies of Arbuzova and coworkers[81-83] showed that cyclolinear polymers are not obtained solely in the interaction between two allyl groups but also in the interaction between an allyl and a maleate group if their conformation in the molecule is favourable for the formation of five- and six-membered rings:



Cyclisation in the interaction between two allyl groups with formation of ten- or eleven-membered rings is less likely for conformational reasons, for example because of internal steric hindrance to ring closure.

6. Copolymerisation

The nature of the involvement of allyl monomers in copolymerisation depends on their low reactivity compared with the majority of vinyl monomers. Analysis of data on the relative reactivities of monomers in copolymerisation shows that in the vast majority of cases the copolymerisation constants for allyl monomers are zero or significantly less than the constants for vinyl monomers. Because of this allyl monomers enter into the copolymer only as separate units and therefore the copolymer cannot contain more than 50 mole % of the allyl monomer. Only in copolymerisation with relatively inactive vinyl compounds (vinyl acetate, maleic anhydride) do allyl monomers exhibit a fairly high reactivity. In the copolymerisation of diallyl phenylphosphonate with lauryl methacrylate at 140°C the composition of the monomer mixture was found to influence the relative reactivities. In the mixture with 39–92 mole % of lauryl methacrylate (M_1), $r_1 = 6.30 \pm 0.30$ and $r_2 = 0.002 \pm 0.3$, while with 27–46 mole % $r_1 = 3.80 \pm 0.40$ and $r_2 = -0.21 \pm 0.02$. It is suggested that this finding and also the appreciable negative value of r_2 can be explained by the effect of the penultimate unit of the chain on the rate of copolymerisation when the unit consists of the allyl monomer.

The copolymers of allyl monomers with unsaturated compounds are of considerable practical importance. This problem will be discussed in detail below.

In conclusion of this section, the following points should be noted. Judging from the copolymerisation constants, the chemical structure of allyl monomers does not influence their reactivity. However, this finding is probably not uncontroversial. All the investigators who have studied the copolymerisation of allyl and vinyl monomers calculated the constants from differential or integral equations for the composition of the copolymers taking into account only those elementary steps which lead to chain propagation but not to chain termination. For the copolymerisation of vinyl monomers, this assumption is to some degree justified. However, in the copolymerisation of allyl monomers the chain termination rate constant is so large that it is probably comparable with the chain propagation rate constant; for this reason, in the calculation of the ratio of the true chain propagation rate constants it must be taken into account. This problem is not dealt with in the literature and still awaits a solution. Only then will it be possible to assess unambiguously the reactivities of allyl monomers and their dependence on chemical structure.

III. POLYMERISATION OF VARIOUS CLASSES OF ALLYL COMPOUNDS

1. Polymerisation of Allyl Ethers

Allyl ethers $CH_2=CHCH_2OR$ were investigated long before their use in polymer chemistry. In 1944 Nichols and Yanovsky[84,85] observed that, on being kept in air, allyl ethers yield infusible and insoluble resins.

This was the beginning of intense studies on the polymerisation and copolymerisation of allyl ethers and their employment in various branches of industry as adhesives, coatings for wood, glass, metal, and textiles, and as moulded articles with exceptional mechanical strength, resistance to wear, thermal and chemical stability, and resistance to the action of solvents and light.

Allyl ethers derived from polyhydric alcohols are polymerised under the action of oxygen at high temperatures[84, 86-90]. As polymerisation proceeds, the solubility of the polymers in acetone diminishes and their viscosity increases.

Prolonged heating of the polymers in the presence of oxygen leads to insoluble infusible resins. Earlier attempts to polymerise allyl ethers in the presence of 5% benzoyl peroxide were unsuccessful[84]. They began to gel only on addition of 15% of benzoyl peroxide. Later papers[91,92] report the preparation of polymers of allyl ethers initiated by peroxide catalysts. In the solid-phase polymerisation of the diallyl ethers derived from tri(hydroxymethyl)propane using peroxide initiators, the products are transparent colourless solid thermoreactive resins insoluble in the majority of organic solvents. The capacity of allyl ethers for polymerisation to thermoreactive resins resistant to the action of solvents, oils, and high temperatures, and their compatibility with a large number of resins and plasticisers permit their employment in the manufacture of resins with high rigidity[93-95] and also as decorative coatings[86,96].

Allyl ethers readily copolymerise with other monomers in the presence of benzoyl peroxide. The copolymerisation of allyl ethyl and allyl butyl ethers with vinyl acetate was reported by Sakurada and Takahashi[97]. Copolymers of allyl glycidyl ether and vinyl acetate have been obtained in benzene at 75°C.[98] Allyl trifluoroethyl ether was copolymerised with maleic anhydride at 70°C in the presence of benzoyl peroxide[99]. The triallyl ether of glycerol and other allyl ethers derived from polyhydric alcohols were copolymerised with vinyl chloride in suspension in an autoclave at 51°C.[100]

Britton and Davis[101] copolymerised vinyl chloride with allyl epoxyalkyl and allyl hydroxyalkyl ethers. Losev[102] employed boron trifluoride together with benzoyl peroxide as a catalyst in the copolymerisation of vinyl chloride with diallyl ethers.

Fisher[103] also reported the use of boron trifluoride as an initiator in the copolymerisation of allyl glycidyl ether with maleic anhydride. The resin formed is then hardened at 110°C for 48–144 h in the presence of benzoyl peroxide. The copolymers may be used as binders for reinforced plastics and as film-forming agents stable up to 260°C. The copolymers of allyl ethers with vinyl acetate, vinyl chloride, vinylidene chloride, styrene, acrylonitrile, butadiene, and acrylic esters have found many applications. The properties of typical copolymers of allyl ethers with other monomers are listed in Table 1.

Table 1. Copolymers of allyl ethers and their properties.

Monomer	Comonomer	Applications of copolymers
Allyloxyethane	Acrilonitrile	Films and fibres with good dyeing properties
Allylpentaerythritol	Acrylonitrile	Thickening agent for non-polar solvents
Allyl glycidyl ether	Vinyl acetate	Surface coatings
Allyl-starch	Styrene	Surface coatings
Diallyl ether of ethylene glycol	Vinyl chloride	Insulation for wires and cables
Triallyl ether of glycerol	Vinyl chloride	Ditto
2-Chloroallyl ether	Methyl methacrylate Butyl methacrylate	Thermosetting coatings for electrical devices, motorcars, and external metallic sheeting
Monoallyl ether of glycerol	Methyl methacrylate Butyl methacrylate	Ditto

Although the copolymerisation of allyl ethers has been as yet inadequately investigated, the use of allyl compounds containing other functional groups (hydroxy-, epoxy-, and ethylene groups) has acquired increasing importance. Even small amounts of allyl ethers added to other monomers considerably improve the physical and mechanical properties of the polymers.

Bifunctional allyl monomers are used for the modification of the existing polymers. They make it possible to obtain copolymers with improved resistance to wear and to the effect of light and solvents.

Valuable polymeric materials have been obtained by the copolymerisation of unsaturated maleate oligoesters with ethers[104–115]. Such compositions harden rapidly in air at room temperature. Light-coloured films with high impact strength, chemical stability, and resistance to wear are obtained. The physical and chemical properties of the copolymers permit their use also in cast compositions, in laminate plastics, and as casting moulds. The copolymers of the unsaturated oligoesters with diallyl phthalate and allyl ethers of glycerol and starch are used[116] as adhesives and binders for emery paper. Allyl ethers of polyhydric alcohols [tri(hydroxymethyl)propane, pentaerythritol, glycerol] react with the unsaturated oligoesters to give copolymers with exceptional water resistance and satisfactory dielectric properties[110,114,115].

Recently much attention has been devoted to unsaturated allyl oligoesters and their copolymers. Unsaturated allyl oligoesters with an allyl bond in the side chain are obtained by the reaction with dibasic acids or their anhydrides of polyhydric alcohols such as allylglycerol and allylglycidol with their hydroxy-groups partly converted into allyl ether groups[117–125].

Such oligoesters are converted into insoluble and infusible polymers by treatment with cobalt naphthenate in the presence of air at room or elevated temperatures[108,111,112,123,125]. However, the homopolymers of allyl oligoesters have not found practical applications.

Sorokin and Gershanova[106] studied the copolymerisation of unsaturated allyl oligoesters with allyl glycidyl ether. They synthesised the oligoesters from allyl glycidyl ether and dibasic acids (maleic, phthalic, and adipic). The copolymerisation was carried out in the presence of redox and peroxide initiators. The authors note that varnish compositions based on the oligoesters obtained from maleic acid and allyl glycidyl ethers harden at room temperature and exhibit fairly satisfactory hardness and degree of solidification. Partial replacement of maleic acid by adipic or phthalic acid in the oligoester lowers the rate of hardening of the varnish compositions.

It has been established by infrared spectroscopy that the copolymerisation involving the double bonds is accompanied by the interaction of the glycidyl groups of the allyl glycidyl ether with the terminal carboxy- or hydroxy-groups of the oligoester.

In their study of mixed allyl-maleic oligoesters, Jenkins et al.[107] showed that an increased content of allyl groups in the oligoester lowers the maximum molecular weight which may be obtained without gelling. This also determines the maximum number of utilisable allyl groups. For the oligoester obtained from propylene glycol, the allyl ether derived from glycerol, and equimolar amounts of maleic and phthalic acids this number is four. When the maleic acid content was less than 25 mole % of the total content of acids, gelling was not observed and it was possible to obtain oligoesters with a high molecular weight.

For polyester varnishes the authors also employed as the allyl component involatile polymerisable compounds of the diallyl ether derived from glycerol and the acetic, adipic, and pyromellitic esters of the diallyl derivative of glycerol.

The copolymerisation of allyl oligoesters with maleic-fumaric oligoesters is described in the publications of Tarasov and coworkers[117–120,126–128] and others[124]. Copolymers with satisfactory physical and mechanical properties have been obtained[117], and may be employed as binders for reinforced plastics. It has been shown[129] that poly(allylglyceryl phthalate-adipate) does not polymerise in the presence of 2% of benzoyl peroxide even at 150°C. The addition of small amounts of the fumaric oligoester (about 10%) leads to the formation of a copolymer even at 80°C. The participation of allyl groups in the copolymerisation reaction has been shown by the fact that the product does not dissolve in organic solvents. Furthermore, bromination of the products of the alkaline hydrolysis of the copolymers reveals the presence of only a fraction of the initial fumaric and allyl double bonds.

2. Polymerisation of Allyl Esters

The allyl esters of mono- and di-carboxylic acids were obtained for the first time in 1885 by Zinin[130] by the double decomposition of the silver salts of aliphatic acids with allyl iodide. Until 1940 there were no data on the use of allyl esters, since allyl alcohol was not readily available. The polymerisation of allyl esters began to acquire practical importance starting with 1941–1942. The allyl esters of carboxylic acids have been used in polymer chemistry in two ways: (1) as monomeric additives to polymers; (2) as partially polymerised thermosetting resins (pre-polymers).

The polymers of allyl esters have found application in those cases where the following properties are necessary: chemical stability, particularly with respect to oxidising agents, exceptionally low dielectric losses, low moisture absorption, low rate of cross-linking after fusion, resistance to wear, and thermal stability.

The allyl esters of phthalic, isophthalic, maleic, fumaric, succinic, diglycolic, itaconic, acetic, and other acids are most frequently used[131-237].

Allyl esters can be polymerised in the presence of various initiating systems (peroxides, ionic polymerisation catalysts, and under the influence of γ-radiation). Among the most widely used and most important monomers are diallyl phthalate and diallyl isophthalate[131-168]. The kinetics of the polymerisation of diallyl phthalate were investigated by Oiwa, Lalau-Keraly, etc.[154-159,168]. They showed that the residual degree of unsaturation in the polymerisation of diallyl phthalate in the presence of benzoyl peroxide and di-t-butyl peroxide depends very little on the catalyst and temperature but does depend strongly on conversion. With increase of conversion, the residual degree of unsaturation falls.

In the initial stage of the polymerisation of diallyl phthalate in the presence of peroxide initiators about 43% of cyclic structures is formed. The structure of the polymer has been confirmed on the basis of the rate of disappearance of C=C bonds revealed by infrared spectroscopy in the region of 1644 cm^{-1}.[165]

In the polymerisation of diallyl phthalate the duration of the hardening process and the contraction of the polymer are very considerable[132]. For this reason, diallyl phthalate is rarely used for the synthesis of a homopolymer. Instead it serves for the preparation of a pre-polymer which is readily moulded, exhibits satisfactory fluidity, and hardens rapidly[147-153]. Diallyl phthalate and diallyl isophthalate pre-polymers are stable on storage and when employed as compositions with catalysts which decompose at high temperatures. On heating and at high pressures (in casting, in the preparation of laminate materials), they soften, flow, and are cross-linked to give three-dimensional insoluble resins.

Diallyl esters of fumaric and maleic acids are also of interest for a wide variety of engineering applications[81-83, 169-183,229]. The mechanism of the formation of polymers based on mono- and di-allyl esters of maleic acid was investigated by Arbuzova et al.[81-83] They established that in the polymerisation of monoallyl maleate and diallyl maleate five- and six-membered lactone units are formed, and with increase of the polymerisation temperature the content of five-membered rings increases. On the other hand, the polymerisation temperature and the nature of the initiator do not affect the degree of cyclisation. With monoallyl maleate, it is 63–64% and, with diallyl maleate, it is almost 100%. The cyclolinear polymers obtained are converted on further polymerisation in the presence of initiators into three-dimensional polymers, which are very hard and exhibit high thermal stability.

The polymerisation of allyl acrylate and allyl methacrylate has been investigated by Schulz, Kawai, Gindin, and others[51,54,74,184-209]. The polymerisation of allyl acrylate in benzene solution with a radical polymerisation initiator yielded a brittle vitreous polymer soluble in benzene and pyridine. The polymer does not soften on heating and hydrolyses only in molten sodium hydroxide–potassium hydroxide. A study of the structure of the polymer showed that 24.2% of the structural units are linked via acrylic groups, 17.2% are linked via allyl groups, and the remaining 58.6% form lactone groups as a result of cyclopolymerisation[186].

The anionic polymerisation of allyl acrylate gives a product with a low molecular weight, which is isotactic to a fairly high degree. Only acrylic double bonds participated in the linear polymerisation; the allyl bonds were involved only in the cross-linking, which occurred when the polymer was stored in air[51]. Similar results were obtained by Gindin et al.[185] in the polymerisation of allyl acrylate under the influence of benzoyl peroxide and ultraviolet light.

Compared with the acrylate, the polymerisation of allyl methacrylate shows certain characteristic features. When azobisisobutyronitrile is used as an initiator, allyl methacrylate polymerises to a product without rings in the chain, which is insoluble in the usual organic solvents[187]. In the polymerisation of allyl methacrylate under the influence of ultraviolet light, Cohen et al.[236] also showed that the polymerisation is not accompanied by cyclopolymerisation. This can be accounted for by resonance stabilisation of the allyl groups as a result of degradative chain transfer, which leads to the cross-linking of the polymer.

In the anionic polymerisation of allyl methacrylate[54] a linear soluble polymer containing allyl groups as branches from the polymer chain is formed. The linear polymers of allyl methacrylate are classified as "self-reactive", yielding polymers which harden on heating or in the presence of radical initiators. Only the copolymers of allyl methacrylate with other monomers have found applications.

Allyl acetate has been homopolymerised[10,18,210-213], largely in order to investigate the kinetics of allyl polymerisation, as mentioned above. This polymer has not found practical application, since it has low molecular weight and poor mechanical properties.

Polymers based on the diethylene glycol–diallyl carbonate system are produced in the presence of free-radical polymerisation initiators as light-coloured castings with exceptional optical properties, high chemical stability, and resistance to wear[237]. The polymerisation of this monomer is inhibited by air and therefore the castings are obtained between glass plates separated by plastic spacers. The diethylene glycol–diallyl carbonate polymers are produced in the manufacture of optical lenses and glass for spectacles, and as coatings for expensive ultraviolet and infrared glasses[6].

Apart from the applications of the polymers of allyl esters, their copolymers with other monomers and unsaturated oligoesters have found many applications in engineering.

The addition of 0.01–0.3% of diallyl phthalates (*o*-, *m*-, and *p*-isomers) to vinyl chloride makes it possible to prepare a polymeric material with mechanical properties 4–10% better than those of poly(vinyl chloride) itself[141]. Diallyl phthalates are frequently used instead of styrene in mixtures with unsaturated oligo-glycol maleates[142]. Articles with homogeneous surfaces and much smaller contraction can be obtained by casting. Diallyl phthalate imparts mechanical strength and thermal stability to oligoester resins and improves their dielectric properties.

The copolymerisation of diallyl maleate and diallyl fumarate with methyl methacrylate and styrene in the presence of a mercaptan and peroxides yields in pregnating powders[183], which can be moulded under pressure of 7 kg cm^{-2}. The copolymer of diallyl maleate with 0.05–0.3% of vinyl chloride is used as an electrical insulator[180]. The copolymer of diallyl maleate and chlorotrifluoroethylene has good adhesive properties[182].

Diallyl fumarate and diallyl maleate are also used with styrene in compositions containing unsaturated oligoesters, which are employed to prepare reinforced plastics[173]. The addition of diallyl phthalate and diallyl maleate to poly(vinyl chloride) imparts hardness to the polymeric materials[176].

Allyl acrylates and allyl methacrylates copolymerise with methyl methacrylate, vinyl chloride, acrylonitrile, polyethylene, etc.[196-208]. The copolymerisation of allyl methacrylate (20%) with methyl methacrylate in the presence of benzoyl peroxide yields polymers with higher softening temperatures than that of poly(methyl methacrylate).[200-202]

The copolymers of allyl furylenemethacrylate with styrene, vinyl acetate, acrylonitrile, and methyl methacrylate have been suggested as plasticisers[197].

The copolymers of acrylonitrile, methyl methacrylate, and methacrylamide, modified with allyl methacrylate, exhibit exceptional mechanical properties (for example, a bending resistance of 1849 $kg\ cm^{-2}$).

The copolymerisation of allyl acrylate (1–15%) with acrylonitrile gives transparent castings[207]. Allyl acrylate is used as a cross-linking agent in the irradiation of polyethylene and polypropylene[209].

The copolymerisation of allyl acetate with other monomers[6,214-216] has been carried out largely to investigate the mechanism of the copolymerisation and to determine the relative reactivities.

3. Polymerisation of *N*-Allyl Derivatives

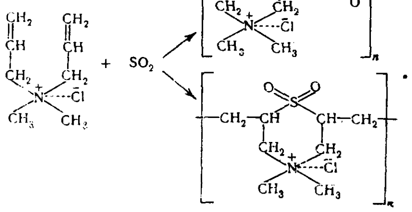
In recent years much attention has been devoted to the study of the polymerisation and copolymerisation of *N*-allyl derivatives (*N*-substituted diallylamines, diallylammonium, salts, *N*-allylamides, *N*-allylimides, triallyl cyanurates, hexa-allylmelamines, etc.)[66,238-289]. The interest in this class of compounds arises from the practical value of the polymers and copolymers of *N*-allyl derivatives (particularly those based on triallyl cyanurate and triallyl isocyanurate).

Butler has shown that the polymerisation of diallylammonium salts in aqueous solutions in the presence of t-butyl hydroperoxide or an azo-initiator leads to the formation of cyclolinear polymers[78,79].

The polymerisation of diallyl- and diallyldimethylammonium bromides[258] yields saturated linear soluble polymers with repeating *N*-substituted piperidinium halide units together with methylene groups.

The ability of diallyl derivatives of quaternary ammonium salts to undergo radical polymerisation is associated with the polarisability of the allyl groups due to the displacement of the π-electron density of the double bond by the electron-accepting nitrogen atom of the ammonium group. In the presence of radical-polymerisation initiators these monomers copolymerise fairly readily with styrene, acrylonitrile, and other monomers.

In the copolymerisation of diallyl-ammonium halides with sulphur dioxide[73], water-soluble cationic polysulphones are formed:



These copolymers do not melt but decompose at 180°C and lose about 40% of their weight at 190°C in 3 h. They are unstable to sodium hydroxide.

The mechanism of the polymerisation of *N*-substituted diallylamines was discussed in detail above[66]. It is noteworthy that the polymerisation of these monomers involves a cyclic mechanism with formation of piperidine rings in the main polymer chain, as in the polymerisation of quaternary diallyl-ammonium salts. Among the cyclic polymerisation products of *N*-substituted diallylamines, *NN*-diallylacetamide, *NN*-diallylbenzamide, *NN*-diallylpropionamide, etc., polyallylcyanamide is of particular interest, being distinguished by low solubility and a high melting point.

Ostroverkhov et al.[238] established that tertiary diallylamines and diallylamides form in the presence of radical initiators polymers with low molecular weights and low softening temperatures which are readily soluble in organic solvents. The low tendency of diallylamides to polymerise can be explained by the vigorous chain termination reaction with participation of the hydrogen atom of the allyl group.

In the presence of anionic and cationic catalysts diallylamides and tertiary diallylamines did not yield polymers either in the solid state or in solution. Allylamines have been recently polymerised by irradiation with cobalt-60 γ-rays.[44] The homopolymers of allylamines and allylamides have not found practical application. It is mainly their copolymers with other monomers and polymers which are used in industry.

The copolymers of triallylamine with acrylic acid have been obtained at 50°C in an atmosphere of nitrogen in the presence of 2% azobisisobutyronitrile. They are excellent thickening agents for latex dyes[242].

The copolymers of diallylamine and acrylonitrile are used as fibres which are more readily dyed than polyacrylonitrile[243].

The copolymers of allylamines with styrene and butadiene have been recommended as hardening agents for epoxy- and ion-exchange resins[239].

Diallylamine introduced into poly(vinyl chloride) in an amount of 0.01–0.3% increases its molecular weight and improves its physical and mechanical properties[230].

Much work has been done on the polymerisation and copolymerisation of triallyl cyanurate, triallyl isocyanurate, and hexa-allylmelamine[248,263-294]. The vitreous polymers obtained in the presence of free-radical polymerisation initiators, are colourless, solid (but brittle), and readily cracked.

Clampitt[265] observed by infrared spectroscopy that in the course of its polymerisation triallyl cyanurate isomerises to triallyl isocyanurate.

Poly(triallyl isocyanurate) has a higher decomposition temperature (377°C) than poly(triallyl cyanurate) (321°C) and higher stability on heating in air and in an atmosphere of nitrogen. Therefore conditions for the hardening of triallyl cyanurate are chosen so that the latter isomerises to triallyl isocyanurate. However, despite their high thermal stabilities, the homopolymers have not found practical application because of their brittleness.

Solid polymeric materials with high thermal stability have been obtained by the copolymerisation of methyl methacrylate (5–50%) with triallyl cyanurate[284,286].

In the presence of peroxide or ionic catalysts allyl derivatives of cyanuric and isocyanuric acids copolymerise with vinyl monomers, dienes, etc. Solid thermostable copolymers insoluble in organic solvents are obtained[282].

The copolymers of triallyl cyanurate, diallyl itaconate, styrene, and methyl methacrylate are used in high-speed military aviation[287]. Triallyl cyanurates and triallyl isocyanurates are introduced into oligoesters to improve their thermal stability and mechanical properties[291–293]. When triallyl cyanurate (2–5 weight units) is introduced into polyethylene to increase the effectiveness of cross-linking, a copolymer with a high melting point is obtained[277].

The polymerisation and copolymerisation of other *N*-allyl derivatives of heterocycles have been less investigated. Only *N*-allyl-α-pyrrolidinone, *N*-allyl-α-piperidinone, and *N*-allyl-α-caprolactam have been polymerised[290]. These monomers hardly polymerise in the presence of 10% benzoyl peroxide at 60°C over a period of 60–100 h. On addition of not less than 5% of azobisisobutyronitrile, *N*-allyl-α-pyrrolidinone and *N*-allyl-α-caprolactam undergo stepwise polymerisation with formation of low-molecular-weight products and trimers in low yields (10–25%). The polymerisation of *N*-allylsuccinimide and *N*-allylphthalimide, in the solid phase and in solution, under the influence of cobalt-60 γ-radiation was reported recently[261]. The polymerisation products have a low molecular weight; the degree of polymerisation is about 10.

4. Polymerisation of Allyl Monomers with Organic Derivatives of Different Elements as Substituents

This class of compound includes allyl derivatives of silicon, titanium, germanium, tin, phosphorus, sulphur, and other elements[7,42,43,68,291–340]. Polymers based on these compounds have attracted attention because they should exhibit high thermal stability and the phosphorus containing polymers should exhibit self-extinguishing properties. The polymerisation of alkenylsilanes containing one allyl or methylallyl group takes place with difficulty[341]. Mironov and Petrov[342] described the polymerisation of alkylmethylallyl- and allyloxy-silanes on platinised charcoal. Later Korshak et al.[343] established that the polymers based on alkylsilanes have different structures depending on the polymerisation initiator. The polymers obtained in the presence of peroxide catalysts contain Si–H bonds, while those obtained in the presence of platinum catalysts do not.

Lyashenko et al.[43] showed that polymers produced in the presence of benzoyl peroxide at 200°C have structures analogous to those obtained at 100°C in the presence of cobalt-60 γ-radiation. The authors observed that the tendency to polymerise increases with the number of allyl groups in alkenylsilanes. Monoallylsilanes exhibit different activities in polymerisation reactions depending on the nature of other groups linked to the silicon atom. Diethylallylsilane does not polymerise in the presence of benzoyl peroxide over a period of 10 h, ethylallylphenylsilane polymerises to a liquid polymer, while ethyldiallylsilane and triallylsilane give crystalline products, the latter being formed in 30 min.

In the polymerisation of diallylsilanes under the influence of cobalt-60 γ-radiation, Gusel'nikov et al.[42] established that the reaction involves inter- and intra-molecular mechanisms. The cyclolinear polymers formed are soluble in organic solvents.

Using Ziegler–Natta catalysts, Topchiev, Bogomol'nyi, Kolesnikov, and others[68,300–303,308] obtained rubberlike products containing unsaturated groups in the side chains. The dominant units in the polymer chain are silicon-containing rings alternating with methylene groups. The copolymers of allylsilanes with other monomers obtained in the presence of Ziegler–Natta catalysts were found to have a constant melting point and high stability when worked. The hardened copolymers did not dissolve in boiling heptane. They have been used as elastomers[305].

There are only isolated data on the polymerisation of the allyl derivatives of titanium, tin, and germanium[50,308,310,311]. A polymer decomposing without fusion above 400°C was obtained from allyl trimethyl titanate in the presence of boron trifluoride or compounds capable of yielding boron trifluoride[50]. The copolymerisation of allyl derivatives of titanium with vinyl acetate gave water-resistant enamels[311].

The polymerisation of diallyldimethylgermane takes place in the presence of triethylaluminium and titanium tetrachloride with formation of a coloured oil in about 50% yield. The molecular weight of the polymer is 270. It is suggested that in this case the main polymerisation product is a cyclic dimer[308].

The polymerisation of phosphorus-containing allyl monomers and their copolymerisation with other monomers and polymers have been investigated by Kamai, Toy, Berlin, Laible, Kennedy, and others[7,67,238,294,296–298,312–334]. The ability of phosphorus-containing allyl monomers to undergo radical polymerisation as a function of the nature of the substituents has been investigated by Kamai[297] and later by Toy[296] using as an example the allyl esters of phosphonic acid. They showed that steric hindrance, the polarity of the substituents, and the presence or absence of inhibiting groups can greatly modify the polymerisation characteristics of the monomers, their effect diminishing on going from allyl to methylallyl esters.

Table 2. Groups of polymerisable diallyl compounds of the type $R-P(O)(OCH_2CH=CH_2)_2$.

First group		Second group	
R	Taft's constant σ^* (Ref.344)	R	Taft's constant σ^*
$H-$	0.49	CH_3-	0
C_6H_5-	0.60	C_2H_5-	—0.1
$C_6H_5CH_2-$	0.22	$n\text{-}C_3H_7-$	—0.115
C_6H_5-O-	2.38	$n\text{-}C_4H_9-$	—0.13
$(CH_3)_2C=CH-$	—	$(CH_3)_2CH$	—0.38

Monomers can be divided into three groups in relation to their capacity for the formation of polymers. The first group includes monomers which polymerise to a solid vitreous product. These are monomers in which the substituent at the phosphorus atom is an electron acceptor. When the substituents are electron donors, the monomers polymerise either to gels or solid but elastic polymers. These constitute the second group (Table 2). The third group includes monomers which polymerise to a liquid product or do not polymerise at all under the influence of peroxide initiators. These are *NN'*-dimethylallylphenylphosphonamide, diallylthiophenylphosphonamide [*NN*-diallylphosphonothionic diamide ? (Ed. of Translation)], diethyl *N*-allylphosphoramidate, and others. The polymerisation passivity of compounds in the third group is due to the inhibiting effect of sulphur and amide groups in the monomers.

Diallyl *NN*-dimethylphosphoramidate ? (Ed. of Translation)] not only does not polymerise but is actually capable of retarding the polymerisation of other diallyl esters.

The interest in polymers of this class arises from their flame-resistant properties.

Toy and Cooper[296] believe that the phosphorus content in allyl monomers is not the sole factor determining the flame-resistant properties of polymers. The polymers of diallyl phenylphosphonate (13% of phosphorus) and diallyl methylphosphonate (17.6% of phosphorus) are more flame-resistant than the polymer of diallyl phosphite (19.2% of phosphorus). However, the authors do not quote other reasons to account for their flame-resistant properties.

In engineering, applications are found mainly for the copolymers of phosphorus-containing allyl monomers with other monomers and polymers. The copolymerisation of diallyl phenylphosphonate with vinyl acetate and methyl methacrylate yielded a transparent polymer with self-extinguishing properties[323].

Phosphorus-containing allyl monomers are introduced into unsaturated oligoesters to make them flame-resistant. The copolymers based on these components have good mechanical and dielectric properties in addition to being flame-resistant[298,333].

5. Polymerisation of Allyl Alcohol and Allyl Halides

Poly(allyl alcohol) was obtained for the first time by the reduction of poly(n-butyl acrylate) with lithium aluminium hydride in dry tetrahydrofuran[345]. The degree of reduction was more than 95%, the molecular weight was 15 900, and the intrinsic viscosity in dimethyl sulphoxide was 0.436.

Poly(allyl alcohol) of low molecular weight is obtained by the polymerisation of allyl alcohol in the presence of a large amount of benzoyl peroxide[346,347]. Poly(allyl alcohol) with an average degree of polymerisation $\overline{DP} = 20$ is soluble in water, methanol, and other organic solvents. With $\overline{DP} = 200$, the polymer shows limited miscibility in water but is readily soluble in methanol, while with $\overline{DP} = 400$ it is soluble only in a mixture of concentrated hydrochloric acid and methanol in dioxan.

Poly(allyl alcohol) of high molecular weight ($\overline{DP} = 370$) has been obtained by irradiating allyl alcohol with cobalt-60 γ-rays. Allyl alcohol with $\overline{DP} = 10^3-10^4$ can be obtained by radiation-induced polymerisation. Poly(allyl alcohol) is a highly branched polymer with a low intrinsic viscosity. It is thermostable and thermoplastic, can be pressed into sheets on heating, and fibres can be readily formed from its melt. Crystalline poly(allyl alcohol) with a melting point of 210–222°C has been obtained by the polymerisation of allyl alcohol in the presence of boron trifluoride at −78°C in petroleum ether[50].

Practical applications have been found mainly for the copolymers of allyl alcohol with other monomers[348-367]. When allyl alcohol is copolymerised with styrene (15–80%), transparent solid polymers are formed and are used as coatings which are colour-fast on heating[353,368]. The copolymers of allyl alcohol and styrene have been used to prepare films with good adhesive properties, resistance to water, dilute alkalis, methanol, and detergents[354,356,357]. These copolymers can serve as binders for the preparation of articles with fibrous fillers[355]. Filled copolymers of styrene, allyl alcohol, and maleic acid are used as facing plates and other constructional materials[359]. Copolymers of allyl alcohol and acrylonitrile have been used as fibres[362].

The polymers of allyl halides (allyl chloride and allyl bromide) are obtained by polymerisation in the presence of peroxides and Ziegler–Natta catalysts and by γ-irradiation[369-375]. High-molecular-weight compounds are obtained only when the monomers are irradiated with cobalt-60 γ-rays.

Polymerisation of allyl chloride on a Ziegler–Natta catalyst yielded a pale-yellow polymer melting at 70–110°C. It contained double bonds formed as a result of the elimination of HCl from the polymer molecules[370].

Polymers of allyl chloride are also obtained in benzene or toluene in the presence of 0.2–0.5% (relative to the monomer) of metallic aluminium[376].

The polymerisation of allyl iodide under the action of γ-radiation yields mainly dimers[370]. The monomers are used in the polymerisation of ethylene to regulate the molecular weight of the polymer[377,378].

6. Polymerisation of Aromatic Allyl Compounds

Korshak and coworkers have investigated the synthesis, polymerisation, and copolymerisation of allyl-containing polyarylates[379-386]. The formation of allyl-containing polyarylate structures under the influence of heat takes place at a temperature in excess of 230°C with a considerable yield of the three-dimensional product. At the beginning of the reaction the β-polymer forms, which is then converted into the γ-polymer. The polymers obtained under conditions ensuring the maximum degree of cross-linking (267°C, 7 h) have an extensive region of elastic deformations, the upper limit of which occurs at temperatures above 500°C. It has been noted that the deformations diminish with increase in the number of cross-links.

The copolymerisation of allyl-containing polyarylates with various vinyl and allyl monomers reduces the thermal stability of the polyarylates. However, in some cases (diallyl phthalate, styrene, etc.) this happens to only a slight extent. It was found that styrene is a poor cross-linking agent and this is why only a small amount of the cross-linked polymer forms at high concentrations of the polyarylate in styrene solution.

Methyl methacrylate, allyl methacrylate, and ethylene dimethacrylate are effective cross-linking agents for allyl-containing polyarylates.

Some of the copolymers have good mechanical and thermal properties. For example, the copolymer with diallyl phthalate has a bending strength of 1190 kg cm^{-2} which hardly changes after 6 h at 250°C. Copolymers of 2-allylphenol with methyl methacrylate and with ethylene dimethacrylate retain a fairly high strength after heat treatment at 300°C in the presence of air. Furthermore, these copolymers exhibit high heat resistance (above 500°C) and thermal stability.

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Institute of Chemistry, The Urals
Branch of the USSR Academy of
Sciences, Sverdlovsk

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Investigation of Solutions of Cellulose

S.N.Danilov, T.I.Samsonova, and L.S.Bolotnikova

This review deals with studies of cellulose solutions. Various solvents for cellulose are characterised in detail. On the basis of the experimental results it is concluded that stable compounds are formed as a results of the reaction of cellulose with complex-containing solvents. The part played by complexes and alkalis present in the solvent in the dissolution of the cellulose is shown.

Various methods of fractionation and the principal relations between the characteristic viscosity and molecular weight of cellulose in various solvents are considered.

In the section dealing with the dimensions and form of the cellulose macromolecules it is shown that cellulose is of much greater dimensions than flexible synthetic polymers, owing to the greater size of the monomeric unit, the considerable extension of the macromolecules in the solution, and the reaction of cellulose with the solvent.

CONTENTS

1. SOLVENTS FOR CELLULOSE

The peculiarities of the structure of cellulose macromolecules, the regularity of its structure, and the strong intermolecular interactions, are due to the presence of hydrogen bonds, which results in cellulose being insoluble in water and organic solvents. It is soluble in aqueous solutions of complexes of bivalent and tervalent metals, certain salts, and concentrated acids (phosphoric acid).

The most widely used of the solvents containing complexes is a solution of the amminecopper complex, first obtained by Schweizer in 1857.[1] This solvent contains compounds formed in the reaction of copper hydroxide with ammonia and of the general formula $Cu(NH_3)_m(OH)_2$, with the tetramminecopper complex $Cu(NH_3)_4(OH)_2$ predominating.

When this solvent is stored in air for even a rather short period there is a change in composition owing to oxidation of ammonia to nitrous acid and beyond, as is shown by the appearance in the solution of ammonium nitrates and nitrites on storage[2] and the copper concentration drops owing to the separation of copper hydroxide. Danilov and coworkers[2-4] investigated the processes in the oxidation of amminecopper solutions of cellulose. In these solutions oxygen attacks both the ammonia and the cellulose as a vigorous carrier of oxygen is present—the copper ion in the tetrammine complex[5,6].

The oxidation of both the solvent itself and of solutions of cellulose in it can be suppressed by the introduction of additions of organic (sucrose, glucose, mannitol, tartaric acid) or inorganic (sulphite, thiosulphate) substances. These additions stabilise the amminecopper complex and lessen the oxidisability of the ammonia. The oxidative degradation of cellulose in a solution of amminecopper complex can be prevented by the addition of metallic copper to the solution, as this vigorously bonds the oxygen[6-12]. Additions of inhibitors greatly reduce the oxidisability of cellulose but do not eliminate it.

Cellulose concentrations of only 3–4% can be obtained by direct dissolution of cellulose in a solution of the amminecopper complex. To prepare more concentrated solutions, cellulose is mixed with a basic copper salt and ammonia solution. As the cellulose dissolves, additional amounts of the basic copper salt pass into the solution. Cellulose solutions with a concentration of over 12% can be obtained in this way. Foreign ions have a considerable effect on the solubility of basic copper salts in ammonia. Thus, copper hydroxide dissolves better in ammonia in the presence of sodium and ammonium sulphates[7].

Traube[12] obtained the ethylenediaminecopper complex by replacing ammonia by ethylenediamine (ED). This system is more stable than the solution of the amminecopper complex and there is less oxidation of solutions of cellulose in it. However, the solubility of cellulose in solutions of the ethylenediaminecopper complex is less than in solutions of the amminecopper complex[13]. According to Marx[14] the maximum possible concentrations of cellulose of various degrees of polymerisation reach 0.6–1.2 g per 100 ml on varying the degree of polymerisation from 6000 to 1500.

Unlike amminecopper solution, where a large excess of ammonia is used, solutions of the ethylenediamine complex dissolve cellulose at a strictly definite ratio of ethylenediamine to copper, en : Cu, which should be 2.[12,15] In instances when this ratio exceeds 2, that is, the en solution is not saturated with copper hydroxide, the solubility of cellulose is less. Since the solvent should always have a strictly defined composition this complicates its preparation. The information about the variation of the characteristic viscosity $[\eta]$ with the composition of the solution of ethylenediaminecopper complex is rather contradictory. Thus, Marx[14] thinks that the en : Cu ratio can be varied from 1.69 to 2.75 (0.5 g-ion copper/litre) without affecting the viscosity. According to Wilson[15], en : Cu should lie within the limits 2.00 ± 0.04, and the copper concentration 1.00 ± 0.1 M, for the change in relative viscosity not to exceed 1%. In studying the formation of the ethylenediaminecopper complex in aqueous solution, Vink[16] found that the existence of complexes of composition $Cuen_2^{2+}$, $Cuen^{2+}$, and $Cuen_3^{2+}$ is possible. He showed that at the ethylenediamine : copper ratio of 1.82 the following complexes can exist in the solution: $Cuen_2^{2+}$ 69.5%, $Cuen_2OH^+$ 9.3%, $Cuen(OH)_2$ 21.2%, that is, the complex $Cuen_2$ predominates in the solution. Like the solutions of amminecopper complex, solutions of the ethylenediaminecopper complex are unstable, although to a lesser degree[17,18]. Measurement of the viscosity of cellulose in solutions of the ethylenediamine complex also must be done in the absence of atmospheric oxygen[18].

Vink[19] observed, in studying the kinetics of oxidative destruction of cellulose in a solution of the ethylenediamine-copper complex, that the cellulose concentration has no effect on the rate of destruction. The rate is a maximum in the first day after the preparation of the solution but then decreases, owing to the formation of inhibitors in the ethylenediaminecopper solution. Two compounds were isolated: glyoxal dioxime HO–N=CH–CH=N–OH and hydroxyiminoacetic acid HO–N=CH–COOH. In investigating these and other oximes it was observed that hydroxyiminoacetic acid has the greatest inhibiting action. In addition to inhibitors, accelerators of the oxidation were found—dimethylglyoxime. It is noteworthy that ethylenediamine itself is not oxidised by oxygen; its oxidation, leading to the formation of inhibitors, takes place only in the presence of copper.

The use of solutions of ethylenediaminenickel[20] and ethylenediaminecobalt[21] complexes as solvents does not have any advantages over the ethylenediaminecopper complex. The presence of nickel and cobalt ions, which can be oxidised from the bivalent to the tervalent state, increases the destruction of the cellulose. Furthermore, these solvents are unstable and they are made in an atmosphere of nitrogen, to avoid the formation of cobalt(III) and nickel(III) hydroxides, which give complexes with ethylenediamine which do not dissolve cellulose. The solubility of the latter in these solvents is low.

Ethylenediamine also forms a complex with zinc and the aqueous solution of this compound dissolves cellulose[22,23]. However, the solvent is stable only at low temperatures.

Unlike the above solvents an aqueous solution of the ethylenediaminecadmium complex[24,25] (Cadoxene) is stable for an almost unlimited time, but cellulose does not oxidise much in it[26,27].

A solution of the ethylenediaminecadmium complex was first obtained in 1957 by Jayme[24,25] by saturating ethylenediamine solutions of various concentrations with basic cadmium salts, cadmium hydroxide at low temperatures, or cadmium oxide at room temperature and at 3–7°C.[28] This can be used as a solvent for cellulose with polymerisation degrees < 1200. To improve the dissolution of the cellulose, Jayme[29] suggested the preliminary swelling of the cellulose in water, but Henley[30] increased the solubility of cellulose by the addition of 0.2–0.5 mole sodium hydroxide to the Cadoxene. It is then possible to dissolve cellulose with a polymerisation degree of 5500. The maximum concentration of cellulose with degree of polymerisation 1200 reaches 4%. Nadziakiewics and Jedlinska[31] also added sodium hydroxide to the solution to improve the solubility of cellulose. However, addition of sodium hydroxide leads to an increase in the destruction of cellulose in Cadoxene[28,32].

Donetzhuber[33] showed the advantage of using a low temperature in the dissolution of cellulose in Cadoxene.

Bolotnikova and Samsonova[34,35] obtained Cadoxene which dissolves cellulose with degree of polymerisation 2000, by saturating a solution of ethylenediamine with cadmium oxide at 0°C for 1 h. In the dissolution of cellulose with a degree of polymerisation > 5000 it is desirable to reduce the temperature to between 0° and −50°C. The maximum concentration of cellulose at DP $\simeq 1200$ is 6–7%.[36]

Cellulose undergoes comparatively little oxidation in a solution of the ethylenediaminecadmium complex[26,34,37]. The presence of foreign ions (Cu^{2+}, Co^{2+}, Fe^{3+}, Ni^{2+}) as impurities accelerates the destruction of cellulose[37], therefore cotton cellulose is oxidised less than sulphite.

Among other methods for making Cadoxene that of Reimers[38] merits note. Ethylenediamine is passed through a column filled with a mixture of sand and cadmium oxide. A solution of the ethylenediaminecadmium complex of the desired cadmium concentration is obtained after 15 min.

An alkaline solution of sodium tartratoferrate complex is another solvent which is used for cellulose. Frank[39] was the first to investigate the complex present in this solvent. The formation of two complexes is possible in the Fe^{III}–tartaric acid–NaOH system, $[(C_4H_2O_6)Fe]Na$ and $[(C_4H_3O_6)_3Fe]Na_6$ at $Fe(OH)_3$: tartaric acid : NaOH molar ratios of 1 : 1 : 1 and 1 : 3 : 6 respectively. Jayme and Verburg[40] found the compositions of mixtures of components with the greatest dissolving power; the complex $[(C_4H_3O_6)_3Fe]Na_6$ is formed. The Na in this can be replaced by K and Li,[41] but the replacement of the tartaric acid by other organic acids: malic, oxalic, lactic, citric, or salicylic, does not lead to the formation of complexes which dissolve cellulose, since the complex is precipitated when the alkali is in excess[42].

Jayme and Bergman[43] proposed two methods for the preparation of a solution of sodium tartratoferrate complex (STFC). The reaction of stoichiometric amounts of an iron(III) salt and tartaric acid in the presence of an excess of sodium hydroxide gives the complex $[(C_4H_3O_6)_3Fe]Na_6$, which is separated by precipitation with alcohol. Then this very hygroscopic complex dissolves in the alkali solution and sodium tartrate is added for stabilisation. However, the most widely used method for making STFC is from tartratoferric acid, insoluble in water[43]. This is dissolved in a solution of alkali and sodium hydrogen tartrate, and the sodium hydrogen tartrate is added in slight excess to stabilise the solution. Two STFC solutions are used for dissolving cellulose with a high degree of polymerisation: one which brings about the swelling of cellulose contains 300 g litre^{-1} STFC, 1.0 N NaOH, and 35 g litre^{-1} sodium tartrate, and the composition of the second solution is 480 g litre^{-1} STFC, 3.0 N NaOH, and 25 g litre^{-1} sodium tartrate. On mixing these two solutions a solvent with optimal dissolving ability is obtained[44]. Valtasaari[45] obtained an alkaline solution of STFC by a simplified method—mixing iron nitrate, tartaric acid, and sodium hydroxide without isolating the pure complex. However, this solvent is suitable only for dissolving cellulose with a degree of polymerisation up to 1500, since foreign ions in this solvent reduce the solubility of cellulose[46]. All other methods for making STFC are only modifications of the methods of Jayme, Bergman, and Valtasaari[47–50]. Solutions of cellulose in an alkaline solution of STFC are fairly stable[51–54]; $[\eta]$ for sulphite cellulose with a degree of polymerisation of 1400 did not change in two days[53], there is only a change in the slope of the relation $\eta_{sp}/c = f(c)$, where c is the concentration in g/100 ml and η_{sp}/c is the reduced viscosity, which shows a change in the interaction of cellulose with the solvent. After 4 days $[\eta]$ had changed by $\sim 6\%$. An investigation of the kinetics of destruction of cellulose in STFC solution[54] showed that it does not depend on the concentration of cellulose in the solution but increases with the temperature. The rates of destruction of cellulose in STFC solution in an atmosphere of nitrogen, air, and oxygen are in the ratio 1 : 3 : 9. An analysis of the oxidation products of cellulose by gas chromatography showed that the oxidation takes place mainly at carbon atoms 2 and 3. Jayme and coworkers[55] later found rather pronounced destruction of cellulose in STFC solutions.

An alkaline solution of biuretcopper complex in which cellulose can also dissolve is formed on mixing copper hydroxide and biuret in 1 : 2 ratio in the presence of potassium hydroxide[56]. Increasing the copper : biuret ratio from 2 to 4 leads to a decrease in the solubility of the cellulose. On replacing the potassium hydroxide by sodium hydroxide the biuretcopper complex dissolves more slowly and to a lesser extent. The solvent is unstable. On storing it for 2–3 weeks the odour of ammonia appears, indicating decomposition of the biuret. The presence of cellulose in the solution of the complex accelerates its decomposition although the solubility of cellulose is unchanged. This is probably because an amminecopper complex is formed in the decomposition of the biuretcopper complex. There has not been a quantitative study of the stability of solutions of cellulose in the biuretcopper complex, although Jayme and Lang[56] noted a significant decrease in the viscosity of cellulose solutions during storage.

As has been shown[57–59], quaternary ammonium bases with a molecular weight over 150 dissolve cellulose, and those with a lower molecular weight cause it to swell. Each organic base can dissolve cellulose only at a definite concentration of the base in water, and this concentration is less the higher the molecular weight of the base. Tetramethylammonium hydroxide ($M = 91$) and trimethylpropylammonium hydroxide ($M = 119$) do not dissolve cellulose at any concentration. Tetraethylammonium hydroxide at a concentration of 35–40% in water dissolves cellulose with $M < 250\,000$. The best solvents are the quaternary ammonium bases containing benzyl radicals[59].

Of the other solvents for cellulose mention must be made of phosphoric acid and sodium hydroxide, but their use is limited, since they only dissolve cellulose with moderate degrees of polymerisation. 82–84% solutions of phosphoric acid have been proposed for the dissolution of cellulose by Ekenstamm[60,61]. In studying the effect of various conditions on the solubility of cellulose in phosphoric acid, Danilov and Gintse[62] found that the solubility curve has two maxima, between which there is a region of incomplete solubility. The position of these maxima correspond to the concentrations of acid at which it exists in the form of monohydrate and hemihydrate. When preliminary swelling of the cellulose in water or dilute phosphoric acid is employed dissolution also takes place in the range of compositions between the maxima. Drawbacks of phosphoric acid as a solvent are its own high viscosity and the fact that it can only dissolve celluloses with polymerisation degrees in the range 700–800, or at lower temperatures degrees of polymerisation up to 1200–1500.[60,61]

At a concentration of 10–12% sodium hydroxide can dissolve specimens of cellulose with a degree of polymerisation up to 350. Solutions of cellulose in alkali undergo strong oxidative destruction[4,63–65].

Cellulose dissolves when heated in solutions of certain salts, such as lower chlorides and thiocyanates, but solutions of cellulose in salts have hardly been investigated.

A quite recent proposal[66] was to dissolve cellulose and other polysaccharides in *NN*-dimethylformamide and *NN*-dimethylacetamide to which N_2O_4 and NOCl have been added. To dissolve cellulose in dimethylformamide the molar ratio of N_2O_4 to cellulose must be greater than 3 : 1 and the ratio of NOCl to cellulose greater than 8 : 1. The cellulose is first suspended in the dimethylformamide and then N_2O_4 or NOCl introduced. In contact with moist air cellulose is precipitated. Cellulose can be isolated from these solutions with water or lower alcohols. In the absence of moisture solutions of cellulose in these solvents are stable.

2. INTERACTION OF CELLULOSE WITH SOLVENTS WHICH CONTAIN COMPLEXES

In dissolving cellulose it is necessary to break the strong intermolecular interactions due to a large number of hydrogen bonds. The weakening of the intermolecular interaction is facilitated by solvation—the reaction of the hydroxyl groups of the cellulose with the solvent with the formation of a monosolvate sheath[67–69]. However, the hydrogen bonds in cellulose are not destroyed completely during solvation. On using solvents which contain complexes of metals a compound of cellulose and the solvent is formed and this together with hydration leads to the breaking of the hydrogen bonds and dissolution of the cellulose.

The greatest number of studies has been devoted to elucidating the mechanism of the dissolution of cellulose in a solution of the amminecopper complex. The first investigations in this direction were made by Traube[70–72] who studied the reaction of the amminecopper and ethylenediaminecopper complexes with tartaric acid and glycerol. He applied the results of his investigations to cellulose and suggested the existence of a complex of cellulose and the amminecopper compound of composition $[(C_6H_8O_5)_2Cu][Cu(NH_3)_4]$, where the ratio $C_6H_{10}O_5 : Cu = 2 : 1$. However, this does not fit in with modern views about the coordination numbers of copper. Hess and Messmer[73,74] also thought that the dissolution of cellulose in a solution of amminecopper complex yielded a compound of the alkoxide type, $[C_6H_7O_5Cu]_2[Cu(NH_3)_4]$, in which copper is present in both the anion and the cation. The formation of an alkoxide compound of copper with cellulose was not demonstrated by these investigators and is not very probable. Their papers do not give any evidence of a different type of bonding of the copper in the cation and anion[75].

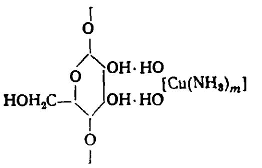
Danilov and Okun'[76–77] investigated amminecopper solutions of cellulose, hydroxyethylcellulose, methyl cellulose, alginic acid, sugars, and polyhydric alcohols. The investigation of electrophoresis and ionic exchange on cation- and anion-exchange resins, and also the study of the composition of precipitates obtained from solutions of cellulose in the amminecopper complex, the investigation of the absorption spectra of a solution of the amminecopper complex, cuprophane and Cellophane films, and solutions of cellulose and other polyhydroxy-compounds showed that copper is not present in the anion. Copper was deposited only on the cathode and exchange of ions on the anion-exchange resin was not observed, whereas the copper and ammonia were completely absorbed on the cation-exchange resin and cellulose was precipitated.

On the basis of their experimental results, Danilov and Okun' concluded that the compound formed in solutions of cellulose in amminecopper complex is not an alkoxide but a molecular compound of variable composition:

$$(C_6H_{10}O_5)_x[Cu(NH_3)_m(OH)_2]_y(H_2O)_z.$$

From a study of the optical rotation and electrical conductivity of amminecopper solutions of 17 glucosides, Reeves[78] suggested that in the solution a cyclic complex is formed between tetra-amminecopper and neighbouring hydroxyl groups of the glucosides. Glucosides without a glycollic grouping do not dissolve in the amminecopper complex.

To find the composition of the compound which is formed in the dissolution of cellulose in a solution of the amminecopper complex, Arkhipov[79] used polarimetric and conductometric methods and also determined the change in the copper concentration on the introduction of cellulose into the water–ammonia–copper hydroxide system. Thermodynamic quantities were calculated: the equilibrium constant of the reaction, the heat of reaction, the free energy change, and the change in entropy of the system. All these results show the formation of a molecular compound:



The nature of the reaction of cellulose with the ethylenediaminecopper complex is thought by Traube[71] and Jolley[80] to be analogous to interaction with the amminecopper complex.

Gralen and Linderot[81] used a spectrophotometric method to determine the optical density of solutions of glucose in solutions of amminecopper and ethylenediamine complexes at wavelength 330 mμm and various molar volumes of the components. These results were compared with optical densities of solutions of the components. Maximal difference in the optical densities was obtained at the glucose : copper ratio of 1 : 1 for solutions of glucose on the amminecopper complex and 4 : 6 for solutions of glucose in the ethylenediamine complex. Gralen and Linderot considered that these results confirmed Hess's alkoxide formula.

Comparatively recently Vink[82] investigated the formation of polysaccharidemetal complexes in solutions of cellulose in ethylenediaminecopper and ethylenediaminecadmium complexes. He subjected the cellulose solutions, diluted with water, to dialysis through Cellophane membranes. The difference in concentration of ethylenediaminecopper complexes on the two sides of the membrane was determined spectrophotometrically. Cellulose and dextran were used. The latter is soluble in water and therefore the composition of the ethylenediaminecopper complex can be varied within wide limits. The use of cellulose is limited to a narrow range of solvent compositions in which it can be dissolved. All the main experiments were made with dextran and then the results of these experiments were extended to cellulose.

Vink began from the assumption that the reaction of cellulose and dextran with ethylenediaminecopper complex can be effected either by the formation of a complex:

$$R'(OH)_2 + Cuen_2^{2+} + 2OH^- \rightleftharpoons R'O_2Cuen + en + 2H_2O, \qquad (1)$$

or by the scheme:

$$ROH + OH^- \rightleftarrows RO^- + H_2O. \qquad (2)$$

The degree of bonding β' of the metals, in this instance copper, was calculated by the formula:

$$\frac{\beta'}{1-\beta'} = K_1[OH^-] + K_2\frac{[Cuen_2^{2+}][OH^-]^2}{[en]}, \qquad (3)$$

where the values of the equilibrium constants K_2 and K_1 determine the relative importance of reactions (1) and (2).

The degree of bonding of the ethylenediaminecopper complex is almost independent of the concentration of the polymer in the solution, although it is somewhat higher for dextran than for cellulose. It was found that at low concentrations of ethylenediamine in the solution (up to 6%) the predominant reaction is the formation of a complex by reaction (1). On increasing the ethylenediamine concentration the second term in Eqn. (3) decreases and complex formation is replaced by reaction according to Eqn. (2), represented by the first term in the right-hand side of Eqn. (3). Cellulose dissolves in ethylenediaminecopper complex at the ratio en : Cu = 2 (6% ethylenediamine, copper concentration 0.5 M). On increasing the en concentration the ethylenediaminecopper complex does not dissolve cellulose. At high ethylenediamine concentrations (~ 25–40%) and a copper concentration of $\nless$ 0.35 M dissolution of cellulose again takes place, which shows the active role of en in the dissolution mechanism.

For solutions of cellulose and dextran in cadmiumethylenediamine complex it was found that within the limits of experimental error the rate constant of the reaction for complex formation is 0. Vink concluded that a complex of cellulose and Cadoxene is not formed, but formation of a compound by reaction (2) occurs. The degree of bonding of cadmium is lower than that of copper, and is the same for cellulose and dextran.

Lindberg and Swan[83] studied the composition of the compound formed in a solution of cellulose in Cadoxene by using the same method as Reeves[78], that is, they studied the change in the optical rotation of solutions of several glucosides and xylosides in Cadoxene and in a 28% solution of en. They think that a complex is formed between the hydroxyls of cellulose and the Cadoxene. A change in the optical rotation of the solution after it had been stored for 24 h was noted. No suggestions were made as to whether this is the consequence of the destruction of the cellulose in the solution or of a change in the state of the solution. A study by paper electrophoresis of a solution of methyl-β-D-glucopyranoside and of several sugars in 10% aqueous solution of Cadoxene (0.55% Cd) showed their low electrophoretic mobility, in good agreement with the results of electrophoresis in aqueous solutions of NaOH.[84]

Vink[82] suggests that the mechanism of dissolution of cellulose in Cadoxene is similar to the mechanism of its dissolution in quaternary ammonium bases. The large $Cden_3^{2+}$ ion in permeating into the cellulose causes its swelling and dissolution. The free ethylenediamine can form molecular compounds with cellulose[85,86].

Jayme and Verburg[41] studied the dissolution of cellulose in alkaline solutions of the sodium tartratoferrate complex[41]. They suggested that the solubility is determined by the swelling of cellulose in NaOH, which in the presence of STFC is so pronounced that dissolution takes place. In carrying out sedimentation and diffusion measurements, Jayme and coworkers[51] started from the fact that reaction between cellulose and STFC ends in addition. By measuring the vapour pressure it was shown that on adding cellulose to the solvent the activity of its components falls. Valtasaari[45] explained the solubility of cellulose in STFC by the direct combination of the cellulose with the iron. Bayer and coworkers[87] studied complex formation in the tartratoferric acid–alkali system from the change in optical rotation and light absorption as a function of the molar ratio of the components. It was found that the optimal Fe^{3+} : tartrate ratio for complex formation is 1 : 4.5. However, a system of this composition does not dissolve cellulose. For good dissolution of cellulose the Fe : tartrate ratio should be 1 : 3. This solution is stable but it contains insufficient tartrate for the complete saturation of the coordinate bonds of the iron. In place of the missing tartrate, water molecules and possibly hydroxide ions from the alkali are bonded with the iron. In the dissolution of cellulose the hydroxyl groups at carbon atoms 2 and 3 displace water molecules and hydroxide ions and form a new chelate compound. In this the hydrogen bonds of the cellulose are broken, destroying the physical structure, and the cellulose enters the solution. Tartrate ions are not displaced from their compounds with iron.

The general structure of the complex, which consists of iron and tartrate ions and of cellulose, cannot be found at present as the nature of the structure existing in the solvent is not known accurately.

3. FRACTIONATION OF CELLULOSE

The molecular weight distribution of cellulose is now mainly determined by the fractionation of its nitrates[88-91]. However, the fractionation of cellulose nitrate under conditions under which the usual polymers are fractionated leads, as Marx showed[92], to destruction, and this is the greater the higher the molecular weight[93]. The fractionation of cellulose nitrate is a long operation and takes 7–10 days. This is also insufficient, since the destruction of cellulose nitrate increases the longer the solution is kept. The breakdown is accelerated by rise in temperature and by alkali metal ions leached out of the glass[93]. In addition it is difficult to obtain completely substituted cellulose nitrate and therefore during fractionation separation will take place both by molecular weights and by degrees of substitution. Therefore it is important to carry out the fractionation of the cellulose by a direct method. Attempts were made to use all the present solvents for the fractionation of cellulose.

In the fractionation by the dissolution method a change in the solubility of cellulose in solutions of alkalis is brought about either by reducing the temperature from 20° to −12°C[94-96] or by change in the alkali concentration[97]. Acetone was used as precipitant in the fractionation of solutions of cellulose in alkalis by the precipitation method[98]. But only cellulose of a moderate degree of polymerisation is soluble in alkali and in alkaline medium it undergoes marked destruction in the presence of air.

Phosphoric acid can be used as solvent in the fractionation of cellulose of moderate degree of polymerisation. The method is based on the fact that at phosphoric acid concentrations from 72 to 83% macromolecules of cellulose of different sizes are dissolved[61]. The solubility of cellulose in phosphoric acid depends on the temperature and increases as the temperature is reduced[99]. According to Akim[100], who studied the polydispersity of celluloses by their fractional dissolution in phosphoric acid, seven or eight fractions can be obtained in 3–4 h. In the fractionation of cellulose in phosphoric acid solutions hydrolysis of cellulose is possible.

The method of fractionating cellulose from its solutions in sulphuric acid[101] is based on the ability of cellulose to be precipitated from such solutions at temperatures from −15° to −20°C on varying the concentration of the acid. A drawback of this method also is the pronounced hydrolysis brought about by the action of sulphuric acid and the possibility of obtaining a total of three or four fractions.

In the fractional dissolution of cellulose in solutions of amminecopper and ethylenediaminecopper complexes a change in the solubility of the cellulose was brought about[102] by the use of amminecopper solutions with different copper concentrations. Coppick and coworkers[98] and Müller and Rogers[103] separately treated several specimens of cellulose with a constant volume of solvent but with different copper concentrations, and Shulyatikova and Mandel'baum[104] varied the absolute amount of copper in the solvent used for dissolving the cellulose. In all the above instances it is thought that dissolution of cellulose with different degrees of polymerisation depends on the concentration of copper in the solution.

Sihtola and coworkers[105] checked this in the following manner. Different amounts of ammonia were added to a solution of cellulose in amminecopper complex, and the concentration of copper in the solution was altered, during which part of the cellulose was precipitated from the solution. Then its characteristic viscosity was determined. Another part of the cellulose left in the solution was precipitated with acid and $[\eta]$ was again measured. It was thus shown that although the concentration of copper in the solution was varied the characteristic viscosity of the precipitates hardly altered, that is, fractional separation did not occur.

The precipitants used for the fractional precipitation of cellulose from its ethylenediammine copper solutions are acids[106] and organic substances (glycerol, propanol, ethanol).[105] As Sihtola and coworkers[105] showed, breakdown of the complex occurs if acid is used to precipitate the cellulose. Usually three or four fractions are obtained, the first of which contains about two-thirds of the weight of the cellulose taken for fractionation. When glycerol and propanol are used to precipitate cellulose from its ethylenediaminecopper solutions the fractionation occurs according to molecular weights. However, it was concluded[105] that solutions of cellulose in the ethylenediaminecopper complex cannot be used for fractionating the cellulose with the aim of determining its molecular weight distribution, owing to the destruction of the dissolved cellulose by atmospheric oxygen.

In recent years Jayme and coworkers used the method of fractional dissolution for fractionation of cellulose from its solutions in Cadoxene[28] and an alkaline solution of the sodium tartratoferrate complex[107]. This was done by adding solvent with various cadmium contents to known weights of cellulose. After shaking for a fixed period the insoluble part was separated by centrifuging. Cellulose was precipitated from the solution left after centrifuging, washed, and its weight and degree of polymerisation determined. The values of $[\eta]$ and the weight of substance extracted were used to construct a molecular weight distribution curve.

Bolotnikova and coworkers[108] used glycerol solutions as precipitants for the fractionation of cellulose from solutions in Cadoxene. It was shown that separation into molecular weight fractions takes place. Specimens of sulphite cellulose with $[\eta] = 4.9$ were separated into 8–10 fractions with $[\eta]$ from 6.1 to 2.2. To decrease the dwell time of the cellulose in the solution centrifuging was used to separate the fractions. In preliminary experiments on the reprecipitation of cellulose from solutions in Cadoxene it was shown that the destruction of cellulose during this is insignificant and $[\eta]$ varies by $\sim 9\%$.

Laamanen and Sihtola[109] used a 75% solution of propanol as precipitant for the fractionation of cellulose from solution in Cadoxene. This method was also employed by Kostnikova and coworkers[110], who showed agreement with the results of fractionation through the nitrates.

A paper recently appeared on the possibility of obtaining a molecular weight distribution curve for cellulose by gel chromatography on polyacrylamide gel[111]. The concentration of cellulose in the eluate was determined by Vasseur's method[112]. Specimens with degree of polymerisation 780, 1180, and 2000 were isolated as were two 50 : 50 mixtures of these specimens having degrees of polymerisation (DP) of 780 and 1180 and of 780 and 2000.

Various precipitants have been used for the fractional precipitation of cellulose from its solutions in the alkaline sodium tartratoferrate complex. Thus glycerol[53,113,114], water–methanol mixture (but up to 20% of the cellulose could not be precipitated with this[115,116]), isopropyl alcohol[117], and glycol[117] have been used. Edel'man observed good agreement between distribution curves obtained in the fractionation of cellulose from solutions in STFC and by the nitrate method, when cellulose solutions taken for fractionation had concentrations $\ngtr$ 0.2 g per 100 ml.

4. RELATION BETWEEN THE CHARACTERISTIC VISCOSITY AND MOLECULAR WEIGHT

The direct determination of the molecular weight of cellulose is hindered by the strongly acid and strongly alkaline nature of its solvents. The determination of molecular weight in solutions of complexes is complicated by the fact that in all the measurements (sedimentation, diffusion, light scattering) the kinetic species is a compound of cellulose with the complex, but as already mentioned there is no single opinion about the composition of the complex.

Gralen[118] determined the molecular weight of cellulose and its derivatives (xanthogenates and nitrates) using sedimentation and diffusion. Polydisperse specimens of cellulose were studied. The molecular weight was determined in the absence of air. Anomalies were observed in diffusion measurements on amminecopper solutions of cellulose but these were not noted for solutions of nitrates and xanthogenates. The diffusion process was retarded and began only after 2–3 days. Such an initial retardation of diffusion is explained[119] by the fact that some part of the copper is bound with the cellulose and diffuses together with it. The concentration of copper in the solution is less than that in the solvent. This also causes an apparent slowing of the diffusion owing to contradiffusion. In calculating the molecular weight Gralen started from Hess's ideas about the structure of the cellulose complex. Gralen gives his observations on the difference between the refractive index determined in sedimentation and diffusion measurements and with the aid of differential prisms. The author suggested that in the first instance the refractive index of the cellulosecopper compound changes, and in the second that of cellulose itself. The approximate conclusion was drawn that this difference corresponds to one atom of copper per glucose residue. From Gralen's results on molecular weight and characteristic viscosity in an amminecopper complex, Hermans[120] derived a relation between $[\eta]$ and molecular weight (M). This relation is shown in Table 1, Eqn. (4).

Michil[121] determined the molecular weight of cellulose from its nitrates when deriving the relation between characteristic viscosity and molecular weight of cellulose in solutions of the amminecopper complex. He calculated the molecular weight of the cellulose nitrate from the relation $[\eta] = f(M)$, determined by Hunt and coworkers[122] and by Holzer and coworkers[123] from results on light scattering. The molecular weights calculated from the relation obtained by Michil for amminecopper solutions of cellulose—Eqn. (5) in Table 1—agree well with the molecular weights measured by Gralen.

Table 1 also gives the relation between $[\eta]$ and M for amminecopper, Eqn. (6), and ethylenediaminecopper, Eqn. (8), solutions obtained by Marx[14]. The degree of polymerisation used in the derivation of these relations was determined from the viscosity of cellulose nitrates and calculated by the Schulz and Marx equation[124]:

$$[\eta]_g = 1.8\cdot 10^{-3} P_w^{0.9}\,\mathrm{cm}^3\,\mathrm{gf}^{-1},$$

where P_W is the weight-mean degree of polymerisation and $[\eta]_g$ was determined at a rate of 500 s^{-1}.

Immergut and coworkers[125] found a relation between characteristic viscosity and molecular weight for solutions of cellulose in amminecopper and ethylenediaminecopper complexes—Eqns. (7) and (9) in Table 1. Polydisperse specimens of cellulose with degrees of polymerisation from 100 to 3000 were investigated. The molecular weights of the cellulose were determined from measurements of the osmotic pressure in solutions of the corresponding cellulose nitrates (polydisperse and fractionated specimens). These investigators attempted to determine the molecular weight of celluloses (DP 408 and 166) in a solution of the ethylenediaminecopper complex with the aid of osmometry. Membranes of poly(vinylbutyral) and poly(chlorotrifluoroethylene) were used. The values of the number-mean molecular weights thus obtained agreed well with those calculated from the relations they obtained.

Table 1. Relation between characteristic viscosity and molecular weight for cellulose in various solvents.

Solvent	Specimens of Cellulose	Temp., °C	Relation $[\eta] = f(M)$, 100 ml g^{-1}	Method	Ref.
Amminecopper complex	polydisperse	25	$[\eta]=0.77\cdot10^{-2}\ P^{0.81}$ (5)	NC_{ls}	121
	ditto	20	$[\eta]=85\cdot10^{-4}\ M^{0.81}$ (7)	NC_{os}	125
ditto	,,	20	$[\eta]=1.7\cdot10^{-4}\ M^{0.77}$ (4)	sd	120
,,	,,	—	$[\eta]=6.8\cdot10^{-2}\ P^{0.9}$ (6)	NC_{sd}	14
Ethylenediamine-copper complex	polydisperse	—	$[\eta]=9.8\cdot10^{-2}\ P^{0.9}$ (8)	NC_{sd}	14
	ditto	25	$[\eta]=1.33\cdot10^{-4}\ M^{0.9}$ (9)	NC_{os}	125
	,,	25	$[\eta]=1.7\cdot10^{-2}\ P^{0.8}$ (10)	os	126
Ditto	polydisperse	25	$[\eta]=1.7\cdot10^{-2}\ P^{0.77}$ (12)	ls	27
,,	hydrolysed	—	$[\eta]=1.8\cdot10^{-2}\ P^{0.77}$ (13)	ls	27
Cadoxene		—	$[\eta]=2.5\cdot10^{-2}\ P^{0.75}$ (11)	sd	27
,,	polydisperse	20	$[\eta]=7.0\cdot10^{-3}\ P^{0.9}$ (14)	NC_{sd}	127
,,	fractionated	20	$[\eta]=5.93\cdot10^{-5}\ M^{0.94}$ (15)	NC_{sd}	127
,,	ditto	20	$[\eta]=9.33\cdot10^{-4}\ M^{0.72}$ (16)	NC_{sd}	127
,,	,,	—	$[\eta]=3.85\cdot10^{-4}\ M^{0.76}$ (17)	ls	130
Alkaline sodium tartratoferrate	polydisperse	25	$[\eta]=6.6\cdot10^{-3}\ P^{1.01}$ (18)	sd	51
	,,	—	$[\eta]=5.31\cdot10^{-4}\ M^{0.78}$ (19)	ls	133

Note. The fifth column gives the method used for determining the molecular weight in the scaling relation $[\eta] = f(M)$: sd, sedimentation and diffusion; ls, light scattering; os, osmometry; NC, molecular weight determined viscosimetrically by conversion of the cellulose into cellulose nitrate; and the subscript shows by which method the relation $[\eta] = f(M)$ was found for cellulose nitrate.

Vink[126] found that solutions of cellulose in the ethylenediaminecopper complex can be diluted with water. Such solutions do not dissolve more cellulose but neither does precipitation of the cellulose take place. Therefore for determining the partial specific volume of cellulose Vink used dialysed solutions and converted the Svedberg formula for calculating the molecular weight of cellulose from sedimentation and diffusion measurements in such a way that the calculation gave the molecular weight not of the cellulosecopper complex (like Gralen), but of the cellulose itself:

$$M = \frac{RTS_x^0}{D_x^0 M_x/M\,(1-\bar{V}_x\rho)},$$

where R is the universal gas constant, T the temperature, S_x^0 the sedimentation constant, and D_x^0 the diffusion constant for the compound of the solvent with cellulose, extrapolated to infinite dilution, ρ the density, $\bar{V}_x$ the partial specific volume, M_x the molecular weight of the compound of cellulose with the solvent. Vink[126] determined the value of

$$\frac{M_x}{M}(1-\bar{V}_x\rho)$$

experimentally by dialysis of cellulose solutions of various concentrations. Anomalies in the diffusion experienced by Gralen[118] were avoided by Vink in the following manner. To prevent counterdiffusion of copper ion from the solvent to the solution he diluted the solvent with a little water. The molecular weights obtained by Vink were compared with those calculated by Marx' equation[14] and showed good agreement. Vink also determined the molecular weights by osmometry and found the relation between $[\eta]$ and M, Table 1, Eqn. (10).

Henley[27] used Vink's method when investigating solutions of cellulose in solutions of the ethylenediaminecadmium complex. The cellulose solutions were diluted with water in 1:1 ratio and contained alkali. Owing to the difficulty in obtaining fractions, Henley used polydisperse specimens obtained by acid hydrolysis of linters with polymerisation 5800. In such treatment a statistical molecular weight distribution with ratio $M_w:M_n = 2$ should be established, where M_w is the weight-mean and M_n the number-mean molecular weight. The relation between the molecular weight and $[\eta]$ obtained by Henley from the sedimentation and diffusion results are given in Table 1, Eqn. (11). Henley also determined the molecular weight of cellulose by a light scattering method. In studying the light scattering of solutions of cellulose in Cadoxene the increment in refractive index was determined after equilibrium dialysis at wavelengths of 5460 and 4358 Å; it was 0.183 and 0.186 ml g^{-1} respectively. The intensity of scattering was measured over the range of angles from 45° to 135°; the $[\eta] = f(M)$ relation—Table 1, Eqn. (12)—was found from the results on molecular weights and $[\eta]$.

Henley employed the usual Cellophane membranes in measuring the osmotic pressure of solutions of cellulose in Cadoxene diluted with water. Since it was assumed that $M_w:M_n = 2$, the values of M_w and M_n gave the viscosity-mean molecular weight and the relation $[\eta] = f(P_v)$, where P_v is the viscosity-mean degree of polymerisation, Table 1, Eqn. (13).

Bolotnikova and Samsonova[127] found the relation between $[\eta]$ and M for fractionated and polydisperse specimens of cellulose in solutions of the ethylenediaminecadmium complex not diluted with water. The molecular weights of cellulose were determined from the viscosity of their nitrates.

The molecular weight of the cellulose nitrates was determined by the relation:

$$[\eta]=2.8\cdot10^{-5}\ M_{ww}^{1.00},$$

obtained by Meyerhoff[128,129] in investigating the sedimentation and diffusion of fractionated and polydisperse specimens of cellulose nitrate in acetone at 20°C. The molecular weights of several specimens of cellulose nitrate were determined by sedimentation and diffusion methods and their values agreed with those calculated by Meyerhoff's equation.

It was observed that there is a decrease in the slope of the relation between lg $[\eta]$ and lg M in the range of high molecular weights. Consequently this relation was found for two ranges of molecular weights. For fractionated specimens of cellulose with a molecular weight up to 400 × 10^3—that is, up to $[\eta] = 10$ g per 100 ml—the relation is described by the equation:

$$[\eta]=5.93\cdot10^{-5}\ M^{0.94}\quad(100\text{ ml g}^{-1}),$$

and in the range of molecular weights greater than 300 × 10^3 by

$$[\eta]=9.33\cdot10^{-4}M^{0.72}\quad(100\text{ ml g}^{-1}).$$

This difference in the values of the constants K and α in the Mark–Kuhn–Houwink equation $[\eta] = KM^{\alpha}$ between the low- and high-molecular weight ranges are due to the fact that at low degrees of polymerisation the final configuration of the coil has not been reached and the asymmetry of the molecules gradually decreases with increase in the molecular weight. Furthermore it can also be explained by the observed deterioration in the quality of the solvent for cellulose with a higher molecular weight. Brown and Wirkström[130] obtained similar results about the different nature of the relation between $[\eta]$ and M; they observed that at DP < 250 the conformation undergoes changes and the behaviour of the molecule departs from the behaviour of the coil. This agrees with the theories of the Kuhns, a verification of whose equations shows[131] that there is a change from the value $\alpha = 1$ in the range of low molecular weights to the value $\alpha = \frac{1}{2}$ in the range of high molecular weights, α being the exponent in the equation $[\eta] = KM^{\alpha}$. This change is due to a change in the trapping of the solvent in the coil of the chain molecule.

Vink[132] studied the behaviour of low-molecular-weight cellulose and oligosaccharides. For the oligosaccharides was determined in water, Cadoxene, and sulphuric acid. For degrees of polymerisation up to 150 a linear relation between $[\eta]$ and M was obtained. At lower degrees of polymerisation (< 100) the slope of the straight line $[\eta] = f(M)$ increases and consequently α also increase; the maximal value being $\alpha = 1.3$ at DP = 15. As has been shown[132], this behaviour of the molecules follows from their tendency to approach a prolate ellipsoidal form as the molecular weight is decreased.

Claesson and coworkers[51] made a diffusion and sedimentation investigation of solutions of cellulose in an alkaline solution of the sodium tartratoferrate complex which had been diluted with water; the relation between $[\eta]$ and M was obtained, Table 1, Eqn. (18). Later Valtasaari[133] obtained the $[\eta] = f(M)$ relation for solutions of cellulose in an alkaline solution of STFC by a light scattering method. This relation is also given in Table 1, Eqn. (19). Other relations between $[\eta]$ and M obtained by calculations from measurements of $[\eta]$ in two solvents, have been published[134].

5. DIMENSIONS AND FORM OF CELLULOSE MACROMOLECULES IN SOLUTION

Cellulose, like many synthetic polymers, is a linear unbranched polymer. However, the properties of cellulose solutions show a difference from those of flexible polymers, for example, those of the vinyl series. Thus it is well known that cellulose has a comparatively high characteristic viscosity ($[\eta]$), low sedimentation constant (S_0) and diffusion coefficient (D_0). Many of these properties, for example, $[\eta]$, are functions of the absolute dimensions of the macromolecules in the solution.

The dimensions and form of the cellulose macromolecules in solution are determined on the one hand by the size and structure of the monomeric unit, which is anhydro-*d*-glucose of cyclic structure, linked by a β-1,4-bond, and on the other hand by the presence of three free hydroxyl groups, which determine the existence of both intra- and inter-molecular hydrogen bonds and also the specific nature of the interaction with the solvent.

To separate the influence of the solvent from the influence of the proper characteristics of the molecules, it is necessary to know the unperturbed dimensions in θ-conditions, that is, when the behaviour of the solution becomes ideal and the second virial coefficient equals zero.

The unperturbed dimensions depend on the size of the monomeric units, the lengths of the bonds between them, the valence angle, and steric and energetic hindrances to rotation around the intermonomeric bond. However, for cellulose it is experimentally difficult to attain the θ-condition, since the complexes in which cellulose is soluble exist in a narrow range of component concentrations and temperatures.

Samsonova and coworkers[135] calculated the unperturbed root mean square distances between the ends of the chain $\langle h_0^2\rangle^{1/2}$ for cellulose in Cadoxene by the Stockmayer–Fixman equation[136], by introducing the additional function $\Phi_0/\Phi(M)$[137]:

$$[\eta]\cdot\Phi_0/\Phi(M) = K_\theta M^{1/2} + 0.51B\Phi_0 M, \tag{20}$$

where

$$K_\theta = \Phi_0\left(\frac{h_0^2}{M}\right)^{3/2}, \Phi_0$$

Φ_0 is the universal Flory constant equal to 2.86×10^{21} for a statistical gaussian coil, $\langle h_0^2\rangle^{1/2}$ is the unperturbed root mean square distance between the ends of the chain, M the molecular weight, B a parameter which characterises the polymer–solvent interaction and is proportional to the second virial coefficient, and $\Phi(M)$ is a function depending on the molecular weight introduced by Eizner and Ptitsyn[138] for the Flory constant with rigid macromolecules which are permeated by the solvent:

$$\Phi(M) = \frac{\Phi_0}{\left[\varphi(\lambda, n) + \frac{45}{32}\sqrt{\frac{2\pi}{3}}\frac{1}{3-\sqrt{2}}\frac{b_0}{r_0}\sqrt{\frac{\lambda}{n}}\right]\varkappa^{1/2}(n/\lambda)}. \tag{21}$$

Here λ is the correlation length, equal to a/b_0, a the persistent length[139], b_0 the "dry" length of monomeric unit, found by an X-ray method to be 5.15 Å, and n is the degree of polymerisation.

It has been shown experimentally[27,140-143] for cellulose and its derivatives that Φ_0 depends on the molecular weight and only becomes constant at rather high molecular weights. This is explained by the great extension of the macromolecules in solution in the range of low molecular weights, so that gaussian statistics are attained only at high degrees of polymerisation when further interaction is small. It can be suggested that a change in Φ arises from the dependence of the permeability of these molecules on molecular weight.

Table 2 gives results on $\langle h_0^2\rangle^{1/2}$. Henley[27] calculated the unperturbed dimensions of cellulose macromolecules from the values of the Flory swelling coefficient α, which characterises the interaction of the polymer with the solvent and is equal to the ratio of the root mean square dimension of the disordered coil to the corresponding dimension of the unperturbed molecule

$$\alpha = \frac{(h^2)^{1/2}}{(h_0^2)^{1/2}},$$

and the value of $\langle h^2\rangle^{1/2}$ is the root mean square distance between the ends of the chain. The Henley swelling coefficient was calculated by the Orofino–Flory equation[144] from the experimental results for the second virial coefficient determined by the light scattering method and from the root mean square radius of gyration of the chain $(\overline{R}^2)^{1/2}$.

Table 2. Dimensions of the macromolecules of cellulose and its derivatives calculated by Eizner and Ptitsyn's theory[138].

System	$[\eta]$	n	λ	$(h^2)^{1/2}$	$(h_0^2)^{1/2}$	$h_{max}/(h^2)^{1/2}$	α
Cellulose in Cadoxene	6.20	2100	13	1100	840	9.1	1.4
	5.50	1730		1000	760	8.3	
	4.50	1260		900	650	6.9	
Solution of cellulose in Cadoxene diluted with water, 1:1 (Ref.27)	6.45	2090	13	1000*	837	10.8	1.4
	5.50	1700		855*	754	10.2	
	4.47	1300		735*	660	9.1	
Cellulose nitrate in acetone	24.1	2940	46	2600	1700	5.8	1.4
	14.7	1800		2100	1300	4.4	
	10.7	1300		1740	1130	3.8	
Ethyl cellulose in ethyl acetate	1.87	331	13	412	260	3.5	1.5
	1.40	246		350	225	3.1	

* The values given are for $\langle h^2\rangle_W^{1/2}$ calculated from $\langle h^2\rangle_Z^{1/2}$ obtained from results on light scattering[27].

Table 3. Dimensions of macromolecules in solutions of cellulose and its derivatives.

System	$[\eta]^{25°}$, dl g^{-1}	n_w	$(R^2)_z^{1/2}$	$(h^2)_z^{1/2}$	$(h_0^2)^{1/2}$	$(h_0^2)^{1/2}/(h^2)_f^{1/2}$	α	Ref.
Solution of cellulose in Cadoxene diluted with water, 1:1	14.15	5820	895	2190	1780	2.47	1.23	27
	6.45	2290	585	1430	1300	2.86	1.10	
	5.50	1780	485	1190	1050	2.62	1.13	
	4.47	1400	445	1090	1010	2 87	1.08	
Hydroxyethyl cellulose in water	10.62	2650	750	1830	1690	3.6*	1.08	141
	10.00	2420	730	1790	1670		1.07	
	8.95	2180	715	1750	1650		1.06	
	1.70	340	305	745	715		1.04	
Hydroxyethyl cellulose in Cadoxene	6.30	2560	620	1520	1070	2.3*	1.42	141
	6.00	2420	600	1470	1140		1.29	
	5.55	2230	575	1405	1020		1.38	
	1.24	330	255	625	575		1.09	
Sodium carboxymethylcellulose in Cadoxene	10.30	4420	835	2040	1400	2.3*	1.46	140
	8.10	3500	735	1800	1280		1.41	
	4.84	2000	550	1350	1040		1.29	
	2.55	1800	330	810	660		1.22	

* The values are approximate, since in calculating $\langle h_0^2\rangle^{1/2}$ the Stockmayer–Fixman theory was used, which cannot be employed in the investigated ranges of molecular weight for cellulose and its derivatives[148].

The value of $(\overline{R}^2)$ is the mean square of the distances r_i of all the elements of mass (atoms) of the chain from its centre of inertia[145];

$$(\overline{R}^2) = \frac{1}{N}\sum r_i^2,$$

where N is the number of units in the molecule. At sufficiently high molecular weights, when a gaussian distribution inside the macromolecule has been reached, statistical theory leads to the following relation:

$$(\overline{R}^2)^{1/2} = \frac{1}{6}h^2.$$

Henley[27] determined $(\overline{R}^2)^{1/2}$ experimentally for solutions of cellulose in Cadoxene diluted with water from the slope of the scattering relation at zero concentration (Table 3) and calculated it from values of S_0, D_0, $[\eta]$, and M. However, good agreement between the calculated and experimentally determined values was not obtained, except for the calculation of $(\overline{R^2})^{1/2}$ from $[\eta]$ and M. Samsonova and coworkers[135] calculated the mean square distance between the ends of the chain according to the Eizner and Ptitsyn theory[138], in which the rigidity and finite length of the chain are allowed for by introducing two functions $\varphi(\lambda,n)$ and $\kappa(n/\lambda)$; $\kappa(n/\lambda)$ takes into account the factor of chain rigidity and the function $\varphi(\lambda,n)$ allows for possible departures from gaussian statistics at low degrees of polymerisation.

Information about the sizes of cellulose macromolecules of various molecular weights is given in Tables 2 and 3, which also gives for comparison the dimensions of cellulose derivatives in various solvents[27,135,140–143]. It also gives values of the swelling coefficient α, which takes into account the contribution of the effect of the interaction of the polymer with the solvent. It was found that the dimensions of the macromolecules of cellulose and its derivatives in solution are appreciably greater than those of synthetic polymers at the same degree of polymerisation. The greater dimensions of the macromolecules of cellulose and its derivatives are due firstly to the greater size of the monomeric units $b_0 = 5.15$ Å (for polystyrene $b_0 = 2.54$ Å), and secondly to the greater elongation of the macromolecules owing to restricted rotation around the C–O bond between monomer units. This was shown for both cellulose[27] and its derivatives[140–143,146] by a comparison of $\langle h_0^2\rangle^{1/2}$ calculated from the experimental results with the values of $\langle h^2\rangle_f^{1/2}$ calculated assuming free rotation around the bond between monomer units. It was found that $\langle h_0^2\rangle_f^{1/2}$ is 2–3 times greater than $\langle h_0^2\rangle_f^{1/2}$ (Tables 3–6) and the ratio $\langle h_0^2\rangle^{1/2}/\langle h^2\rangle_f^{1/2}$ increases with decrease in molecular weight, showing the change in the elongation of the macromolecule with M. Furthermore, the restriction of rotation around the intermonomeric bond is shown by the high values of $\cos\Phi$[27,140–143] which is a parameter of steric hindrance. At sufficiently high values of n an analysis of hindrances to rotation can be made by using the equation:

$$h_0^2 = N\bar{b}_0^2\left(\frac{1-\cos\theta}{1+\cos\theta}\,\frac{1+\cos\Phi}{1-\cos\Phi}\right), \tag{22}$$

where N is the total number of units, θ the oxygen valence angle in cellulose and its derivatives (~ 110°), and Φ the angle between the planes of successive bonds. When rotation around the C–O bond is unrestricted, $\cos\Phi = 0$, and in the absence of free rotation with maximal elongation $\cos\Phi = 1$. For cellulose $\cos\Phi = 0.78$,[27] that is, the steric hindrances in the cellulose chain should be one of the factors which determine the form of the cellulose molecules in the solution. For amylose $\cos\Phi = 0.81$[147] and for hydroxyethyl cellulose[143] $\cos\Phi = 0.89$. In the last instance the high value of $\cos\Phi$ is due to the presence of additional hindrances, owing to the hydroxyethyl side-groups having approximately the same length as the monomeric unit b_0.

Table 5. Comparison of A_m and b for cellulose and its derivatives.

System	A_m, Å	b, Å	Method	Reference
Solution of cellulose in Cadoxene diluted with water (1 : 1)	54 147 107	24 23 23	sd visc. ls.	27
Cellulose in Cadoxene	100	25	visc.	135
Hydroxyethylcellulose in water	51 182 176 180	23 27 30 30	sd. visc. ls. ls.	143 143 143 141
Hydroxyethylcellulose in Cadoxene	124	25	ls.	141
Ethyl hydroxyethylcellulose in water	120 216	— 37	sd visc.	154 154
Methyl cellulose in water	87	—	sd	27
Ethyl cellulose in ethyl acetate	100	23	visc.	135
Cellulose nitrate in ethyl acetate	234	35	ls.	122

Table 4 gives the dimensions of the macromolecules of various polysaccharides calculated by the Eizner–Ptitsyn theory[128,135,137,149–153]. On comparing the results given in Tables 2–4 we see that the dimensions of almost all the polysaccharides, except cellulose nitrate and hydroxyethyl cellulose in water, are approximately the same at the same degrees of polymerisation, as is shown by the almost equal values for the correlation lengths λ and for the persistent length a. This shows that polysaccharides having a β-1-4

Table 4. Dimensions of the macromolecules of various polysaccharides calculated by the Eizner–Ptitsyn theory.

No.	Polymer	Solvent	M_0	Range of $[\eta]$, dl g^{-1}	Range of SP	λ	a	$(R^2)_z^{1/2}$, Å	Reference
1	birch xylan	90% DMSO	149	0.24—0.88	55—194	6.6	34.2	48—102	149
2	Canadian spruce xylan	alkali borates	137	0.37—0.57	174—406	2.7	14.2	69—102	150
3	cellulose acetates	trifluoroethanol	249	0.46—1.11	46—136	11.0	55.6	49—101	150
4	cellulose acetate	acetone	249	0.27—2.30	33—377	11.5	59.3	39—190	150
5	cellulose acetate	acetone	260	1.23—5.05	190—1000	14.7	75	150—375	137
6	cellulose	Cadoxene	162	1.47—14.15	1390—5830	13.8	70.8	405—839	27
7	cellulose	STFC	162	2.85—15.15	385—3950	13.8	71.9	206—695	133
8	cellulose trinitrate	acetone	294	0.36—15.30	44—2142	25.5	132	56—684	128
9	cellulose xanthogenate diethylacetamide	90% DMSO	238—336*	1.79—2.67	473—1190	10.5	54.0	203—378	151
10	cellulose caproate	dioxan	459	0.32—3.80	86—3160	9.3	47.7	72—514	150
11	galactomannan triacetate	acetonitrile	432	0.44—9.45	171—1236	11.2	57.8	118—1106	152
12	glucomannan triacetate	nitroethane	288	2.28—6.25	1130—4080	10.7	55.3	323—620	150
13	polystyrene	benzene	52.1	0.27—0.90	433—2260	13.2	20.4	64—153	153
14	"	cyclohexane	52.1	0.18—0.40	433—2260	6.0	9.8	44—103	153

bond, and also an α-1-6 bond in the example of galactomannates, have the same configuration, which is almost independent of the lateral substituent groups.

The small differences in λ, for example, for acetylcellulose ($\lambda = 11-14.7$) can be explained by the difference in the degrees of polymerisation, since with increase in n the effect of excluded volume begins to be apparent. An especially pronounced dependence of λ on DP was observed for cellulose nitrate[135]. The lower rigidity of pentosans compared with hexosans can be explained by the fact that xylan, which has five carbon atoms has greater free rotation around the ether bond than hexosans. True, at the low value of $\lambda = 6.6$ xylan can have too low a DP. The value of $\lambda = 2.7$ for xylan from canadian spruce is thought to be erroneous by the investigators themselves[150], probably owing to errors in the molecular weight determination by the light scattering method, where the effect of lignin impurities and of the aggregation of the particles should appear.

Table 6. Parameters which characterise the undisturbed state for cellulose and its derivatives in Cadoxene and polystyrene in toluene.

Polymer	b, Å	A_m, Å	A_m, mol. units	$(\overline{h_0^2})^{1/2}/(\overline{h^2})_f^{1/2}$	Reference
Cellulose	19	70	14	2.7	27
Hydroxyethylcellulose	18	62	12	2.4	141
Sodium carboxyethylcellulose	18	60	12	2.4	140
Polystyrene in toluene	8.6	33	13	2.2	156, 157

The comparatively low value of λ for cellulose caproate is explained by the fact that it was obtained under θ-conditions.

The other values given in Tables 2 and 5, show the degree of elongation or the flexibility of the macromolecules. The relation $h_{\max}/\langle h^2\rangle^{1/2}$ characterises the degree of convolution of the macromolecules, where $h_{\max}$ is the contour length of the completely extended molecule $= nb_0$. $A_m = h^2/h_{\max}$ is the effective length of the Kuhn statistical segment, which is a measure of the short-range interactions affecting the length of the segment and characterising the chain "rigidity". Here the "rigidity" of the chain signifies the elongation owing to restricted rotation around the intermonomeric bond rather than resistance to deformation. $b = (h^2/n)^{1/2}$ is the effective length of the monomeric unit just as the persistent length a[139] is a measure of the "rigidity" of the chain.

A comparison of these quantities shows that cellulose has the same degree of convolution, or the inverse quantity, degree of elongation, as its derivatives, with the exception of cellulose nitrate and of hydroxyethyl cellulose in water. The great extension of the macromolecules of cellulose nitrate is due to the presence of the strongly polar NO_2 groups, and that of hydroxyethyl cellulose in water to the presence of intramolecular hydrogen bonds, which have a considerable effect on free rotation around the intermonomeric bond. Here solutions of hydroxyethyl cellulose in water are very stable; they can be heated to boiling or large quantities of precipitant (salts or dimethyl sulphoxide) can be added without precipitation of the polymer—a difference from methyl cellulose[154]. The addition of precipitant has no effect on the change in the molecular elongation of the hydroxyethyl cellulose. This independence of the composition of the solvent can be explained by the presence of intramolecular hydrogen bonds, which play a large part in the form of the macromolecules in solution. An increase in the hydrophobic nature of the substituents in ethylhydroxyethylcellulose leads to less extension, and an increase in the degree of substitution in methyl cellulose (28% methoxy-groups) to a more compact structure.

For sodium carboxymethylcellulose the dimensions and form of its macromolecules in solution depend on the ionic strength of the solvent. At a high ionic strength (in Cadoxene and 1 N NaCl) the CMC molecule behaves like cellulose and other uncharged derivatives of cellulose in Cadoxene and has the same dimensions. It is less extended than hydroxyethyl cellulose in water. With decrease in the ionic strength the dimensions of the coil increase considerably, by approximately a factor of 2 (for a change in ionic strength from 0.2 M NaCl to 0.005 M NaCl) owing to interaction between the charged groups.

The great dimensions of the macromolecules of cellulose and of derivatives in real, that is, non-ideal, solutions is due to the considerable spreading of the molecules due to interaction with the solvent, which has been characterised[27,135,140–143] by the swelling coefficient α, which is the effective excluded volume. Here the nature of the interaction with Cadoxene is the same for both cellulose and those derivatives which are soluble in the solvent.

The swelling coefficient is rather high (1.4) but less than the values given in the tables for specimens with low n, which suggests that a gaussian distribution of the segments inside the coil is not achieved. The low value of α for hydroxyethyl cellulose in water again suggests a more elongated form for the macromolecules.

Water has a great affinity for the hydroxyl groups and forms a compact solvate layer around the macromolecule which decreases with increase in temperature.

The size of the cellulose macromolecules in Cadoxene is also affected by the fact that Cadoxene does not simply solvate the cellulose but forms a more stable compound with it than the solvates. The existence of a compound of cellulose with the solvent the electronic polarisability of which is sufficiently high suggests a high value for the increment in refractive index dn/dc which is approximately 0.18 for cellulose in Cadoxene[27] and in sodium tartratoferrate complex[52].

The second virial coefficient for cellulose[27] and its derivatives in Cadoxene[140–143] is rather high ($A_2 = 10-17 \times 10^{-4}$) which suggests good interaction of the polymer with the solvent. Since the presence of hydrogen bonds in cellulose requires very polar solvents for its dissolution, it is natural that after the cellulose has dissolved these solvents become "good" in the thermodynamic sense in relation to the cellulose macromolecules. An analysis of the thermodynamic parameters for the interaction of the polymer with the solvent showed that cellulose and its derivatives have a negative entropy of mixing[142,155], which shows the compact arrangement of the solvent molecules around the polymer segments. The nature of the interaction of cellulose and its derivatives with the solvent depends on the degree of polymerisation, the temperature, the degree of substitution (in the cellulose derivatives) and also the nature of the solvent.

The strongly negative temperature coefficient of the characteristic viscosity for cellulose and its derivatives shows a decrease in the elongation of the macromolecules with increase in temperature, which is mostly connected with the weakening of the polymer–solvent bond. This is also shown by the change in α with temperature. Furthermore, the values of α and A_2 depend on the degree of polymerisation[27,140–143,146].

On comparing the unperturbed dimensions of cellulose and its derivatives with polystyrene we see that the flexibility of cellulose in solution is not very different from the flexibility of polystyrene, the number of monomeric units in the equivalent Kuhn statistical segment is almost the same but a greater degree of polymerisation for cellulose and its derivatives is needed only to achieve the conformation of a statistical coil.

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Institute of High-molecular-weight
Compounds, Academy of Sciences
of the USSR, Leningrad

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Types of Reaction Undergone by Coordinated Ligands and the Factors Influencing the Change in Their Reactivity†

Yu.N.Kukushkin

The influence of the following factors on the reactivity of coordinated ligands (chiefly nitrogen-containing ligands) is examined: 1) the nature of the metal ion; 2) displacement of the electrons of the ligand to the central ion; 3) change in the stability of the complexes formed in the reaction relative to that of the original complexes; 4) the charge of the ionic complexes; 5) the influence of π-dative bonding by one ligand to the central atom on the reactivity of another ligand in the same complex; 6) stabilisation of one of the tautomeric forms of a ligand as a result of complex formation with metal ions; and 7) stabilisation of the deprotonated form of a ligand by complex formation. Examples of the masking of individual functional groups by complex formation and the manifestation of new chemical properties of the ligand as a result of coordination are examined. It is shown that in a number of instances the metal ion can be regarded as a matrix on which the synthesis of an organic molecule takes place. Reactions involving "insertion" into a metal-ligand bond are discussed. The bibliography contains 93 references.

CONTENTS

I. INTRODUCTION

In recent years, chemists in various countries have been paying increasing attention to the study of the chemical behaviour of molecules or ions in the inner sphere of complex compounds of various metals; a number of reviews[1-5] and a collection of papers[6] have been published. The chief aim of the study of the reactivity of coordinated ligands is the development of a theory of homogeneous catalysis involving metal complexes. A recent review[7] published in the Soviet Union contains material which is also directly related to this question.

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† This review is based on a paper presented at a symposium on "The Properties of Organic Ligands in Complexes with Metals", held at Zelenogorsk (Leningrad) in December, 1968.

The aim of the present review was not to present all the factual material available in the literature. The author has tried, on the basis of specific examples, to demonstrate the factors influencing the reactivity of chiefly nitrogen-containing ligands.

II. CHANGE IN THE ACID-BASE PROPERTIES OF LIGANDS UNDER THE INFLUENCE OF A METAL ION

One of the first chemists to raise the question of the change in the properties of ligands when they are introduced into a complex with metal ions was A. A. Grinberg. As early as 1927, he presented a paper entitled "The Change in the Reactivity of Molecules Bound in Complexes".

No one is now surprised by the fact that ammonia, on entering a complex, "loses" its basic properties and exhibits acidic properties. The theory of the acid-base properties of complex compounds was to a considerable extent developed by Grinberg[8]. It is quite familiar, and there is no need to dwell on it.

The influence of the difference in the mobilities of the protons on the nitrogen atom in various reactions of coordinated ammonia can be demonstrated for the example of its reaction with chlorine. It has been established that an ammonia molecule in the inner sphere of Pt^{IV} complexes can be converted into dichloroamine[9]:

$$[PtCl_3(NH_3)_3]^+ \xrightarrow{Cl_2} [PtCl_3(NH_3)_2(NCl_2H)]^+$$
$$[PtCl_3(NH_3)_2(NCl_2H)]^+ \rightarrow [PtCl_3(NH_3)_2(NCl_2)]^0 + H^+$$

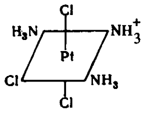
The hydrogen atom in the dichloroamine is so labile that complexes containing the dichloroamido-group NCl_2^- are usually isolated in the solid phase.

Table 1. Acidic dissociation constants of amine complexes of Pt^{IV} and the instability constants of their silver and thallium salts.

Type of complex	$K^*_{H^+}$	K_{Ag^+}	K_{Tl^+}
$[PtCl_2(NH_3)_3(NH_2M)]^{2+}$	6.0×10^{-12}	–	1.5×10^{-4}
$[PtCl(NH_3)_4(NH_2M)]^{3+}$	7.9×10^{-9}	1.3×10^{-8}	(2.0×10^{-6})
$[PtBr(NH_3)_4(NH_2M)]^{3+}$	5.6×10^{-9}	1.2×10^{-8}	–
$[Pt(NH_3)_5(NH_2M)]^{3+}$	1.2×10^{-7}	4.9×10^{-8}	3.6×10^{-4}
$[PtCl(NH_3)_3Py(NH_2M)]^{3+}$	1.2×10^{-7}	5.7×10^{-7}	3.7×10^{-4}
$[PtCl(NH_3)_2Py_2(NH_2M)]^{3+}$	1.6×10^{-6}	2.2×10^{-5}	5.5×10^{-4}
$[PtClPy_4(NH_2M)]^{3+}$	6.0×10^{-5}	3.2×10^{-5}	3.2×10^{-3}

*The acidic dissociation constants are taken from Refs. 19 and 20. The constants for the hexammine is taken from more accurate data[21].

Of the three ammonia molecules in the ion



the greatest lability is shown by the molecule of the Cl–Pt–NH_3 axis. It is this molecule which is converted into dichloroamine. It has been shown[10,11] for a large number of examples that when several coordinated molecules are present, conversion into chloroamines (or bromoamines) is undergone first of all by the molecules in which the protons have the highest lability.

The establishment of the relationship between the acidic properties of complex compounds and the ability of amines to undergo conversion into chloroamines led to the prediction[12,13] of the possibility of preparing chloroamine compounds from amine compounds of palladium(IV), gold(III), and various other metals. A chloroamine compound of palladium was prepared by Babaeva and Khananova[14], and a gold compound by Kukushkin and Zorina[15].

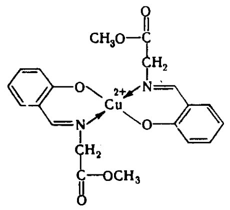
In joint work with Grinberg[16] it was shown that in Pt^{IV} complexes the hydrogen atoms of the ammonia molecules can be replaced by silver, and in work with Rabinovich and Goloseeva[17,18] it was established that this replacement can also be achieved with thallium. It was also shown[17,18] that with increase in the acidic properties of the ammines there is a decrease in the stability of both the silver and the thallium derivatives. For the thallium derivatives, a levelling of the instability constants was observed, but the overall tendency for the stability to change remained.

It can be seen from Table 1 that the silver derivatives are much more stable than the thallium compounds. This corresponds to the stabilities of silver and thallium ammines. The instability constant of $Ag(NH_3)^+$ is 6.3 × 10^{-4}, and that of $Tl(NH_3)^+$ is 8.3.

The factors determining the acidic properties of amine complexes probably retain their significance in the dissociation of the corresponding silver salts. Two of the main factors influencing the acidic properties of inner-sphere ligands are the charge of the central ion and the charge of the ionic complex. It will be seen from what follows that both of these factors are extremely important for the reactivity of coordinated ligands.

III. CHANGE IN REACTIVITY AS A RESULT OF THE DISPLACEMENT OF THE ELECTRONS OF THE LIGAND TO THE CENTRAL ATOM

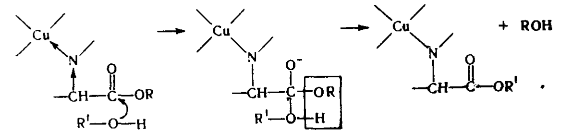
Pfeiffer and coworkers[22] carried out the trans-esterification of the ester fragment of the Schiff's base of an aminoacid, coordinated to the bivalent copper ion. These trans-esterifications took place at a much higher rate within the complex



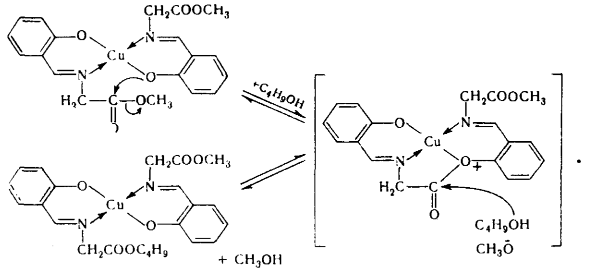
than in the free esters. For example, the replacement of the methoxy group by the butoxy group took place in 10 min in the complex dissolved in butanol.

Much later, Verter and Frost[23] continued Pfeiffer's studies with this and similar compounds. In addition to a large number of trans-esterifications within the complexes, Verter and Frost were able to carry out the amidation of coordinated Schiff's bases; in particular, they were able to replace the methoxy group CH_3O by the butylamino group C_4H_9NH.

There are two views regarding the mechanism of these reactions. Martell and Calvin[24] attribute this marked increase in the rate of trans-esterification to the displacement of electrons from the carbonyl carbon towards the copper atom under the influence of the donor–acceptor bond between the ligand and the central atom. This displacement should facilitate the reaction of the electron-donating oxygen atom of the solvent molecule with the carbon of the carbonyl group. The mechanism of this reaction can be represented schematically as follows:

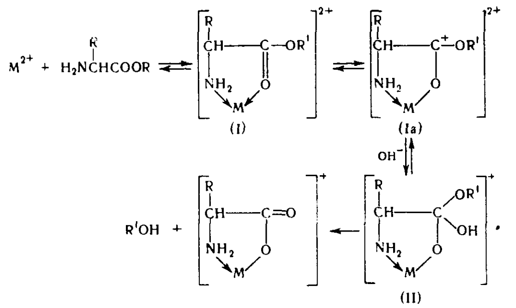


The reaction mechanism proposed by Verter and Frost[23] assumes the mutual influence of the ligands in the complex



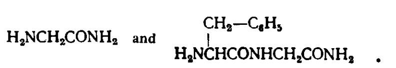
The carbonyl of the ester group is attacked by the oxygen atom of the aldehyde fragment of another ligand with the formation of an intermediate structure of the lactone type. This reaction should be reversible, but with the high active mass of the solvent alcohol it moves preferentially in one direction.

Kroll[25] studied the catalytic action of bivalent heavy metal ions on the hydrolysis of the esters of aminoacids. The rates of these reactions are extremely low in the absence of metal ions, which produce a marked increase in the reaction rates. In Kroll's opinion, the catalytic increase in the rate of hydrolysis of the aminoesters can be explained schematically as follows:



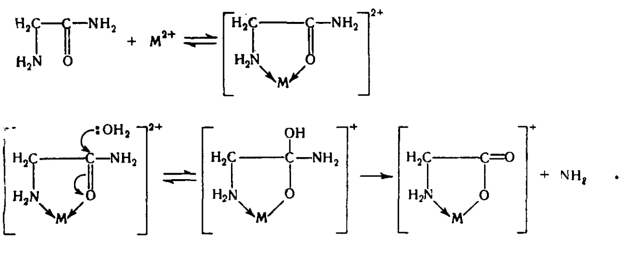
The proposed mechanism is based on the principle that the ligand in the coordinated state (I) and (Ia) exhibits a higher affinity for the hydroxide ion than the free ester. In other words, coordination increases the electrophilic nature of the reaction centre. The intermediate unstable complex (II) decomposes to the alcohol and the complex of the aminoacid, dissociation of which completes the cycle of catalytic reactions. For a series of bivalent ions, Kroll established a correspondence between the tendency to form complexes and the catalytic effect of the ions.

The catalytic influence of Cu^{II} on hydrolysis and isotopic exchange of oxygen in aminoesters was also studied by Bender and Turnquest[26]. Meriwether and Westheimer[27] studied the catalytic influence of bivalent copper, nickel, and cobalt ions on the hydrolysis of the amides

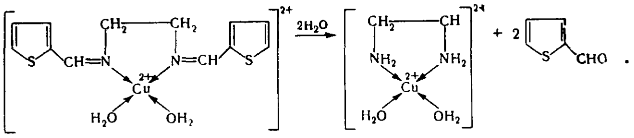


$$H_2NCH_2CONH_2 \text{ and } H_2N\underset{}{\overset{CH_2-C_6H_5}{\overset{|}{C}}}HCONHCH_2CONH_2 \ .$$

The views of these authors[26,27] regarding the mechanism of the catalysis of these reactions essentially coincide with the mechanism put forward by Kroll[25]. The catalysis of the hydrolysis of aminoacetamide can be represented as follows:

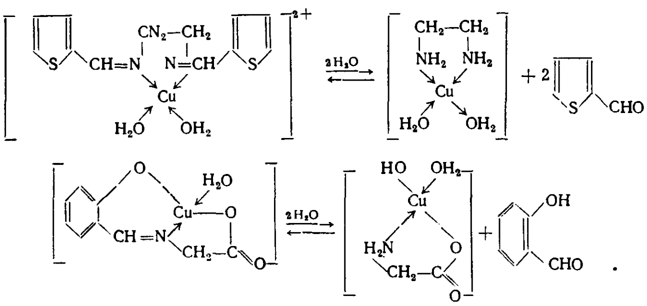


Bailar and Eichhorn[28] established the catalytic action of copper ions on the hydrolysis of the Schiff's base formed from thiophene-2-aldehyde and ethylenediamine:



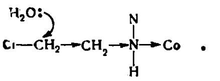
Under similar conditions but in the absence of Cu^{II}, the hydrolysis of this Schiff's base is very slow. Bailar (like Kroll) considers that the catalytic influence of copper is due to the increase in the electrophilic character of the unsaturated carbon atom as a result of the formation of a donor–acceptor bond. This facilitates attack on the reaction centre by a water molecule.

Eichhorn[29] studied the influence of complex formation on the stability, with respect to hydrolysis, of the Schiff's bases formed by thiophene-aldehyde with ethylenediamine and by salicylaldehyde with glycine. He established that copper facilitates the hydrolysis of the former and hinders the hydrolysis of the latter. The hydrolysis of the copper complex of the Schiff's base formed by thiophene-aldehyde with ethylenediamine gives the ethylenediamine complex. Both the initial and the final complexes contain one ring, and the factor determining the relative stability of these complexes is the electron distribution.



As a result of the hydrolysis of the Schiff's base formed by salicylaldehyde and glycine, the complex is converted from a dicyclic to a monocyclic compound. The difference in the stabilities of the dicyclic and monocyclic complexes probably has a greater influence on the reactivity of the original compound than the change in the polarisation of the nitrogen atom. Thus this example shows the need to make allowance for another factor—*the stabilities of the original complexes and reaction products.*

The influence of coordination on the hydrolysis of halogenoalkylamines has been studied[30]. It has been established that in the ionic complex $[Co(H_2O)(Cl-CH_2-CH_2-NH_2)en_2]^{3+}$ the hydrolysis of β-chloroethylamine is 50 times more rapid than the hydrolysis of the free halogenoalkylamine. The displacement of the electron pair of the nitrogen atom towards the cobalt as a result of the formation of a donor-acceptor bond acts like an inductive effect

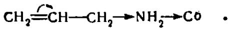


The influence of the coordination of unsaturated aliphatic amines on the addition of hydrogen halides to the amines has been studied[31]. It has been shown that allylamine in the complex *cis*-$[CoClen_2(NH_2CH_2CH{=}CH_2)]Cl_2$ gives a mixture of the γ- and β-isomers. The relative quantities of the isomers obtained from free and coordinated allylamine are given in Table 2.

Table 2. Influence of coordination on the order of attachment of hydrogen halides to allylamine.

Compound	Hydrogen halide	Relative concentration	
		β-isomer, %	γ-isomer, %
$CH_2{=}CHCH_2NH_2$	HCl	55	45
$[CH_2{=}CHCH_2N(C_2H_5)_3]Cl$	HCl	17	83
cis-$[CoCl(CH_2{=}CHCH_2NH_2)en_2]Cl_2$	HCl	42	58
cis-$[CoBr(CH_2{=}CHCH_2NH_2)en_2]Br_2$	HBr	38	62

Thus the displacement of electrons towards the cobalt directs the addition along a path which does not correspond to Markovnikov's rule

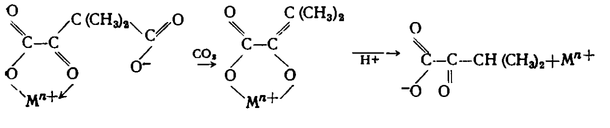


The effect of coordination to the cobalt atom, however, is much weaker than the effect produced by the attachment of a proton to the amino-group.

A large number of published papers have been devoted to the catalytic decomposition of ketoacids under the influence of both enzymes and ions of various metals. Catalysis of the decarboxylation by metal ions is observed for di- and tricarboxylic ketoacids. The rate of the decarboxylation of monocarboxylic ketoacids or nitroacetic acid is not increased by metal ions, and is sometimes even decreased[32,33].

The decomposition of α,α-dimethyloxalacetic acid[34,35] and oxalacetic acid[32,36-42], and the catalytic decarboxylation of acetonedicarboxylic acid[43] and oxalosuccinic acid[37] have been studied.

The mechanism of the decarboxylation is probably the same for these acids. Many authors are of the opinion that an intermediate chelate complex is formed in the decarboxylation. This was first shown in Refs. 34, 35, and 37. A decarboxylation mechanism was proposed by Steinberger and Westheimer[35], who consider that the formation of coordinate bonds by the dicarboxylic acid with the metal ions leads to withdrawal of the electrons from the non-coordinated carboxyl group. This is the reason for the increase in the ease of decarboxylation:

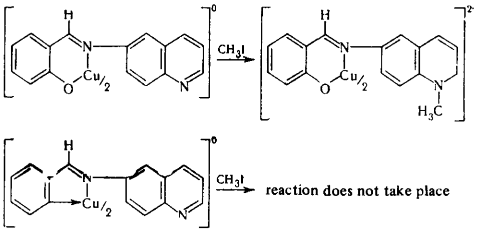


With ketoacids, which can give an enol form, the initial formation of an enol chelate is assumed.

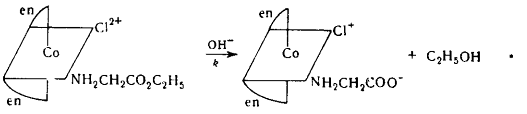
Pedersen[33,38] also considers that a reason for the spontaneous decomposition of nitroacetic acid is the displacement of the electrons from the carboxyl group to the nitro-group. The mechanism of catalysis examined above explains the decrease in the rate of decarboxylation of monocarboxylic acids (or the absence of catalysis) under the influence of metal ions. In this instance the attachment of the metal leads to a displacement of electrons towards the carboxyl group.

IV. INFLUENCE OF THE CHARGE OF THE IONIC COMPLEX ON THE REACTIVITY OF A COORDINATED LIGAND

A striking example of the influence of the charge of an ionic complex on the reactivity of a ligand is provided by the alkylation of the nitrogen atom in a quinoline group. Thus it has been shown[44] that the alkylation of this group by methyl iodide in a neutral complex is comparatively rapid, whereas almost no alkylation takes place in a cationic complex



Hay and coworkers[45,46] showed that in a cationic complex with Co^{III}, ethyl glycinate is hydrolysed with a rate constant $k = 3.5 \times 10^3$ litre mole^{-1} min^{-1}:



Under the same conditions, the rate constant for the the hydrolysis of the free ester is $k' = 38$ litre mole^{-1} min^{-1}:

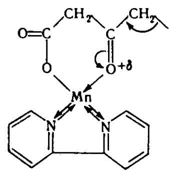
$$H_2NCH_2CO_2C_2H_5 + OH^- \xrightarrow[k']{} H_2NCH_2CO_2^- + C_2H_5OH \; .$$

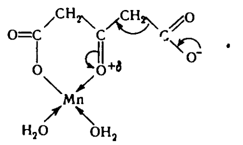
Thus the introduction of the ester into an ionic complex of Co^{III} with a charge of +2 increases the reaction rate by a factor of about 100. This effect can be attributed to electrostatic interaction: the positive charge of the complex facilitates attack by the hydroxide ion.

V. INFLUENCE OF π-DATIVE BONDING BY ONE OF THE LIGANDS TO THE CENTRAL ATOM ON THE REACTIVITY OF ANOTHER LIGAND IN THE SAME COMPLEX

It has been established[43,47] that the 1,10-phenanthroline complexes of Mn^{II} have a much higher catalytic activity with respect to the decarboxylation of dicarboxylic acids than the hydrated maganese ion. An analogous phenomenon was observed by Hay and Leong[48], who showed that the decarboxylation of acetonedicarboxylic acid in the

2,2′-bipyridyl complex of Mn^{II} is about 10 times more rapid than that in the corresponding aquo-complex.



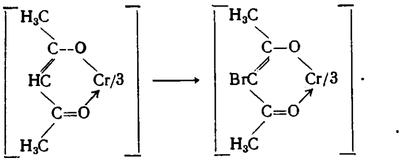


The authors cited consider that the increase in the reaction rate is due to the formation of a π-dative bond by manganese with 1,10-phenanthroline or 2,2′-bipyridyl. The formation of a π-dative bond should increase the positive effective charge of the central ion and hence facilitate decarboxylation.

VI. STABILISATION OF ONE OF THE TAUTOMERIC FORMS OF A LIGAND BY COMPLEX FORMATION WITH METAL IONS

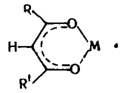
Grinberg and coworkers[49] studied the hydrolysis of dimethyl hydrogen phosphite in the free state and in a platinum(II) complex, and concluded that in dimethyl hydrogen phosphite coordinated to Pt^{II}, the phosphorus atom is in the tervalent state, whereas in the free acid it is in the quinquevalent state. As a result, the coordinated acid has a much stronger acidity than the free acid.

β-Diketones provide the classical example of keto–enol tautomerism. The enol forms have a high tendency to form complexes. The first study of the reactivity of coordinated β-diketones (more accurately, their enol forms) was apparently that of Reihlen[50], who established that the action of bromine on the acetylacetonato-compound of chromium (in alcoholic solution) leads to the replacement of the hydrogen on the central carbon atom by bromine:

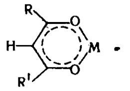


At the time, Reihlen regarded this reaction as confirming Mayer's hypothesis regarding the reactivity of keto–enol forms in tautomeric equilibrium.

In recent years, the complexes of metals with β-diketones have been attracting the attention of chemists from the theoretical viewpoint. Structural data show that the C–C, C–O, and M–O distances in β-dicarbonyl chelates are equivalent[51]. On this basis, the β-dicarbonyl chelates are regarded as forms stabilised by resonance:

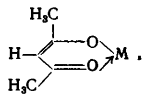


Some authors go further, and regard the β-dicarbonyl complexes of metals as pseudo-aromatic compounds[52]:



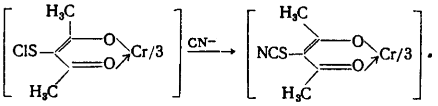
On this basis, many authors are studying the replacement of hydrogen in the pseudo-aromatic ring: halogenation, acetylation, nitration, and the introduction of thiocyanato-groups into the aromatic ring[52–58].

Kluiber[59] studied the action of sulphur dichloride on compounds with the general formula

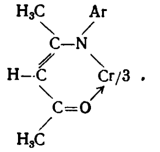


This reaction was studied for the acetylacetonato-compounds of Al^{III}, Cr^{III}, Co^{III}, and Be^{II}. This study showed that the hydrogen on the central carbon atom can be replaced by the –SCl group. An interesting feature is that the usual products of the reaction of sulphur dichloride with enols similar to acetylacetone are sulphides. It is believed that sulphides are formed through an intermediate R–SCl compound. In Kluiber's opinion, the preservation of the –SCl group in this instance is due to the steric protection of this group by the adjoining methyl groups.

The action of cyanide ions on the chromium complex obtained in this way converts the –SCl group into a thiocyanato-group according to the scheme



The same chromium compound was also obtained by the direct reaction of the acetylacetonato-compound of chromium with thiocyanogen. Collman and Kittleman[60] prepared a large number of complexes of Cr^{II} with β-ketoimines with the general formula



The central carbon atom in the β-ketoimines in the chromium complexes, as in the complexes formed by β-diketones, undergoes bromination by N-bromosuccinimide. Nitration and formylation of inner-sphere β-ketoimines does not take place, however, because of the lower stability of the ketoimine complexes compared with the compounds formed by the diketones.

VII. STABILISATION OF THE DEPROTONATED FORM OF A LIGAND BY COMPLEX FORMATION

It is known that the azo-coupling of derivatives of phenol and diazonium ions takes place more readily in alkaline medium, because of the high reactivity of the corresponding phenolato-compounds. Azo-coupling often does not take place at all in acid medium. Kuznetsov[61] gives a number of examples of the influence of complex formation on the ability of various derivatives of phenol to undergo azo-coupling. Thus pyrocatechol in acid solutions is almost unable to couple with diazobenzenesulphonic acid. In the presence of salts of gallium, aluminium, and more particularly zirconium and germanium, azo-coupling takes place even in the presence of mineral acids. Moreover, the production of azo-compounds from, for example, pyrocatechol in alkaline medium is made difficult by its oxidation under the influence of the diazonium ion, and this decreases considerably the yield of the product. In the presence of the ions of the above metals, oxidation of pyrocatechol by diazonium salts does not take place. The influence of metals on this reaction is associated with the formation of inner-complex salts, in which the proton of the phenol group is replaced by a metal ion.

Like pyrocatechol, 8-quinolinol undergoes almost no coupling with diazobenzenesulphonic acid in mineral acid, but this coupling takes place when the 8-quinolinol is combined in a copper complex.

Azo-coupling is not facilitated by complex formation with all metals, however. The rate of the reaction of 8-quinolinol with diazobenzenedisulphonic acid is decreased by aluminium salts. In the presence of aluminium salts, this reaction takes place very slowly, even in the presence of sodium acetate. Kuznetsov attributes this to the difference in the nature of the O–Cu and O–Al bonds. This sharp difference, however, may be due to the higher charge of the aluminium complex compared with the copper complex. A higher positive charge on the complex should hinder the attack of the diazonium cation on the coordinated 8-quinolinol molecule.

An example of the influence of a metal ion on reactivity as a result of stabilisation of the deprotonated form of a ligand is provided by the reaction of 4-dimethylaminophenyldiazonium chloride with chromotropic acid. The dye is obtained in 58% yield, the substitution taking place in the 4-position of chromotropic acid (1,8-dihydroxynaphthalene-3,6-disulphonic acid). When the calcium complex of this acid is used, the yield can be increased to 90%.[62]

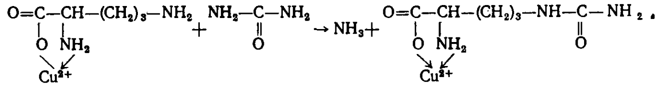
The halogenation (chlorination and bromination) of 8-quinolinol in its complexes with Cr^{III}, Co^{III}, Fe^{III}, and Cu^{II} gives the same products as the halogenation of free 8-quinolinol (for example, 5,7-dichloro-8-quinolinol). Jones[63] reports that in the chlorination of free 8-quinolinol, the yield of the dichloro-derivative does not exceed 30%. In the chlorination of inner-sphere 8-quinolinol, however, the yield of the dichloro-derivative is 80–90%. Jones also attributes this to the presence of the phenolato-form in the complex. Moreover, the metal protects the functional groups from oxidation.

Fernando and coworkers[64] emphasise that the influence of complex formation on the reactivity of aromatic ligands should be estimated not only from the reaction products, but also on the basis of a quantitative comparison of the reaction rates[65,66]. Quantitative studies[64] showed that the rate of the iodination of 8-quinolinol-5-sulphonic acid decreased on formation of complexes. The influence of the complex-forming species was established, and it was also possible to arrange the metal ions in the order of their decreasing influence: $Cu^{2+} > Ni^{2+} > Co^{2+} > Fe^{2+} > Zn^{2+} > Mn^{2+}$.

VIII. ELIMINATION OF THE CHARACTERISTIC PROPERTIES OF LIGANDS AS A RESULT OF COORDINATION AND THE USE OF THIS PHENOMENON TO MASK INDIVIDUAL FUNCTIONAL GROUPS

On coordination, amines may lose the properties associated with the presence of the free pair of electrons. The nitro-group in Pt^{IV} complexes can no longer be oxidised by permanganate. The toxicity of the cyanide ion is reduced or eliminated completely. The fact that complex formation may eliminate completely the ability of various functional groups to react, without altering significantly the reactivity of non-coordinated functional groups, particularly if these are at a distance from the point of coordination, makes it possible to use this phenomenon in preparative work.

For example, it is believed that citrulline $H_2NCONH(CH_2)_3CH(NH_2)COOH$ is present in various proteins, in which it takes part in the formation of urea. Kurtz[67,68] carried out this reaction in the opposite direction by means of complex formation. He prepared the copper complex of ornithine (as a result, the α-amino-group was masked) and carried out the condensation of this complex with urea:



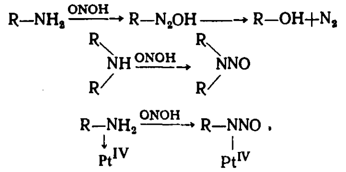
$$O{=}C{-}CH{-}(CH_2)_3{-}NH_2 + NH_2{-}\underset{\displaystyle O}{\underset{\|}{C}}{-}NH_2 \rightarrow NH_3 + O{=}C{-}CH{-}(CH_2)_3{-}NH{-}\underset{\displaystyle O}{\underset{\|}{C}}{-}NH_2\,,$$

The copper was then removed from the complex by the action of hydrogen sulphide, to give citrulline. Kurtz prepared various aminoacids in this way. The efficiency of the masking action of the metal ions depends to a marked extent on the stability of the complex.

IX. MANIFESTATION OF NEW CHEMICAL PROPERTIES BY THE LIGAND AS A RESULT OF COORDINATION

An example of the manifestation of new chemical properties by a ligand is provided by the azo-coupling of 1,10-phenanthroline and diazosulphanilic acid. 1,10-Phenanthroline cannot couple with diazonium salts, but in its complex with bivalent iron it undergoes vigorous coupling with the diazonium salts of sulphanilic acid and *p*-nitroaniline-*o*-sulphonic acid[69].

It is well known that the nitrosylation of free primary amines gives unstable diazo-compounds, which decompose with the formation of an alcohol and the liberation of nitrogen, whereas secondary amines form stable nitroso-compounds:



$$R{-}NH_2 \xrightarrow{ONOH} R{-}N_2OH \longrightarrow R{-}OH+N_2$$

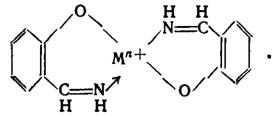
$$R_2NH \xrightarrow{ONOH} R_2NNO$$

$$\underset{\displaystyle Pt^{IV}}{\underset{\downarrow}{R{-}NH_2}} \xrightarrow{ONOH} \underset{\displaystyle Pt^{IV}}{\underset{|}{R{-}NNO}}\,,$$

Chernyaev and Andrianova[70] showed that coordinated primary amines may exhibit the properties of secondary amines in nitrosylation. For example, aliphatic amines in a Pt^{IV} complex form stable nitroso-compounds. They exhibit the properties of secondary amines because of the fact that the nitrogen forms a bond with the platinum atom, instead of a second alkyl radical.

X. CHANGE IN THE REACTIVITY OF COORDINATED SCHIFF'S BASES

Complexes of metals with Schiff's bases are extremely widely encountered. They are obtained both from previously prepared Schiff's bases and by the action of aldehydes and ketones on the amino-complexes of metals. Sometimes, complex formation leads to the stabilisation of aldimines which are unstable in the free state. Thus Pfeiffer[71] prepared salicylideneimine in complexes of zinc, copper, and nickel. The complexes can be represented by the following general formula:



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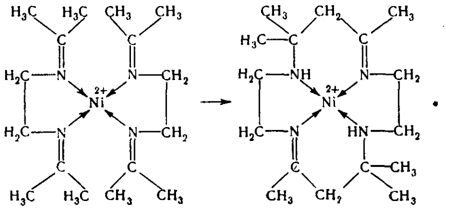
Salicylideneimine is unstable in the free state and cannot be prepared.

An interesting series of studies was carried out by Curtis and coworkers[72-77] on the reaction of cyclic amine-complexes of nickel and copper with acetone and aliphatic aldehydes. They established that the Schiff's bases formed initially undergo inner-complex aldol condensation with the formation of a macrocyclic ligand. This condensation is catalysed by bases:

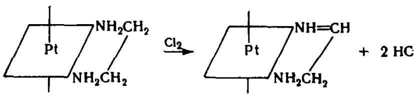


Since the reaction of aldehydes with inner-sphere amines leads to the formation of water, these reactions should most probably be carried out in anhydrous media. The amine-complexes of platinum are generally sparingly soluble in non-aqueous solvents. Various chloroamine-complexes of platinum, however, are soluble in polar organic solvents. In particular, the complex $[PtCl(NO_2)_2(NCl_2)(NH_3)_2]$ is soluble in acetaldehyde.

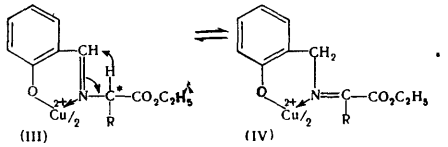
It has been established[78] that an inner-sphere ammonia molecule in $[PtCl(NO_2)_2(NCl_2)(NH_3)_2]$ is converted into acetaldimine on reaction with acetaldehyde. In the presence of active chlorine, however, the inner-sphere acetaldimine is converted into acetonitrile. The reactions can be represented schematically as follows:

$$\begin{array}{c}
Cl_2N{-}Pt \leftarrow NH_3 + CH_3CHO \rightleftarrows Cl_2N{-}Pt \leftarrow NH{=}CHCH_3 + H_2O \\
Cl_2N{-}Pt \leftarrow NH{=}CHCH_3 + 2H_2O \rightleftarrows H_3N \rightarrow Pt \leftarrow NH{=}CHCH_3 + HClO + ClO^- \\
H_3N \rightarrow Pt \leftarrow NH{=}CHCH_3 + OCl^- \rightarrow H_3N \rightarrow Pt \leftarrow N{\equiv}C{-}CH_3 + H_2O + Cl^- \\
\hline
Cl_2N{-}Pt \leftarrow NH_3 + CH_3CHO \rightarrow H_3N \rightarrow Pt \leftarrow N{\equiv}C{-}CH_3 + HClO + Cl^-
\end{array}$$

The dehydrogenation of inner-sphere ligands under the influence of chlorine was observed earlier[79]. It was established that the reaction of chlorine with ethylenediamine in a Pt^{IV} complex may lead to the formation of aminoacetaldimine:



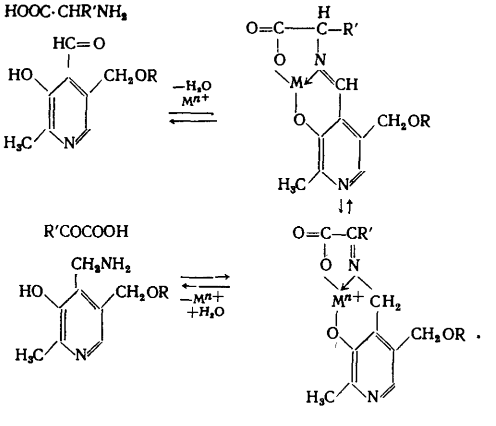
The important role of complex formation in the change in the reactivity of Schiff's bases is shown by the work of Pfeiffer and coworkers[80], who showed that when a chelate Cu^{II} complex is formed with an optically active Schiff's base formed from an aminoester and salicylaldehyde, rapid racemisation takes place. This can be attributed to the existence of an inner-complex tautomeric equilibrium:



(III) (IV)

The loss of the asymmetry of the optically active carbon atom takes place on formation of structure (IV). The reverse conversion of complex (IV) the complex (III) should produce equal quantities of the two optically active antipodes.

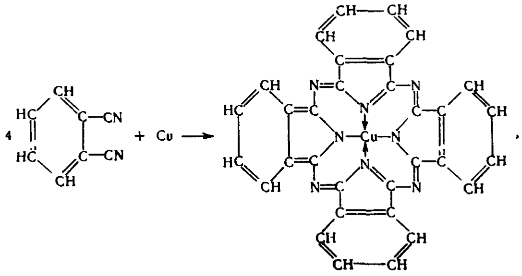
An inner-complex tautomeric equilibrium is the chief stage in the mechanism of catalytic trans-amination between pyridoxal and an aminoacid, proposed by Snell[81]. In his opinion, trans-amination gives a Schiff's base, stabilised by coordination to the metal ion, after which the double bond is displaced to the carbon atom of the aminoacid:



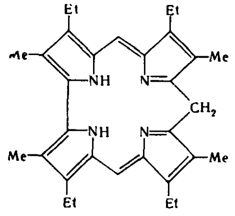
It is considered that trans-amination is extremely important in biology, since it provides an extremely probable means of producing a bond between carbohydrates and proteins.

XI. THE METAL IONS AS A MATRIX ON WHICH AN ORGANIC MOLECULE IS SYNTHESISED

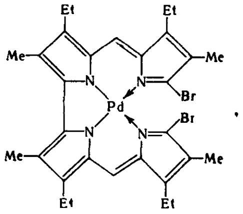
The preparation of metal-containing phthalocyanines from a metal and the dinitrile of phthalic acid takes place much more readily than the direct preparation from the free bases[3]:



A striking example of the matrix effect of a complex-forming metal is provided by the preparation of compound (V). This compound could not be prepared for a long time, but was eventually readily prepared by the reaction of formaldehyde with the palladium(II) complex (structure VI):[82]



(V)

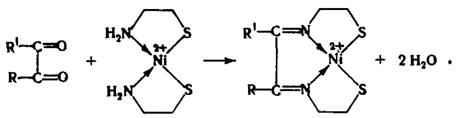


(VI)

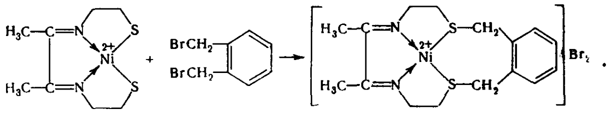
It is assumed that by following the route of ring closure in complex (VI), it is possible to introduce O, NH, or S in place of the methylene group.

The reaction between β-mercaptoethylamine and α-diketones usually gives thiazolidines as chief product, with only small quantities of the α-diimines[83]. Busch[84] showed that if the β-mercaptoethylamine is present in an

Ni^{II} complex, it reacts with α-diketones to form the inner-sphere α-diimine in 70% yield:



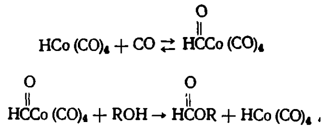
Busch then used this complex as a template for the subsequent preparation of a polycyclic chelate[85]. He carried out the following reaction:



which was made possible by the fixation of the sulphur atoms in the cis-position.

XII. REACTIONS INVOLVING "INSERTION" INTO A METAL- LIGAND BOND

Extensive material has now accumulated on reactions involving the "insertion" of various molecules in a metal–ligand bond. The "insertion" of carbon monoxide, alkenes, acetylene derivatives, etc. has been studied[86]. For example, the reaction of carbon monoxide and methanol with cobalt carbonyl hydrides leads to the formation of an ester of formic acid. It is considered[87–89] that the reaction mechanism can be represented as follows:



$$HCo(CO)_4 + CO \rightleftarrows HC(=O)Co(CO)_4$$

$$HC(=O)Co(CO)_4 + ROH \rightarrow HC(=O)OR + HCo(CO)_4\,.$$

An interesting reversible carbonylation of an alkyl manganese pentacarbonyl was carried out by Coffield and coworkers[90]:

$$CH_3Mn(CO)_5 + Co \rightleftarrows CH_3COMn(CO)_5\,.$$

It was subsequently shown[91] that the "insertion" into the manganese–alkyl bond involves chiefly a carbonyl which is already coordinated to manganese, and not a carbonyl from the outer sphere.

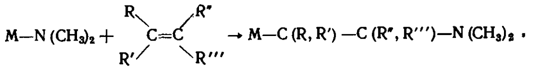
Booth and Chatt[92] carried out the carbonylation of alkyl and aryl compounds of platinum and palladium. The following are examples of the reactions which they carried out:

$$trans\text{-}[PdCH_3X(PEt_3)_2] \rightarrow trans\text{-}[PdCOCH_3X(PEt_3)_2]$$

$$[Pt(CH_3)_2(PEt_3)_2] \xrightarrow{CO} [Pt(COCH_3)_2(PEt_3)_2]\,.$$

Chandra and coworkers[93] showed that "insertion" into a metal–nitrogen bond can be carried out. They carried out a number of reactions of two types:

$$M{-}N(CH_3)_2 + RC{\equiv}CR' \rightarrow M{-}C(R){=}C(R'){-}N(CH_3)_2$$



$$M{-}N(CH_3)_2 + RR'C{=}CR''R''' \rightarrow M{-}C(R,R'){-}C(R'',R'''){-}N(CH_3)_2\,.$$

When the hydrocarbons contain groups which show a clearly defined ability to attract electrons, these reactions take place under mild conditions.

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In conclusion it should be noted that other factors, in addition to those listed above, influencing the reactivity of ligands may be detected. The detection of additional factors may be made primarily by analysing data on the reactivity of unsaturated organic molecules, since almost no discussion of π-complexes has been given in the present review.

It has already been noted that the change in the reactivity of ligands in complexes sometimes results from several factors. This is apparently the most widely encountered case. The author has encountered considerable difficulty in selecting examples which might illustrate individual factors as far as possible in pure form. Thus the assignment of reactions to various classes may be a subject for discussion.

From the viewpoint of the development of a theory of homogeneous catalysis involving metal complexes, quantitative data characterising the change in reactivity are of considerable importance. Unfortunately, few data of this kind have yet been published. It is to be hoped that with increase in the interest of this problem, the work carried out will be more quantitative in character. One possible approach to this is by the extensive use of correlation equations of the type corresponding to Hammett's equation.

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Lensovet Leningrad
Technological Institute

U.D.C. 541.571.9

The Intramolecular Hydrogen Bond and the Reactivity of Organic Compounds

I.D.Sadekov, V.I.Minkin, and A.E.Lutskii

Numerous new data on the effect of intramolecular hydrogen bonds on the reactivity of organic compounds are reviewed systematically.
The bibliography comprises 200 references.

CONTENTS

1. INTRODUCTION

An enormous number of investigations have been made recently on the nature and properties of hydrogen bonds. In the vast majority of these the effects of hydrogen bonds on different physical properties (on electronic, vibration, and NMR spectra, dipole moments, etc.) are investigated. A number of monographs and reviews are devoted to data obtained in this field. There is much less information about the effect of hydrogen bonds on the chemical properties of the molecules involved in them. Such information is scattered in various sources and only two attempts have been made to review it[1,2]. Subsequently many new communications on the role of hydrogen bonds in various chemical reactions appeared. The principal aim of the present review is to give a general and systematic account of these data.

In view of the large number of new facts, the scope of the review had to be restricted to only one type of hydrogen bond—the intramolecular hydrogen bond (i.h.b.). The qualitative nature of the available literature data on the effect of intramolecular hydrogen bonds on the reactivity of organic compounds and as a rule the lack of sufficiently systematic studies precludes the treatment of these data on the basis of any one general concept. Numerous conclusions concerning the effect of intramolecular hydrogen bonds on chemical properties arrived at in this review or by the authors of the papers quoted are based on comparisons and analogies, the generality of which cannot always be demonstrated, for example those based on the identification of the properties of hydroxy- and alkoxy-derivatives, *o*- and *p*-substituted benzenes, etc.

However, this approach reflects not only the level attained in the modern analysis of the effect of intramolecular hydrogen bonds on reactivity but also the exceptional complexity of the problem. In principle, the difficulty of investigating this problem consists in the fact that the intramolecular hydrogen bond, the effect of which on reactivity has to be elucidated, should be regarded as a comparatively small perturbation in relation to factors which determine the mode and type of reaction, since usually the energy of the intramolecular hydrogen bond is almost ten times smaller than the energy of activation for the corresponding chemical reactions.

Bearing this in mind, our aim was to collect the principal facts relevant to the problem under consideration and to describe them systematically.

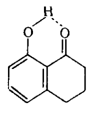
2. EFFECT OF THE INTRAMOLECULAR HYDROGEN BOND ON THE ACIDITY OF THE HYDROXY-GROUP

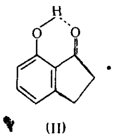
The hydrogen atom of the hydroxy-group involved in an intramolecular hydrogen bond is linked to the molecule much more strongly than in the absence of such a bond. As a result, the removal of such a proton from the molecule is more difficult than in the case of a non-chelated hydrogen atom. For this reason *ortho*- or *peri*-hydroxy-compounds with substituents capable of functioning as electron acceptors are weaker acids than the analogous compounds with *para*-substituents. Salicylaldehyde which contains a strong intramolecular hydrogen bond[3,4] has $pK_a = 8.14$ (in water), while the pK_a of the isomeric *p*-hydroxybenzaldehyde is 7.45.[5,6] If it is assumed that the transmission of electronic effects from the *ortho*- and *para*-positions is approximately the same, it becomes clear why 4-chloro-2-hydroxybenzaldehyde ($pK_a = 7.18$) is a weaker acid than 2-chloro-4-hydroxybenzaldehyde ($pK_a = 6.60$), which has no hydrogen bond[7].

The acidity of *o*-hydroxyacetophenone is lower than that of *p*-hydroxyacetophenone (their pK_a's are 10.07 and 7.87 respectively[6,8]). The higher dissociation constant of salicylaldehyde compared with *o*-hydroxyacetophenone is consistent with the relative strengths of the intramolecular hydrogen bonds, which can be estimated from the infrared spectra ($\Delta\nu_{C=O}$, determined by the intramolecular hydrogen bond, is 38 cm^{-1} for the first compound and 45 cm^{-1} for the second). The relative p*K*a's of α-naphthol derivatives have been determined[9]. 1-Hydroxy-2-naphthaldehyde (pK_a = 8.85) and 1′-hydroxy-2′-acetonaphthone (pK_a = 10.9), which have powerful intramolecular hydrogen bonds[2], are weaker acids than 1-hydroxy-4-naphthaldehyde (pK_a = 8.75) and 1′-hydroxy-4′-acetonaphthone (pK_a = 9.6) where a hydrogen bond is impossible.

Although the acid dissociation constants of the *o*-hydroxycarbonyl compounds were measured by different investigators and under different conditions, nevertheless it is clear that the *o*-hydroxycarbonyl derivatives of naphthalene are usually weaker acids than the corresponding benzene derivatives. The explanation of this should be sought in the greater strength of the hydrogen bond in the naphthalene series compared with benzene derivatives.

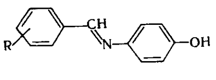
The strong intramolecular hydrogen bond in 8-hydroxy-1-tetralone(I) is the reason why this compound is a weaker acid (pK_a = 11.14) than 6-hydroxy-1-tetralone (pK_a = 7.74) and similarly 7-hydroxy-1-indanone (II) is a weaker acid (pK_a = 8.43) than 5-hydroxy-1-indanone (pK_a = 7.53):[10]


(I)


(II)

As a result of the strong intramolecular hydrogen bond between hydroxy- and nitro-groups, the acidity of 2-nitro-1-naphthol is lower than that of 4-nitro-1-naphthol[5]. According to spectrophotometric determinations[11,12], the p*K*a of 2-nitro-1-naphthol is 8.72, which corresponds to a dissociation constant 8 times higher than for 1-naphthol, while the p*K*a of 1-nitro-2-naphthol is 9.02, i.e. the dissociation constant is 14 times higher than that of 2-naphthol. This non-equivalent increase of acidity has been attributed to a stronger intramolecular hydrogen bond in 1-nitro-2-naphthol compared with its isomer. It is noteworthy that, apart from the intramolecular environment, acid dissociation constants are greatly influenced by the solvent in which the p*K*a is determined. Thus, the anomalously low acid dissociation constants of 2,4- and 2,5-dinitrophenols in benzene compared with their values in water have been explained as the result of a stronger hydrogen bond in the molecules of these substances in benzene solution[13].

An example characterising the effect of intramolecular hydrogen bonds of different strengths on acidities is quoted by Minkin et al.[14], who measured the p*K*a's of Schiff bases of four types (III–VI):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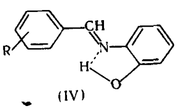
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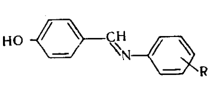
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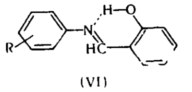
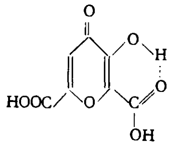

(VI)

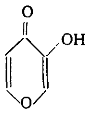
The corresponding p*K*a's (in 98% methanol) are listed in Table 1. The reduced acidity of (VI) compared with (V) and of (IV) compared with (III) is undoubtedly associated with the effect of the hydrogen bond. The order of magnitude of the p*K*a values is consistent with the concept of the greater strength of the hydrogen bond in the six-membered ring of (VI)[15,16,17] compared with the five-membered ring of (IV).[18,19,20]

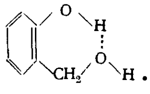
Table 1.

Type of Schiff base	pK_a					
	$R=N(CH_3)_2$	$R=OCH_3$	R=H	$R=CH_3$	R=I	$R=NO_2$
III	10.60	10.49	10.42	—	10.33	10.18
IV	11.02	—	10.88	10.92	—	10.71
V	—	9.84	9.73	9.79	9.63	—
VI	—	—	11.03	11.09	10.95	10.82

The presence of intramolecular hydrogen bonds in hydroxy-acids increases the dissociation constant of the carboxy-group but significantly lowers that of the chelated hydroxy-group. Whereas $K_a = 3.5 \times 10^{-10}$ for the phenolic hydroxy-group in *p*-hydroxybenzoic acid, salicylic acid, in which there is a strong intramolecular hydrogen bond, has $K_a = 1.5 \times 10^{-14}$. The same thing is also observed for the esters of *p*- and *o*-hydroxy-benzoic acids: the p*K*a's of the *o*- and *p*-isomers are 9.2 and 8.34 respectively[21]. The sharply reduced ionisation constant of the phenolic hydroxyl in meconic acid (VII) ($K_a = 1.5 \times 10^{-10}$) compared with pyromeconic acid (VIII) ($K_a = 2.2 \times 10^{-8}$) is evidence[22] of the presence of intense chelation in the first compound between the OH and COOH groups:


(VII)


(VIII)

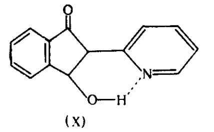

(IX)

The *peri*-sulpho-groups in phenylazonaphthols behave similarly[23].

It has been found that not only powerful electron-accepting groups such as >C=O, $-NO_2$, >C=N–, and –COOH, which form strong hydrogen bonds, are capable of reducing the acid strength. Even a weak electron-accepting substituent, such as the hydroxymethyl group, forms an intramolecular hydrogen bond with the phenolic hydroxyl in (IX) and weakens its acid properties. The p*K*a of *p*-hydroxymethylphenol is lower by 0.1–0.15 units than the p*K*a of phenol itself. (9.94 for phenol and 9.82 for *p*-hydroxymethylphenol)[24]. If the effect of the hydroxymethyl group in compound (IX) were mainly inductive, one might expect that the p*K*a value for this compound would be approximately the same as for the *para*-isomer. However, the p*K*a of *o*-hydroxymethylphenol (IX) is lower by only 0.02–0.05 units than the value for phenol itself. The reason for this is the presence of an intramolecular hydrogen bond in compound (IX).[25,26]

A similar situation exists also in di-(*o*-hydroxyphenyl)-methanes[27,28]. The behaviour of 2,2′-dihydroxybiphenyl is very similar to that discussed above. Whereas the higher value of the first ionisation constant of this compound (pK_{a1} = 7.56)[29] compared with *o*-phenylphenol (pK_a = 9.97)[30] may be attributed to an intramolecular hydrogen bond in the neutral molecule[31], the much lower value of the second ionisation constant (K_{a1}/K_{a2} = 106) can be accounted for by a strong hydrogen bond in the monoanion.

The effect of the intramolecular hydrogen bond is shown in the fact that many phenols with such a bond do not form normal salts under the usual conditions. Thus 2-(2′-pyridyl)indane-1,3-dione (X) is insoluble in aqueous sodium bicarbonate and is not titrated with alkali in an aqueous dioxan mixture[32]. Certain *peri*-hydroxyazo-dyes (XI) behave similarly. They are all insoluble in aqueous solutions of alkali[33]. Many other examples of similar behaviour of phenols have been quoted[1-4,34]: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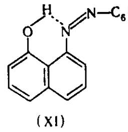
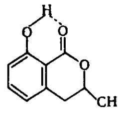

(XI)

3. ALKYLATION OF HYDROXY-COMPOUNDS

The presence of an intramolecular hydrogen bond in the molecule is the reason for the difficulty and sometimes the impossibility of obtaining ethers derived from the hydroxy-groups involved in the hydrogen bond by treatment with diazomethane under the usual conditions. This property of chelated groups is sometimes used to establish the structures of hydroxyanthraquinones, hydroxyflavones, hydroxyxanthones, etc., although in certain cases such *peri*-chelated hydroxyls may be methylated by prolonged heating with a large excess of diazomethane. A particular example of such "normally" methylated compounds, is mellein—3,4-dihydro-8-hydroxy-3-methylisocoumarone (XII).[35] Under the action of diazomethane, it is readily converted into the methoxy-derivative, although its OH group is involved in a strong hydrogen bond: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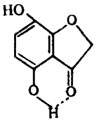
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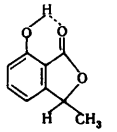
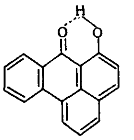

(XIV)

Other compounds where the proton of a chelated hydroxy-group can be comparatively readily replaced by methyl under the action of an ethereal solution of diazomethane are 4,6-dihydroxy-3-coumarone (XIII),[36] 7-hydroxy-3-methylphthalide (XIV),[37] 3,6-dihydroxyphthalic anhydride, 3,6-dihydroxyphthalimide,[38] 1-benzoyl-2-naphthol, and 6-hydroxymesobenzanthrone (XV):[39]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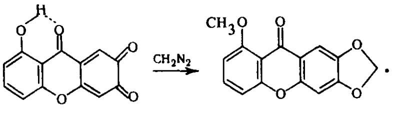
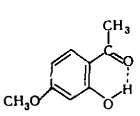

(XVI) (XVII)

8-Hydroxy-2,3-quinoxanthone (XVI) is methylated in an unusual way, being converted under the action of diazomethane in an ethereal solution into compound (XVII).[40] It is interesting that in the majority of the normally methylated compounds the carbonyl group is located in a five-membered ring.

The vast majority of chelated phenols are not methylated, and in the presence of several hydroxy-groups in the molecule only those not involved in hydrogen bonding are substituted. *o*-Hydroxyacetophenone, *o*-hydroxybenzophenone, 2-hydroxy-4-methoxyacetophenone (XVIII),[39] 1-hydroxy-9-xanthone (XIX),[41] and the diethyl ester of meconic acid[22] are not methylated at all by diazomethane in ethereal solution: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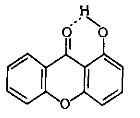
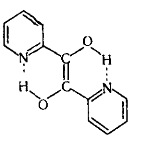

(XIX)

All attempts to methylate 2-pyridoin (XX)[42,43] were also unsuccessful. Diazomethane in ether has altogether no effect on this compound and in the reaction with sodium and methyl iodide or with dimethyl sulphate and alkalies, the only products are picolinamide in the first case and methyl picolinate in the second.

Examples of this kind among quinones are fairly numerous. The hydroxy-groups of alizarin methylated in the 2-position[1], 6,11-dihydroxy-5, 12-naphthacenequinone (XXI),[44] and 2-methoxyjuglone (XXII)[45] do not react with diazomethane: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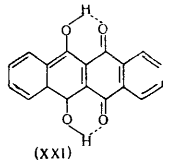
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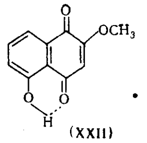
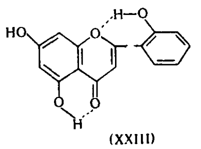

(XXII)

A very characteristic feature of polyhydroxy-compounds is selective alkylation of the free hydroxyls. In chromanone, flavanone[46], and polyhydroxyflavone[40] derivatives diazomethane methylates all the hydroxy-groups with the exception of the group in the 5-position. Similar results were obtained in the reaction with dimethyl sulphate in alkali at room temperature[46]. It has been shown[47] that the 2′-hydroxy-group in flavanones behaves similarly to the 5-hydroxy-group. Thus methylation of 2′,5,7-trihydroxyflavanone (XXIII) with dimethyl sulphate in acetone in the presence of potassium carbonate gives only 2′,5-dihydroxy-7-methoxyflavanone: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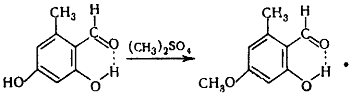
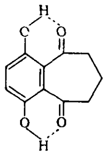

(XXIV) (XXV)

The only product of the methylation of 2,4,5-trihydroxyacetophenone with dimethyl sulphate is 2-hydroxy-4,5-dimethoxyacetophenone[48], while 2,4-dihydroxydeoxybenzoin yields only 2-hydroxy-4-methoxydeoxybenzoin[49]. A similar situation exists in substituted resacetophenones and nitroresorcinols where methylation with dimethyl sulphate of the hydroxyl chelated with the nitro- or carbonyl group is very difficult[49,50]. Methylation with dimethyl sulphates of the *o*-orsellinaldehyde (XXIV) leads to everninaldehyde (XXV).[51]

Sometimes the inability of chelated hydroxy-groups to be methylated is used for their protection in many syntheses. Thus Baker and Savage[52] showed that the 1,2-methylene ether of pyrogallol can be obtained by converting pyrogallol into pyrogallol-4-carboxylic acid, which yields 2-hydroxy-3,4-methylenedioxybenzoic acid under the action of dimethyl sulphate. The decarboxylation of this compound on heating with copper chromite gave the required product. The 1,2-dimethyl ether of pyrogallol was synthesised similarly.

Similar results were obtained in the study of the methylation[45] of a series of derivatives of polyhydroxy-1,4-naphthoquinones: juglone (5-hydroxy-1,4-naphthoquinone) and naphthazarin (5,8-dihydroxy-1,4-naphthoquinone). Under all the conditions investigated, the *peri*-hydroxy-groups in the 5- and 8-positions, which are linked by strong hydrogen bonds, are not methylated by diazomethane, while all other hydroxy-groups are readily converted into methoxy-groups. Thus, in the reaction with diazomethane 2-hydroxyjuglone gives 2-methoxyjuglone, 3-hydroxyjuglone gives 3-methoxyjuglone, and 6-ethyl-7-hydroxy-2-methoxyjuglone gives 6-ethyl-2,7-dimethoxyjuglone. Hydroxynaphthazarins behave similarly.

The behaviour of polyhydroxyindanones, tetralones, and 1,2-benzocycloheptanones is unusual. Like all *peri*-chelated hydroxy-ketones, 1′,4′-dihydroxy-1,2-benzocyclohepta-3,7-dione (XXVI) does not react with diazomethane[53]. However, 1′,2′,3′,4′-tetrahydroxy-1,2-benzocycloheptan-3-one (XXVII) is readily converted into the 2′,3′,4′-trimethyl ether, the *peri*-hydroxy group of which cannot be alkylated,[54]:



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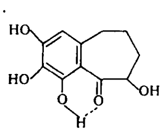

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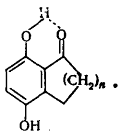


(XXVIII)

At the same time, 5,8-dihydroxytetralone is not methylated with diazomethane even at the free hydroxy-groups in the 5-position[55]. An anomalous feature is that the reaction of diazomethane with 4,7-dihydroxyindanones (XXVIII, $n = 1$), 4,7-dihydroxytetralones (XXVIII, $n = 2$), and 4,7-dihydroxybenzocycloheptanones (XXVIII, $n = 3$) does not result in the methylation of any of the hydroxy-groups even on prolonged contact at low temperatures in various solvents[38]. The behaviour of these compounds in reactions with phenyl isocyanate is also anomalous[38].

4. THE STRENGTH OF CARBOXYLIC ACIDS

When hydrogen bonds are formed in molecules of organic carboxylic acids, the dissociation constants of the latter may increase or decrease. They increase when the carboxy-group behaves as a proton acceptor (by virtue of its carbonyl oxygen) and they decrease in those cases where the hydroxyl of the carboxy-group behaves as a proton donor in the hydrogen bond. Examples of compounds of the first type are the *o*-hydroxy-acids of the benzene and naphthalene series. Salicylic acid is much stronger than the *m*- and *p*-isomers[21,56–58]. The introduction of a second hydroxy-group in the *o*-position results in an even greater increase of the dissociation constant. 2,6-Dihydroxybenzoic acid is stronger than phosphoric acid. The acid dissociation constants K_a in water are listed in Table 2.

The much higher dissociation constant of salicylic acid [compared with isomers (Ed. of Translation)] cannot be explained by the electronic effect of the hydroxy-group, since it should be approximately the same for the *o*- and *p*-positions. Nor can one invoke the *ortho*-effect to account for this phenomenon[59]. Although the higher dissociation constants K_a of the *o*-substituted benzoic acids compared with the *p*-isomers due to the destabilisation of the unionised acid by steric factors[57] is observed also on introduction of other *o*-substituents, incapable of formation of hydrogen bonds, the increase is much less. Thus, whereas the K_a values for the *o*-isomers of toluic and chlorobenzoic acids, for example, exceed the values for the *p*-isomers by factors of 2.9 and 10.5,[60] K_a for *o*-monohydroxybenzoic acid is higher than the corresponding value for the *p*-isomer by a factor of 40. Nor should one forget that the bulk of the hydroxy-group is much smaller than that of the majority of other *o*-groups and yet its effect on K_a is much greater. The polar effect is itself too small to account for the considerable difference between the dissociation contants of *o*- and *p*-hydroxybenzoic acids. This is evident from the fact that the K_{a1} for *o*- and *p*-phthalic acids, which are 1.1×10^{-3} and 2.9×10^{-4}, and for *o*- and *p*-aminobenzoic acids, 1.1×10^{-5} and 1.4×10^{-5}, differ much less than in the case of hydroxy-acids[60].

Table 2.

Acid	$10^5 K_a$	$K_a/K_{a(C_6H_5COOH)}$
Benzoic	6.30	1
m-Hydroxybenzoic	8.33	1.32
p-Hydroxybenzoic	2.62	0.42
o-Hydroxybenzoic	105	16.7
2,6-Dihydroxybenzoic	6000	952

The only acceptable explanation of the anomalously high K_a value for salicylic acid is the existence of an intramolecular hydrogen bond in its molecule[3]. The intramolecular hydrogen bond is of course present both in the undissociated acid and in the anion[61,62]. However, since it is to be expected that it is stronger in the anion than in the acid, the stabilisation of the former will be significant and the equilibrium will be displaced towards the dissociated form. An indirect confirmation of this hypothesis is provided by the dissociation constants of methoxybenzoic and 3-methoxy-2-naphthoic acids[21] listed in Table 3.

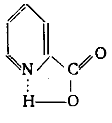
Table 3.

Acid	$10^5 K_a$	$K_{a(OH)}/K_{a(OCH_3)}$
p-Methoxybenzoic	3.20	0.81
o-Methoxybenzoic	8.06	13.00
3-Methoxy-2-naphthoic	15	13.1

It should be noted, that on the basis of K_a measurements for substituted salicylic acids in benzene, Dunn and Penner[63] regard the above explanation of the unusual strength of salicylic acid as a serious oversimplification.

The anomalously high pK_a values for methylsubstituted pyrrole-2-carboxylic acid compared with the 3-isomers (Table 4)[64,65] have been attributed to the existence of intramolecular hydrogen bonds in the anions of the former compounds. Although intramolecular hydrogen bonds of this kind have not been found in the corresponding ester or in 2-acetylpyrrole, the more pronounced nucleophilic properties of the carboxylate anion may result in this type of interaction[64].

While in the examples considered above the intramolecular hydrogen bond is responsible for the increase of the acid dissociation constant, in many 2-substituted acids with heterocyclic substituents the hydrogen bond has the opposite effect. The σ-constant of the 2-pyridyl group calculated from the K_a of picolinic (XXIX) and pyridine-2-acetic (XXX) acids proved to be anomalously low compared with the σ-values calculated from data for other reaction series. This is explained by the presence of an intramolecular hydrogen bond between the hydrogen atom of the hydroxy-group and the nitrogen atom, which stabilises the acid and increases the pK_a value[66]:



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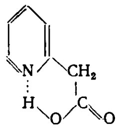
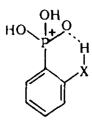


(XXX)

Table 4. pK_a values for substituted pyrrolecarboxylic acids.

Position of COOH	R	pK_a
2	H	4.40
3	H	4.95^{18}; 5.00^{56}
2	3-CH_3	4.60
2	4-CH_3	5.10
2	5-CH_3	5.00
3	2-CH_3	5.80
3	4-CH_3	5.60
3	5-CH_3	5.35

Jaffe's examination of the acid dissociation constants of *o*-substituted phenylphosphonic acids[67] led to the hypothesis that, depending on the nature of the *o*-substituent, the P=O group can behave as an acceptor [compound (XXXI)] or a donor [compound (XXXII)] in the hydrogen bond:



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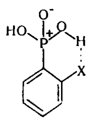

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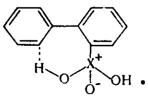


(XXXIII)

When the P=O group behaves as an acceptor, the negative charge of its oxygen atom decreases and the acid strength increases. This effect is clearly seen in 2-hydroxy-4-nitrophenylphosphonic acid, where the difference between the experimental pK_a and the value calculated on the assumption that the polar and inductive effects are the same in the *o*- and *p*-positions reaches −0.18 in water and −0.64 in 50% alcohol.

On the other hand, if the P=O group behaves as a donor in the hydrogen bond, its oxygen atom assumes a partial negative charge and therefore the first dissociation constant of the phosphonic acid increases. This effect, which is weaker than the first, obtains in *o*-methoxyphenylphosphonic acid (ΔpK_a in water +0.10 and in alcohol +0.25). The effect of substituents on the second dissociation constants of the above compounds is also interpreted from the standpoint of this mechanism.

Hydrogen bonds with benzene rings as proton acceptors are fairly weak[68–73]. Nevertheless the large differences between the pK_a values of *o*-biphenylylphosphonic (XXXIII, X = P) (pK_a = 3.78) and phenylphosphonic (pK_a = 1.83) acids[67,74] and *o*-biphenylylarsonic (XXXIII, X = As) (pK_a = 4.29) and phenylarsonic (pK_a = 3.47) acids[75] have been attributed to the intramolecular hydrogen bonds between the acid hydroxy-groups and the π electrons of the aromatic system[67].

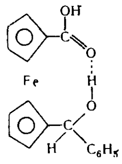
Intramolecular hydrogen bonds have some effect also on the dissociation constants of organic acid salts. When a hydroxy- or amino-group capable of formation of hydrogen-bonded bridges is present in the salt anion, the dissociation constant of the salt is greatly increased. This has been found, in particular, for magnesium, calcium, strontium, and barium salts of glycollic acid, glycine, etc.[76]

5. ESTERIFICATION REACTIONS

The rate and mode of esterification reactions depends significantly on the presence of intramolecular hydrogen bonds in the reactant molecules. Measurements of the rate constants for the interaction of substituted benzoic acids with *p*-tolyldiazomethane in toluene or ethyl acetate solutions showed that salicylic acid is the most reactive[77]:

$$RCOOH + N_2C(C_6H_4CH_3)_2 \rightarrow RCOOCH(C_6H_4CH_3)_2 + N_2.$$

In an analogous reaction with diphenyldiazomethane in toluene at 30°C, among all ferrocenecarboxylic acids with heteroannular CH_3CO, C_2H_5, C_6H_5, $C_6H_5CH_2$, and $C_6H_5CH(OH)$ substituents, 1-(α-hydroxybenzyl)ferrocene-1′-carboxylic acid was esterified with the highest rate constant[78]. It has been shown[79] that diphenyldiazomethane attacks the carboxy-group at the O–H bond. Therefore the high reactivities of salicylic acid[77] and 1-(α-hydroxybenzyl)ferrocene-1′-carboxylic acid (XXXIV)[78] can be explained by the formation of an intramolecular hydrogen bond between the hydroxy-group of the substituent and the carbonyl oxygen, which inhibits the rotation of the COOH group and increases the rate of its reaction with diaryldiazomethanes:



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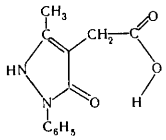

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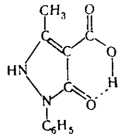


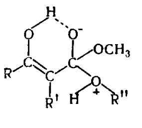
(XXXVI)

The sharp difference between the reactivities of *cis*- and *trans*-2-hydroxycyclohexane-1-carboxylic acids and their derivatives is attributed to the presence of a hydrogen bond in the *cis*-isomer[80]. The higher rate of reaction with diazomethane of antipyrineacetic acid (XXXV) compared with antipyrinecarboxylic acid (XXXVI) is a consequence, according to the author[81], of the greater lability of the seven-membered chelate ring in compound (XXXV) compared with the six-membered ring in compound (XXXVI). It is believed that the higher reactivity of β-keto-esters in transesterification reactions (RCOOR′ + R″OH → RCOOR″ + R′OH) may be due to a hydrogen bond in the transition state (XXXVII) of the reaction[82,83]. Indeed, while the transesterification of methyl- and ethyl-substituted β-keto-esters takes place under mild conditions in the absence of a catalyst, the transesterification of disubstituted β-keto-esters incapable of enolisation and hence of the formation of intramolecular hydrogen bonds does not take place under these conditions.

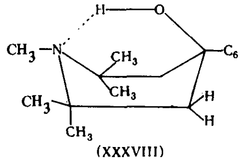
A chelated phenolic hydroxyl is probably more readily acylated than alkylated[40]. However, the formation of esters (particularly under the usual conditions) is also anomalously slow or does not occur at all when the molecule contains hydrogen-bonded hydroxyls. Thus in the benzoylation of phenol and its substituted derivatives it was found that *o*-nitrophenol is esterified at the lowest rate, while the esterification of the *m*- and *p*-isomers is somewhat faster than that of phenol itself[1]. In polyhydroxyanthraquinones the chelated *peri*-hydroxyls are acetylated much more slowly than others[1].

Many compounds with a strong intramolecular hydrogen bond are not acetylated at all under the usual conditions (acetylation with acetic anhydride at room temperature with addition of several drops of pyridine). This has been established for 4-chlorosalicylaldehyde[1], 5-fluoro-2-nitrophenol[1], 2-hydroxy-3-methyl-5-nitrobenzaldehyde[49], 2,3,5-trinitrophenol[49], and α-hydroxybenzylideneacetophenone[49].

The unsuccessful attempts to obtain the acetyl derivatives of compound (XXXVIII) are due to the presence of the strong intramolecular hydrogen bond in the latter ($\Delta\nu_{OH} = 205\ cm^{-1}$).[84]

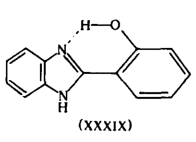


(XXXVII)



(XXXVIII)

The selective acetylation of hydroxy-groups in polyhydroxy-compounds is also due to the involvement of some of these in intramolecular hydrogen bonds. Thus in the acetylation of 2,4-dihydroxybenzoic acid and the corresponding aldehyde only the 4-acetoxy-2-hydroxy-derivative is obtained[1] and 2,4,6-trihydroxybenzaldehyde gives only the 4,6-diacetyl derivative[1]. Acetylation of polyhydroxy-substituted flavones, isoflavones, chromones, and flavanones under mild conditions does not involve the hydroxy-groups in the 5-position because of its strong hydrogen bond with the *peri*-carbonyl oxygen atom[40] (under more severe conditions—heating at 100°C—this hydroxyl is also acetylated). Acetylation with acetic anhydride of 1′,2′,3′,4-tetrahydroxy-1,2-benzocycloheptan-3-one (XXVII) gives 2′,3′,4-triacetoxy-1-hydroxy-1,2-benzocycloheptan-3-one[84], while the acetylation of 2-(*o*-hydroxyphenyl)benzimidazole (XXXIX) takes place at the nitrogen atom[85] (there is a strong intramolecular hydrogen bond between the hydroxy-group and the imine nitrogen atom[86]):



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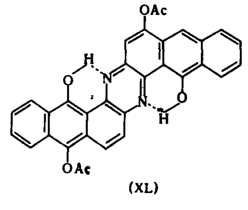


(XL)

The reductive acetylation (with zinc and acetic anhydride) of the non-linear isomer of indanthrone yields only the diacetyl derivative (XL) since the remaining hydroxy-groups are linked by strong hydrogen bonds[87].

To elucidate the effects of intramolecular hydrogen bonds on the rate of acetylation, the kinetics of the reaction of certain cholinolytic substances with acetyl chloride have been investigated[88] at 30°C in chloroform solution. The kinetic data together with infrared spectroscopic data[89] are presented in Table 5. A particularly important feature of these results is that the spectroscopic measurements were made approximately under the same conditions (carbon tetrachloride as a solvent) as the kinetic experiments.

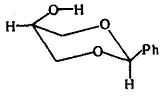
Table 5.

Compound	ν_{OH}, cm^{-1}	$k_{acetylation}$, litre $mole^{-1}$ min^{-1}
(1) $(C_6H_5)_2C(OH)CH_2OC_2H_5$	3484^*_{33}	0.50
(2) $(C_6H_5)_2C(OH)C_2H_5$	—	0.50
(3) $(C_6H_5)_2C(OH)COOCH_2CH_2N(C_2H_5)_2$	3534_{31} 3610_{64}	1.42
(4) $(C_6H_5)_2C(OH)COSCH_2CH_2N(C_2H_5)_2$	3534_{57} 3610_{30}	9
(5) $(C_6H_5)_2C(OH)CONHCH_2CH_2N(C_2H_5)_2$	3378_{38} 3623_{73}	1.50
(6) $(C_6H_5)_2C(OH)CON(CH_3)CH_2CH_2N(C_2H_5)_2$	3378_{33} 3610_{80}	1.90
(7) $(C_6H_5)_2C(OH)CH_2OCH_2CH_2N(C_2H_5)_2$	3155_{38} 3610_{75}	0.29
(8) $(C_6H_5)_2C(OH)CH_2CH_2N(C_2H_5)_2$	3226_{34} 3610_{84}	0.35

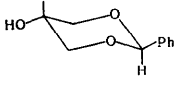
*The subscripts denote the percentage transmission in 0.02 M solutions in carbon tetrachloride.

The complexity of the structures of the compounds chosen and the presence in them of substituents of different electronic types complicates the interpretation of the results. Nevertheless it is clear that the rate of acetylation of the thioester (4) is much higher than that of the ester (3), while the rates for the corresponding amides are much lower. This is fully consistent with the spectroscopic finding that the hydroxyl in (4) is less strongly linked and those in (5) and (6) are more strongly linked by intramolecular hydrogen bonds than the hydroxyl in (3). One cannot of course dismiss the possibility of some influence of the ester, thioester, and amide groups on the lability of the hydrogen atom in the hydroxy-group. Similarly the lower rate of reaction of (7) and (8) compared with (1) and (2) respectively can be explained by stronger intramolecular hydrogen bonds in the latter.

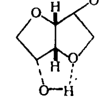
The accelerating effect of hydrogen bonds on the esterification of alcohols has also been described. Such an effect has been noted by Buck et al.[90] in a study of the esterification of 5-hydroxy-1,3-dioxan derivatives with *p*-phenylazobenzoyl chloride. *cis*-5-Hydroxy-2-phenyl-1,3-dioxan (1,3-benzilideneglycerol) and (XLI) reacts with *p*-phenylazobenzoyl chloride almost six times faster than the *trans*-isomer (XLII). This is because the intramolecular hydrogen bond in compound (XLI) (in carbon tetrachloride solutions $\Delta\nu_{OH_{cis}} = 3590\ cm^{-1}$ and $\Delta\nu_{OH_{trans}} = 3633\ cm^{-1}$) increases the basicity of the oxygen atom of the hydroxy-group and thereby increases the rate of esterification:



(XLI)



(XLII)



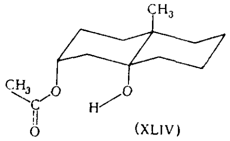
(XLIII)

This is confirmed by the behaviour of 4-phenylcyclohexanols. Since only intermolecular hydrogen bonds may exist in solutions of these compounds, the reactivity of both isomers should be enhanced, but, since in the *cis*-isomer the hydroxy-group is sterically more inaccessible, the greatest increase in rate should be expected for the *trans*-isomer. Indeed, at 37°C *trans*-4-phenylcyclohexanol reacts almost 7 times faster than the *cis*-isomer.

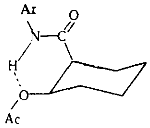
Of the two hydroxy-groups in 1,4,3,6-dianhydro-α-gluticol (XLIII) the 5-hydroxy-group, involved in an intramolecular hydrogen bond, is the more reactive. In particular, the formation of the *p*-toluenesulphonyl derivative involves mainly the 5-hydroxy-group (after interaction with *p*-toluenesulphonyl chloride for 46 h the mixture has the following composition: 11.7% of the 2-monosubstituted derivative, 11.7% of the 2,5-disubstituted derivative, and 45.4% of the 5-monosubstituted derivative [91]); in the esterification with *p*-phenylazobenzoyl chloride the 5-monosubstituted derivative is also mainly formed (after 22 h the reaction mixture contains 12% of the 2-monosubstituted derivative, 9% of the 2,5-disubstituted derivative, and 36% of the 5-mono-substituted derivative [90]).

6. HYDROLYSIS OF ESTERS

Barton [92] established that esters of equatorial alcohols of the cyclohexane series are hydrolysed more readily than the epimeric axial esters. However, this general rule does not hold if the hydroxy- and ester-groups in the monoesters of the diols approach one another under the influence of the molecular environment to such an extent that an intramolecular hydrogen bond is formed. Such a hydrogen bond greatly facilitates the hydrolysis of axial esters compared with the equatorial esters. This phenomenon was discovered for the first time by Henbest and Lovell [93,94]. In a study of the hydrolysis of 3-acetoxy-5-hydroxysteroids in aqueous potassium bicarbonate they found that the *cis*-diaxial hydroxy-esters of the cholestane and coprostane series are hydrolysed (under the same conditions) to a much greater extent than the corresponding equatorial esters. These results were explained by the formation of a six-membered ring with a hydrogen bond between the hydroxyl in the 5-position and the alcoholic oxygen of the axial ester (XLIV):



(XLIV)



(XLV)

According to the authors, such a hydrogen bond increases the reactivity of the ester group in relation to the nucleophilic agent introduced into the reaction [94]. The decrease of the OH and $\geqslant$C–O vibration frequencies and the increase of the carbonyl frequency in the infrared spectra of acetoxy-alcohols of type (XLIV) confirmed the hypothesis that intramolecular hydrogen bonds of this type are present.

A study of the infrared spectra (with high resolution in the region of the hydroxyl stretching vibrations) of certain 1,3-hydroxy-acetates of the bicyclononane and bicyclononene series was carried out by Johnson and coworkers [95]. The authors believe that the slight shift of the hydroxyl band ($\Delta\nu_{OH}$ = 15 cm^{-1}) cannot be assigned to the hydrogen bond with the carbonyl oxygen because, like Henbest and Lovell [93,94], they attribute this shift to the hydrogen bond with the ester oxygen. Furthermore, the >C=O frequency in the intramolecularly hydrogen-bonded compounds investigated is usually enhanced, while involvement in an intramolecular hydrogen bond always reduces it.

The hydrogen bond is also responsible for the higher reactivity of derivatives of *cis*-2-hydroxycyclohexanecarboxylic acid compared with the *trans*-isomers. Thus the *cis*-acetoxy-*p*-toluidide (XLV) is hydrolysed much more rapidly than the corresponding *trans*-isomer [80].

Similarly the base-catalysed methanolysis of 7- and 16-acetoxy-derivatives of germine is facilitated by the presence of hydroxy-groups in the 14- and 20-positions [96], while the methanolysis of the 16-acetoxy-derivative of cevine is facilitated by the hydroxy-group in the 20-position [97].

Table 6.

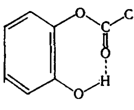
Compound	10^3k, litre mole^{-1} s^{-1}
3β-Methoxycholestan-4β-yl acetate	2.7
4β-Hydroxycholestan-3β-yl acetate	22
3β-Hydroxycholestan-4β-yl acetate	24
Cholestan-3β-yl acetate	1.3

A study has been made [98,99] of the kinetics of the alkaline hydrolysis of cholestan-3β-yl acetates at 30°C in 20% aqueous dioxan containing sodium hydroxide. The results are presented in Table 6, which shows that the rate of hydrolysis of the 3β-acetate increases by a factor of 8 or 9 when a 4β-hydroxy-group is introduced into the molecule. The replacement of the 3β-hydroxy-group by a methoxy-group (the inductive effect of which is approximately the same as that of the hydroxy-group) reduces the rate of hydrolysis of the 4β-acetate by a factor of 19.

In a study of the rate of alkaline hydrolysis of a number of monoglycyl derivatives of *cis*- and *trans*-tetrahydrofuran-3,4-diols it was found [100] that, whereas the *trans*-hydroxy-group increases the rate of alkaline hydrolysis (at 30°C) by a factor of 2.3, the increase due to the *cis*-hydroxy-group is by a factor of 6.7. However, in contrast to Henbest and Lovell [93,94], the enhanced reactivities of the monoglycinates derived from the *cis*-3,4-diols are attributed [100] to a hydrogen bond with the carbonyl oxygen. It is noteworthy that, although Johnson and coworkers [95] do assert on the basis of infrared spectroscopic measurements that the hydrogen bond in the ground state is formed with the ester oxygen, they believe nevertheless that the kinetically important species may be those where the carbonyl oxygen behaves as the proton acceptor.

The sharp increase of the rate of hydrolysis on formation of a hydrogen bond between a hydroxy-group and a carbonyl or methoxy-carbonyl group was noted in a study of the hydrolysis of indole alkaloids [101,102]. However, because of the complexity of the compounds (yohimbine, corynanthine, methyl reserpate, etc.), the rate of hydrolysis of which is influenced considerably not only by the intramolecular hydrogen bond but also by the concentrations of the conformers and the rates of their interconversions, it is difficult to interpret the quantitative data obtained in this investigation. Examples of the acceleration of alkaline hydrolysis of esters are known also for many other types of compound [103]. Hansen [104] investigated the rate of alkaline hydrolysis of a number of phenols at 25°C in 0.07 M $KClO_4$. The value of lg k_2 (k_2 is a second-order rate constant in litre mole^{-1} s^{-1}) are listed in Table 7.

The much higher rate of hydrolysis of phenyl acetate (by a factor of 700) compared with the *o*-hydroxyphenylacetate (XLVI) is due to the presence in the latter of a strong intramolecular hydrogen bond ($\Delta\nu_{C=O}$ in carbon tetrachloride solutions is 30 cm^{-1}). The intramolecular hydrogen bond in *o*-carboxyphenyl-β-D-glucose (XLVII) explains why it is hydrolysed 10^4 times faster than the *p*-carboxyphenyl-derivative[105]:


(XLVI)

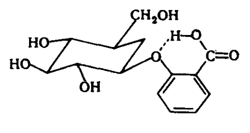
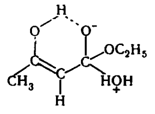
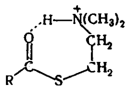

(XLVII)

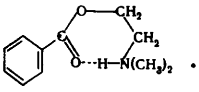
Table 7.

Compound	lgk_2
Phenyl acetate	0.22
o-Methoxyphenyl acetate	0.01
o-Hydroxyphenyl acetate	3.07
o-Phenylene diacetate	0.97

The stabilisation of the transition state (XLVIII) by the intramolecular hydrogen bond is the cause of the rapid hydrolysis of ethyl acetoacetate in water at 90°C:[106]


(XLVIII)


(XLIX)


(L)

Hansen[107] noted an appreciable effect of hydrogen bonds involving a nitrogen atom on the hydrolysis of esters. In the alkaline hydrolysis (pH 7–10) of two thioesters—2-(*NN*-dimethylamino)ethyl thioacetate $CH_3CH_2C(O)SCH_2CH_2NH(CH_3)_2$ (XLIX) and $CH_3CH_2C(O)SCH_2CH_2\overset{+}{N}(CH_3)_3$—it was found that the first ester is hydrolysed 240 times faster than the second. This may be due to a hydrogen bond in (XLIX). The same causes are responsible for the somewhat smaller increase (approximately by a factor of 20) of the rate of hydrolysis of the 2-(*NN*-dimethylamino)ethyl benzoate (L) compared with the 2-(*NNN*-trimethylamino)ethyl ester[108].

The enhanced (by a factor of 20–30) rate of hydrolysis of tertiary 2- and 3-dialkylaminoalkyl acetates compared with the corresponding quaternary compounds is also due to the existence of an intramolecular hydrogen bond in the former, as shown by spectroscopic data[109].

The kinetic data obtained in a comparative study[110] of the alkaline hydrolysis of esters with the general formula $C_6H_5COOCH_2R$ at a constant pH at 25°C in 50% ethanol are presented in Table 8, which shows that the esters capable of forming an intramolecular hydrogen bond with a carbonyl oxygen are hydrolysed many times faster than their analogues without such bonds. Thus compound (2) is hydrolysed 22 times faster than compound (1) and compound (6) is hydrolysed 1000 times faster than compound (5).

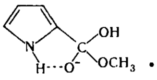
Many other examples of the effect of intramolecular hydrogen bonds on the rate of hydrolysis have been adduced[111,112]. In a spectrophotometric study of the acid hydrolysis of a number of aromatic Schiff bases in aqueous alcohol it was found that the rate constant for the hydrolysis of *o*-hydroxybenzylidene-*p*-toluidine (k_1 = 0.021) is 9.6 times lower than that of *p*-hydroxybenzylidene-*p*-toluidine (k_1 = 0.202).[111] On the other hand, *o*-methoxybenzylidene-*p*-toluidine (k_1 = 0.680) hydrolyses three times faster than *p*-methoxybenzylidene-*p*-toluidine (k_1 = 0.220). Clearly the markedly lower rate of hydrolysis of the *o*-hydroxy-isomer compared with the *p*-isomer is due to an intramolecular hydrogen bond in the former.

Table 8.

Substituent R	Presence of i.h.b.*	k, mole^{-1} min^{-1}
(1) $-C{\equiv}C-CH_2-N(C_2H_5)_2$	—	7.46
(2) $-C{\equiv}C-CH_2-NH-C_2H_5$	+	167
(3) $-C{\equiv}C-CH_2-\overset{+}{N}(C_2H_5)_2-CH_3$	—	32.1
(4) $-C{\equiv}C-$	—	12.8
(5) $-CH_2-N(C_2H_5)_2$	—	2.48
(6) $-CH_2-\overset{+}{N}H(C_2H_5)_2$	+	2500
(7) $-CH_2-\overset{+}{N}(C_2H_5)_3$	—	69.8

*A minus sign denotes the absence of a hydrogen bond and a plus sign denotes its presence.

This bond reduces the basicity of the imino-nitrogen and hinders its protonation:

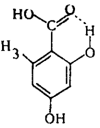

(LI)

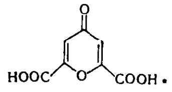
The hydrogen bond has an accelerating effect on the alkaline hydrolysis of methyl pyrrole-2-carboxylate (LI) compared with the isomeric methyl pyrrole-3-carboxylate[64], the rate constants for their hydrolysis in aqueous acetone being 0.41 × 10^{-3} and 0.059 × 10^{-3} respectively. The explanation is that the transition state in the hydrolysis of compound (LI) is stabilised by an intramolecular hydrogen bond of the type >N–H. . . O<.

The ease of hydrolysis of 1-quinolinium derivatives to the corresponding quinolines is attributed[112] to the presence of an intramolecular hydrogen bond in 4-dialkylaminoalkylaminoquinolines[113].

7. DECARBOXYLATION REACTIONS

The decarboxylation reaction requires a weakening of the bond between the carboxyl carbon atom and the atom in the ring (or chain) to which it is linked. This happens to some extent on acid dissociation and the rate of reaction is determined mainly by the rate of decomposition of the anion[114–116]. Since acids with the carbonyl group involved in a hydrogen bond with *o*-hydroxy-groups are much stronger than their isomers, they should be decarboxylated much more readily than the latter. Thus, while benzoic acid is not decarboxylated up to 400°C and *p*-hydroxybenzoic acid is decarboxylated at about 300°C, salicylic acid splits off carbon dioxide on heating in water to 220–230°C,[49] 2-hydroxynaphthoic acid, which has a strong intramolecular hydrogen bond[117], is decarboxylated at 120°C,[49] and orsellinic acid (LII) decomposes into orcinol and carbon dioxide even on boiling in methanol[49]:


(LII)

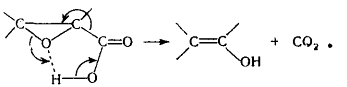

(LIII)

Similarly, meconic acid, the carboxy-group of which is chelated, splits off carbon dioxide above 120°C, while chelidonic acid (LIII) which does not have a hydrogen bond of this kind is decarboxylated only at 300°C.

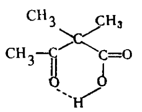
Some of these acids, for example, phloroglucinoldicarboxylic and *o*-nitrosalicylic acids, are extremely unstable in a free form and therefore cannot be isolated[49]. On the other hand, isomers of *o*-nitrosalicylic acid are quite stable.

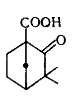
Pyridine-2-acetic[118,119] and quinoline-2-acetic[118] acids are decarboxylated very readily below 100°C. On the other hand, the isomeric 3-acetic acids are decarboxylated with considerable difficulty. This may appear strange if one remembers that the 2-isomers are weaker acids than the 3-isomers by virtue of an intramolecular hydrogen bond with the nitrogen atom[66]. One of the possible explanations of this finding is that the decarboxylation takes place in fact via the hydrogen-bonded cyclic form of the molecule. Thus the optically active methylethylpyridine-2-acetic acid is resistant to decarboxylation in acid and alkaline media and is readily decarboxylated in a neutral medium (maximum chelation) with formation of racemic 2-s-butylpyridine.

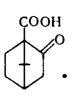
It has also been suggested[120] that the thermal decomposition of glycidic acid to carbonyl compounds is accompanied by the intermediate formation of the chelate compound (LIV):


(LIV)

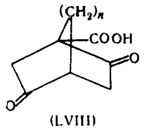
It has been established experimentally[121] that the non-catalysed decarboxylation of β-keto-acids, for example, dimethylacetoacetic acid (LV), is independent of the dielectric constant of the solvent. Therefore the rate-determining stage of the reaction cannot be the decomposition of strongly polar intermediate species. On this basis, and also because the primary product of the cleavage of compound (LV) is the enolic form of isopropyl methyl ketone, Westheimer and Jones[121] suggested that the reaction involves the intermediate formation of the chelate species (LV):

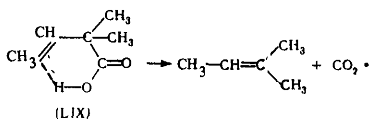

(LV)


(LVI)


(LVII)

The validity of this hypothesis is indicated by the fact that β-keto-acids incapable of enolisation (because of the considerable steric strain on formation of the enol), for example, camphenic (LVI) and ketopinic (LVII) acids, are not decarboxylated above 300°C, while derivatives of bicyclo[3,3,1]nonane (LVIII) are not decarboxylated even on vacuum sublimation at 150°C.[122] According to Arnold et al., the decarboxylation of βγ-unsaturated acids, for example 2,2-dimethylbutane-3-carboxylic acid (LIX),[123] also proceeds via a cyclic chelate formed in which the double bond behaves as a proton acceptor:


(LVIII)

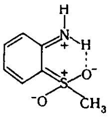

(LIX)

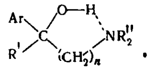
The unusual resistance to decarboxylation of styrylacetic acid and αα-dimethylstyrylacetic acid is explained by the fact that the loss of carbon dioxide with subsequent migration of the double bond leads to the breakdown of the conjugated system[123].

Similar mechanisms have been proposed for the decarboxylation of malonic acid and its half-esters and also the half-esters of 2,5-dimethylcyclopentanedicarboxylic acid[124].

8. INTRAMOLECULAR HYDROGEN BONDS AND BASICITY

Whereas fairly extensive data have accumulated on the effect of intramolecular hydrogen bonds on the acid properties of individual groups, the effect of the hydrogen bond on basicities has been investigated very much less. It may be supposed that the involvement of an atom or group of atoms with basic properties in a hydrogen bond should result in a weakening of the basic properties if the given group plays the role of a donor in the hydrogen bond. Thus *o*-aminophenyl methyl sulphone is a weaker base than the *p*-isomer although the steric effect of the methanesulphonyl group should increase and not decrease the strength of the *o*-base compared with the *p*-isomer. The reason for this is the flattening of the molecule as a result of the contribution of the resonance structure (LX) with an intramolecular hydrogen bond[125]:


(LX)

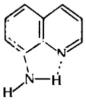

(LXI)

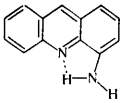
The less pronounced basic properties of 2-amino-4-trifluoromethylphenyl phenyl sulphone compared with the 4-amino-2-trifluoromethylphenyl isomer can be explained similarly[126].

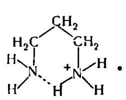
o-Hydroxybenzylidenepentylamine (pK_a = 12.15 in acetonitrile), which, like all *o*-hydroxybenzylidenealkylamines, has a strong intramolecular hydrogen bond[127], is a weaker base than *p*-hydroxybenzylidenepentylamine (pK_a = 14.80).[128]

In a study of amino-alcohols (LXI)[129,130] it was found that there is a reciprocal relation between the strength of the intramolecular hydrogen bond (displacement of the OH band in the infrared spectrum in carbon tetrachloride solution) and the basicity of amino-alcohols (in nitrobenzene)[130]: the stronger the hydrogen bond the lower is the basicity of the amino-group and, within the limits of each series, the frequency shift is fairly well correlated with the relative basicity of the amino-alcohol.

The intramolecular hydrogen bond has a considerable influence on the basicity of the ring nitrogen atoms in 8-aminoquinoline (LXII) and 1-aminoacridine (LXIII):[131,132]


(LXII)


(LXIII)


(LXIV)

Among all the aminoquinolines and aminoacridines, compounds (LXII) and (LXIII) are the weakest bases. The reason for this is the presence in them of intramolecular hydrogen bonds, demonstrated by spectroscopic data[133].

The reduced basicity of the amino-group in the monocation of trimethylenediamine (LXIV) compared with other diamines has also been attributed[134] to the presence of an intramolecular hydrogen bond.

9. REDUCTION REACTIONS

a. Reduction of the Carbonyl Group

The presence of a hydroxy-group in the *ortho*-position relative to a carbonyl group considerably alters the activity of the latter. In the polarographic reduction of a series of quinones in aprotic solvents it was noted[135] that electron-donating groups displace the half-wave reduction potential towards more negative values. At the same time hydroxy-groups linked to >C=O groups via an intramolecular hydrogen bond shift the potentials towards more positive values (Table 9).

Table 9.

Quinone	Substituent	Solvent	$E_{1/2}$, V
	H	CH_3CN	—0.71
		DMF*	—0.72
1,4-Naphthoquinone	2-CH_3	CH_3CN	—0.77
	2-NH_2	CH_3CN	—0.92
	2-OH	DMF	—0.64
		CH_3CN	—0.52
	5-OH	DMF	—0.51
	H		—0.98
9,10-Anthraquinone	2-C_2H_5	DMF	—1.12
	1-OH	DMF	—0.77
	1.8-$(OH)_2$	DMF	—0.64

*DMF = dimethylformamide

An analogous effect was noted[136] also in a series of aromatic ketones: the carbonyl group in *o*-hydroxyacetophenone is reduced appreciably more readily than in the *para*-isomer. Thus the intramolecular hydrogen bond greatly increases the electron affinity of the molecule.

b. Reduction of the Nitro-group

The presence of the hydrogen bond in *o*-nitro-compounds not only increases the ease of reduction of the nitro-group but is also the reason why the reduction products are not always amines. Thus *p*-nitrophenol and nitrocresols [(3) and (4) in Table 10], which have no intramolecular hydrogen bonds, are fully reduced to the amines at any pH, while the presence of intramolecular hydrogen bonds in the *ortho*-isomers [(1), (5), (6), and (7) in Table 10] stabilises the intermediate hydroxylamine derivative and inhibits further reduction at a dropping mercury electrode[137,138]. At the same time, dihydroxynitrobenzenes [(10)–(12) and (14) in Table 10], which have weaker hydrogen bonds than *o*-nitrophenol, are reduced to the amines at any pH.[139]

Table 10.

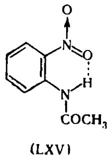
Compound	$E_{1/2}$, V		
	pH 2.2	pH 3.6	pH 6.4
(1) *o*-Nitrophenol	—0.34	—0.52*	—0.73**
(2) *p*-Nitrophenol	—0.54	—0,68*	—0.86**
(3) 6-Nitro-*m*-cresol	—0.35	—0.42	—0.58
(4) 5-Nitro-*o*-cresol	—0.30	—0.35	—0.52
(5) 3-Nitro-*p*-cresol	—0.21	—0.27	—0.42
(6) 3-Nitro-*o*-cresol	—0.20	—0.22	—0.37
(7) 4-Nitro-*m*-cresol	—0.20	—0.24	—0.42
(8) 2-Nitro-*p*-cresol	—0.28	—0.32	—0.50
(9) 4-Nitro-*o*-cresol	—0.23	—0.30	—0.48
(10) 2-Nitroresorcinol	—0.17***	—0.25	—0.36
(11) 4-Nitroresorcinol	—0.26	—0.36	—0.54
(12) 3-Nitrocatechol	—0.16	—0.24	—0.37
(13) 4-Nitrocatechol	—0.34	—0.45	—0.57
(14) 2-Nitrohydroquinone	—0.20	—0.25	—0,38

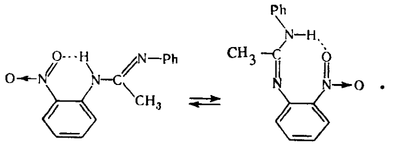
*Determination at pH 4.0
**Determination at pH 7.0
***Determination at pH 2.1.

The half-wave potentials for the reduction of *o*-nitrophenol and its substituted derivatives and also dihydroxynitrobenzenes with intramolecular hydrogen bonds [(10)–(12) and (14) in Table 10] are much more positive than for the *para*-isomers and *o*-methoxynitrobenzenes in an acid medium, but are approximately the same in alkaline solutions where there is no intramolecular hydrogen bond. This is evidently due to the fact that the hydrogen bond is formed only with one oxygen atom of the nitro-group. This makes the oxygen atoms non-equivalent and facilitates the reduction of the oxygen atom not involved in chelation. The half-wave potentials for the reduction of different nitrophenols, nitrocresols, and dihydroxynitrobenzenes are listed in Table 10.

The kinetics of the reduction of substituted nitrobenzenes with titanium trichloride in aqueous alcohol were investigated by Newton et al.[140], who showed that the *p*-hydroxy-group lowers the rate of reduction of the nitro-group by a factor of 4 compared with nitrobenzene, while the *o*-hydroxy-group increases it by a factor of 16.5. At the same time, *o*- and *p*-methoxynitrobenzenes react at almost identical rates. It is therefore clear that the enhanced reactivity of *o*-nitrophenol is a consequence of the presence of an intramolecular hydrogen bond.

Chelation can also account for the greater ease of reduction of *o*-nitroacetanilides (LXV) compared with nitrobenzene and *m*- and *p*-nitroacetanilides[141]:


(LXV)

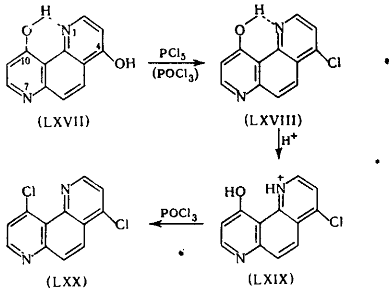

(LXVI)

The possibility of chelation of this type is demonstrated by the fact that *o*-nitroacetanilide is more volatile than the *meta*- and *para*-isomers, is less associated in naphthalene[142], and has a number of other properties typical for chelated systems[143]. At pH 8 and 12 the differences between the reduction potentials of the *ortho*- and *para*-isomers are +0.15 and +0.13 V respectively, while at pH 7 the half-wave potential for compound (LXV) is more negative by 0.04 V than for *p*-nitroacetanilide (in a highly alkaline medium there is no chelation). Similar results were obtained in a study of the polarographic and catalytic reduction of *o*-nitrophenylacetamidine (LXVI) and its isomers[144]. In the pH range between 2.2 and 7 the differences between the half-wave potentials for the reduction of the *meta*- and *para*-isomers are insignificant, while the value for (LXVI) is much less negative. The greater ease of reduction of (LXVI) compared with its isomers, due to the presence of an intramolecular hydrogen bond, was confirmed also by catalytic hydrogenation in methanol using Raney nickel as a catalyst. The times required for the complete reduction of the nitro-group in the *ortho*-, *meta*-, and *para*-isomers are in the ratios $o:m:p = 1:4:6$.

The greater ease of reduction of 4(7)-nitrobenzimidazole[145] and 4(7)-nitrobenzotriazole[146] compared with their isomeric 5(6)-nitroderivatives without intramolecular hydrogen bonds is explained by the chelation between the hydroxy- and nitro-groups in these compounds.

10. SUBSTITUTION REACTIONS

The intramolecular hydrogen bond has a considerable influence on certain substitution reactions. When 4,10-dihydroxy-1,7-phenanthroline (LXVII) is treated with phosphorus pentachloride or phosphorus oxychloride, the hydroxy-group in the 4-position is the first to be replaced by chlorine to give compound (LXVIII). Such preferential substitution of the hydroxyl can be accounted for by the "masking" of the hydroxy-group in the 10-position by the intramolecular hydrogen bond with the nitrogen atom in the 1-position[147]:



(LXVII) (LXVIII) (LXX) (LXIX)

The conversion of (LXVII) into (LXX) is achieved by prolonged heating of the former with $POCl_3$. The addition of a small amount of H_2O or HCl to the reaction mixture greatly increases the rate of reaction and the yield of the product, since under these conditions the intramolecular hydrogen bond breaks in consequence of the protonation of the ring nitrogen atoms. In a study of the reaction

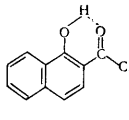
$$R{-}C_6H_4CH{=}N{-}C_6H_4R' + R''{-}C_6H_4{-}CHO \rightarrow R''{-}C_6H_4{-}CH{=}N{-}C_6H_4{-}R' + R{-}C_6H_4{-}CHO$$

it was found that among aromatic aldehydes the most reactive is salicylaldehyde[148], which may be attributed to the presence of an intramolecular bond.

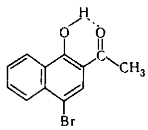
It is well known that *o*-halogenonitrobenzenes react with primary and secondary amines much more rapidly than their *para*-isomers. Thus *o*-chloronitrobenzene reacts with piperidine in xylene at 102°C 80 times faster[149,150] and in benzene 47–51 times faster[150,151] than the *para*-isomer. In polar solvents, for example, alcohols or aqueous dioxan, this ratio is much less, but always greater than unity[150]. The greater reactivity of *o*-halogenonitrobenzenes compared with the *para*-isomers is explained[152] by the fact that in the transition state of these reactions there is a hydrogen bond in the case of the *ortho*-isomers, which facilitates the process. Other explanations for this phenomenon have also been proposed[149].

An important argument in favour of the hypothesis of the decisive role of the intramolecular hydrogen bond is provided by the reaction of 1,4-diazabicyclo[2,2,2]octane with *o*-chloronitrobenzene in which there is no hydrogen bond in the transition state. This compound reacts with *p*-chloronitrobenzene in benzyl alcohol at 500°C hundreds of times faster than with the *ortho*-isomer. At the same time di-n-butylamine reacts with the *ortho*-isomer 16 times faster than with the *para*-isomer. These data support the hypothesis of the formation of a hydrogen bond in the transition state. Similarly the presence of a hydrogen bond between a hydrogen atom of the amino-group and the fluorine atom accounts also for the greater reactivity of *o*-fluoronitrobenzene compared with other *o*-halogenonitrobenzenes[154,155].

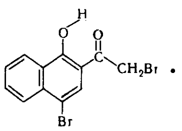
The presence of intramolecular hydrogen bonds explains the characteristics of certain electrophilic substitution reactions. Chang and Yang[156] found that 2-acetyl-1-naphthol (LXXI) is readily brominated at room temperature to 2-acetyl-4-bromo-1-naphthol (LXXII) and bromination with an excess of bromine gives 4-bromo-2-bromoacetyl-1-naphthol (LXXIII). However, 2-acetyl-4-bromo-1-naphthol does not react further with bromine if it is first isolated from the reaction mixture:



(LXXI)



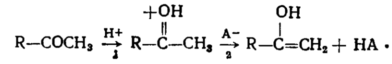
(LXXII)



(LXXIII)

This behaviour of (LXXI) becomes clear if one considers the formation of the dibromo-derivative (LXXIII): (LXXI) + $Br_2 \xrightarrow[1]{} (LXXII) + HBr \xrightarrow[2]{Br_2} (LXXIII) + HBr$. It follows from this mechanism that the formation of the dibromo-derivative (LXXIII) takes place only in the presence of hydrogen bromide formed in the first stage of the reaction. Indeed (LXXII) is brominated successfully when HBr is passed through its solution in acetic acid. This antagonistic effect on bromination is shown by both 4-bromo- and 4-nitro-derivatives of 2-acetyl-1-naphthol and is common to this group of compounds. It appears logical to attribute this behaviour to the interaction between the hydroxy- and oxo-groups.

The principal stages in the acid-catalysed bromination of ketones are as follows:



$$R{-}COCH_3 \underset{1}{\overset{H^+}{\rightarrow}} R{-}\overset{\overset{+OH}{\|}}{C}{-}CH_3 \underset{2}{\overset{A^-}{\rightarrow}} R{-}\overset{\overset{OH}{|}}{C}{=}CH_2 + HA\,.$$

Chelation should interfere with the formation of the intermediate ion and should lower the rate of bromination. The addition of a proton to the carbonyl oxygen breaks the hydrogen bond and permits further bromination. The behaviour on bromination of the methyl ether and acetate derived from (LXXI), in which there are no intramolecular hydrogen bonds, confirms this. None of these compounds requires the addition of acids for the bromination of the acetyl group.

11. REACTIONS OF *o*-HYDROXY-ALDEHYDES

One of the most thoroughly investigated reactions, the kinetics of which are significantly influenced by the presence of hydrogen bonds, is the reaction of aromatic *o*-hydroxy-aldehydes with reagents for carbonyl compounds. Studies of this kind were carried out for the first time by Vavon[157]. It was found that salicylaldehyde and *o*-vanillin, which have strong intramolecular hydrogen bonds, react with hydroxylamine hydrochloride 13 and 11 times faster respectively than the isomeric *p*-hydroxybenzaldehyde and *p*-vanillin[158]. This behaviour persists also in the interaction of other *o*-hydroxy-aldehydes with the hydrochlorides of hydroxylamine, phenylhydrazine, and semicarbazide,[158], and with melamine[159]. Thus 2-hydroxy-1-naphthaldehyde reacts with hydroxylamine hydrochloride 120 times faster and with phenylhydrazine hydrochloride 53 times faster than 4-hydroxy-1-naphthaldehyde which has no intramolecular hydrogen bond. It is interesting to note than *o*-methoxybenzaldehydes react with carbonyl reagents much faster than the *p*-methoxy-derivatives. For example, *o*-methoxybenzaldehyde reacts with hydroxylamine hydrochloride 150 times faster than anisaldehyde.

Table 11.

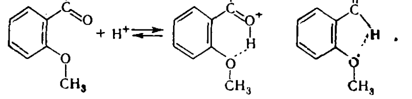
Substituent	$10^3 k_1$, s^{-1}	
	$NH_2OH \cdot HCl$	$C_6H_5NHNH_2 \cdot HCl$
o-OH	42.8	16.3
p-OH	5.9	0.8
m-OH	15.8	2

Knorre and Emanuel'[160] made a more rigorous kinetic study of this reaction. They investigated the kinetics of the interaction of hydroxy- and nitro-benzaldehydes with hydroxylamine and phenylhydrazine hydrochlorides in 95% methanol. The rate constants obtained for the reactions of hydroxybenzaldehydes are listed in Table 11, which shows that salicylaldehyde reacts with hydroxylamine hydrochloride 7.2 times faster and with phenylhydrazine hydrochloride 8.2 times faster than *p*-hydroxybenzaldehyde. On the other hand, the isomeric nitrobenzaldehydes react with these reagents for the carbonyl group at virtually identical rates (*o*-nitrobenzaldehyde even a little more slowly than the others).

The results of polarographic studies of the kinetics of the reactions of a large number of benzaldehydes with aniline in a buffer solution at pH 10.5 in 50% methanol[161] agree with those quoted above. Salicylaldehyde reacts with aniline 58 times faster than *p*-hydroxybenzaldehyde and *o*-chlorobenzaldehyde, in which there is no intramolecular hydrogen bond, reacts somewhat more slowly than *p*-chlorobenzaldehyde. It is surprising that *o*-aminophenol is very much more reactive in the reaction with benzaldehyde (by a factor of approximately 30) than *p*-aminophenol. This behaviour of *o*-aminophenol may be attributed to the greater stabilisation (by the intramolecular hydrogen bond) of benzylidine-*o*-aminophenol produced compared with the product formed by the *para*-isomer.

The data of Wolfenden and Jencks[162] on the formation of semicarbazones from aromatic aldehydes indicate a greater reactivity of *o*-aldehydes in general (*o*-Cl, *o*-OH, *o*-NO_2, *o*-CH_3) compared with the *para*-isomers. Thus the vast majority of data indicate that *o*-hydroxy- and *o*-methoxy-benzaldehydes are more reactive than their *para*-isomers, the ratio of the rate constants for the reactions of the *ortho*-isomers to those for the reactions of the *para*-isomers exceeding the analogous ratios for other substituents.

Knorre and Emanuel'[2] believe that the higher reactivity of the *o*-hydroxy- and *o*-methoxy-groups in an acid medium can be explained in the following way. The substituent in the *ortho*-position in relation to the aldehyde group affects its basicity by the stabilisation of the conjugate acid of the aldehyde as a result of the formation of a hydrogen-bonded bridge, as in compound (LXXIV):



(LXXIV) (LXXV)

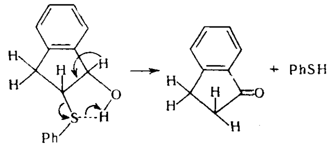
Such stabilisation depends in the first place on the capacity of the substituent for the formation of hydrogen bonds. Gordy's data[163] on the shift of the OD stretching vibration frequencies on dissolution of CH_3OD in solvents with different functional groups were used to obtain quantitative characteristics of this capacity. According to these results, $\Delta\nu$ is 200 cm^{-1} for hydroxy-compounds, 70 to 110 cm^{-1} for methoxy-compounds, and 30–50 cm^{-1} for nitro-compounds (for example). Consequently the enhancement of the basic properties of the carbonyl compound will be a maximum for the hydroxy-substituent and a minimum for the nitro-substituent.

A different explanation of the greater reactivity of *o*-hydroxy- and *o*-methoxy-benzaldehyde was put forward by Vavon and Montheard[157,158,164,165], who suggested that the rate of reaction is determined by the concentration of the conformers of compound (LXXV) with exceptionally high reactivity. The possibility of the existence of hydrogen bonds of this type has been indicated by Pinchas[166,167] on the basis of infrared spectroscopic measurements for a number of benzaldehydes. However, in later studies by Forbes[168] certain characteristics of the infrared spectra of *o*-nitrobenzaldehyde and related compounds were attributed not to intramolecular hydrogen bonds but to steric interactions. In general it is difficult to believe that such weak hydrogen bonds (if they exist at all) have so great an effect on the rate of reaction. Finally, Wolfenden and Jencks[162] suggested an explanation, based on a detailed study of the kinetics on the formation of semicarbazones, for the enhanced reactivity of *o*-substituted benzaldehydes in general and not only the hydroxy- and methoxy-derivatives, namely that the transmission of electronic effects by a resonance mechanism from the *para*-position is more effective than from the *ortho*-position.

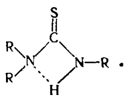
Evidently further data are required for a final choice between these hypotheses.

12. INTRAMOLECULAR HYDROGEN BONDS AND CERTAIN SPECIFIC REACTIONS

The intramolecular hydrogen bond influences also certain other types of chemical reactions, for example certain decomposition and condensation reactions. In particular, *cis*-2-phenylthioindanol (LXXVI) undergoes spontaneous decomposition. Since the *trans*-isomer is comparatively stable, such behaviour of (LXXVI) must be attributed to its intramolecular hydrogen bond, the presence of which has been demonstrated spectroscopically[169]:



(LXXVI)



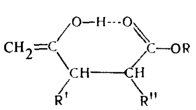
(LXXVII)

The fact that the product of the addition of sodium bisulphite to salicylaldehyde decomposes much more rapidly than the products of bisulphite additions to other *o*-aldehydes can be explained by "proton transfer" from the hydroxy-group to the sulphite group being eliminated, probably via a hydrogen-bond bridge[170].

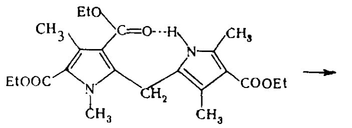
In a study of the kinetics of the decomposition of thiourea and its methyl derivatives in aqueous solution, Shaw and Walker[171,172] concluded that the reaction proceeds via a chelate cyclic species (LXXVII). This mechanism is confirmed by the finding that tetramethyl-thiourea, which is incapable of forming intramolecular hydrogen bonds, is not decomposed in aqueous solutions[173].

The effect of various types of intramolecular hydrogen bonds on the rate of cleavage of the –N=N–bond in azodyes under the influence of yeast has been noted[174].

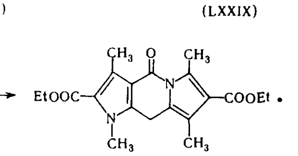
Since it has been established experimentally that the reactivity of the butyl ester of levulinic acid in the Claisen condensation is higher than that of the methyl ester[175], while in the hydrolysis of the esters the ratio of the reaction rates has the usual value (the rate for the butyl ester is higher), the ionic mechanism of the Claisen condensation has been rejected[176]. The authors suggest that the active form of levulinic acid in this condensation is the seven-membered chelate ring (LXXVIII):



(LXXVIII)



(LXXIX)

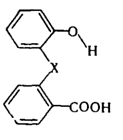


(LXXX)

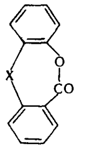
In consequence of the increasing +*I* effect in the series $CH_3 < C_2H_5 < C_3H_7 < C_4H_9$, the negative charge at the carbonyl oxygen also increases, which tends to increase the stability of the intramolecular hydrogen bond and accelerates the reaction.

The ready cyclisation of dipyrrolylmethanes (LXXIX) to cyclic amides with the dipyrrolopyridine structure (LXXX)[177] is probably due to the mutual approach of the reaction centres in compound (LXXIX) caused by the intramolecular hydrogen bond, the presence of which has been demonstrated by infrared spectroscopy[178].

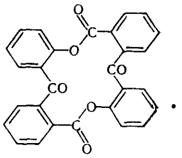
It is suggested that the intramolecular hydrogen bond is responsible also for the formation of various reaction products in the intramolecular cyclisation of compounds of type (LXXXI).[179,180] The dehydration of 2-carboxy-2′-hydroxybenzophenone (LXXXI, X = CO), 2-carboxy-2′-hydroxy-5′-methylbenzophenone, and 2-carboxyphenyl 2′-hydroxyphenyl ether (LXXXI, X = O) by acetic anhydride gives almost quantitative yields of the seven-membered lactones (LXXXII), while other dehydrating agents [P_4O_{10}, $POCl_3$, $(CF_3CO)_2O$] lead to the formation mainly of 14-membered lactides (LXXXIII):



(LXXXI)



(LXXXII)



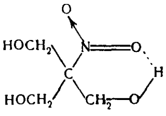
(LXXXIII)

This is explained by an intramolecular hydrogen bond in compound (LXXXI), which forces these molecules into a configuration which is unfavourable for lactone formation, favouring instead the formation of lactides. In fact 2-carboxy-2′-hydroxydiphenylmethane, in which an intramolecular hydrogen bond of this kind cannot exist, yields only a lactone under all conditions[180].

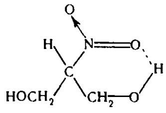
13. INHIBITION OF CHEMICAL REACTIONS BY INTRAMOLECULAR HYDROGEN BONDS

Numerous data showing that intramolecular hydrogen bonds can retard and sometimes prevent a number of chemical reactions have been published. The inhibition of alkylation and acetylation reactions by intramolecular hydrogen bonds has already been mentioned (Sections 2 and 4). In some cases the inhibition of chemical reactions by intramolecular hydrogen bonds can be explained by the fact that the latter stabilise conformations in which the reaction centres are separated and therefore the reaction cannot occur.

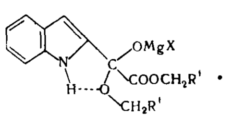
Thus the ability of nitro-groups to form strong hydrogen bonds is responsible for the ready formation of cyclic acetals and ketals from tri(hydroxymethyl)nitromethane (LXXXIV), which has free hydroxy-groups, while di(hydroxymethyl)nitromethane (LXXXV), where one of the hydroxy-groups is chelated, form these derivatives with great difficulty or not at all[181]:



(LXXXIV)

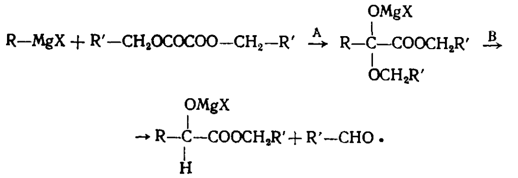


(LXXXV)



(LXXXVI)

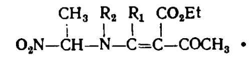
Metal alkoxide halides formed in the reactions of oxalic esters with organomagnesium compounds [reaction (A)] and containing the α-indolyl group differ sharply in their thermal stability from compounds with any other substituents. The latter break down by reaction (B) in the range 40–110°C, while (LXXXVI) remains completely unchanged at these temperatures[182]. This is explained by the stabilising effect of the intramolecular hydrogen bond on the complex formed, as shown for compound (LXXXVI). The presence of a hydrogen bond of this type in the compound is confirmed by infrared spectra:



$$R{-}MgX + R'{-}CH_2OCOCOO{-}CH_2{-}R' \xrightarrow{A} R{-}\underset{OCH_2R'}{\overset{OMgX}{C}}{-}COOCH_2R' \xrightarrow{B}$$

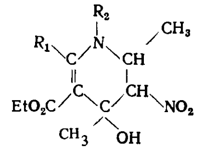
$$\rightarrow R{-}\underset{H}{\overset{OMgX}{C}}{-}COOCH_2R' + R'{-}CHO.$$

A very interesting case of the inhibition of chemical reactions by hydrogen bonds is the cyclisation of compounds of the type[183]

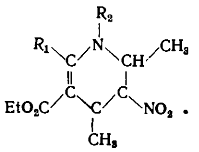


$$O_2N{-}\underset{}{\overset{CH_3}{CH}}{-}\overset{R_2}{N}{-}\overset{R_1}{C}{=}\overset{CO_2Et}{C}{-}COCH_3\ .$$

The compound with $R_1 = R_2 = H$ does not cyclise although the steric conditions should favour the formation of the cyclicaldol (LXXXVII) or its dehydration product (LXXXVIII):

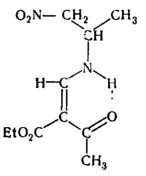


(LXXXVII)

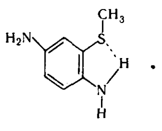


(LXXXVIII)

Evidently the aldol condensation may be hindered if the initial molecule contains an intramolecular hydrogen bond, as in compound (LXXXIX):



(LXXXIX)



(XC)

Indeed, when $R_1 = R_2 = H$ or $R_1 = CH_3$ and $R_2 = H$, the compounds are not cyclised under a wide variety of conditions, which suggests that their hydrogen-bond bridge is exceptionally stable, and as a result the molecule exists in the conformation unfavourable for cyclisation, since the reaction centres (the carbonyl and methylene groups) are distant from one another. This is confirmed by the behaviour of the compound with $R_1 = H$ and $R_2 = CH_3$ in which the formation of intramolecular hydrogen bonds is impossible and which therefore is instantly cyclised to 5-ethoxycarbonyl-4-hydroxy-1,2,4-trimethyl-3-nitro-1,2,3,4-tetrahydropyridine (LXXXVII).

Hydrogen bonds have a marked influence on the course and final products of condensation and substitution reactions. Thus 4-amino-3-methylthioazobenzene can be readily synthesised by the condensation of nitrosobenzene with 2-methylthio-1,4-phenylenediamine (XC). As a result of the presence of an intramolecular hydrogen bond in the initial compound, the condensation involves preferentially the free amino-group, so that the ratio of the condensation product involving the free and hydrogen-bonded amino-groups is 21 : 1.[184]

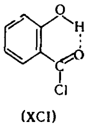
In a study of the condensation of aromatic aldehydes with benzyl carbamate[185], it was found that the reaction gives satisfactory yields with nitro- and methoxy-benzaldehydes but does not take place at all with salicylaldehyde and vanillin, owing to the presence of intramolecular hydrogen bonds in the molecule of the latter compounds. In contrast to these aldehydes, 3-nitrosalicylaldehyde, in which an analogous situation would appear to exist, gave *NN*-dibenzyloxycarbonyl-2-hydroxy-3-nitrobenzylidenediamine in high yield. However, one should not forget that in this compound the hydrogen bond is formed mainly between the hydroxy- and nitro-groups and therefore the reactive aldehyde group remains free.

The inhibiting effect of the *o*-hydroxy-group in the aldehyde component is observed also in the condensation of various aromatic aldehydes with phenylacetic acid[186].

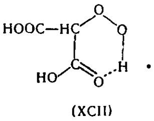
As already mentioned, the involvement of the hydroxyl in a hydrogen bond greatly reduces its tendency to enter into other reactions. The authors believe that the presence of a strong intramolecular hydrogen bond is the reason why *o*-nitrophenol does not form compounds with 8-hydroxyquinoline[187], acetamide[188], urea[189], acetone, and dimethyl sulphoxide[190].

14. THE ROLE OF INTRAMOLECULAR HYDROGEN BONDS IN THE STABILISATION OF ORGANIC MOLECULES

Intramolecular hydrogen bonds are known to be a factor stabilising molecules. In some cases the presence of intramolecular hydrogen bonds in molecules is the principal cause of their stability. Thus, owing to the presence in its molecule of a strong intramolecular hydrogen bond, salicyloyl chloride (XCI) can be isolated in a pure form[194,195], in contrast to its *meta*- and *para*-isomers which readily undergo polyesterification reactions. The existence of this type of hydrogen bond has been demonstrated spectroscopically[196]:



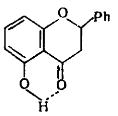
(XCI)



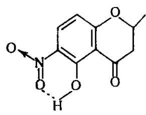
(XCII)

The impossibility of determining (with the aid of the usual reagents) of the hydroperoxy-group in hydroperoxymalonic acid obtained in the ozonolysis of acetylenedicarboxylic acid in concentrated formic acid is probably associated with the presence of a strong intramolecular hydrogen bond in compound (XCII).[197]

Hydrogen bonds have a marked influence also on the stability of certain *o*-hydroxychalcones and their cyclisation products—flavanones. While flavanone rings are usually readily opened by alkalies, 5-hydroxyflavanone (XCIII), in which there is a strong intramolecular hydrogen bond, is fairly stable[198]:



(XCIII)

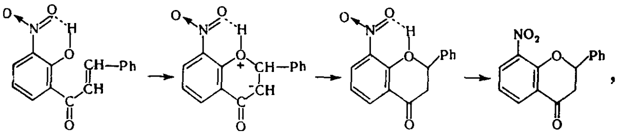


(XCIV)

At the same time 5-hydroxy-6-nitroflavanone (XCIV), where the hydroxy-group is hydrogen-bonded mainly on the nitro-group, readily undergoes ring opening under the action of alkalies[199].

The high stability of nitrochalcones of type (XCV) (low rate of cyclisation to flavanones) has been attributed to an intramolecular hydrogen bond between the hydroxy- and nitro-groups[199].

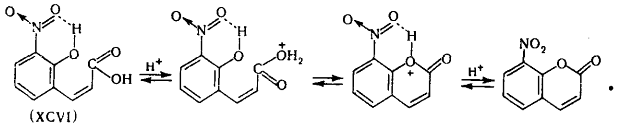
From the standpoint of the mechanism of the cyclisation of chalcones to flavanones adopted at the present time:



(XCV)

such behaviour of compound (XCV) is explained in the following way. The hydrogen bond between the nitro- and hydroxy-groups prevents the elimination of the proton in the last stage and stabilises the nitrosulphones in relation to the corresponding flavanones.

A similar stabilising effect of the nitro-group is observed with 3-nitro-*o*-coumaric acids[200]. This effect can be understood by considering the mechanism of the cyclisation of coumaric acids to coumarones:



(XCVI)

The formation of an intramolecular hydrogen bond, as in the case of hydroxynitrochalcones, prevents the loss of a proton in the last cyclisation stage. Therefore 3-nitro-*o*-coumaric acids are very stable in aqueous solutions. This explanation of the stability of compound (XCVI) is confirmed by the behaviour of 4-methyl-3-nitro-*o*-coumaric acid. The introduction of a methyl group breaks down the coplanarity of the ring and the nitro-group, as a result of which the hydrogen bond between the latter and the hydroxy-group is greatly weakened and the acid is relatively unstable in aqueous solution.

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Rostov-on-Don State University
Lenin Kharkov Polytechnic Institute

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Intramolecular Coordination in Organic Derivatives of the Elements

A.K.Prokof'ev, V.I.Bregadze, and O.Yu.Okhlobystin

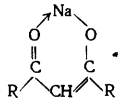
For the first time, the data on the problem of intramolecular coordination in organic derivatives of the elements have been compiled and a systematic and critical account has been given. A definition of intramolecular coordination in its various forms is proposed. It has been shown that intramolecular coordination may constitute the driving force of a number of reactions of such organic derivatives (α-, β-, and γ-elimination).
The bibliography comprises 210 references

CONTENTS

I. INTRODUCTION

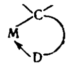
The concept of intramolecular coordination between a metal atom with vacant orbitals and an electron-donating atom in the same molecule has been recently put forward with increasing frequency to account for a number of physical anomalies associated with the structure of organometallic molecules and also in the interpretation of many of their reactions. Since the possibility of such coordination exists in principle, it is frequently postulated on the basis of purely intuitive considerations without more serious justification.

A typical example, dating back to as early as 1925, is the attribution of a chelate structure with covalent bonds to sodium enolates of β-dicarbonyl compounds on the basis of their relatively low melting points and appreciable solubility in aprotic solvents[1]:



Subsequently Brändström[2,3] attempted to use these concepts to explain the dual reactivity of alkali metal enolates.

The aim of the present review is to give a systematic account of the most important postulates put forward in connection with intramolecular coordination and to assess their possible role in organometallic reactions. It is scarcely useful to consider here also the numerous and well known cases of donor–acceptor interaction between two adjacent atoms (for instance, boron and nitrogen atoms in systems of the type of borazole, $d_\pi - p_\pi$ interaction in silylamines, etc.), although they can in fact be regarded as a special case of intramolecular coordination. Chelate compounds in which the electron-donating atom is in a side chain while the chain itself is separated from the metal by a heteroatom (acetylacetonates and related compounds) also will not be considered in detail if they are not truly organometallic compounds, i.e. do not contain at least one direct metal–carbon bond. Attention will be concentrated on compounds in which the carbon chain with the electron-donating atom is linked to the metal via a carbon atom:

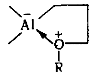


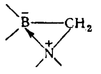
where D is the electron-donating atom.

Frequently in cases where intramolecular coordination in a non-reacting molecule is rejected for some reason, a hypothesis of this kind is suggested for the transition state. Cases of this kind will also be considered briefly.

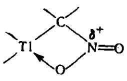
II. THE CONCEPT OF INTRAMOLECULAR COORDINATION

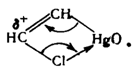
So far a serious theoretical basis for an intramolecular bond of this kind is lacking. Apparently the majority of investigators who postulated it agree that this is donor–acceptor interaction of the "hydrogen bond type". Nevertheless it is evident that in reality extreme cases are possible which could be regarded as qualitatively different. On the other hand, D → M interaction may be equivalent to almost complete charge transfer, i.e. the transfer of two electrons; we are then dealing with a stable intramolecular complex of the "reverse onium" type (ate-complex). In this class of intramolecular organometallic complexes, one may include, for example, the γ-alkoxy-derivatives of aluminium and certain amine complexes of boron, for example:



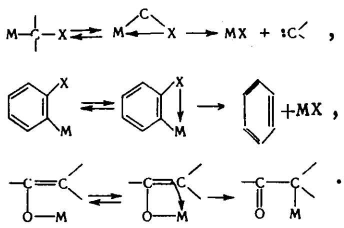


The charge transfer may not be quite so complete; such compounds resemble more the classical electron-deficient molecules (diborane, trimethylaluminium) containing three-centre bridge bonds, where the bond between the three nuclei is formed by two electrons. In this case a coordination-unsaturated metal atom and an atom with a considerable positive charge produced by its electronegative substituents serve as the electron-deficient centres. Such are, for example, the α-nitroalkyl derivatives of thallium and *cis*-β-chlorovinylmercury chloride:

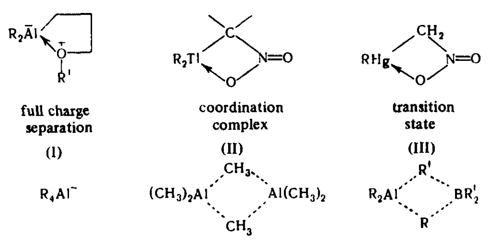




The similarity of these structures to the four-centre transition states in $S_E i$ reactions is not merely formal: there is finally a possibility of the case where a cyclic structure with a coordinate intramolecular bond is formed only as a transition state. These are the well known reactions involving the formation of carbenes and dehydrobenzene and O–C rearrangements of non-ionic enolates.



Thus it is possible to distinguish three different types of intramolecular coordination reactions in organometallic compounds. Firstly, coordination interaction with full charge separation, as in compounds such as the tetra-alkylaluminium salts, secondly, coordination complexes analogous to the trimethylaluminium dimer with bridge bonds, and, thirdly, intramolecular coordination occurring only in transition states, similar to the bridge type transition states in radical exchange reactions involving many organoaluminium and organoboron compounds:



However, it is important to remember that in all the above cases the driving force in the formation of bonds, possible rearrangements, or eliminations is the same: the coordination unsaturation of the metal atom which tends to make good its electron deficit at the expense of a donor in the same molecule, their interation (D → M) taking place through space in addition to a conjugation or induction chain.

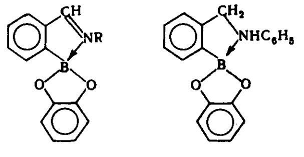
III. INTRAMOLECULAR COORDINATION AND PHYSICAL PROPERTIES OF THE MOLECULES

There is no doubt that the occurrence of intramolecular coordination may affect the physical properties of organometallic molecules. Indeed, in many cases the characteristic features of NMR and NQR spectra and dipole moments, the anomalous effects of *ortho*-substituents, etc. are attributed to such coordination interaction. Analysis of the literature data leads to the conclusion that in fact none of the usual methods can alone provide an answer as to the presence or absence of intramolecular coordination. Evidently such coordination can be reliably inferred only on the basis of consistent data derived by a number of methods. The situation is complicated also by the fact that factors such as intramolecular association (particularly in crystals), inductive and resonance effects, electrostatic attraction or attraction through space ("field effects"), etc. are superimposed on intramolecular coordination interaction.

Vibration Spectra

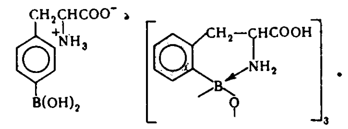
The presence of intramolecular coordination is frequently inferred from optical spectra of organic boron derivatives which show a distinct tendency towards the attainment of the tetrahedral sp^3 configuration.

B → N coordination interactions are therefore suggested for compounds of the type

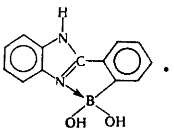


on the basis of a broad absorption band at 1220 cm^{-1}, which can be accounted for by B → N vibrations. The authors also postulate the possibility of intermolecular interaction.

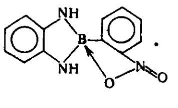
Comparison of the infrared spectra of boron-containing phenylalanines shows that the spectrum of the *ortho*-derivative exhibits, in contrast to the *para*-derivative, an intense broad band at 1710 cm^{-1}, which is characteristic of an unionised carboxylic acid:



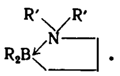
B → N intramolecular coordination has been proposed[6] for 2-(2-boronophenyl)benzimidazole on the basis of the high melting point (> 320°C) and the presence of $\lambda_{max} \simeq$ 310 nm in the ultraviolet spectrum (in 95% ethanol), while 2-(2′-methylphenyl)benzimidazole has $\lambda_{max} = 277$ nm. The absence of intense absorption in the region 7.2–7.8 μm is evidence that the boron atom is coordinated to four groups:



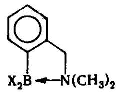
In view of the lower absorption intensity in the region of 350–400 nm of the ultraviolet spectra of 2-phenylbenzo-1,3,2-diazaborolines, compared with unsubstituted 2-(nitrophenyl)benzimidazoles, O → B intramolecular coordination, which is absent from the corresponding *meta*- and *para*-nitro-derivatives, is postulated[7]:



The dependence of the strength of the B → N coordinate bond on substitutents has been determined for γ-aminopropyl compounds[8,9]:

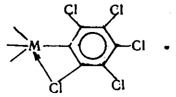


In the unsubstituted amine (R′ = H) coordination is postulated on the basis of the bathochromic shift of the NH_2 stretching vibration bands (3292 and 3350 cm^{-1}), which is characteristic of compounds with a B ← N coordinate bond. The occurrence of such interaction is supported also by the resistance to disproportionation (up to 200°C), which is high for asymmetric boron trialkyls, the relative stability in air, and high dipole moments (4.0–4.2 D). The substitution of a hydrogen atom at the nitrogen atom by dialkyl groups or the introduction of an alkoxy-group at the boron atom lowers the strength of the B ← N bond, while in the compound $(EtO)_2BCH_2CH_2CH_2NEt_2$ there is probably no coordination at all ($\mu = 1.44$ D). Similar coordination has been proposed[10] for compounds of the type

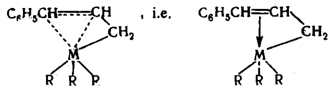


where X = OH or $N(CH_3)_2$. These compounds are relatively resistant to hydrolysis; furthermore, diamineboron distils in a vacuum (75–76°C/0.4 mmHg).

The ultraviolet spectra of pentachlorophenyl derivatives of silicon and tin show a much more intense absorption than the spectra of their hydrogen analogues; in view of this, intramolecular coordination was suggested as the explanation of many unusual properties of these compounds[11]:

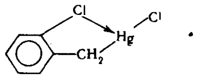


Substitution of the β-methyl proton in *trans*-β-methylstyrene by a $(C_2H_5)_3M$ group (where M = Si, Ge, or Sn) gives rise to a bathochromic shift, which has been explained[12] by an increase in the delocalisation of the π electrons of the allyl double bond through overlap with the vacant *d* orbitals of the metal



where M = Si, Ge, or Sn and R = C_2H_5.

A split Hg–Cl frequency (314, 364, and 251 cm^{-1}) in the infrared spectrum of *o*-chlorobenzylmercury chloride is accounted for by the existence of several rotational isomers[13]. The most intense band (314 cm^{-1}) is attributed to a conformation with possible intramolecular interaction:

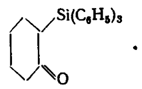


Recently, extensive experimental data have accumulated on the spectra of α-carbonyl organometallic compounds[14]. In the α-carbonyl derivatives of mercury and tin the carbonyl absorption in the infrared spectra is displaced towards lower frequencies (1686–1660 cm^{-1}) and in the ultraviolet spectra a slight displacement of the CO band towards longer wavelengths and a considerable increase of the intensity (by a factor of 200–300) compared with the carbon analogues has been observed, which suggests that these compounds have properties approaching those of conjugated systems. These data, together with the observed dual reactivity of α-metallated aldehydes and ketones, led to the conclusion that there is σ,π-conjugation in compounds of this kind[15,16]. However, Japanese investigators[17] believe that the considerable shift of the carbonyl frequency (ν_{CO} = 1645 cm^{-1}) in $Hg(CH_2CHO)_2$ and $ClHgCH_2CHO$ spectra can be explained by CO → Hg intramolecular coordination (the formation of a polymer is also possible), since in the spectra of acetaldehydemercury ν_{CH} = 2720 cm^{-1}, which corresponds to the normal vibrations in aldehydes; furthermore, this compound undergoes the usual reactions typical of the aldehyde group.

The lowering of ν_{CO} in the spectrum of $(C_6H_5)_3SiCH_2COC_6H_5$ (1667 cm^{-1}) compared with the carbon analogue (1698 cm^{-1}) has been explained by the inductive effect of silicon on the carbonyl group[18].

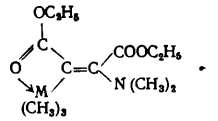
Thus the unusual spectroscopic properties of α-metallated ketones and aldehydes cannot be explained by any one effect. For this reason, attempts have been made in a number of investigations to discover the principal effect resposible for these anomalies. The significant difference between the observed and calculated frequencies of the carbonyl groups (the calculation was based on Thompson's equation $\nu_{CO} = 1720 + 15\Sigma\sigma^*$ cm^{-1}) [19] in $(CH_3)_3SiCH_2COCH_3$ (1698 and 1716 cm^{-1}) and $(CH_3)_3CCH_2COCH_3$ (1723 and 1717 cm^{-1}) suggested that intramolecular coordination in $(CH_3)_3SiCH_2COCH_3$ predominates over the inductive effect of silicon[20]. However, Thompson's relation was derived for compounds of the type CCl_3COCl, in which the field effect and other factors can be more important than inductive effects. Therefore this relation cannot be extended without modifications to the ketones considered above. The same workers later interpreted the higher intensity of the $n \rightarrow \pi^*$ transition (by a factor of 4–5) in α-silylketones relative to their carbon analogues as confirmation of the presence of intramolecular CO → Si coordination, since they believe that the intensity of this transition in related ketones cannot be accounted for by steric and inductive effects[21]. However, the study of β-substituted ketones shows that the exaltation of the $n \rightarrow \pi^*$ transition in these compounds can be explained by many factors and not necessarily the same ones which are responsible for the shift of the carbonyl frequency[22,23].

An attempt has been made to separate the inductive effects from other effects influencing the frequency of the carbonyl absorption in the spectrum of α-triphenylsilylcyclohexanone[24]:

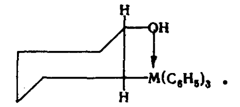


Since the frequency of the CO group in the spectrum of this compound in liquid paraffin is represented by a singlet at 1678 cm^{-1} and in the spectrum of the carbon analogue at 1709 cm^{-1}, it was concluded that Fermi resonance is unlikely. In carbon tetrachloride solution the singlet corresponding to the carbon compound is observed at 1720 cm^{-1}, while in the case of the silicon derivative it is split into two bands (1682 and 1692 cm^{-1}). The splitting is independent of concentration in the range 0.2–10%, which excludes intermolecular interaction. The splitting can be accounted for by a conformational equilibrium, since the relative intensities of the two peaks vary with temperature. The inductive effect of silicon should not depend on the conformation of the cyclohexane ring, whereas intramolecular coordination is possible only in the conformation where the silicon is equatorial. The results may be explained by the cooperative effect of the intramolecular CO → Si coordination and the inductive effect of silicon.

Intramolecular coordination has been proposed also for α-ethoxycarbonyl derivatives of Group IV elements, although it should be weaker than in the corresponding α-ketones. In organotin diazo-esters $R_{4-n}Sn[C(N_2)COOC_2H_5]_n$ (n = 1,2) it has been proposed on the basis that the dipole moment μ = 2.2 D (for n = 1 and R = CH_3) and also a considerable shift of the carbonyl (2070–2045 cm^{-1}) and diazo- (1675–1655 cm^{-1}) frequencies compared with the carbon analogues[25]. Intramolecular coordination is responsible for the splitting of the C=O bands (1735 and 1680 cm^{-1} for the silicon derivative, 1739 and 1698 cm^{-1} for the germanium derivative, and 1740 and 1705 cm^{-1} for the tin derivative) and the bands due to C=C vibrations (1570 and 1550 cm^{-1} for the silicon derivative, 1590 and 1555 cm^{-1} for the germanium derivative, and 1625 and 1590 cm^{-1} for the tin derivative) in the infrared spectra of compounds of the type[26]:



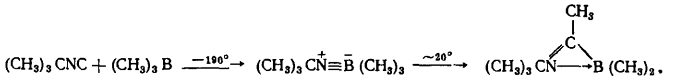
1,2-Disubstituted cyclohexanols of the type 2-$(C_6H_5)_3MC_6H_{10}OH$ (M = Si or Ge) have been found to have a higher acidity[24] than 1-triphenylmethyl-2-cyclohexanol in view of the greater changes in the vibration frequencies of the hydroxy-group on addition of dimethyl sulphoxide and tetrahydrofuran. Since the electropositive effect of silicon and germanium should reduce the acid strength, the above anomalous increase of acidity is explained by an intramolecular interaction between oxygen and the metal



A similar interaction is postulated on the basis of the changes under analogous conditions in the infrared spectra of the silicon and germanium analogues of 1,1,1-triphenylethanol[27].

Radio-frequency Spectroscopy

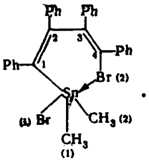
Attempts have often been made to demonstrate the presence of intramolecular coordination in organoboron compounds by proton resonance. The product of the addition of trimethylboron to t-butyl isocyanate isomerises at room temperature to a three-membered chelate complex which is resistant to the action of oxygen and moisture[28]:



The PMR spectrum of the complex in benzene consists of three peaks δ: 2.57 p.p.m. (very broad), 1.18 p.p.m. (sharp), and 0.20 p.p.m. (broad) in proportions of 1 : 3 : 2, which correspond to the groups $=\overset{|}{C}-CH_3$, $-\underset{|}{\overset{|}{C}}-CH_3$, and $>B-CH_3$. In the infrared spectrum there is no frequency due to the stretching vibrations of the $\overset{+}{N}\equiv\overset{-}{C}$ group (2247 cm^{-1}) but there is a $\nu_{N=C}$ frequency at 1548 cm^{-1}. The mass spectrum of the complex corresponds to a monomeric structure†. The formation of a three-membered ring is undoubtedly caused by a steric factor, since less hindered isonitriles dimerise with formation of 2,5-dibora-2,5-dihydropyrazines[29].

Intramolecular (and intermolecular) coordination[30] is postulated in the molecule of dimethylaminomethylboron $(CH_3)_2BCH_2NH_2$. This compound is a weak acid and a weaker base than the corresponding monofunctional derivative; in the PMR spectra δ_{CH_2} is displaced towards stronger fields—0.24 p.p.m. (60 MHz) (δ_{CH_2} for cyclopropane is 0.20 p.p.m.).

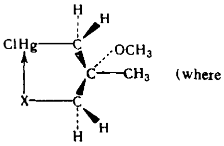
Intramolecular Sn ← Br interaction has been most convincingly demonstrated for 4-bromo-1,2,3,4-tetraphenyl-*cis*-*cis*-1,3-butadienyldimethyltin bromide[31]:



At 36°C the PMR spectra of this compound in carbon tetrachloride has a doublet with components of equal intensity due to the methyl protons (δ = 0.48 and 0.98 p.p.m.), which merges into a singlet at 87°C. There is a pronounced solvent effect: the addition of bases (pyridine, ethers, alcohols, etc.) to a solution of the compound in carbon tetrachloride gives rise to a singlet at δ = 0.73 p.p.m. At the same time in thionyl chloride (strongly ionising solvent) the temperature at which the doublet merges into a singlet is close to that for carbon tetrachloride. The non-equivalence of the methyl protons in the diene has been explained by intramolecular Sn ← Br interaction which stabilises the non-planar cisoid conformation and prevents rotation about the C(2)−C(3) bonds at low temperatures in non-basic solvents. The barrier to rotation about the C(2)−C(3) bonds, determined from the PMR spectra, is equivalent to 18.3 ± 0.23 kcal $mole^{-1}$. The hindered rotation of the diene and the non-equivalence of the methyl protons can be eliminated by breaking the weak coordinate bond Sn ← Br, which is observed experimentally on heating the specimen, the addition of a base competing with Br(2) in the coordination with Sn, and replacement of Br(2) by hydrogen. The suggested conformation of the diene has been confirmed by X-ray analysis[31].

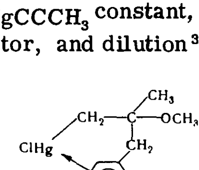
The formation of an intramolecular complex in the Reformatskii reagent derived from $BrCH_2COOC_2H_5$ is suggested on the basis of the shift to higher fields of the signal due to CH_2 protons in the NMR spectrum with increasing solvating power of the solvent[32].

The formation of a ring by an intramolecular donor–acceptor interaction between mercury and halogen atoms in γ-halogenopropyl derivatives of mercury is the cause of the non-equivalence of the methylene protons [Δν (CH_2Br) = 19.1 Hz, Δν (CH_2Hg) = 13.6 Hz]:[33]



(where X = Cl, Br) .

This non-equivalence diminishes sharply if a solvent such as pyridine, capable of breaking the coordinate bond, is employed. This entails also a decrease of the spin–spin coupling constant J_{HgCCCH_3} (36 Hz in deuterochloroform and 20 Hz in pyridine). The intromolecular π-coordination of the phenyl group with the mercury atom has been demonstrated for 2-methoxy-2-methyl-3-phenylpropylmercury chloride on the basis of the non-equivalence of the methylene protons, the J_{HgCCCH_3} constant, the effect of solvents, the temperature factor, and dilution[34]:



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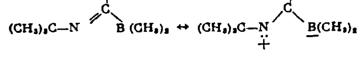
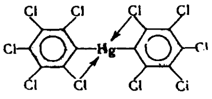
† On the basis of the mass spectra, the authors believe that a preferable structure is the resonance hybrid:



NMR spectroscopy has proved to be a powerful method for the investigation of intra- and inter-molecular coordination. The splitting of the lines due to the chlorine atoms in the CCl_3 group in the ^{35}Cl NMR spectra of the compounds Cl_3CHgBr (37.590, 37.893, 38.794, and 39.032 MHz), Cl_3CHgCl (37.604, 37.968, 39.032, and 39.172 MHz), and $(Cl_3C)_2Hg$ (37.037, 37.681, 38.675 MHz), which is considerable (> 2%), exceeding the limiting crystallographic splitting for molecular crystals with van der Waals interaction between molecules[35], has been explained by intramolecular interaction between one of the chlorine atoms of the CCl_3 group and the mercury atom[36,37]. However, this coordination, which has been confirmed by X-ray diffraction analysis[37], readily breaks down on formation of complexes of the above mercury compounds with dimethoxyethane (the appreciable line splitting vanishes from the ^{35}Cl NMR spectra)[38]. It is interesting that complexes are not formed with ethyl ether. Intramolecular coordination in Cl_3SnCH_2Cl has been proposed on the basis of spectroscopic data[39] and has been confirmed[40] by ^{35}Cl NMR spectra. The spectrum corresponding to the $SnCl_3$ group consists of two lines with intensity ratios of 1 : 2 and a splitting of 6% (23.072, 23.072, and 21.832 MHz), which is three times greater than the maximum possible crystallographic splitting. The non-equivalence of the chlorine atoms can be explained by the coordination interaction Cl → Sn in the $Cl{-}\underbracket{Sn{-}CH_2{-}Cl}$ plane. The cryoscopic determination of the molecular weight in benzene shows that there is no association. Furthermore, the possibility of coordination is not inconsistent with the results of studies of the ^{35}Cl NMR spectra of Cl_3SnCH_2Cl in benzene and ether (1 : 1 and 1 : 2).[41] For test compound : solvent molar ratios of 1 : 1 and 1 : 2, the spectra of Cl_3SnCH_2Cl proved to be identical and therefore only 1 : 1 complexes are formed.

The complex $SnCl_4.2(C_2H_5)_2O$ consists of a tetragonal bipyramid in which four chlorine atoms are located at the base and the ether group are at the vertices[42]. The number of lines and their splitting, assigned to the $SnCl_3$ group in the complexes of Cl_3SnCH_2Cl with benzene and ether, is very similar to that in the spectrum of $SnCl_4.2(C_2H_5)_2O$. Therefore one may suppose that these complexes too have the structure of a tetragonal bipyramid in which three chlorine atoms are located at the base. Probably one of the vertices of the bipyramid is occupied by the coordinated chlorine of the CH_2Cl group and the other by a ligand molecule (Fig. 1).

The intramolecular coordination of chlorine atoms in the 2,2′- or 6,6′-positions of di(pentachlorophenyl)mercury (38.220, 38.220, 38.094, 37.828, and 36.421 MHz), where the evidence for this type of coordination comes also from the crystallographic equivalence of the chlorine atoms in the 3,4,5- and 3′,4′,5′-positions, has been demonstrated by the same method. A similar conclusion was reached also for compounds of the series C_6Cl_5HgX (X = Cl, C_6H_5, or CH_3) in view of the anomalously high frequency shifts in the ^{35}Cl NMR spectra compared with the usual substituents, of the *o*-chlorides compared with the *m*- and *p*-chlorides[43].



On the basis of ^{35}Cl NMR data[44], dipole moments[45], and the relative capacities for complex formation[46] of *cis*- and *trans*-β-chlorovinylmercury chlorides, it has been suggested that there is powerful intramolecular coordination in the *cis*-chloride molecule. Crystals of the *cis*-chloride (m.p. 55°C) are amorphous to X-rays and their ^{35}Cl NMR spectrum shows a single C−Cl frequency (33.132 MHz), which excludes the possibility of intramolecular coordination of the type occurring in the *trans*-chloride crystals. While the dipole moment of the *trans*-chloride (1.82 D in benzene at 25°C) agrees satisfactorily with the value calculated for the ideal model (1.92 D), for the *cis*-chloride there is a considerable discrepancy between the observed and calculated moments (2.92 and 3.57 D respectively). This last finding can be probably accounted for only by a considerable decrease in the angles ClCC and CCHg in consequence of intramolecular coordination. In contrast to the *trans*-analogue, the *cis*-chloride does not form a complex with pyridine, which shows that the mercury atom is coordination-saturated; the capacity of the *cis*-isomer to eliminate acetylene under the action of nucleophilic reagents is also sharply reduced[45].

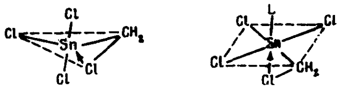
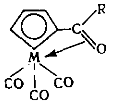


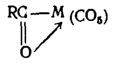
Figure 1. Structures proposed for Cl_3SnCH_2Cl and its ether and benzene complexes.

The conclusion that there is direct intramolecular interaction between the metal atom and the substituent is based[47] on the increase of the asymmetry parameter (η) in the ^{55}Mn, ^{187}Re, and ^{185}Re NMR spectra on introduction of a group COR (R = CH_3, CF_3, or C_6H_5) into the cyclopentadienyl ring of cyclopentadienylmetal tricarbonyls:



(M = Mn, Re) .

Interaction of the same type between the oxygen of the acyl group and the metal has been postulated for acyl derivatives of manganese and rhenium pentacarbonyls on the basis of the infrared spectra[48] in combination with X-ray structural data[49,50]:



Structures

X-Ray diffraction analysis is used comparatively rarely to determine the structures of organometallic compounds with intramolecular coordination.

It has been found[51] that phenylsilatrane $C_6H_5\underbracket{Si(OCH_2CH_2)_3N}$ consists of a distorted trigonal bipyramid with the nitrogen and carbon (from the phenyl group) atoms located at the vertices. The N−Si−C atoms lie almost on a straight line [deviation 0.016 Å (0.016°? Ed. of Translation)]. The silicon atom deviates from the plane of the oxygen atoms by 0.204 Å towards the phenyl carbon atom: ∠ C−Si−O (mean) = 97.1°; ∠ O−Si−O (mean) = 118.5°; l_{SiO} = 1.638−1.665 Å; l_{SiN} = 2.193 Å.

Ethylgermanatrane has a similar configuration[52]. The germanium atom deviates from the plane of the oxygen atoms by 0.23 Å towards the ethyl carbon atom: $\angle$N–Ge–C = 176°; l_{GeN} = 2.25 Å. In view of the experimentally established fact that the structures of the ethylgermanatrane and ethylsilatrane crystals are isomorphous, ethylsilatrane has a similar structure with corrections for the different covalent radius of silicon.

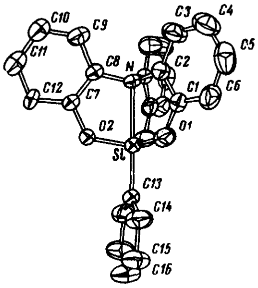


Figure 2. (2, 2′, 2″-Nitrilotriphenoxy)phenylsilane.

(2,2′,2″-Nitrilotriphenoxy)phenylsilane $C_6H_5Si(OC_6H_4)_3N$ also has the configuration of a distorted trigonal bipyramid[53]. The angle $\angle$C–Si–O (mean) = 100.0° is much greater than the analogous angle for the triethoxy-analogue (97.3°) and lies approximately halfway between 90° (for the ideal trigonal bipyramid) and 109.5° (in the tetrahedron). The angle $\angle$N–Si–C = 180° and the Si–N distance is 2.344 Å (2.179 Å in the triethoxy-analogue), which is 0.5 Å longer than the normal Si–N bond (Fig. 2).

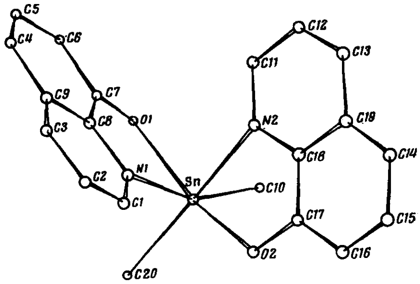


Figure 3. Di-(8-hydroxyquinolato)dimethyltin.

The configuration of di-(8-hydroxyquinolinato)dimethyltin $(CH_3)_2SnOx_2$ (Ox = 8-hydroxyquinoline) has also been determined[54] and found to be a highly distorted octahedron with the methyl groups in the *trans*-positions and the following bond lengths (Å): Sn–C 2.15 and 2.17, Sn–O 2.10 and 2.11, and Sn ← N 2.31 and 2.38; the angle $\angle$CSnC is almost tetrahedral (110.7° ± 0.80°) (Fig. 3).

The intramolecular Sn ← Cl coordination interaction has been found unexpectedly in bipy(OC)$_3$ClMoSnCH$_3$Cl$_2$.[55] Tin in the crystals of this compound may be regarded as having a distorted trigonal bipyramidal environment in which Cl(1) and Cl(3) are linked to tin and molybdenum respectively; Cl(1)SnCl(3) = 168°. The chlorine atom linked to molybdenum is at a distance of 2.81 Å from the tin atom and is clearly linked to both metals (Fig. 4).

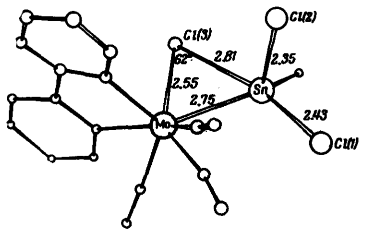


Figure 4. The structure of bipy(OC)$_3$ClMoSnCH$_3$Cl$_2$.

X-Ray diffraction analysis confirmed the occurrence of the intramolecular interaction Sn ← Br proposed for (4-bromo-1,2,3,4-tetraphenyl-*cis*-*cis*-buta-1,3-dienyl)dimethyltin bromide[31]. The presence of a weak coordinate Sn ← Br bond with a length of 3.769 ± 0.007 Å, which is shorter by 0.4 Å than the sum of the van der Waals radii of tin and bromine, has been demonstrated. For this interaction to be possible, the angle $\angle$ C(1)SnCH$_3$(1) has increased to 130.3° from the normal tetrahedral value of 109.5°.

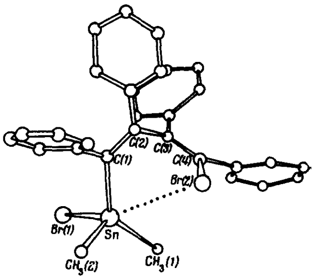
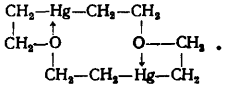


Figure 5. (4-Bromo-1,2,3,4-tetraphenyl-*cis*-*cis*-buta-1,3-dienyl)dimethyltin.

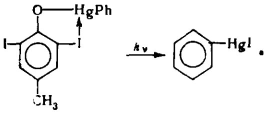
Furthermore, the lengths of the bonds involving Sn have increased from their normal values and also the bond C(4)–Br(2) has become appreciably longer. Normal bond lengths have also been observed (Å): Sn–Br(1) 2.507 ± 0.007 (2.46), Sn–C(1) 2.19 ± 0.04 (2.14); Sn–CH$_3$(1) = Sn–CH$_3$(2) 2.24 ± 0.04 (2.18), and C(4)–Br(2) 2.01 ± 0.04 (1.89) (see Fig. 5).

The crystal structures of α-substituted CCl_3HgBr, CCl_3HgCl,[37] $CBr_2ClHgBr$,[56] and CBr_3HgBr,[57] β-substituted (*trans*-ClCH=CHHgCl,[58] *trans*-ClCH=CHHgBr,[59] and $ClHgCH_2CHO$,[56] and γ-substituted $(CH_3)_2C(OC_2H_5)C(CH_3)_2\cdot CH_3HgSCN$,[60] $(CH_3)_2C(OCH_3)C(CH_3)_2CH_2HgI$, $(CH_3)_2C(OCH_3)C(CH_3)_2CH_2HgSCN$,[61] *o*-$ClC_6H_4CH_2HgCl$,[56] and *p*-$CH_3C_6H_2(I_2)OHgC_6H_5$ [62] derivatives of organomercury compounds have been investigated. It has been found that in compounds with chlorine and oxygen atoms in the α-, β-, and γ-positions the Hg...X interaction does not usually result in Hg...X distances markedly different from those normally observed when different molecules come into contact. An exception is the dimeric molecule of ββ'-oxidodiethylmercury[63], where the mercury atom is coordinated to an oxygen atom as well as two carbon atoms (Hg...O distance 2.21 Å):

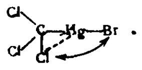


When the α-, β-, and γ-substituents are bromine, sulphur, and iodine atoms, intramolecular interaction in this case leads to a deviation of the Hg...X distances from the values corresponding to different molecules in contact: in CBr_3HgBr we have 3.00 Å for $Hg...Br_I$, 3.36 Å for $Hg...Br_{II}$, and 3.40 Å for $Hg...Br_{III}$; in derivatives of dithizone $Hg(C_{13}H_{12}N_4S)_2.2C_5H_5N$ the mercury atom has a nearly tetrahedral configuration: in the environment of the mercury atom there are two sulphur atoms at a distance of 2.4 Å and two sulphur atoms at a distance of 2.5–2.6 Å, with the valence angles SHgS = 155° and NHgN = 102°.

In the compound p-$CH_3C_6H_2(I)_2OHgC_6H_5$ the Hg...I intramolecular interaction leads to the photochemical decomposition of the crystals under the action of X-rays and the formation of phenylmercury iodide[62]:

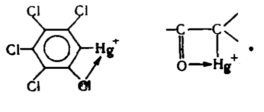


Under the action of X-rays, one of the chlorine atoms in the CCl_3 group in CCl_3HgBr crystals is replaced by bromine[37]:

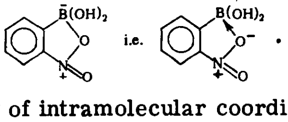


Other Methods

The low rate constants for the electrochemical reduction of β-carbonyl and pentachlorophenyl derivatives of mercury have been explained by the reduced positive charge at the mercury atom due to intramolecular coordination[64]:



The anomalously low acidity of *o*-nitrophenylboronic acid ($K_a = 0.56 \times 10^{-6}$) compared with the *meta*-isomer ($K_a = 6.9 \times 10^{-9}$) and the *para*-isomer ($K_a = 9.8 \times 10^{-9}$) has been explained[65] by the formation of the cyclic compound

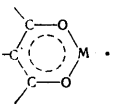


The possibility of intramolecular coordination, suggested in the compound $(C_2H_5)_3SnCH_2COCH_3$ in view of the appreciable quadrupole splitting in the GR spectrum (Moessbauer effect)[66–68], was investigated for different α- and β-carbonyl-containing stannanes[69]. Appreciable quadrupole splitting has been found for α-stannylcarbonyl compounds. It cannot be accounted for by the inductive effect of the halogenomethyl group, because it is absent even in the case of fluorine[70]. The enolate structure $R_3Sn{-}O{-}C\genfrac{}{}{0pt}{}{\diagup\!\!\diagup}{\diagdown}$ is excluded by spectroscopic data. In addition the GR (Moessbauer) spectra of alkoxystannanes are significantly different. The mass spectra are also consistent with intramolecular CO → Sn coordination. There is no quadrupole splitting in the case of β-carbonyl derivatives of tin, in good agreement with infrared spectroscopic data, which show that, in contrast to stannyl ketones, the carbonyl frequency (1718 cm^{-1}) is the same as for the carbon analogues.

"Atranes" and Related Compounds

Organic derivatives of the elements in which the chain with the electron-donating atom is linked to the metal via a non-carbon atom constitute a somewhat distinct group. It includes diketone, diazene, dithiocarbamate, etc. derivatives. Data on compounds of this kind touch upon the main subject of the present review and are briefly described below.

X-Ray diffraction studies on acetylacetonates[71,72] have shown that the acetylacetonate rings are planar and that the pairs of M–O, C–O, and C–C bonds are of equal length:



It has been shown that these systems undergo a wide variety of electrophilic substitution reactions characteristic of aromatic systems[73].

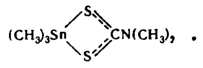
Intramolecular M ← N coordination interaction has been investigated in considerable detail for mono-, di-, and tri-ethanolamine derivatives of boron and silicon. Compounds of this kind were obtained for the first time in 1933[74] and in the course of 30 years boron compounds were investigated almost exclusively. The presence of the B ← N bond has been demonstrated on the basis of the monomeric structure[75], high dipole moments[76,77], high solubilities in water[78,79], and the absence of appreciable electron-donating properties of the nitrogen atom[80]. The presence of the Si ← N bond has been demonstrated using similar data[81] and also infrared[81,82] and PMR[81] spectroscopy and X-ray diffraction analysis[52,53]. The silicon compounds exhibit high biological activity: phenylsilatrane $C_6H_5\underline{Si(OCH_2CH_2)_3N}$ proved to be several times more toxic than hydrocyanic acid[81]. The existence of the Sn ← N bond in stannatranes has been demonstrated by PMR and GR (Moessbauer) spectroscopy[83]. Exhaustive data on all known compounds of this type are presented by Prokof'ev[41].

The chelate salts of nitrilotriacetic acid of the type $X_{n-3}\overline{M(OCOCH_2)_3N}$ should also be included in this class of compounds[84,85]. They have been found to have high biological activity[86].

The presence of the Sn ← N bond in the 8-hydroxyquinolinates $R_nSn(Ox)_{4-n}$, suggested because of the appearance of a yellow colour, the infrared, ultraviolet, and PMR spectrosopic data[87,88,89], and the monomeric nature of the compound[89], has been confirmed by X-ray diffraction analysis[54].

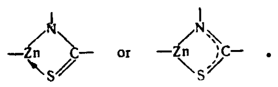
Organotin carboxylates of the type $R_2Sn(OCOR')_2$ exist in the fused and crystalline states as polymers with hexacoordinate tin atoms in which two carboxy-groups are located between adjacent tin atoms (according to infrared spectra)[90]. However, in non-polar solvents intermolecular coordination breaks down and the dicarboxylates form an asymmetric chelate structure with a non-linear skeleton (according to infrared and PMR spectra)[90,91]. Carboxylates of the type $R_3SnOCOR'$ also consist of polymers in crystalline and fused states[92-94]. However, in substituted carboxylates of the type $ClR_2SnOCOR'$ in solution intramolecular CO → Sn coordination is suggested (according to infrared spectroscopic data)[95].

A chelate structure has also been proposed for trimethyltin *NN*-dimethyldithiocarbamate on the basis of infrared spectroscopic studies in liquid paraffin and in solution and also in view of the monomeric form of the compound in benzene[96]:

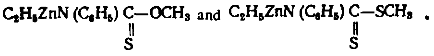


It is surprising that its oxygen analogue has a polymeric structure.

A similar difference between sulphur and oxygen in their capacity for forming an intramolecular coordinate bond was noted[97] in a comparison of the PMR spectra of *N*-(ethylzinc)acetanilide $C_2H_5ZnH(C_6H_5)COCH_3$ and its sulphur analogues. The considerably higher chemical shift of the methyl protons in *N*-(ethylzinc)thioacetanilide and its complexes with pyridine and *NNN'N'*-tetramethylethylenediamine constitutes, according to the authors, significant evidence in favour of the coordination of the thiocarbonyl groups to the zinc atom:

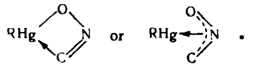


Similar coordination has also been proposed for other sulphur-containing compounds:

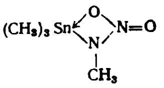


$C_2H_5ZnN(C_6H_5)\underset{\overset{\|}{S}}{C}-OCH_3$ and $C_2H_5ZnN(C_6H_5)\underset{\overset{\|}{S}}{C}-SCH_3$.

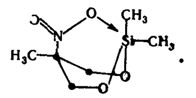
Interaction of this type has also been postulated for organomercury fulminates on the basis of preliminary structural data and characteristics of their chemical behaviour[98,99]:



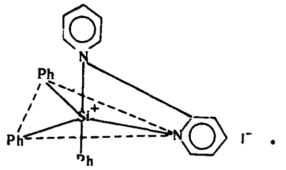
A transannular coordinate bond between one of the oxygen atoms of the nitro-group and the metal atom has been proposed for a number of organometallic nitro-compounds too. In organotin nitroamines $R_3SnN(NO_2)R'$ it is suggested in view of the pale brown colour, low melting points, stability in air, low conductivity in nitrobenzene, and infrared and Gr (Moessbauer) spectra[100]:



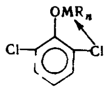
and in 2,2,5-trimethyl-5-nitro-2-sila-1,3-dioxan on the basis of the splitting of the signals due to the methylene protons in the PMR spectrum (in contrast to the analogous compounds without a nitro-group)[101]:



A chelate structure has been proposed for triphenyl(dipyridyl)siliconium iodide[102] and diphenyl(2,2'-dipyridyl)boronium perchlorate[103] but the proposed structures have not been adequately proved:



Intramolecular M ← Cl coordination interaction probably occurs also in organometallic derivatives of 2,6-dichlorophenol, since the ^{35}Cl NMR spectra showed two different signals for the chlorine atoms in the 2- and 6-positions in the aromatic ring and the splitting between these signals is 0.13 – 0.45 MHz for the tin and lead derivatives (i.e. is within the limits of the crystallographic effect), while for mercury it is 0.83 – 1.2 MHz (i.e. 2 – 3% of the measured quantity. If it is assumed that the splitting is proportional to the intensity of the coordination interaction, then it follows that in the above compound organotin groups exhibit a higher capacity for coordination[104]. However, the authors do not exclude completely the possibility of intermolecular interaction in these systems:



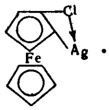
(M = Hg, Sn, Pb) .

Similar coordination has been proposed also for organometallic derivatives of 2,6-dibromo-4-fluorophenol[105] in view of the increase of the chemical shift of fluorine-19 under the influence of the groups Et_3SnO and PhHgO in the ^{19}F NMR spectra compared with the spectra of 4-fluorophenol derivatives without bromine. In these systems too the coordination is more intense for the organomercury group.

IV. CHEMICAL CONSEQUENCES OF INTRAMOLECULAR COORDINATION

The chemical effects of intramolecular coordination may be extremely varied. It is logical to expect that it will be reflected mainly in anomalous reactions because of a different distribution of electron density in the molecule compared with "normal" reactions of related compounds where intramolecular coordination is known to be absent.

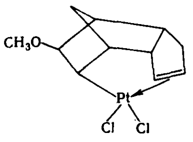
The first of the problems which arise here is the effect of intramolecular coordination on the strengths of metal–carbon bonds and hence the stability of the molecule as a whole. The views expressed in this connection reflect at least two, at first sight contradictory, trends. On the one hand, attempts are made to explain by intramolecular coordination the anomalous stability of many compounds which according to *a priori* estimates should not be so stable. The silver derivatives of chloroferrocene described by Nesmeyanov et al.[106] are typical examples of this kind; the authors explain their stability, unusual for organic silver σ-derivatives, by the Cl → Ag coordination:

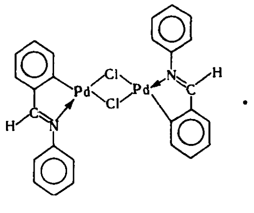


On the other hand, the hypothesis of intramolecular coordination is being increasingly put forward to account for the thermal instability of organometallic compounds with functional substituents, particularly to account for the elimination reactions and the mechanism of metallotropic rearrangements[107,108].

Apparently there is no contradiction between these two points of view. Among transition metals (or silver, copper, and gold which resemble them) intramolecular coordination, like intermolecular coordination, should indeed enhance the stability of the metal–carbon σ-bonds. The same bonds formed by a non-transition metal are polarised under the influence of coordination, which greatly increases their reactivity and hence makes the compound chemically more labile[109].

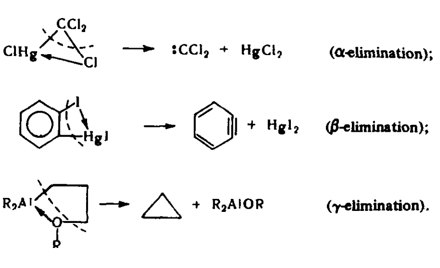
On the basis of X-ray diffraction[110] and infrared[111] and NMR[112] spectroscopic data, the stabilisation of the usually unstable σ-derivatives of transition metals as a result of intramolecular coordination interaction between the vacant orbitals of the metal atoms and the π-electron bonds or free electron pairs of other atoms is postulated, for example:





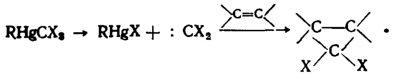
Similar intramolecular complexes or transition states corresponding to them are considered in Jones's review[113] and a number of later publications[114-117].

The presence of intramolecular coordination in the non-reacting molecule or its occurrence in the course of the incipient reaction may be regarded as a kind of "pre-existence" of the fragment to be eliminated:

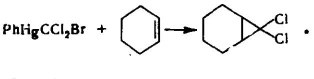


α-Elimination

As already mentioned (p. 200) the presence of intramolecular coordination in the trichloromethylmercury chloride molecules follows from X-ray diffraction analysis[37] and ³⁵Cl NMR spectra[38]. The capacity of compounds of this kind for α-elimination with the removal of a mercury halide and a dihalogenocarbene is not therefore surprising[118-138]:



Usually dihalogenocarbenes are readily formed in the thermolysis of trihalogenomethyl derivatives of mercury at 80°C in an inert solvent (benzene). However, some of them split off dihalogenocarbenes at a satisfactory rate even at room temperature. Thus the compounds $PhHgCCl_2Br$, $PhHgCClBr_2$, $PhHgCBr_3$, and $PhHgCCl_3$ decompose very slowly[132]:



The yields of 7,7-dichloronorcarane amount to 3, 12, and 66% after 3 h, 24 h, and 11 days respectively. Trihalogeno-derivatives of organomercury compounds, which are at least formally donors of dihalogenocarbenes, include also $PhHgCX_3$ (X = Cl or Br)[118-123], $Cl_3CHgCCl_3$, Cl_3CHgCl,[124] $PhHgCX_2Br$ (X = Cl or Br)[125], $PhHgCCl_2Br$,[120,121,126-136] $PhHgCClBr_2$,[121,127] $XC_6H_4HgCCl_2Br$,[137] and $Hg(CBr_3)_2$.[138]

Other α-halogenomethyl derivatives of organometallic compounds undergo the same type of thermal decomposition: ICH_2MgI,[139] $IZnCH_2I$,[140] $Zn(CH_2X)_2$ (X = Cl or I),[141,142] $Cd(CH_2I)_2$,[141] ICH_2HgI, $Hg(CH_2Br)_2$,[143] Et_2AlCH_2Cl,[144] and $In(CH_2I)_3$.[141] Monohalogenocarbenes CHX (X = Cl or Br) are eliminated in the decomposition of a number of organometallic compounds: $LiCHCl_2$,[145] $Zn(CHCl_2)$,[145] and $C_6H_5HgCHXBr$.[146,147]

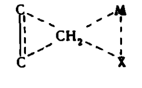
Under very mild conditions (−65°C), dichloronorcarane is formed from $LiCCl_3$ and cyclohexene[148-151] and at 80°C also from $(C_6H_5)_3PbCCl_3$.[143] The stability of organometallic compounds of this type depends on the metal. Dichlorocarbenes are formed in high yield on refluxing $(CH_3)_3SnCCl_3$ and $(CH_3)_3SnCCl_2Br$ in cyclo-octene[152], while trichloromethyltrichlorosilane gives rise to them only at 250°C.[153] Difluorocarbene is eliminated at 180–220°C from tris(trifluoromethyl)arsine and tris(trifluoromethyl)stibine[154] and at 100–200°C from trifluoromethyl derivatives of pentavalent phosphorus: $(CF_3)_nPF_{5-n}$ ($n = 1-3$).[155,156]

Dihalogenocarbenes may be formed as a result of the exchange of a halogen for a metal in tetrahalogenomethanes, for example in the reaction between methyl-lithium and trifluoroiodomethane[157] or in the reaction of n-butyl-lithium and dibromodifluoromethane[158]. However, there are no reliable data about the intermediate formation of organometallic compounds in such reactions and therefore they will not be considered here.

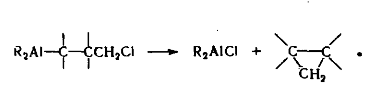
The interaction of the carbenes $:CZ_2$ (Z = H or halogen) with olefins, which leads to cyclopropanes, takes place stereospecifically and constitutes a *cis*-addition; this means that the carbenes entering into the reaction are in a singlet form.

Several different mechanisms have been proposed to account for the formation of cyclopropanes.

1. A bimolecular single-stage transfer of $:CZ_2$ in which the organometallic reagent reacts directly with the olefin via a five-centre transtion state[140,141]:



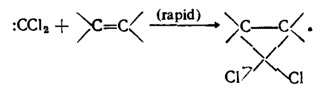
2. A bimolecular two-stage process via the addition of the organometallic reagent to the olefin with subsequent elimination of the metal halide[142]:



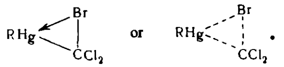
However, in this case it is difficult to reconcile the selectivity of the addition and elimination reactions and also the configurational stabilities of the intermediate organometallic compounds with the stereospecifity of the addition of carbenes to olefins.

3. A process in which the rate-determining stage (possibly reversible) is the decomposition of the organometallic compound to the carbene with subsequent rapid reaction of the latter with the olefin and formation of the cyclopropane. The carbene mechanism proposed by a number of investigators[153,156,159] and investigated in detail by Seyferth and coworkers[132,137] can be represented by the following equations:

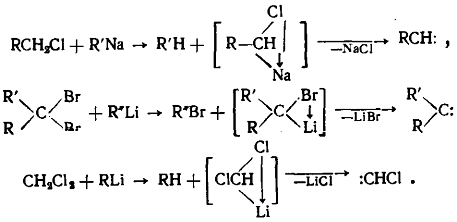
$$C_6H_5HgCCl_2Br \underset{\text{(rapid)}}{\overset{\text{(slow)}}{\rightleftarrows}} C_6H_5HgBr + :CCl_2,$$



The intermediate formation of carbenes has been demonstrated by kinetic experiments in a number of cases. Thus carbene is formed as a result of α-elimination, which requires an internal nucleophilic attack by the halogen atom on the metal via the following transition state:



The principal syntheses of alkyl(aryl)-, dialkyl(diaryl)-, and monohalogeno-carbenes are based on the α-elimination of intermediate organometallic compounds, for example:



For a detailed account of the chemistry of carbenes, see the monographs by Kirmse[160] and Hine[161].

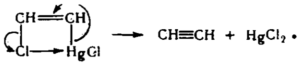
It is suggested that α-elimination from polyhalogenoalkyl compounds of various elements with expulsion of a carbene is a common reaction[153]. This is confirmed by the thermal instability of compounds of this kind. Trifluoromethylmagnesium iodide begins to decompose at a temperature as low as −60°C;[162] perfluoropropyl-lithium[157] and perfluoropropylmagnesium[163] and perfluoropropylzinc[164] iodides decompose at 40°, above 20°, and at 130−150°C respectively:

When any halogen except fluorine is in the α-position, the organometallic compounds of alkali and alkaline earth metals cannot be isolated at all[160,161,164]. Very slow decomposition of αα-dihalogenodialkyl compounds of mercury is observed even at room temperature, the process being sharply accelerated at 100°C:[165]

$$RR'CHCCl_2HgCHRR' \xrightarrow{100-140°} RR'C{=}CHCl + RR'CHHgCl.$$

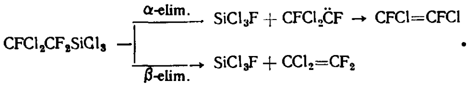
β-Elimination

The β-elimination reaction has been very thoroughly investigated among organomercury compounds[166]. If the reaction takes place under the influence of an extraneous reagent, β-elimination is usually explained by the Nesmeyanov mechanism[16] involving the transfer of the reaction centre along the σ, π- or σ,σ-conjugation chain. Until very recently, the possibility of coordination interaction through space, i.e. by-passing the conjugation chain, was not taken into account in such cases. Nevertheless the existence or formation of an intramolecular coordination bond is in some measure equivalent to nucleophilic attack on the metal atom, which results in a closed ring and the σ,σ- or σ,π-conjugation chain becomes "incorporated" as in the usual nucleophilic attack:

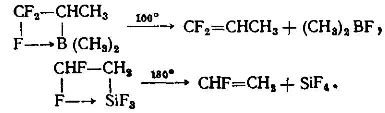


Evidently spontaneous and thermal β-elimination reactions should be treated in the same way. In those cases where coordination within the same molecule is impossible, a similar effect is achieved by intermolecular coordination, which occurs, for example, in the decomposition of *trans*-β-chlorovinylmercury chloride.

If the halogen in the polyhalogenoalkyl derivatives of silicon is present in both α- and β-positions, α-elimination is accompanied by simultaneous β-elimination, albeit to a much lesser extent, for example[153,167]:



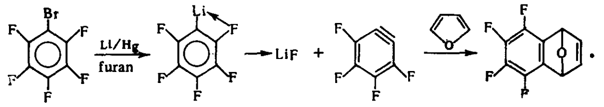
At 185°C the yields of CFCl=CFCl and CCl_2=CF_2 are 80 and 7% respectively. In the absence of a halogen in the α-position, β-elimination takes place, as shown for polyfluoroalkyl compounds of boron[168] and silicon[153]:



When the fluorine atom in polyfluoroalkylsilicones and polyfluoroalkylpolysiloxanes is present in both the α- and β-positions, thermal decomposition is accompanied by α- and β-elimination, both processes yielding an olefin[169]:

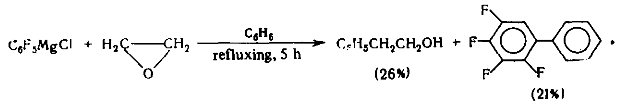
$$(CHF_2CF_2SiO_{1.5})_n \rightarrow n\,CHF{=}CF_2.$$

In contrast to the perfluoroalkyl organometallic compounds, the corresponding pentafluorophenyl derivatives are as a rule more stable. This applies particularly to lithium derivatives. Pentafluorophenyl-lithium[170] is an excellent starting material for the synthesis of other pentafluorophenyl metal derivatives. Being more stable than *o*-fluoro- and *o*-bromo-phenyl-lithium, pentafluorophenyl-lithium nevertheless decomposes with formation of tetrafluorodehydrobenzene, probably as a result of intramolecular coordination interaction between lithium and fluorine atoms. The intermediate formation of tetrafluorodehydrobenzene has been demonstrated by the reaction with bromine and chlorine and also by the isolation of a Diels–Alder adduct in the reaction with furan:



The formation of 2-bromononafluorobiphenyl from bromopentafluorobenzene and pentafluorophenyl-lithium has also been explained[171] by the intermediate formation of tetrafluorodehydrobenzene, since usually direct attack on compounds of the type C_6F_5X by nucleophilic reagents leads to *para*- and not *ortho*-substitution. The intermediate formation of tetrafluorodehydrobenzene in this reaction has been confirmed also by other investigators[172].

The study of the products of the reaction of pentafluorophenyl organomagnesium derivatives also indicates the intermediate formation of tetrafluorodehydrobenzene. The interaction of pentafluorophenylmagnesium chloride with epoxyethane in benzene yields 2,3,4,5-tetrafluorobiphenyl, which is probably formed as a result of the abstraction of hydrogen from benzene[173]:



When cyclohexane is used as a solvent in this reaction and furan is added to the reaction mixture, the furan adduct mentioned above is formed. Pentafluorophenylmagnesium bromide refluxed in toluene also yields tetrafluorodehydrobenzene[174].

In trifluoromethyl derivatives of tin the tendency of the metal atom to enter into coordination interaction with the fluorine atom is considerable and trimethyltrifluoromethyltin is thermally unstable due to the migration of the fluorine to the tin atom[159]. However, pentafluorophenyl compounds of this type are much more stable; thus trimethylpentafluorophenyltin is stable at 250°C and decomposes only at 350°C.[175]

The unusual decomposition of potassium pentafluorophenyltrifluoroborate can also be explained by the coordination interaction between fluorine and boron atoms[176]:

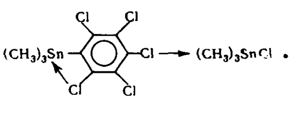
$$K^+[C_6F_5BF_3]^- \xrightarrow{300°} KBF_4 + \text{perfluoropolyphenylenes.}$$

Perfluoropolyphenylenes are probably obtained as a result of the intermediate formation of tetrafluorodehydrobenzenes.

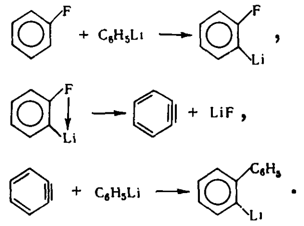
Prolonged pyrolysis of di-(π-cyclopentadienyl)di(pentafluorophenyl)titanium in a vacuum at 150°C leads to the migration of the fluorine atom to the titanium atom and partial decomposition of the substance:

$$(\pi\text{-}C_5H_5)_2\,Ti\,(C_6F_5)_2 \rightarrow (\pi\text{-}C_5H_5)_2\,Ti\,(C_6F_5)\,F\,.$$

Pentachlorophenyl organometallic compounds have not been investigated quite so widely as the pentafluorophenyl derivatives but here too results have been obtained which may be a consequence of the intramolecular coordination of the metal atom with the chlorine atom in the *ortho*-position. Thus pentachlorophenyltrimethyltin decomposes at 300°C with formation of trimethyltin chloride[177]:

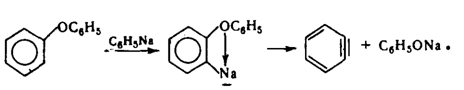


In all the above examples of coordination interaction between metal and halogen atoms the intermediate formation of dehydrobenzene derivatives has been demonstrated. Therefore such decomposition of pentafluoro- and pentachloro-phenyl derivatives of organometallic compounds may be regarded as a special case of a general tendency of aromatic compounds with metal and halogen atoms in the *ortho*-positions to decompose with formation of dehydrobenzenes. Wittig[178,179] was the first to postulate the formation of dehydrobenzene as an intermediate in the formation of 2-lithiumbiphenyl from fluorobenzene and phenyl-lithium:



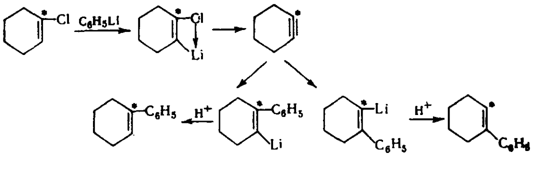
The rate-determining stage of the reaction is the elimination of lithium fluoride as a result of intramolecular coordination interaction leading to the formation of dehydrobenzene. The fact that, when labelled [^{14}C]-1-fluorobenzene is used, a mixture of almost equal amounts of the two isomeric biphenyls is obtained, suggests the intermediate formation of dehydrobenzene[180].

The existence of dehydrobenzene has also been demonstrated in the interaction of phenyl ether with phenylsodium[181,182]:



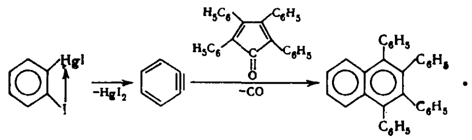
The elimination of sodium phenoxide in this reaction is probably caused by intramolecular coordination interaction of the ether oxygen with the sodium atom.

Similar elimination of MX fragments leading to analogues of dehydrobenzene is known also for the olefin series. Thus 1-phenylcyclohexene, which is obtained in the reaction between 1-chlorocyclohexene and phenyl-lithium in ether[183,184], and 1-phenylcyclopentene formed similarly from 1-chlorocyclopentene[185] are both probably produced via an intermediate cyclohexyne and cyclopentyne. This is confirmed by the finding that, when a labelled carbon atom in 1-chlorocyclohexene is employed, almost equal amounts of two phenylcyclohexenes, with substituents at both olefinic carbon atoms, are obtained[186]:

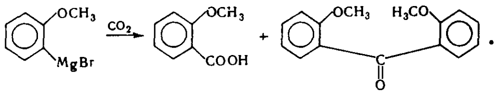


The coordination interaction between magnesium and bromine is probably responsible for the formation of cyclohexyne from the organomagnesium derivative of 1,2-dibromocyclohexene[187].

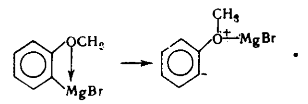
Irradiation with ultraviolet light leads to fairly intense coordination interaction between the mercury atom and the iodine atom in the *ortho*-position in 1-iodo-2-iodomercuribenzene. This results in the formation of mercury(II) iodide and dehydrobenzene, which was identified by the reaction with tetraphenylcyclopentadienone, giving a 25% yield of tetraphenylnaphthalene[188,189]:



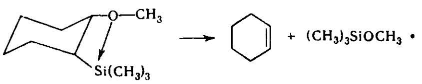
Reactions between carbon dioxide and Grignard reagents obtained from *o*-methoxybenzyl chloride, *o*-dimethylaminobromobenzene, and *o*-bromo(methylthio)benzene yielded both acids and ketones[190]. For example, *o*-methoxybenzoic acid and 2,2-dimethoxybenzophenone were obtained from *o*-methoxyphenylmagnesium bromide:



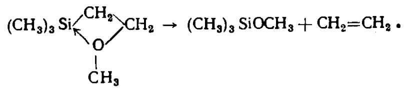
Under the same conditions, Grignard reagents obtained from *m*- or *p*-bromomethoxybenzene *β*-(*o*-methoxyphenyl)-ethyl chloride, *o*-bromomethylbenzene, and *γ*-methoxypropyl bromide give rise only to the corresponding acids. The anomalous reactions leading to the formation of ketones were accounted for by the formation of strained planar rings as a result of intramolecular coordination:



Thermal decomposition of the methyl ether derived from *cis*-2-trimethylsilylcyclohexanol (first-order reaction)[191] gives a quantitative yield of cyclohexene and methoxytrimethylsilane:



Ethylene is evolved in quantitative yield in the pyrolysis of ethylmethoxytrimethylsilane (first-order reaction)[191]:



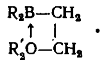
$$(CH_3)_3Si(CH_2CH_2)(OCH_3) \rightarrow (CH_3)_3SiOCH_3 + CH_2{=}CH_2.$$

2-Alkoxyethyl derivatives of boron are thermally unstable and readily eliminate olefins[192]. Thus tri-(2-ethoxyethyl)boron begins to evolve ethylene at a temperature as low as −10°C:

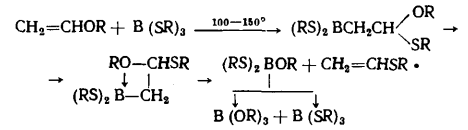
$$(C_2H_5OCH_2CH_2)_3B \rightarrow (C_2H_5OCH_2CH_2)_2BOC_2H_5 + CH_2{=}CH_2.$$

2-Ethoxyethyldiethoxyboron decomposes at a higher temperature (160–170°) than the butyl ester of di-(2-ethoxyethyl)boronic acid. Consequently thermal stability increases as 2-alkoxyethyl groups are replaced by alkoxy-groups.

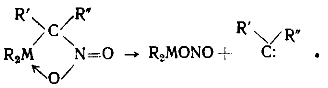
The reaction of dipropyldeuteroborane with *cis*-1-ethoxy-2-phenylethylene at 0°C gives a 40% yield of *trans*-*β*-deuterostyrene when the mixture is allowed to stand after the reaction at room temperature for 1 h. In this case *cis*-elimination takes place although the initial olefin does not isomerise on reaction with the normal borane[193]. It is interesting that, on replacing oxygen by sulphur in the initial olefin, the non-catalysed elimination reaction does not occur. The thermal instability of 2-alkoxyethyl derivatives of boron was explained by intramolecular coordination:



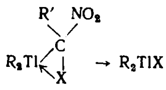
Similar coordination can account for the reaction of thioborates with vinyl ethers which yields alkyl vinyl sulphides and alkyl borates[194]:



Intramolecular coordination interaction is suggested for *α*-nitroalkyl derivatives of mercury and thallium, which decompose on heating with formation of nitrites and probably carbenes[195]:



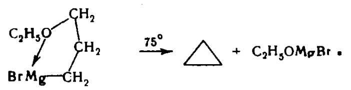
When halogen atoms are bonded to the *α*-carbon atoms of *α*-nitroalkyl derivatives of thallium, a competing intramolecular interaction takes place and in a number of cases the corresponding halide and not the nitrite is formed:



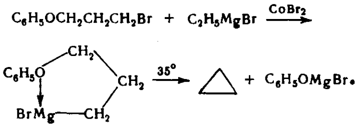
where X = F or Cl.

γ-Elimination

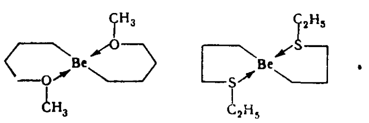
Intramolecular coordination can explain the thermal instability of 3-alkoxy-derivatives of Grignard reagents, as a result of which cyclopropane and its derivatives are readily formed[196,197]:



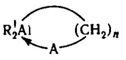
Cyclopropane is also formed in the double decomposition of Grignard reagents with 3-phenoxypropyl bromide in the presence of cobalt(II) salts (the Kharasch reaction)[198]:



Di-(*δ*-methoxybutyl)beryllium and di-(*γ*-ethylthiopropyl)-beryllium[199] are probably chelate salts, since they can be distilled in a vacuum:

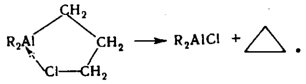


Convincing evidence has been adduced for intramolecular coordination in γ-amino-, γ-alkoxy-, γ-hydroxy-, γ-alkylthio-, γ-halogeno, and also δ-alkoxy-derivatives of aluminium[144,200,201]:



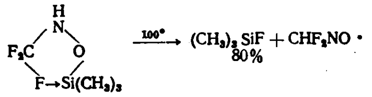
(n = 3, 4; A = RO, RS, R_2N, Hal).

γ-Halogenalkyl derivatives of aluminium readily eliminate cyclopropane[144]:

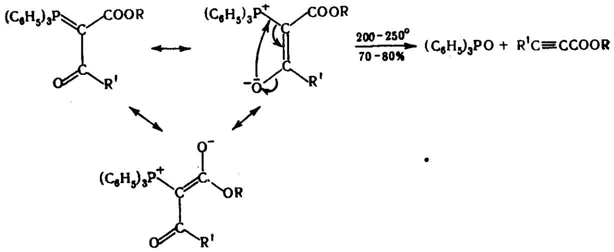


The evidence for coordination in the remaining compounds is based on their monomeric form in benzene and the absence of intermolecular coordination with ethyl ether; in the case of amines the evidence is based on the absence of electron-donating properties at the nitrogen atom (a quaternary compound is not formed with methyl iodide)[200,201]. When the fluorine atom is in the γ-position, the thermal and hydrolytic stability of the corresponding polysiloxanes is very high and $(CF_3CH_2CH_2SiO_{1.5})_n$ is not cleaved by alkalis at 20–80°C, while $(CF_3CH_2CH_2)_3B$ is stable at 100°C.[168]

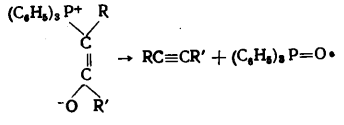
On the other hand, if the halogen atom is separated from the metal by a heteroatom (in *N*-trifluoromethyl-*O*-trimethylsilylhydroxylamine), γ-elimination can probably occur)[202]:



A surprising example of the effect of the possible intramolecular coordination on reactivity is provided by substituted phosphoranes[203]. Acylalkoxycarbonylmethylenetriphenylphosphoranes, the stability of which is explained by resonance, decompose at 220–250°C, yielding the corresponding propiolic esters and triphenylphosphine oxide:



On the basis of the resonance formulae, this reaction may be regarded as an intramolecular Wittig synthesis. In the reaction of betaines, in which R and R′ are not hydrogen atoms but any electron-accepting group, high yields of disubstituted acetylenes are obtained[204,205]:



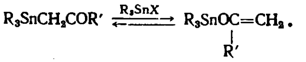
On the other hand, when R = $-C{\equiv}C-R'$, diacetylenes may be obtained in this way.

Metallotropy

Intense studies on various metallotropic rearrangements, including metallotropic photomerism, were begun recently. In all these investigations the concepts of intra- and intermolecular coordination, usually postulated for the transition state, are always employed. There is scarcely any sharp qualitative distinction between a transition complex of a clearly coordination type and coordination (intra- or inter-molecular) interaction in a system which has not yet reacted. The occurrence of such interaction, leading, for example, to the preferential formation of the conformation required for the rearrangement, should undoubtedly facilitate the rearrangement itself, lowering the required activation energy.

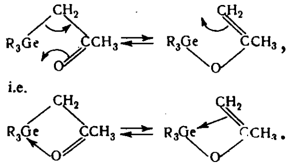
Such metallotropic rearrangements include, for example, the rearrangement of α-silylketones to silylenolates on heating[107,108] or in the presence of mercury and zinc salts and chlorosilanes[108,206]. The thermal rearrangement must be molecular, since, in the first place, the rearrangement of $(C_6H_5)_3SiCH_2COC_6H_5$ is a first-order reaction[107] and, in the second place, on heating mixtures of $(C_2H_5)_3SiCH_2COCH_3$ with $(CH_3)_3SiCH_2COC_6H_5$ and of $(C_2H_5)_3SiO(CH_3O)C{=}CH_2$ with $(CH_3)_3SiCH_2COC_6H_5$, it proved impossible to isolated intermolecular rearrangement products[108]. It is believed that the rearrangement proceeds via a four-centre activated complex[107,108], which is of the intramolecular coordination type:

The rapid catalytic rearrangement of a number of similar tin compounds is of the equilibrium type[207]:



$$R_3SnCH_2COR' \xrightleftharpoons{R_3SnX} R_3SnOC(R'){=}CH_2 .$$

The corresponding trialkylgermane derivatives constitute a true metallotropic tautomeric system with a relatively low (about 1 month) rate of attainment of equilibrium. It may be supposed that here too the rearrangement proceeds via a four-membered coordination complex[208,209]:



The explanation of the recently discovered metallotropic tautomerism of organometallic derivatives of p-nitrosophenols[210] is similarly based on the concept of intermolecular coordination.

The above review shows that the concept of intramolecular coordination is employed to account for a wide range of phenomena associated with the structure and reactivity of organometallic compounds. Nevertheless the experimental proof of the occurrence of intramolecular coordination interaction is in many cases clearly inadequate and the concept itself is frequently merely a useful hypothesis. However, this new trend in the chemistry of organic derivatives of the elements promises to become extremely fruitful and consequently deserves extensive and impartial development.

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Institute of Organic Derivatives
of the Elements,
USSR Academy of Sciences,
Moscow

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Reactions of Epoxy-compounds by a Radical Mechanism

A.P.Meleshevich

Data on various methods for the initiation of radical reactions of epoxy-compounds, including their homopolymerisation, are reviewed systematically.
The bibliography comprises 134 references.

CONTENTS

I. INTRODUCTION

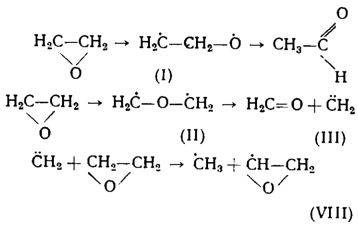
Much work has been done on the chemistry of epoxy-compounds. The reactions of these very simple heterocyclic compounds are treated from the standpoint of ionic mechanisms. With rare exceptions [5,13,14], no attention is devoted to radical reactions of epoxy-compounds in any of the monographs, reviews, and textbooks dealing with their chemistry [1-13]. Many investigators believe that such reactions are altogether impossible [15-18]. Similar views have been expressed by Staudinger and coworkers [15-17], who reported in the 1930's that radical type initiators, ultraviolet light, and sunlight do not influence epoxy-compounds and their reactions, in particular polymerisation, "occur only under the influence of appropriate catalysts". This situation did not alter in the course of the succeeding decade. Sorensen and Campbell [18] assert that only ionic catalysts are effective initiators of the polymerisation of epoxy-compounds. From time to time this view has been supported by new reports. Hopff and Zaner [second author not traced—name transcribed from Russian (Ed. of Translation)] [19] and also Oku et al. [20] did not observe the formation of acetophenone or a polymeric product from epoxyethylbenzene when azodi(isobutyronitrile) or benzoyl and lauroyl peroxides were used as initiators. The attempts to polymerise isoprene oxide [1,3-epoxy-2-methylbutane] by a radical mechanism in the presence of peroxides and azo-compounds were unsuccessful [21]. Epoxyethane does not react either with hydrogen peroxide (30%) or with lead dioxide, or with benzoyl peroxide [22]. In a recently published monograph dealing with the polymerisation of cyclic oxygen compounds [23] and also in the review by Frunze and Kurashev [14] the lack of reports on the homopolymerisation of epoxyalkanes initiated by radicals is pointed out.

Nevertheless, as early as 1918, Bodforss [24,25] obtained data which, in the light of modern concepts, may be explained as reactions of epoxy-compounds by a radical mechanism. The number of studies in which the reactions of epoxy-compounds are considered from the standpoint of radical processes has greatly increased in recent years. The investigation of chemical reactions of epoxy-compounds with participation of radicals is not only of theoretical but also of practical interest, since they have found application in many branches of the national economy.

The present review is a first attempt at a systematic account of reactions of epoxyalkanes involving a radical mechanism. Together with the description of the thermal, chemical, and photochemical initiation of the reactions, data are presented on the radiolysis of epoxy-compounds—a new branch of the radiation chemistry of heterocycles.

II. FORMATION OF RADICALS IN THE PYROLYSIS OF EPOXY-COMPOUNDS

Rice and Johnston [26] were some of the first investigators who noted the formation of radicals in the thermal decomposition of epoxy-compounds. Rice and Rice [27] detected free radicals in the pyrolysis of epoxyethane with the aid of a "metallic mirror". The rate of disappearance of the "metallic mirror" was higher than in the decomposition of other organic compounds, in particular acetaldehyde—a structural isomer of epoxyethane. Hence the authors concluded that a large number of radicals are formed in the decomposition of epoxyethane and proposed a mechanism of consecutive and parallel reactions [reactions (1)–(3)] in the pyrolysis of epoxyethane with participation of radicals of five types[†] (Table 1): ethylenoxy-radical [biradical (I)], hydroxydimethylene (II), carbene [methylene (III)], and methyl and epoxy-radicals (VIII).



$$\underset{\diagdown O \diagup}{H_2C{-}CH_2} \rightarrow \underset{(I)}{H_2\dot{C}{-}CH_2{-}\dot{O}} \rightarrow CH_3{-}C\overset{O}{\underset{H}{\lessdot}} , \tag{1}$$

$$\underset{\diagdown O \diagup}{H_2C{-}CH_2} \rightarrow \underset{(II)}{H_2\dot{C}{-}O{-}\dot{C}H_2} \rightarrow H_2C{=}O + \underset{(III)}{\ddot{C}H_2} , \tag{2}$$

$$\ddot{C}H_2 + \underset{\diagdown O \diagup}{CH_2{-}CH_2} \rightarrow \dot{C}H_3 + \underset{(VIII)}{\underset{\diagdown O \diagup}{\dot{C}H{-}CH_2}} . \tag{3}$$

There does not exist a unanimous view concerning the structure and reactions of pyrolytic free radicals. Rice

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[†] There does not exist a single accepted terminology for the radicals arising in the cleavage of the epoxy-ring. In the present study an attempt is made to give a systematic account of such radicals and to name them on the basis of the nomenclature of organic compounds adopted by IUPAC [28,29]. In some cases the names of radicals adopted by individual authors were chosen and a number of trivial names have been proposed. Some of the radical names adopted in the original literature and not included in the Table have been retained in the text.

and Stalibaumer[30], Schumacher[31], Steacie[32], and Zimakov[13,33] give preference to radical (II). According to Zimakov[37], the biradicals (II), which are formed in the singlet state, influence the process only slightly since their lifetime is very short (about 10^{-13} s) and the metastable biradicals with a lifetime of 10^{-8} s make the main contribution to the pyrolytic reaction. To justify his view, Zimakov invoked Terenin's theory[38] of metastable biradicals produced as a result of the reversal of the spin of one of the two electrons and a transition of the biradical from the singlet to the triplet state, which in the case of epoxyethane can be represented as follows:

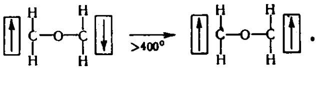
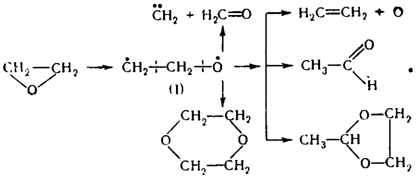


Table 1. Radicals formed from epoxy-compounds

№	Formula	Radical	References
(I)	$\dot{C}R_1R_2-CR_3R_4-\dot{O}$	Alkyl(aryl)ethyleneoxy	—
	$\dot{C}H_2-CH_2-\dot{O}$	Ethyleneoxy (biradical)	29
(II)	$\dot{C}R_1R_2-O-\dot{C}R_3R_4$	Oxydi[alkyl(aryl)]methylene	—
	$\dot{C}H_2-O-\dot{C}H_2$	Oxydimethylene	29
(III)	$\ddot{C}R_1R_2$	Carbene	28,34
	$\ddot{C}H_2$	Methylene	28
(IV)	$\overset{\quad O}{\overset{/\!\!/}{\dot{C}}}-H$	Formyl	29
(V)	$O=\dot{C}-CH_3$	Acetyl	29
(VI)	$R-\dot{C}H-\overset{\quad O}{\overset{/\!\!/}{C}}-H$	Alkylformylmethyl	29
(VII)	$R-\underset{O}{\underset{\parallel}{C}}-\dot{C}H_2$	Keto-radical	20,35
		Acetonyl, R = CH_3	29
		Phenacyl, R = C_6H_5	29
(VIII)	$\underset{\diagdown O \diagup}{\dot{C}H-CH_2}$	Epoxy	36
		1,2-Epoxyethyl	29
(IX)	$\underset{\diagdown O \diagup}{\dot{C}H-CH}-CH_3$	1,2-Epoxy-1-propyl	—
(X)	$\underset{\diagdown O \diagup}{CH-\dot{C}}-CH_3$	1,2-Epoxy-2-propyl	—
(XI)	$\underset{\diagdown O \diagup}{CH_2-CH}-\dot{C}H_2$	Glycidyl (2,3-epoxypropyl)	—
(XII)	$\underset{\diagdown O \diagup}{CH_2-CH}-CH_2-\dot{O}$	Oxyglycidyl (2,3-Epoxypropyloxy)	—
		(2,3-Epoxypropoxyl)	—
(XIII)	$CH_3-\overset{OH}{\overset{\vert}{C}}H-\dot{C}H_2$	2-Hydroxypropyl	29
(XIV)	$\dot{C}H_2-CH_2-OH$	2-Hydroxyethyl	29
(XV)	$H-\underset{O}{\underset{\parallel}{C}}-\dot{C}H_2$	Formylmethyl	29

Zimakov frequently emphasised[33,37,39] that "the formation of the stable dimethylene oxide biradical (II) in the pyrolysis of epoxyethane should in fact account for *all the characteristic features* (my italics—A. M.) of the pyrolytic reactions" of epoxyethane and various substances in its presence.

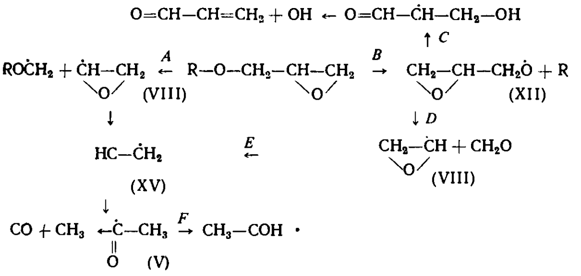
Malinovskii and Baranov demonstrated the inadequacy of the evidence for the decisive role of the biradical (II) in the pyrolysis of epoxyethane and epoxypropane in the presence of catalysts[40,41]. By adducing a number of pieces of evidence based mainly on the study of the composition of liquid-phase and gaseous decomposition products, Malinovskii and Baranov proposed other radical mechanisms for the pyrolysis of the above epoxy-compounds without the participation of oxydimethylene. Their mechanisms are based on the ethyleneoxy-biradical (I):



(4)

The authors note that the ethyleneoxy-biradical (I) is formed as an intermediate in the thermal decomposition of epoxyethane since "*only in this way* (my italics—A. M.) is it possible to explain" the presence of free oxygen and a large amount of ethylene and the formation of acetaldehyde and a cyclic acetal. The interpretation of the pyrolysis of epoxyethane and epoxypropane on the basis of the participation of ethyleneoxy-biradicals (I) provides a more convincing explanation of the formation of the final products, since the hypothesis of the oxydimethylene biradical (II) cannot account for the formation of all the reaction products.

In a series of studies by Neiman, Kovarskaya, Akutin, and coworkers[36,42–46] the thermal degradation of unhardened and hardened epoxy-resins was investigated. The composition of the gaseous pyrolysis products from the resins was the same for both hardened and unhardened resins regardless of the type of hardening agent employed (polyethylenepolyamine and maleic anhydride). According to the authors[36,42–46], the decomposition of the resin at 200–500°C is a free-radical process, which begins with the scission of the terminal part of the molecule and the formation of the epoxy-radical (VIII) (pathway *A*) and the oxyglycidyl radical (XII) (pathway *B*) according to the mechanism:



(5)

The radical (XII) can react in two ways: it can either isomerise via pathway *C* with formation of acrolein or it can decompose via pathway *D* into formaldehyde and the epoxy-radical (VIII). The latter isomerises via the formyl radical (XV) (pathway *E*) to the acetyl radical (V), which can in turn combine with hydrogen and form acetaldehyde or break down into carbon monoxide and a methyl radical. The suggested mechanism[36,42–46] does not postulate the cleavage of the three-membered ring at the C–C bond. The views of Neiman and coworkers on the isomerisation processes in the pyrolysis of epoxy-resins are shared by Anderson[47].

According to the literature, the mechanism of the thermal degradation or even the simplest epoxy-compound (epoxyethane) still remains controversial. This is indicated by (a) the difference between the radical and molecular pyrolysis products (furthermore, the complete set of products is not quoted in the reports of various workers), (b) the different interpretation of the formation of the same products, for example, carbon monoxide, methane, acetaldehyde, ethylene, acrolein, etc., and (c) the divergent views of investigators concerning the role of the methyl radical: some believe that it interacts with the epoxyethane molecule, while others reject this hypothesis, etc. The considerable qualitative and quantitative differences between the reaction products from which inferences concerning the processes occurring were in fact mainly drawn led to the situation where almost every investigator proposes his own mechanism for the pyrolysis of epoxyethane. Malinovskii[5] rightly remarked that this state of affairs arose because of failure to take into account completely the reaction products and frequently because the experiments were performed under non-comparable conditions (purity of the products, design of the reactor, static or dynamic process conditions, different temperatures and pressures, presence and type of catalyst, etc.).

Furthermore, because of serious practical difficulties, epoxy- and other radicals have not been identified and it is so far impossible to distinguish between the conceivable involvement of radicals (I) and (II) in the pyrolysis of epoxyethane, for example. One cannot exclude the possibility that they coexist in different proportions, which are determined either by the electronic and molecular structure of the epoxy-compound or by the experimental conditions.

Speaking of epoxy-radicals, attention must be drawn to the following factors. The considerations concerning the formation of the oxydimethylene biradical described earlier[33,37,39] are based on the fact that in the epoxyethane molecule the C–C bond is least stable and therefore, on raising the temperature, is the first to break:

C-H	87.3 kcal mole^{-1}
C-O	70.0 kcal mole^{-1}
C-C	58.6 kcal mole^{-1}.

Table 2. Dissociation energies of the C–O bond in oxygen-containing heterocycles

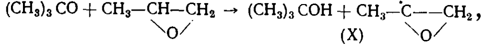
Compound	Biradical formed	Bond dissociation energy, kcal mole^{-1}	No. of atoms in ring
Tetrahydropyran	$\dot{C}H_2(CH_2)_4\dot{O}$	71.2	6
Tetrahydrofuran	$\dot{C}H_2(CH_2)_3\dot{O}$	68.6	5
Trimethylene oxide	$\dot{C}H_2(CH_2)_2\dot{O}$	—	4
Epoxypropane	$\dot{C}H_2CH(\dot{O})CH_3$	51.5	3
	$\dot{O}CH_2\dot{C}HCH_3$	50.5	
Epoxyethane	$\dot{C}H_2CH_2\dot{O}$	47.7	3

It is stated that the above estimates of bond strengths are consistent with the data of Gel'man[48] and Pauling[49]. However, more reliable studies[50] on the strength of the C–O bond in which account was taken of the ring size in cyclic ethers and epoxy-compounds yielded significantly different results. Table 2 shows that the maximum strength of the C–O bond is observed in six-membered cyclic ethers, where it reaches 71.2 kcal mole^{-1}. This value was in fact adopted[33,37,39] for the three-membered epoxy-ring. Actually, experiment shows[50] that, as the size of the ring of the heterocyclic oxygen-containing compound diminishes, the dissociation energy of the C–O bond falls sharply and for epoxy-compounds becomes approximately 50 kcal mole^{-1}. Thus the weakest bond in the epoxy-ring is C–O and not C–C as was believed[33,37,39]. In the vast majority of published reports and reports considered in the present review the preferential cleavage of the C–O bond in the epoxy-ring is noted, which agrees with the data of Gray and Williams[50].

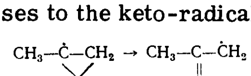
III. RADICAL REACTIONS OF EPOXY-COMPOUNDS INITIATED BY PEROXIDES

Probably the first communication where it was noted that the epoxy-ring may be opened with formation of a polymer by a radical mechanism in the presence of initiators was that of Conant and Peterson[51] published in 1932. Even under severe conditions (12 000 atm., 168 h, 2% of benzoyl peroxide), epoxycyclohexane polymerised with difficulty, yielding a viscous liquid. After degassing in a vacuum at 100°C, a solid polymer soluble in benzene, chloroform, and ethyl and allyl ethers and insoluble in ethyl alcohol, acetone, and acetic anhydride was obtained.

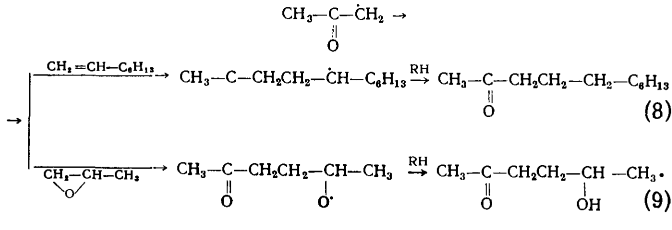
The work of Conant and Peterson remained unnoticed and it was not until 30 years later that the radical reaction between epoxypropane and oct-1-ene initiated by t-butyl peroxide at 150°C was described[52]. According to gas–liquid chromatographic data, the reaction product is a ~ 4 : 1 mixture of 2-undecanone and 5-hydroxy-2-hexanone. The t-butoxy-radical formed in the decomposition of the peroxide abstracts a hydrogen atom from the second carbon atom [of epoxypropane (Ed. of Translation)] with formation of a 1,2-epoxy-2-propyl radical (X):


(6)

which then isomerises to the keto-radical (VII):


(7)

The radical (VII) attacks both the double bond of the olefin and the ring of the epoxy-compound, initiating the parallel competing reactions (8) and (9). 2-Undecanone is formed by reaction (8) from the keto-radical and oct-1-ene and 5-hydroxy-2-hexanone is formed by reaction (9) from the keto-radical and epoxypropane:



To test their hypothesis concerning the pathway followed in the formation of the hydroxy-ketone, Gritter and Wallace investigated the reactions of epoxypropane with t-butyl peroxide in the presence of compounds with active hydrogen atoms and butyl groups. Large fragments—the residues of radicals (VII) and (XIII)—appeared in the final reaction products. The addition of 1,2-epoxybutane, 1,2-epoxyoctane, and epoxyethylbenzene to oct-1-ene by reaction (8) has also been achieved[53]‡. Aldehydes are absent from the reaction products, ketones alone being detected. This suggests a preferential removal of the hydrogen atom from the methine group in the epoxy-radical and its subsequent isomerisation to radical (VII).

Free radicals may abstract hydrogen from epoxy-compounds not only at the α- but also at the β-carbon atoms in relation to the oxygen atom, i.e. atoms in the allyl position with respect to the three-membered ring. This type of radical attack was observed by Sabatino and Gritter[54] in the reaction of t-butyl peroxide with epoxycyclohexane. It was suggested that, in consequence of the decyclisation and

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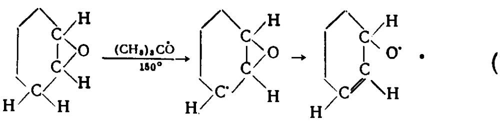
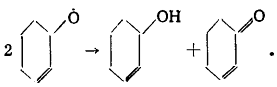
‡ The radical copolymerisation of epoxy-compounds is considered in the review of Frunze and Kurashev[14].

electronic isomerisation of the epoxy-ring, the initially formed radical isomerises to an unsaturated radical:

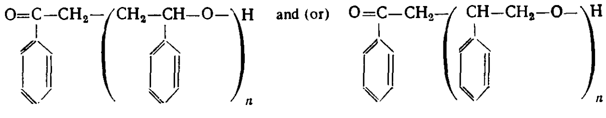

(10)

The authors explain the removal of a hydrogen atom from the β-carbon atom in the epoxycyclohexane molecule by postulating that the epoxy-ring behaves as a pseudo-olefin and the allyl position in olefins is known to be reactive with respect to radical attack[55,56]. Since cyclohex-2-en-1-one and cyclohex-2-en-1-ol are formed in small but approximately equal amounts, it may be supposed that the principal reaction undergone by the cyclohex-1-en-1-oxy-radical is disproportionation:

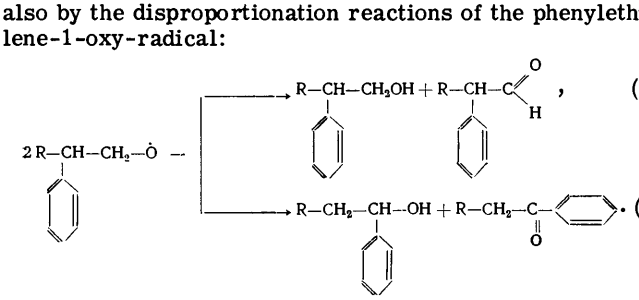

(11)

The main product of the reaction of t-butyl peroxide with epoxycyclohexane is cyclohexanone.

Using t-butyl and benzoyl peroxides as radical initiators, Oku et al.[20] achieved, in contradiction of the data of Hopff and Zaner[19], the polymerisation of epoxyethylbenzene and glycidyl phenyl ether. The only low-molecular-weight product isolated in the polymerisation of epoxyethylbenzene was acetophenone, which indicated the formation of the keto-radical (VII) as an intermediate. Polyepoxyethylbenzene had a molecular weight of 1500–2000. The infrared spectra of the polymer showed absorption bands at 3500 cm^{-1} (hydroxyl), 1720 and 1680 cm^{-1} (carbonyl), and 1030–1100 cm^{-1} (ether bond). These data suggest that the structure of the products formed by reaction (9) may be assigned to the polymer:

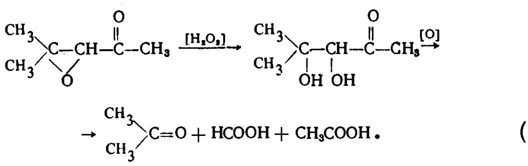


However, it has been established that there are about two hydroxy- and 1.5 carbonyl groups per polymer molecule. Probably these differences can be accounted for not only by the branching of the polyepoxyethylbenzene molecules but also by the disproportionation reactions of the phenylethylene-1-oxy-radical:

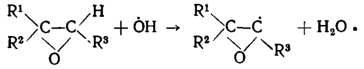

(12)
(13)

A similar mechanism of radical polymerisation in the presence of t-butyl peroxide has been suggested for glycidyl phenyl ether.

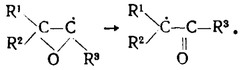
Razuvaev, Etlis, and coworkers investigated the interaction of hydroxy-radicals with a number of epoxyalkanes[57–60]. Since the carbonyl group lowers the reactivity of the oxygen atom of the epoxy-ring, t-butyl peroxide reacts with 3,4-epoxy-4-methylpentan-2-one with difficulty. However, the reaction of 3,4-epoxy-4-methylpentan-2-one with hydrogen peroxide takes place readily. A different reaction mechanism is proposed in this case: initially the epoxy-ring opens with formation of a keto-glycol, which is then oxidised to acetone and formic and acetic acids:


(14)

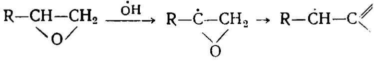
However, in most cases[57–59] the reactions of epoxy-compounds with hydrogen peroxide take place only on irradiation with ultraviolet light, which decomposes the peroxide into hydroxy-radicals. The hydroxy-radical formed abstracts a hydrogen atom with formation of a trialkylaryl-substituted epoxy-radical:


(15)

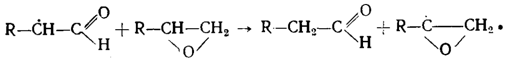
The latter may isomerise to a keto-radical. When an epoxyethane in which all the substituents were different was used, it was established[57] that the isomerisation is not accompanied by the migration of the R^1 or R^2 group to another carbon atom in the ring but takes place as a result of ring opening:


(16)

Unfortunately the authors do not consider the effect on the isomerisation process of the delocalisation of the unshared electron, which may alter to a considerable degree depending on the substituent. Thus the interaction of hydroxy-radicals with monosubstituted 1,2-epoxyalkanes also leads to the formation of epoxy-radicals but these isomerise to alkyl(aryl)formylmethyl radicals (VI) with migration of a hydrogen atom in the ring:


(17)

In contrast to trisubstituted epoxy-compounds, the products in this case are not ketones but aldehydes, which are probably formed by the reaction:

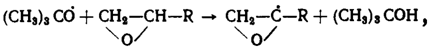

(18)

Furthermore, it is interesting to note that the products of the reactions of monosubstituted epoxy-compounds in which the substituents contain oxygen atoms (ether bond) include neither ketones nor aldehydes. Aldehydes may form in the isomerisation of epoxy-radicals but not the epoxy-compounds themselves, since the formation of propionaldehyde was not observed on irradiation of an aqueous solution of epoxypropane with ultraviolet light[59].

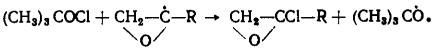
The oxidation of the aldehyde and (or) α-hydroxy-aldehyde formed as a result of the addition of a hydroxy-radical to radical (VI) probably leads to the formation of the corresponding acid, the reaction of which with the epoxyalkane yields an ester.

Photochemical liquid-phase chlorination of epoxyethane and epoxypropane with t-butyl hypochlorite was described by Walling and Fredricks[61] and that of epoxytrimethylethane and epichlorohydrin, by Razuvaev et al.[62] Epoxyethane, epoxypropane, and epoxytrimethylethane are converted under these conditions into monochloroepoxyethane, 2-chloroepoxypropane, and chloroepoxytrimethylethane

$$(CH_3)_3COCl \xrightarrow{h\nu} (CH_3)_3C\dot{O} + Cl\,, \qquad (19)$$

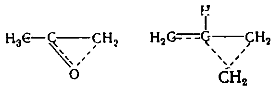


$$(CH_3)_3C\dot{O} + CH_2{-}CH{-}R \rightarrow CH_2{-}\dot{C}{-}R + (CH_3)_3COH, \quad (20)$$



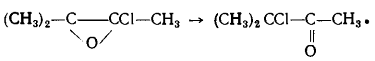
$$(CH_3)_3COCl + CH_2{-}\dot{C}{-}R \rightarrow CH_2{-}CCl{-}R + (CH_3)_3C\dot{O}. \quad (21)$$

In the photochemical chlorination of the above epoxy-compounds with t-butyl hypochlorite there is preferential attack on the three-membered ring, the removal of a hydrogen atom from the ring, and the formation of α-chloro-epoxy-compounds, while in the chlorination of methylcyclopropane the chlorine atom enters the methyl group. It is suggested[61] that the attack on the epoxy-ring is due to the high electron availability adjacent to the ether oxygen. Furthermore, the epoxy-radical (1,2-epoxy-2-propyl) formed in this process is evidently more stable than the isomeric glycidyl radical:



However, in the photochemical chlorination of epichlorohydrin with t-butyl hypochlorite, the former behaves like methylcyclopropane, since in this case the main product was 3,3-dichloroepoxypropane[62], i.e. the glycidyl radical (XI) and not the epoxy-radical was formed.

Furthermore, in contrast to the observations of Gritter and Wallace[52], the radical (X) formed by reaction (20) did not isomerise to the keto-radical but reacted with t-butyl hypochlorite or its decomposition products to form α-chloroepoxy-compounds. These compounds then readily isomerised to carbonyl compounds with migration of the chlorine atoms to an adjacent carbon atom: chloroepoxyethane was converted into chloroacetaldehyde, and chloroepoxytrimethylethane into chloroisopropyl methyl ketone[62]:



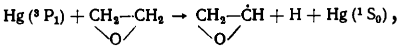
$$(CH_3)_2{-}C{-}CCl{-}CH_3 \rightarrow (CH_3)_2CCl{-}\underset{\underset{O}{\|}}{C}{-}CH_3. \quad (22)$$

These data confirm yet again the view that the mechanism of the isomerisation of epoxy-compounds is determined primarily by their electronic structure.

The experimental data examined above show that the free-radical reactions of epoxy-compounds in the presence of initiators may be divided into three types: (1) reactions with ring opening as a result of attack by a free radical; (2) reactions involving the abstraction of a hydrogen atom from the α-carbon atom of the ring; (3) reactions involving the abstraction of hydrogen atoms in the allyl position with respect to the oxygen atom of the epoxy-ring, i.e. in the β-position with respect to the ring. The products contain hydroxy- and carbonyl-groups. The formation of carbonyl compounds from epoxy-compounds is due to the isomerisation of epoxy-radicals.

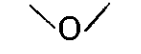
IV. PHOTOCHEMICAL REACTIONS OF EPOXY-COMPOUNDS BY A RADICAL MECHANISM

The photochemical decomposition of epoxyethane in the gaseous state was investigated by Phibbs et al.[63] Since epoxyethane has only one absorption band at 1713 Å,[64,65] its decomposition was sensitised by mercury vapour. The principal reaction products proved to be hydrogen, carbon monoxide, acetaldehyde, and a polymer; smaller amounts of methane, formaldehyde, and C_2 hydrocarbons were also detected. Bearing in mind the composition of the photolysis products and only slight dependence of their yield on pressure, the authors[63] believe that the isomerisation and decomposition processes are based on the reactions of excited epoxyethane molecules,



$$Hg(^3P_1) + CH_2{-}CH_2 \rightarrow CH_2{-}\dot{C}H + H + Hg(^1S_0), \quad (23)$$

and the polymerisation process has a free-radical mechanism. Homer and Noyes[66] carried out direct photochemical decomposition of epoxyethane at a wavelength < 2000 Å in the gas phase (10–100 mmHg, 27–250°C) and in a mixture with dimethylmercury. The reaction products were hydrogen, carbon monoxide, methane, ethane and smaller amounts of formaldehyde, acetaldehyde, and more complex aldehydes. The primary decomposition products are probably methyl and formyl radicals:



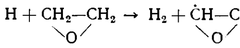
$$CH_2{-}CH_2 \xrightarrow{h\nu} \dot{C}H_3 + H\dot{C}O. \quad (24)$$

(IV)

Since the heat of dissociation of the formyl radical (IV) is close to zero and therefore its thermodynamic stability is almost independent of temperature, it should decompose as follows:

$$H\dot{C}O \rightarrow CO + \dot{H}. \quad (25)$$

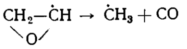
The methyl radical mainly abstracts a hydrogen atom forming methane and to a lesser extent dimerises to ethane. With increase of the intensity of illumination and temperature, the methane : ethane ratio increases. The contribution of the reaction



$$H + CH_2{-}CH_2 \rightarrow H_2 + \dot{C}H{-}CH_2 \quad (27)§$$

(VIII)

also increases with temperature. Part of the epoxy-radicals (VIII) decompose with elimination of carbon monoxide:

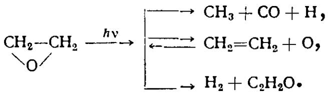


$$CH_2{-}\dot{C}H \rightarrow \dot{C}H_3 + CO \quad (28)$$

while others are stabilised by combining with other radicals and atoms.

The photochemical decomposition of epoxyethane sensitised by mercury[67] involves the formation of hydrogen, methane, ethane, propane, ethylene, carbon monoxide, acetaldehyde, higher homologues of acetaldehyde, and small amounts of a ketone. Cvetanovic[67] believes that the principal primary step is the decomposition of the excited epoxyethane molecule by reactions (23)–(25). He also postulates the molecular breakdown of epoxyethane into hydrogen and keten to a slight extent.

Evidently the mechanism of the photolysis of epoxyethane is complex and inadequately investigated. In order to avoid the effect of secondary reactions, Roquitte[68] subjected epoxyethane, tetradeuteroepoxyethane, and their mixtures to pulse photolysis at an effective wavelength of 1900 Å and energies of the light pulse up to 2160 J with the lifetime of a single pulse 44 ms. Hydrogen, methane, ethane, ethylene, carbon monoxide, and carbon dioxide were found among the photolysis products, but there were no aldehydes. The author believes that three parallel competing processes take place under these conditions:



$$CH_2{-}CH_2 \xrightarrow{h\nu} \begin{cases} \rightarrow CH_3 + CO + H, & (29) \\ \rightleftarrows CH_2{=}CH_2 + O, & (30) \\ \rightarrow H_2 + C_2H_2O. & (31) \end{cases}$$

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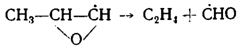
§ Eqn. (26) is missing in the original Russian text (Ed. of Translation).

The principal stage of the process is reaction (29), since a high yield of carbon monoxide and its increase with light intensity are observed. Furthermore, 70% of hydrogen is also formed by reaction (29) and 30% as a result of the primary molecular reaction (31). The authors believe that the effect of reaction (30) is slight because of its reversibility. The relative quantitative contributions of reactions, (29), (30), and (31) to the pulse photolysis of epoxyethane are estimated as 2.3 : 1 : ≪ 1. Reaction (29) is analogous to the process described for photolysis with a low intensity of illumination[66] and reactions (30) and (31) were discussed by Cvetanovic[67,69]. In the photolysis of an equimolar mixture of C_2H_4O and C_2D_4O it was established[68] that 82% of the methane was formed from methyl radicals [reaction (29)] and 17.5% was formed with participation of methylene. The appearance of methylene can be explained by the decomposition of the excited keten molecule formed by reaction (31):

$$CH_2{=}C{=}O^* \rightarrow \dot{C}H_2 + CO. \qquad (32)$$

Carbonyl compounds, carbon monoxide, hydrogen, ethylene, and alkanes were the products of the photochemical decomposition of *trans*-2,3-epoxybutane in the gas phase[70]. When oxygen was added (about 0.5 mmHg), methanol was the principal photolysis product. An increase of pressure in the irradiation of pure *trans*-2,3-epoxybutane sharply reduces the yields of carbon monoxide, ethylene, propane, and particularly carbonyl compounds. It is believed that, with increase of pressure, the fragment C_3H_5O loses its excess energy in collisions and is stabilised by conversion into radical (IX), while at a low pressure it can isomerise to radicals (VI) and (VII) or decompose by the reaction

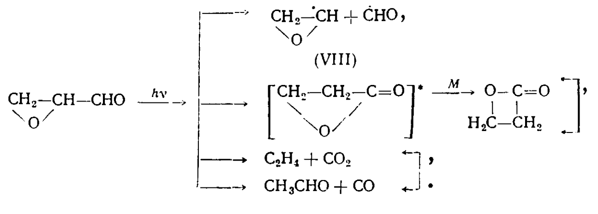


(33)

and further by reaction (25) or it can form $CH_3{-}C\substack{/\!\!/O \\ \backslash H}$ and $C_2H_5{-}C\substack{/\!\!/O \\ \backslash H}$ by reacting with $\dot{C}H_3$ and $\dot{C}_2H_5$.[67]

With increase of pressure, the quantum yield of the main photolysis product (isobutyraldehyde), formed at a low pressure [by the reaction of radicals (VI) with $\dot{C}H_3$] diminishes, since under these conditions the concentration of radicals (VI) falls. Cvetanovic and Doyle postulated the dissociation of the C–O bond in the epoxy-ring in the photolysis of *trans*-2,3-epoxybutane and the formation of "triplet biradicals" (I), similar to those which arose in the reaction between oxygen atoms and but-2-ene isomers $(CH_3{-}\underset{\dot{O}}{CH}{-}\dot{C}H{-}CH_3)$.[71] These radicals underwent intramolecular rearrangement and hardly decomposed. The dissociation of the C–H bond in the molecules of the epoxy-compound investigated was not observed during photolysis.

The gas-phase photolysis of glycidic aldehyde, one of the simplest of the bifunctional epoxy-compounds, was investigated by Goodspeed and Blacet[72] (irradiation at wavelengths of 3130 and 2654 Å, pressure 16–27 mmHg, 77–127°C). The decomposition of the aldehyde was represented by the following mechanism:

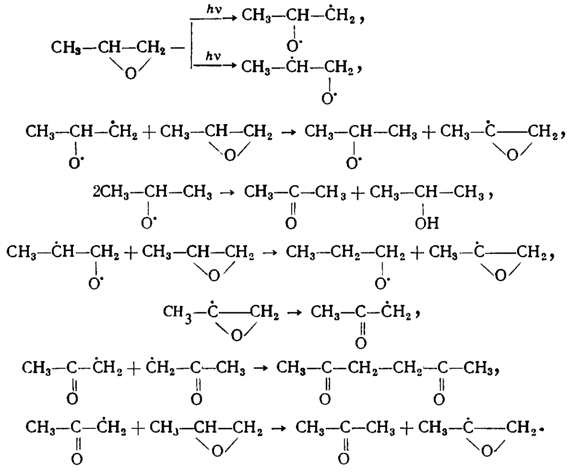


(34)
(35)
(36)
(37)

The radical (VIII) decomposes by reaction (28) and methyl and formyl radicals react with glycidic aldehyde giving rise to methane, carbon monoxide, $CH_3\dot{C}O$, and hydrogen and to carbon monoxide and $CH_3\dot{C}O$ respectively. It was established that at 3130 Å reactions (36), (37), and (34) consume 75%, 5%, and 10% of the energy absorbed respectively. Photochemical dissociation reactions (36) and (37) of the liquid propiolactone are also suggested.

In contrast to previous studies, where the epoxy-compounds were photolysed in the gaseous state, Sabatino and Gritter[54] initiated the free-radical reactions of a number of epoxy-compounds in the liquid phase at a wavelength of 2537 Å. The authors believe that pulse illumination and low conversions reduced the likelihood of secondary reactions. Epoxypropane was irradiated both in the presence and absence of oct-1-ene; epoxycyclohexane and epoxyethylbenzene were irradiated in a pure form. The reaction products suggested that the decomposition of all the epoxy-compounds was of the same type.

Like Cvetanovic[70], Gritter and Sabatino¶ believe that the most important factor is the primary homolytic cleavage of one or other C–O bond in the ring with formation of biradicals of type (I). To account for the radical mechanism of the photolysis of epoxypropane, for example, and the formation of a ketone, aldehydes, an alcohol, and a dimer, they suggest the following sequence of stages:



(38)
(39)
(40)
(41)
(42)
(7)
(43)
(44)

Referring to Walling[73], the authors state that the rearrangement of the initially formed biradicals into a ketone and an aldehyde, involving the migration of a hydrogen atom, is exceptionally fast. The acetonyl radical interacts with oct-1-ene by reaction (8). Although the authors attempted to exclude the occurrence of secondary reactions, Table 3 shows that in the photolysis of epoxypropane it was impossible to achieve this completely. The high content of acetone in the photolysis products (about 70% when acetonylacetone is allowed for) introduces additional difficulties into the interpretation of the mechanism of the photolysis, since acetone may be consumed in the photosynthesis of acetonylacetone[74,75]. Under the experimental conditions where the system was irradiated with light corresponding to the absorption band of ketones, acetone may also have served as a source of acetonyl radicals but this possibility was not taken into account; the effect of oxygen on various radicals and the process as a whole is obscure (the report does not state that the photolysis was carried out in a vacuum).

¶ J. Org. Chem., 29, 1965 (1964) (Ed. of Translation).

Although the suggested mechanism, as in very many other cases, is speculative and controversial and requires experimental confirmation, nevertheless the important role of acetonyl radicals in it and the preferential dissociation of C–O bonds are noteworthy. If 1-C–H and especially 2-C–H bonds were dissociated (which does not entail the isomerisation of the ring), it would be difficult to account for the formation of alcohols, while the dissociation of the C–C bond excludes the formation of even one of the observed reaction products.

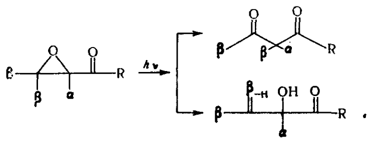
Table 3. Composition of the photolysis products of epoxypropane, epoxycyclohexane, and epoxyethylbenzene

Reactant	Reaction products	Site of dissociation	Conversion, %
Epoxypropane	acetone	C–1–O	0.28
	isopropyl alcohol	C–1–O	0.21
	acetonylacetone	C–1–O	0.22
	propionaldehyde	C–2–O	0.01
	propyl alcohol	C–2–O	0.01
Epoxycyclohexane	cyclohexanone	C–O	0.23
	cyclohexanol	C–O	0.14
Epoxyethylbenzene	acetophenone	C–1–O	0.03
	2-phenylethanol	C–1–O	0.14
	1-phenylethanol	C–2–O	0.13

Earlier it was noted that the absorption band of the epoxy-group in the electronic spectrum is in the far ultraviolet and the position of its absorption maximum does not differ markedly from that corresponding to the ethylene double bond. The conjugation of the ethylene double bond with the carbonyl group in the molecule of an $\alpha\beta$-unsaturated carbonyl compound results in a considerable shift of the absorption bands of both groups towards longer wavelengths[76]. A similar effect may be observed in $\alpha\beta$-epoxy-ketones where the ethylene double bond is replaced by an epoxy-group[72,77], which makes it possible to carry out the photolysis with ultraviolet light at longer wavelengths.

One of the first investigations of the photochemical reactions of $\alpha\beta$-epoxy-ketones was carried out by Bodforss[24,25].

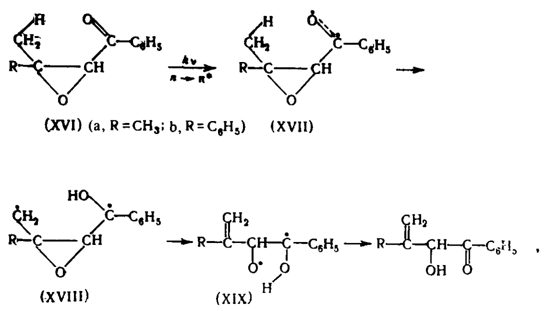
The photochemical rearrangement of $\alpha\beta$-epoxy-ketones may lead to the formation of a β-diketone [reaction (45)][24,78–81] or a keto-alcohol [reaction (46)][79]:



(45)

(46)

The formation of β-diketones entails the migration of the substituent from the β-carbon atom in relation to the carbonyl group to the α-carbon atom. The possibility of absorption of ultraviolet light by the epoxy-ring is disregarded and its cleavage is attributed to the effect of the carbonyl group[79,81]. The opening of the epoxy-ring in 1,2-epoxy-2-methylpropyl phenyl ketone (dimethylacrylophenone oxide) (XVIa) and 1,2-epoxy-2-phenylpropyl phenyl ketone (dypnone oxide) (XVIb) takes place as a result of the $n\rightarrow\pi^*$ excitation of the carbonyl group and subsequent rearrangement of the molecule by mechanism (47).[79] As a result of intramolecular photochemical dehydrogenation, in which the excited carbonyl group of compound (XVII) abstracts a hydrogen atom from the methyl group, the biradical (XVIII) is formed. The presence of an unpaired electron at the methylene group linked to the epoxy-ring favours the homolytic dissociation of the C–O bond, giving rise to the biradical (XIX) in which the semiquinone group $>\dot{C}{-}OH$ derived from the carbonyl group responsible for the photochemical dehydrogenation remains unchanged. In the last stage intramolecular disproportionation leads to the final reaction product:



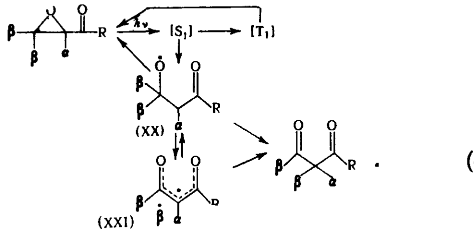
(47)

Together with the intermolecular photochemical dehydrogenation reactions known previously, reaction (47)[82] may be used for preparative intramolecular photochemical dehydrogenation of $\alpha\beta$-epoxy-ketones[79].

As a result of the photochemical reaction involving the excitation of the non-bonding electrons of the oxygen atom in the carbonyl group, 3,4-epoxy-4-phenyl-2-pentanone and 3,4-epoxy-4-methyl-2-pentanone rearrange to β-diketones [reaction (45)] with migration of the methyl group[78,79,83] in contrast to reaction (47). In a discussion of the reactivity of the carbonyl group in the excited $n\rightarrow\pi^*$ state it was noted[79,84,85] that the groups attached to the carbon atom adjoining the excited C=O group may undergo homolytic cleavage. Evidently reaction (45) does in fact begin with such cleavage. The cleavage of the C–O bond in the epoxy-ring, in contrast to the abstraction of a hydrogen atom from the γ-carbon atom in compound (XVI), is attributed[79] to an excited π^* electron which is more localised at the carbonyl group of 3,4-epoxy-4-methyl-2-pentanone and 3,4-epoxy-4-phenyl-2-pentanone and to the greater probability of C–O dissociation, since in compound (XVI) the excited electron is delocalised over both the carbonyl and phenyl groups and its effect is reduced.

In a study of the photochemical rearrangements of $\alpha\beta$-epoxy-ketones to β-diketones, an unusual sequence of various β-groups as regards their capacity for migration was observed[78,79,81,86,87]: diphenylmethyl and benzyl > hydrogen > methylene > methyl > phenyl.

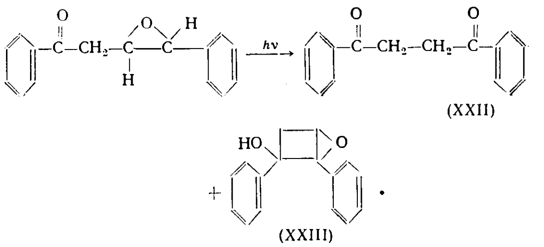
An important aspect of the mechanism of the photochemical rearrangement of epoxy-ketones was established by Markos and Reusch[81] [reaction (48)][81], who observed that the photochemical reactions of $\alpha\beta$-epoxy-ketones take place via the singlet excitation of the molecule [S] and the intermediate state (XX), bypassing the triplet state [T], since the rearrangement of epoxy-ketones proved to be insensitive to the presence of oxygen, a change of solvent, and the addition of reagents quenching triplet states.



(48)

To account for the anomalous capacity for migration and the formation of fragmentation products, it was assumed that the migrating group is a radical and that a radical pair is formed in the cage (XXI) from the intermediate state (XX). Unsaturated $\alpha\beta$-epoxy-ketones were much more stable in relation to the $n \rightarrow \pi^*$ excitation of the carbonyl groups than their saturated analogues[87].

The photochemical rearrangement of $\beta\gamma$-epoxy-ketones, for example *trans*-3,4-epoxy-1,4-diphenylbutan-1-one, leads to the formation of a γ-diketone (XXII) and an alcohol to which the structure (XXIII) is attributed:



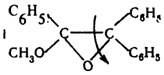
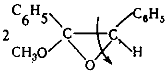
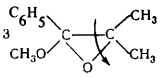
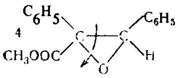
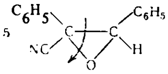
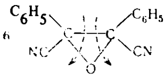
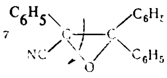
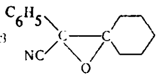
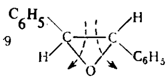
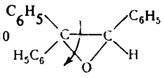
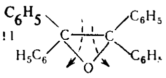
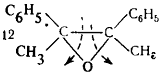
(49)

It is suggested[88] that epoxycyclobutane may be formed by reaction (47) with the sole difference that the semiquinone reacts with the unshared electron of the γ-carbon atom, forming a new C–C bond.

Temnikova and coworkers[89–93] and a group of American investigators[94–100] obtained new, novel data on the radical mechanism of the photolysis of epoxy-compounds. They made the interesting observation of the intermediate formation of carbenes on irradiation with ultraviolet light of a number of epoxyethane derivatives (Table 4). The arrows indicate the chemical bonds in the three-membered ring which are preferentially cleaved during photolysis, i.e. the arrow separates the carbene formed. The remaining molecular fragment rearranges very rapidly to the corresponding carbonyl compound. As a rule, all the epoxy-compounds were irradiated in methanol or olefin solution. The type of solvent was probably dictated by the endeavour to demonstrate the existence of carbenes on the basis of the composition of the product formed by typical secondary reactions. Indeed, irradiation of epoxy-compounds 1 and 11 (Table 4) in methanol gave an almost quantitative yield of methoxydiphenylmethane[89,94], while irradiation of a solution of epoxy-compound 5 gave α-methoxyphenylacetonitrile[99]. In the presence of olefins the photolytic decomposition of epoxy-compounds takes place with formation of the corresponding cyclopropane derivatives, which is generally regarded as proof of the presence of carbenes. Thus the photolysis of the cyanoepoxy-compound 6 (Table 4) in tri- and tetra-methylethylene gave good yields (80%) of cyclopropane derivatives with the cyano-group attached to the three-membered ring. This process has been suggested as a preparative method for the synthesis of phenylcyanomethylene[92].

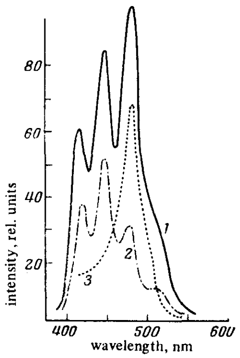
Convincing direct evidence for the formation of carbenes in the photolysis of epoxy-compounds was obtained recently. The carbenes were identified by a luminescence technique and by an ESR method in irradiated epoxy-compounds 10 and 11 (Table 4) at −196°C in methylcyclohexane solution. The Figure shows the luminescence spectrum of the irradiated epoxy-compound 11 (Table 4). The authors[100] showed that part of the total luminescence spectrum corresponds to the phosphorescence of benzophenone (the carbonyl-containing fragment of the molecule of compound 11 after its photochemical decomposition) and another part to the fluorescence of the diphenylcarbene biradical (III). The latter spectrum corresponded fully to the luminescence spectrum of diphenylcarbene obtained by a different method[101,102]. According to the ESR spectra of the irradiated solution of compound 11, diphenylcarbene has a triplet ground state (the spins of the free electrons are parallel), i.e. it may be regarded as a biradical.

Table 4. Epoxy-compounds yielding carbenes on photolysis

Formula	Epoxy-compound	Solvent, concn.	decomp. path way	References
1 	epoxy-1-methoxy-1,2,2-triphenylethane	methyl alcohol, trimethylethylene	*B*	89
2 	epoxy-1-methoxy-1,2-diphenylethane	trimethylethylene, tetramethylethylene	*B*	91
3 	epoxy-1-methoxy-2,2-dimethyl-1-phenylethane	trimethylethylene	*B*	89
4 	epoxy-1-methoxycarbonyl-1,2-diphenylethane	methyl alcohol, trimethylethylene	*A*	93,99
5 	1-cyanoepoxy-1,2-diphenylethane	trimethylethylene, tetramethylethylene, methyl alcohol (0.1 M), 2,3-dimethylbut-2-ene (0.5 M)	*A*	91,94 98,99
6 	1,2-dicyanoepoxy-1,2-diphenylethane	trimethylethylene, tetramethylethylene	*A*, *B*	92
7 	1-cyanoepoxy-1,2,2-triphenylethane	methyl alcohol (0.3 M), 2,3-dimethylbut-2-ene (0.3 M), 2-methylbut-2-ene	*A*	94,98 99
8 	1-cyanoepoxy-2,2-pentamethylene-1-phenylethane	methyl alcohol (0.3 M), 2,3-dimethylbut-2-ene (0.3 M)	*A*	99
9 	*trans*-epoxy-1,2-diphenylethane *trans*-(stilbene oxide)	2-methylbut-2-ene	*A*,*B*	94
10 	epoxytriphenylethane	methylcyclohexane (10^{-4} M), 2-methylbut-2-ene + benzene, 2-methylbut-2-ene	*A*	94,100
11 	epoxytetraphenylethane	methyl alcohol + benzene and methylcyclohexane (10^{-4} M)	*A*,*B*	94,100
12 	epoxy-1,2-dimethyl-1,2-diphenylethane		*A*,*B*	96

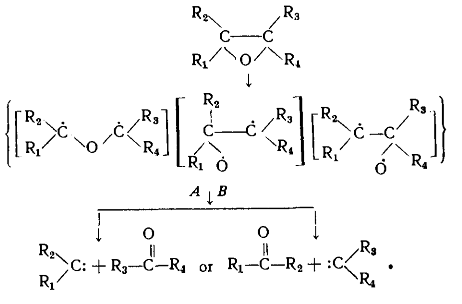
Thus, together with photolytic cleavage of diazo-compounds and ketones, a new source of biradicals with a wide variety of substituents has been found, namely epoxy-compounds. The photochemical method for the generation of carbenes from epoxy-compounds was discovered recently and is therefore not included in Kirmse's monograph[34].

The experimental data from the investigations considered[89-99] permit certain conclusions concerning the radical mechanism of the photolysis of epoxy-compounds. Although in all these investigations[89-99] without exception, starting with the first report by Kristinnsson and Griffin[94], the dissociation of the C–C bond is suggested as the primary step in the photolysis of the epoxy-rings, there is no convincing evidence for the reaction by this pathway. It appears desirable to represent the photolysis of epoxy-compounds by mechanism (50). We may also note that later Griffin and Kristinnsson changed their view on the primary stage of the process[100].



Luminescence spectra of the photolysis products of epoxytriphenylethane: *1*) overall luminescence spectrum; *2*) phosphorescence spectrum; *3*) fluorescence spectrum (the difference between the total luminescence and phosphorescence). Conditions of photolysis: 10^{-4} M solution of epoxytetraphenylethane in methylcyclohexane; temperature 77°K; duration of irradiation 20 s; wavelength 2537 Å.

The nature and number of substituents of the epoxy-ring are of decisive importance for the occurrence of reaction (50) by pathways *A* and *B* and for the very possibility of the formation of the carbene. Examination of data on the photochemical reactions of epoxy-compounds shows that carbenes are not formed from epoxyethane and its monosubstituted derivatives. On the other hand, methylene appearing in the photolysis of epoxyethane is not a product of the direct breakdown on the epoxy-compound [reaction (32)] but is formed in subsequent reactions[68]:



(50)

The determination of the sequence of the dissociation of the C–C or one of the C–O bonds in the epoxy-ring under the influence of ultraviolet light constitutes a very complex problem, which requires solution and a theoretical treatment. The mode of photochemical decomposition of the epoxy-ring is determined by the electromeric effect of the ring substituents[89-91,93] and the degree of weakening of the bonds in the ring. Furthermore, account must be taken of the isomeric structure of the molecules[90,94,99] and the effect of reactive solvents, for example, acetone[72] or methanol, both on the reaction and the polarisation of the C–O bonds in the three-membered ring, which has been scarcely investigated. Different views have been expressed about the effect of methanol on the epoxy-group. In one case[103] such an effect was noted (a shift of the band due to the hydrogen bond in the infrared spectrum of the same order of magnitude as for the methanol–acyclic ether pair, namely 80–99 cm^{-1}), while in another case[104] such an effect was denied (the infrared spectra of mixtures of epoxyalkanes and alcohols failed to reveal any interaction between them). In a third communication[105] it is stated that the interaction of the hydroxy-group with the ring involves the electrons of the C–O bond and that it occurs when the hydroxy group approaches not the apex of the ring but its plane. Account must also be taken of the effect of the size of the incident quanta, the duration of the irradiation, and the sensitisers used. Although compounds 10 and 11 (Table 4) do not absorb light at wavelengths higher than 3000 Å, their irradiation with light at a wavelength of 2537 Å for only 5 s is sufficient to cause further photolysis on irradiation with light at a wavelength of 3500 Å, which suggests a sensitising effect by the photochemical decomposition products[100]. The introduction into the reaction medium of photosensitisers, for example benzophenone (a decomposition product of compound 11, Table 4), leads to an increase of the yield of diphenylcarbene compared with non-sensitised photolysis. Possibly the photosensitiser arising in the photochemical decomposition of epoxy-compounds facilitates the transition of diphenylcarbene as well as other carbenes to a triplet state, as in the formation of triplet methylene in the presence of benzophenone[106], and thereby influences the reaction.

V. RADICAL PROCESSES IN EPOXY-COMPOUNDS INDUCED BY HIGH-ENERGY RADIATION

The radiation-chemical reactions of epoxy-compounds are the least investigated branch of the chemistry of three-membered heterocycles. The explanation is that the radiolysis of epoxy-compounds began to be investigated only in recent years and the radiation processes are extremely complex, since they involve the simultaneous occurrence of reactions with participation of radicals, radical-ions, ions, etc. These factors make it difficult to elucidate the mechanisms of the radiation-chemical reactions of epoxy-compounds.

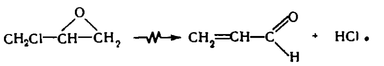
One of the first tasks undertaken in the study of radiation-induced reactions of epoxy-compounds consisted in the investigation of their polymerisation. For this purpose, epoxyethane was irradiated. However, it did not polymerise either in the liquid[107,108] or solid[109,110] phases or in methylene chloride solution[107]. A polymer was obtained in 0.22% yield by irradiating epoxyethane in the solid phase (dose 8 Mrad, dose rate 15.5 rad s^{-1}, −80°C, vacuum)[111]. By changing the irradiation conditions (41.6 Mrad, 50 rad s^{-1}, room temperature), the yield of the polymer was increased to 1.37%. The addition of inorganic oxides (ZnO, SiO_2, MgO, and As_2O_3) had little effect on the yield of the polymer.

Hoshino et al.[112] observed the formation of a polymer and acetaldehyde from epoxyethane and determined their yields. The gaseous products evolved were analysed. They concluded that the radiation-induced decomposition of epoxyethane involves both radical and molecular mechanisms, the polymerisation reaction predominating.

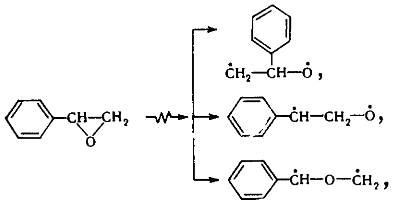
Frequent attempts to achieve the radiation-induced polymerisation of pure epoxypropane by a radical mechanism were unsuccessful[107,109,110,113-115]. Nevertheless the absence of a polymeric product in the irradiated epoxypropane cannot be regarded as proof that radical processes are impossible. An ESR study of the radiolysis of epoxypropane (between −140° and −170°C) established the formation of two types of radicals and their structure. Trofimov and Chkheidze[116] showed that the ESR spectrum of irradiated epoxypropane is produced by the superposition of a triplet with $\Delta H_T = 18$ Oe and the spectrum with a line width $\Delta H_{tot} = 82$ Oe. The glycidyl radical (XI) ($\Delta H_\alpha = 18.5$ Oe, $\Delta H_\beta = 0$) makes the main contribution with a small contribution by the epoxy-radical (VIII) (hyperfine structure splitting of 82 Oe). Radicals formed as a result of the opening of the three-membered ring were not detected.

Tabata[114] and Tabata and Sobue[117,118] described the synthesis of a homopolymer of epoxypropane in the liquid and solid phases mixed with epoxyethylbenzene. Whereas previously the authors considered the radiation-induced polymerisation of epoxypropane in the presence of epoxyethylbenzene from the standpoint of a radical mechanism, in their latest publication[115] they concluded that the process has an ionic mechanism (low activation energy, the absence of an effect by radical inhibitors).

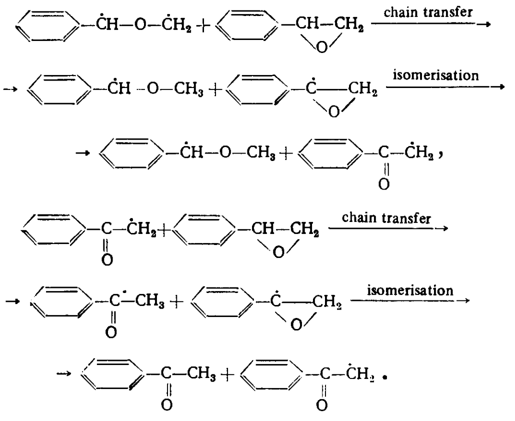
Radiation-induced polymerisation of epichlorohydrin (ECH) in the solid[110] and liquid states[119,120] was not observed. The infrared spectra of irradiated epichlorohydrin show new bands at 3450 cm^{-1} (hydroxy-groups) and 1720 cm^{-1} (carbonyl group) (cobalt-60 radiation, 400 Mrad). It has been noted[121] that the epoxy-ring is opened on radiolysis of epichlorohydrin with formation of carbonyl and hydroxy-groups and probably ether bonds (band with a maximum at 1065–1120 cm^{-1}). The viscosity of epichlorohydrin increases in the course of irradiation. Dichlorohydrin, acrolein and water (liquid phase) and hydrogen, methane, ethane, propane, and an unknown substance (gas phase) were detected among the radioysis products. One of the possible pathways in the formation of dichlorohydrin is as follows. H or Cl radicals are split off during the radiolysis and either recombine to HCl or abstract chlorine and hydrogen respectively from the epichlorohydrin molecule. Further reaction of hydrogen chloride with epichlorohydrin takes place by the familiar mechanism[122]. Acrolein may be formed from epichlorohydrin as a result of the elimination of hydrogen chloride:


(51)

Epoxyethylbenzene polymerises on cobalt-60 irradiation (8–54 rad s^{-1}) or irradiation with accelerated electrons (8×10^4–2×10^5 rad s^{-1}) at temperatures between −196° and 140°C in the solid and liquid phases[114,115,117]. The rate of radiation-induced polymerisation of epoxyethylbenzene and its conversion increase with temperature. The radiation-chemical yield at 140°C is $G_{-M} = 1000$. The overall activation energy for the liquid-phase process is 6.25 kcal $mole^{-1}$. An increase of the dose increases the yield of the polymer and the degree of polymerisation. Benzoquinone (2%, 20°C, dose rate 23.8 rad s^{-1}) inhibits the reaction over a period of 150 h. All these data support a radical chain mechanism of the radiation-induced polymerisation of epoxyethylbenzene. In their discussion of the process mechanism, the authors postulate the formation of three types of biradicals arising on dissociation of the principal bonds of the epoxy-ring:


(52)
(53)
(54)

and suggest that the reaction takes place simultaneously by several pathways. In one of these the interaction of the primary radical with the monomer is represented by the following mechanism taking into account repeated chain transfer (abstraction of hydrogen atoms) and isomerisation:



(55)
(56)

The importance of the role of fast chain transfer and isomerisation reactions in this mechanism appears to be significantly responsible for the low rate of propagation and for the presence of stages in the reaction[118].

Colichman and Strong[123] did not observe any changes in an epoxy-resin after irradiation (cobalt-60, 100 Mrad, 55 rad s^{-1}, 38°C) and decided that radiation cannot promote the interaction in resins involving epoxy-groups. Nor was polymerisation observed after the irradiation of the pure diglycidyl ether of 2,2-di(*p*-hydroxyphenyl)propane[119].

On the other hand, it has been shown that epoxydian† resins (EDS) of types ED-5, ED-6, EDP, and EDL not only polymerise but are also cross-linked under the influence of high-energy radiation at room temperature without the use of hardening agents[124-128]. The study of the radiation-chemical reactions of these resins showed that the epoxy-group is the most sensitive unit in their molecule. The rate of decomposition of the epoxy-rings in the resins of all types was the same, being proportional to the dose both in a vacuum and in the presence of atmospheric oxygen. It is independent of the phase state (under the usual conditions, the ED-5 and ED-6 resins are liquid and EDP and EDL are solid) and the molecular weight of the resin in the range 370–1200, of the initial content of epoxy-groups in

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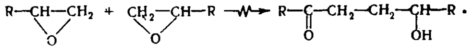
† Dian = di(*p*-hydroxyphenyl)dimethylmethane (Ed. of Translation).

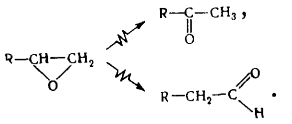
the resins (9–22%), and of the dose rate. The radiation-chemical yield of the reactions of the epoxy-groups proved to be 2.66 groups/100 eV. The rate of decomposition of epoxy-groups increases with temperature. The increase of the density, refractive index, and molecular weight varies linearly with the dose. These changes convincingly demonstrate the occurrence of radiation-induced polymerisation of unhardened epoxydian resins.

The nature of the radiation-chemical reactions of the epoxy-rings were inferred, in particular, from the changes in the infrared spectra. The intensity of the 915 cm^{-1} band (epoxy-groups) decreased, the band in the region of 3500 cm^{-1} became broader and more intense (hydroxy-groups and intermolecular hydrogen bonds), and a new band appeared at 1720 cm^{-1} (carbonyl groups). The formation of carbonyl groups and the increase of the concentration of hydroxy-groups cannot be attributed to radiation-induced oxidation reactions. There is a genetic relation between the decomposition of epoxy-groups and the formation of carbonyl groups and also the increase of the concentration of hydroxy-groups. Possibly it is revealed in the interaction of the epoxy-groups of two molecules of an epoxydian resin:


(57)

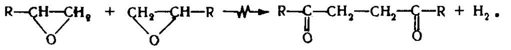
As already mentioned, the formation of carbonyl groups from epoxy-rings is evidence of the occurrence of radical processes.

One of the causes of the low rate of radiation-induced polymerisation of the resin is intramolecular rearrangements, which in fact lead to the consumption of epoxy-groups but do not give rise to an increase of the molecular weight. Depending on the site of the homolytic cleavage of the ring, ketones and aldehydes may be formed:


(58)

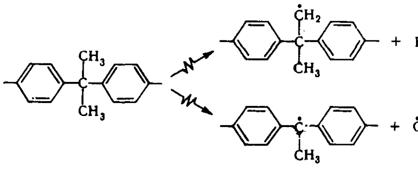
(59)

The formation of carbonyl groups, which is accompanied by the breakdown of epoxy-groups and a linear increase in the length of the resin molecules, can also occur as a result of the following reaction:


(60)

The radiation-chemical yield of the total gaseous product is smaller by a factor of almost 36 than the decomposition yield of the epoxy-groups and amounts to 0.074 mol./100 eV. The gaseous mixture consists mainly of hydrogen, but since $(G_{\text{-ep.gr.}}/2)/G_{\text{gas}} \ll 1$, reaction (60) occurs relatively rarely even if it is assumed that it is the sole source of hydrogen.

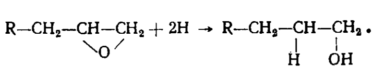
The molecular-structural changes in solid epoxydian resins were investigated by Bakaeva et al.[120] (cobalt-60, 1500 Mrad, 84–2100 rad s^{-1}).[120] In view of the similarity of the ESR spectra of irradiated 2,2-di(*p*-hydroxyphenyl)-propane and the resin, the authors believe that the primary radiation-chemical steps in the resins are the following radical reactions:


(61)

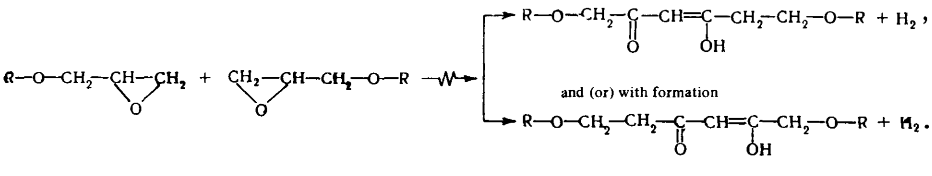
(62)

As assumed by Bakaeva et al.[120], the formation of bonds between resin molecules occurs only as a result of the interaction between radicals formed by reactions (61) and (62). However, such a reaction is complicated by the rigidity of the *p*-phenylene unit[129,130] and of the entire resin molecule[126], i.e. a sharp decrease in mobility and greater inhibition of the rotation of all the units of the molecular chain, when the resin solidifies[131]. Furthermore, a change in the type of substituent or an increase in the length of the side chain at the central dian atom might lead to a change in the ultraviolet spectrum of the compound when the concentration of new bonds is sufficiently high[132]. However, after irradiation with a dose of 500 Mrad the ultraviolet spectra of the resins proved to be identical with those of the non-irradiated resins. This indicates, firstly, a low probability of the reactions of the above radicals with one another, secondly, the absence of reactions involving addition to the benzene ring in the *o*- and *m*-positions, and, thirdly, the high radiation stability of the bond between the quaternary carbon atom and the phenyl rings in the resin molecules[128].

Like Colichman and Strong[123], Bakaeva et al.[120] do not postulate a linear growth of the resin molecules and the participation of the epoxy-groups in this process. They believe[120] that the epoxy-groups decompose by reaction (58) or form a primary alcohol as a result of hydrogenation:


(63)

The radiation-chemical reactions of the diglycidyl ether of ethylene glycol (DEG) obey very largely the same relations as the reactions of epoxydian resins[125,127,128]. The absence of aromatic rings from DEG favours more vigorous gas evolution ($G_{\text{gas}} = 0.95$ mol./100 eV) and decomposition of epoxy-groups ($G_{\text{-ep.gr.}} = 5.66$ groups/100 eV). On the basis of chemical analyses and ultraviolet and infrared spectra, it has been suggested that, on irradiation of DEG, the enol of a β-diketone is formed apart from the occurrence of reaction (57):



(64)

(65)

Polyfunctional epoxy-compounds the molecules of which contain, in addition to epoxy-rings, various other reactive groups, for example, double bonds are of definite interest. Glycidyl methacrylate (GMA) polymerise in the solid state (cobalt-60, 0.4 Mrad, 3–600 rad s^{-1}) by a radical chain reaction with bimolecular chain termination[133]. After 10–15% conversion, a gel fraction is formed. The appearance of a three-dimensional structure is regarded as proof of the involvement in the reaction of both functional groups, since it is well known that monofunctional monomers, for example, methyl methacrylate and butyl methacrylate (the closest analogues of GMA) are degraded and not cross-linked by radiation. In the initial stage of the process the polymerisation of GMA involves mainly the double bonds. But even in this stage the epoxy-groups are involved also.

The data presented show that, under the action of high-energy radiation, radical processes occur in epoxy-compounds as a result of which they can polymerise via the epoxy-groups, isomerise to carbonyl compounds, and give rise to ethers and hydroxy-groups. Despite some analogy with the double bond[134], the three-membered epoxy-ring is much less reactive.

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The data presented show that under certain conditions epoxy-compounds may react by a radical mechanism. Despite the various methods of initiation of the radical reactions of epoxy-compounds, the results are the same in most cases—cleavage of the C–O bond of the ring. The site of the dissociation of the bond is little affected by the form of activation: nuclear vibrations (pyrolysis), electron excitation (photochemistry), radical attack (chemical initiation), and radiation-induced reactions. The electronic structure of their molecules plays a decisive role in the mode and rate of the reactions of epoxy-compounds. It is reasonable to expect that the epoxy-ring may be cleaved at different sites, since the strength of the bonds in it depends on the substituents. Consequently one of the most important tasks in the study of the mechanism of the radical processes involving epoxy-compounds is the identification of the intermediate products in order to establish the site of the dissociation of the chemical bonds in the epoxy-ring and the effect on the cleavage of the number and nature of the substituents at the ring carbon atoms.

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Institute of Physical Chemistry,
Academy of Sciences of the
Ukrainian SSR, Kiev

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Aromatic Polyethers

V.V.Kopylov

Aromatic polyethers which have found industrial application are surveyed. The formation, structure, and properties of poly(phenylene oxides) are described. A list of 361 references is included.

CONTENTS

I. INTRODUCTION AND CLASSIFICATION

Aromatic rings and ether bonds are among the chemical groupings which possess great resistance to heat and to thermal oxidation. It is not surprising, therefore, that aromatic polyethers—poly(arylene oxides)—have found wide application as high-temperature materials. Furthermore, the benzene rings in phenyl ethers are not coplanar, but are inclined at an angle to one another[1]. Such arrangement results in absence of resonance conjugation between these rings, so that they can easily rotate relative to one another through a solid angle of 120°.[2] Because of this combination of stability and mobility the arylene oxide unit is very frequently used to confer flexibility on the macromolecules of thermostable polymers. The introduction of such units into macromolecules usually results in an improvement in the solubility and the elasticity of the polymer, while its mechanical and thermal stability are maintained, as has been confirmed experimentally on series of such polymers as the polybenzimidazoles, polybenzothiazoles, polybenzoxazoles[3], polypyromellitimides[4-7], polythiazoles[8], polycarbonates[9-12], polyamides[13], poly-1,3,5-triazines[14], polyester–amides[15], polyquinoxalines[16], polysulphones[17-20], polysulphonamides[21], polybenzylenes[22,23], polyperfluorobenzylenes[24], polyphenylenes[25,26], poly(phenylene borates)[27], etc.

The Dowtherm high-temperature heat-transfer agents—eutectic mixtures of diphenyl ether with biphenyl and naphthalene—which have been known since the 1930s, may be regarded as the first industrial materials of this type[28,29]. The principal subsequent developments on these lines have been due mainly to chemists working for the Dow and Monsanto firms, and in recent years the General Electric Company.

Poly(arylene oxides) are met in Nature only in the form of poly(phenylene oxide) resins having molecular weights up to 5000, in which the ether bonds are oriented in the *meta*-position relative to one another. These resins can be isolated from certain petroleums by repeated reprecipitation with petroleum ether from oxolan solution[30]. No such results are yet available for the *para*-isomers. The possibility of the existence of poly-(*o*-phenylene oxides) is doubtful because of steric hindrance, although they are mentioned in some patents.

With few exceptions the aromatic polyethers which have hitherto been synthesised and investigated have been benzene derivatives. In the literature they are denoted by several different terms. In the present Review we shall use the name *phenylene oxides*. The reason for this choice is that, although all the terms equally reflect the chemical structure of the compounds, only the above name corresponds to those adopted in the chemistry of macromolecular compounds, such as poly(phenylene sulphides), poly(phenylene sulphoxides), polyphenyleneimines, etc.

Phenylene oxides of low and of high molecular weight differ substantially in methods of preparation, properties, and fields of application, and merit separate consideration. In the present Review, therefore, all phenylene oxides are divided into three classes—(*a*) oligomeric phenylene oxides, containing up to 10 benzene rings in the molecule, (*b*) meso(phenylene oxides), containing 10—100 benzene rings, and (*c*) poly(phenylene oxides), containing more than 100 benzene rings, and exhibiting all the properties of high polymers.

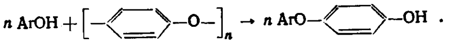
II. OLIGO(PHENYLENE OXIDES)

Oligo(phenylene oxides) can in turn be provisionally divided into two groups—neutral, consisting only of ether bridges and benzene rings having alkyl or halogen substituents; and functional derivatives, containing such groups as hydroxyl, carboxyl, amino, sulpho, etc. in the framework.

1. Synthesis of Neutral Oligo(phenylene Oxides)

The chief method of synthesis consists in building up the chain step by step by the Ullmann condensation of alkali-metal phenoxides or phenoxyphenoxides with aryl halides in the presence of catalytic quantities of copper powder[31-33]. A mechanism of heterolytic substitution had been suggested earlier for this process, but evidence has recently been obtained that the reaction involves the formation of free radicals of phenoxyl type[34,35]. A search for optimum conditions for the synthesis of oligo(phenylene oxides) has shown that, in order to increase the purity and the yield of the required product, the process must be conducted in solution or in suspension in a highly polar organic solvent having a high boiling point, especially in one which is a single-electron carrier, whether in the form of a solvated electron (ether)[36,37] or in the form of a radical-anion (ketone)[38,39]. In several cases copper salts and their complexes are used instead of metallic copper as catalyst. It is sometimes useful to activate the reaction with ultraviolet radiation, iodine, or a free-radical catalyst[40].

The structure of the oligomers is determined by that of the initial compounds: isomerisation has not been observed during synthesis. The initial phenoxyphenols are usually obtained also by Ullmann condensation. A promising method of preparing phenoxyphenols is the "radical acidolysis" of poly(phenylene oxides)[41],[42]:



The aryl halides are prepared by the usual methods, and if necessary are isomerised by means of aluminium chloride[43]. The greatest influence on the reactivity of phenoxyphenols in the Ullmann condensation is exerted by substituents located *ortho* and *para* to the hydroxy-group, the reactivity being diminished by electron-acceptor substituents, and increased by electron-donor substituents. The halogen in the aryl halide and the process conditions have a considerably greater effect. It has been found that the activity sequence of the halogens is $I \simeq Br > Cl \gg F$ [44]; in the synthesis of the polyethers $I > Br > Cl$ and *para* > *ortho* ≫ *meta*.

It has been noted several times that the synthesis of oligo(phenylene oxides) is accompanied by several side-reactions. The effect of oxygen is especially injurious, quinones and biphenylquinones being formed in its presence. Since these impurities catalyse decomposition of the oligomers, purification of the final product becomes particularly important. Ordinary fractional distillation and recrystallisation are usually ineffective. The best results are obtained by treatment with silica and alumina in a flow system (chromatography) or in solution with subsequent filtration and fractional distillation, by zone melting, or by treatment with ion-exchange resins or alkali metals[45-50].

2. Synthesis of Oligo(phenylene Oxides) containing Functional Groups

Functional groups are introduced into oligo(phenylene oxides) either by the choice of appropriate initial compounds containing protected functional groups, e.g. alkoxylated aromatic compounds, the protection being removed after condensation, or by appropriate chemical treatment of the neutral oligomers. Since an aromatic ether bond possesses great chemical stability, both methods are quite effective. Thus dihydroxylated oligo(phenylene oxides) have been obtained[10],[51] by hydrolysing the dimethoxy-compounds, diepoxy-derivatives[52], and sulpho-derivatives, by treating neutral oligomers with oleum[53], etc. A mixture of mono- and di-hydroxylated oligomers is formed by the action of aqueous alkali on a monochlorodiphenoxide in the presence of copper at 250–350°C.[54] An interesting and evidently promising method for the synthesis of the monohydroxylated oligomers is the oxidative polycoupling of phenols terminated in its early stages. It has been shown experimentally[55-57] that oligomers containing 2–7 benzene rings and one terminal hydroxyl can be obtained in this way. The decomposition of poly(phenylene oxides) of high molecular weight may also yield oligomers containing one or two terminal hydroxy-groups[58],[59].

3. Physical Properties of Oligo(phenylene Oxides)

Almost all known oligo(phenylene oxides) are clearly identified chemical compounds. The series of *para*-isomers are crystalline solids, and the *meta*-isomers are viscous liquids at room temperature. The characteristics of some of these compounds are listed in Table 1.

X-Ray examination of a series of oligo-(*p*-phenylene oxides) has shown that the parameters of the unit cell are independent of the length of the molecular chain. All these compounds give the same indices of type *h*, *k*, 0, corresponding to interplanar spacings of 6.79, 5.05, 4.58, 4.22, 3.94, 3.42, 3.67, 2.88, 2.71, 2.56, 2.32, 2.12, 1.89, 1.82, 1.66, 1.60, and 1.50 Å, which represent a crystal lattice having the parameters $a = 9.6$ Å, $b = 6.45$ Å, and $\gamma = 90°$.[60]

Table 1. Characteristics of oligo(phenylene oxides) of general formula $C_6H_5.[OC_6H_4]_n.H$.

n	M.p., °C	B.p., °C	Ref.
	para-Isomers		
2	77	—	2
3	111.0—1.5	—	60
4	153.0—3.5	—	60
5	180.0—1.0	—	60
6	211	—	60
7	222	—	61
	meta-Isomers		
2	61.5	220/0.18	33.62
3	—	214—7/0.7	63
4	—	292—4/2.8	63
5	—	280—3/0.15	63
6	—	318—24/0.15	63
p-$(C_6H_5OC_6H_4)_2$	53.5—4.5	245—811.5	64—66

All neutral oligo(phenylene oxides) are excellent dielectrics, having volume resistivities of the order of 10^{11}–10^{12} ohm cm. The electrical conductivity of the series of *meta*-oligomers over this range can be explained by convection currents[67]. A more interesting rule has been observed in the series of *para*-oligomers, whose conductivity at room temperature diminished with increase in the length of the molecular chain; it varied exponentially with rise in temperature, the activation energy being 5.2–7.2 eV, and near the melting points reached a value of the order of 10^{-9} ohm^{-1} cm^{-1}, which was approximately the same for all the compounds investigated[60].

The viscosity of the oligomers diminishes with rise in temperature, but nevertheless remains sufficiently high for them to be used as high-temperature lubricants. In order to obtain oligo(phenylene oxide) lubricants which do not thicken at low temperatures, halogen atoms[68],[69] or alkyl groups[70],[71] are introduced around the phenylene oxide chain, or else ester or carbonyl groups are included in the chain itself[72-74].

The dielectric properties of the oligomers are preserved over wide ranges of frequency and temperature. Thus *p*-*p*′-chlorophenoxyphenyl phenyl ether has a dielectric constant of 4.57–5.98, a dielectric loss angle of $\tan^{-1} 0.001-0.0071$, and a volume resistivity of 3.1×10^{10} to 3×10^{12} ohm cm.[75]

The infrared spectra of oligo(phenylene oxides) contain all the typical absorption bands of aromatic compounds having the given type of substitution. The characteristic bands due to an aromatic ether bond lie in the range 1210–1230 cm^{-1} and in the region of 1270 cm^{-1} in the cases of the *para*- and *meta*-oligomers respectively. The mass spectra of several of the oligomers have also been investigated[78].

The high radiation stability of the oligomers is especially interesting. According to various workers oligo(phenylene oxides) withstand, without appreciable change in viscosity, irradiation with γ-rays and neutrons of total dosages up to 10^8 rad at temperatures up to 140°C.[79-81] The addition of 1–10% of an acylate, dialkyldithiocarbamate, or a dialkyl phosphorodithioate of an alkaline-earth metal, mercaptobenzothiazole, or a dithiol enables the stability of the oligomers to be raised to 10^9–10^{10} rad.[81-85]

The mechanical properties of the oligomers have been discussed in a review[86].

4. Chemical Properties of Oligo(phenylene Oxides)

As has been stated above, the ether bond in oligo(phenylene oxides) is very inert chemically. It is cleaved only by the action of alkali-metal amides in liquid ammonia[87] or (by a radical-anion mechanism) by interaction with alkali metals in an aprotic solvent in an inert atmosphere[88-90]. In the former case a phenol and an amine are formed, and in the latter case a phenol and biphenyl.

Substitutions in the benzene ring of the oligomers are almost identical with the corresponding reactions in the aromatic series. The ether bridges in the oligomers are able to form complexes with aluminium bromide and several other electron acceptors; the heat of formation of the complex depends on the structure of the oligomer[91,92].

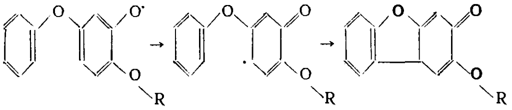
The great resistance of the oligomers to the action of oxidising agents at high temperatures is especially interesting. In air oxidation begins only above 300°C. This stability is responsible for several special applications of oligo(phenylene oxides) (see below). The standard method for testing the oligomers for thermo-oxidative degradation consists[93-95] in bubbling air or oxygen at different rates through a portion of the molten oligomer at a constant temperature, preferably 315°C, for 24 and 48 h. This method is used to determine the relative stability of different oligo(phenylene oxides), the stabilising effect of additives, the influence of contact with various metals on the course of the process and on the corrosive power of the oligomers under these conditions.

Results obtained by different workers indicate that oligo(phenylene oxides) are thermally stable up to 300–450°C and withstand oxidation up to 200–300°C. Wilson and Smith[96] investigated the thermo-oxidative degradation of the oligomers labelled with deuterium and tritium, and found the process to be accompanied by the detachment of hydrogen atoms, predominantly from terminal groups, with the participation of phenyl and hydroxyl radicals, the formation of new C–C bonds, and in the later stages new C–O–C bonds, as a consequence of which macromolecular compounds of phenylene oxide structure are observed among the products of oxidative degradation.

The thermal and thermo-oxidative degradation of unsubstituted, neutral oligo(phenylene oxides) has been investigated systematically by Archer and Bozer[97]. They found the *meta*-oligomers to be considerably less stable than the corresponding *para*-isomers: the latter exhibit self-stabilisation, evidently as a consequence of the formation of dibenzofuran structures in the early stages of oxidation. The tetrameric and pentameric oligo(*m*-phenylene oxides) are thermally stable up to 420°C; after 336 h in air at 315°C the *para*-isomers have absorbed one-tenth of the oxygen absorbed by the *meta*-isomers during 150 h under the same conditions. Mass-spectroscopic and chromatographic examination of the products of thermo-oxidative degradation has shown them to include a bisphenoxyphenyl ether (in the case of the pentamers), a diphenoxybenzene, *o*- and *p*-phenoxyphenol, diphenoxide, phenol, benzoquinone, benzofuran, dibenzofuran, 2-phenoxybenzofuran, and traces of benzenediols, carbon dioxide, and water. Monomeric products constituted 34–48% of the total organic products; the yields of carbon dioxide and water were respectively 0.0003 and 0.0006 mole per gramme of the initial oligomer.

The authors suggested a mechanism of oxidative degradation of oligo(phenylene oxides) initiated by the oxidation by oxygen of an *ortho*- or *para*-position in a terminal benzene ring to a hydroperoxide, which then breaks down into hydroxyl and aryloxyl radicals. The former radical abstracts a hydrogen atom from the next molecule, and the resulting phenyl radical undergoes recombination or adds oxygen; the peroxy-radical thus formed detaches a hydrogen atom from another molecule, and then breaks down into a hydroxy-radical and a new aryloxy-radical, which results in branching of the kinetic chain. Termination of this chain by the coupling of phenyl and hydroxyl radicals will give phenols containing a hydroxyl end-group.

Initial attack by oxygen on an inner benzene ring in the oligo(phenylene oxide) by a somewhat different mechanism yields the same final situation: the initial ether is converted into a number of phenoxyl radicals and substituted phenols. Thus the role of oxygen in this process reduces to the formation of phenoxy-radicals. According to the authors the subsequent course of degradation is determined solely by these radicals. In the case of the *para*-isomers there are two possibilities: if the initial attack takes place *ortho* to the ether bond, the molecule undergoes a quinonoid rearrangement, and then a dibenzofuran structure is formed which stabilises the system:



when the initial attack occurs at the *para*-position, elimination of *p*-benzoquinone followed by chain growth is more probable. Furthermore, the authors accept the possibility of the formation of *o*-benzoquinone, without detailing the mechanism.

Much attention has been paid to the problem of improving the thermo-oxidative stability of oligo(phenylene oxides) by means of various additives or special treatments. As noted above, the stability of the oligomers is substantially influenced by their purity. Further treatment of the oligomers with alkali[98] or alkaline-earth[99] metals, or their oxides or hydroxides[100,101], lengthens the period of service of the oligomers at 300–350°C. A favourable effect is produced by the addition of aryltin halides, trifluoroacetates, or thiocyanates[102-109], arylhalogenoplumbanes and lead acylates[110,111], or triphenylphosphine oxide and tri-*p*-chlorophenylphosphine oxide[112,113]. Among organic compounds the best stabilisers for the oligomers were compounds containing at least one sulphur or halogen atom in the molecule[114], including halogenophenols[115,116], and also phthalimide, anthraquinone, phenyl benzoate, diphenyl phthalate, benzanilide, acenaphtho[1,2-*a*]acenaphthylene, or Schiff bases from 3-aminorhodamine[117-123]. However, organic salts and complexes of metals have proved to be more effective, such as the benzoates and naphthenates[112,124], dithiocarbamates[125], acetylacetonates[108,126,127], and bis-2-*N*-phenylformimidoyl-5-nitrophenoxides[128] of nickel and cobalt, tricarbonyltristriphenylphosphinyliron[129], and aryl-ferrocenes or -titanocenes[130,131]. The standard mixture of oligo(phenylene oxides) for testing the stabilising action of additives comprised 65% of *mm′m″*-, 30% of *mm′p″*-, and 5% of *pm′p″*-pentaphenylene tetroxide. The same mixture is most widely employed in industry when oligo(phenylene oxides) are used as hydraulic liquids, heat-transfer agents, coolants in atomic reactors, high-temperature lubricants, etc.

5. Uses of Oligo(phenylene Oxides)

Oligo(phenylene oxides) are used either alone or with various additives in many fields besides those mentioned above. Oligomers containing 4 – 6 benzene rings enable heat transfer to be effected by direct contact between a gas stream and the heat-transfer agent[132]. A study has been made[133] of the dependence of heat transfer on the composition of the oligomer, the character of the surface, the properties of the flow, etc.

In No. 102 diffusion pumps the *meta*-pentamer ensures that a vacuum down to 10^{-9} torr can be obtained[134,135].

Oligo(phenylene oxides) can be used as operating liquids in hydraulic systems at 400°C for up to 600 h, and at 480°C for 80 min[136,137], withstanding loads up to 30 kbar[138]. This has enabled them to be used as fireproof hydraulic liquids for submarines[139].

Elastodynamic film lubricants, greases for gas turbines, and other lubricants based on the oligomers are able to function at 315°C for more than 100 h. Partial fluorination of the oligomers, or the addition of polyphenylenes or chloroperfluoroacylates of heavy metals, enhances the fire-resistance and the oxidative stability of these lubricants, and also improves their properties at high pressures[140–148].

Lubricating greases based on the oligomers, suitable for operating at speeds up to 20 000 rev/min and temperatures up to 300°C, are obtained by introducing into the oligo(phenylene oxide) 5 – 40% of an acylate of an alkali or an alkaline-earth metal[149,150], 1 – 2% of a polymethacryate containing C_{22-24} alkyl groups[151], a mixture of 30% of silica gel with 0.5% of asbestos[152,153], 25 – 50% of esters of polyols with higher fatty acids[154], or a mixture of oligomeric poly(phenylene sulphides)[155].

Oligo(phenylene oxides) are used as lubricants in the machining of thin aluminium sheet and foil at 350 – 450°C.[156] In several cases their application is determined by their specific chemical properties. It has been noted earlier that sulphonic acids based on the oligomers are surface-active agents[53]. Hydroxy-derivatives of the oligomers are used as strong antiseptics and herbicides[157], and alkylthio-derivatives as pesticides[158]. In combination with substituted phenols and compounds of Group IVa metals oligo(phenylene oxides) stabilise polypropylene to the action of ultraviolet rays[159]. An oligomer can be used as cocatalyst for the Ziegler polymerisation of alkenes[160]. Functional derivatives of the oligomers have been used to obtain polymers of enhanced thermal stability[161].

III. MESO(PHENYLENE OXIDES)

Meso(phenylene oxides) have acquired hardly any intrinsic value in technology. However, considerable experience has been gained in the course of studying their synthesis and properties, and this has subsequently led to the successful synthesis of poly(phenylene oxides).

1. Syntheses from Halogenated Phenols

The first person to obtain a synthetic meso(phenylene oxide) was probably Benedict, who in 1879 investigated the decomposition of 2,4,6-tribromophenol at 130°C, and obtained an amorphous powder whose composition corresponded to the formula $C_6H_2Br_2O$.[162] As Hunter showed later, this was undoubtedly a polymeric product of not very high molecular weight. A similar result was obtained by Castle[163].

The polycondensation of halogenated phenoxides was investigated later by a group of chemists under the direction of Hunter[164]. They found that britle amorphous polymers were formed when suspensions of the 2,3,6-trichloro-, 2,4,6-tribromo-, and 2,4,6-tri-iodophenoxides, 2,4,6-tribromo-3-methoxyphenoxide, and other halogenated phenoxides of silver were heated in benzene or in ethyl iodide at 60°C or in the form of the dry powders. Silver 2,4,6-tribromophenoxide reacted with ethyl iodide to form a dark blue solution, which gradually became brownish yellow, and then deposited silver bromide; alcohol precipitated from the solution an amorphous product of molecular weight 6600 and empirical formula $C_6H_2Br_2O$. A systematic study of the process revealed the following rules: (*a*) in the case of the trihalogenated compounds the reaction took place predominantly in the *para*-position; (*b*) the activity of the halogens diminished in the sequence iodine – bromine – chlorine; and (*c*) only those halogen atoms which were attached directly to a hydroxylated benzene ring reacted under the conditions investigated.

Conclusions (*b*) and (*c*) are confirmed by the dehalogenation by mercury of 2,6-dibromo-4-(4-chloro-2, 6-di-iodophenoxy)phenol and 4-(4-chloro-2, 6-di-iodophenoxy) phenol: only bromine is abstracted from the former compound, whereas the latter does not react at all. The colour of the meso(phenylene oxides) obtained is probably due to the formation of biphenylquinonoid units in the chain, for it disappears on reduction of the polymer. Additional confirmation has been obtained by means of infrared spectroscopy.

"Mesomeric" phenylene oxides of the same type are formed also by (i) the action of mercury on 2,4,4,6-tetrabromocyclohexa-2, 5-dienone, (ii) the action of iodine on potassium trichlorophenoxide in aqueous or benzene medium, and (iii) the electrolysis of silver halogenophenoxides.

Golden[165] has prepared several meso(phenylene oxides) of this type using a modification of Hunter's method. The properties of the products are listed in Table 2. From solutions they all yield only brittle films, as was to be expected for polymers of low molecular weight. The possibility of the formation of dibenzodioxan was also noted in the course of this work; with pentachlorophenol the reaction could be controlled to give mainly polymers in which the unit was either C_6Cl_4O or 2,3,4,5,7,8,9,10-octachlorodibenzodioxan.

Rainford and LeRosen[166] obtained a dark blue meso(phenylene oxide) of molecular weight 1800 by heating sodium 2,4,6-tribromo-3-fluorophenoxide. Blanchard and his coworkers[167] developed Hunter's work further, and found that 2,4,6-tribromo-3-methoxyphenol in the presence of iodine in benzene, and 2,4,4,6-tetrabromocyclohexa-2,5-dienone in the presence of metallic mercury, give initially a green polymer, which when subsequently dissolved in benzene and allowed to stand became decolourised. At the same time the molecular weight of the polymer doubled, probably as a result of coupling and the formation of dienone structures.

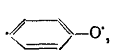
Table 2. Meso(phenylene oxides) synthesised by Golden[165].

Phenoxide		Polymer		
substituents	metal	yield, %	softening point, °C	mol. wt.
p-Chloro-	K	4	356—260	2800
2,4-Dichloro-	Na	45	270—273	—
2,4-Dibromo-	Na	81	240—245	—
2,4,5-Trichloro-	Na	37	215—220	—
2,4,6-Trichloro-	Na	90	185—186	4800
2,4,6-Trichloro-	Ag	79	185—188	9600
2,4,6-Tribromo-	K	60	244—246	3200
2,3,4,6-Tetrachloro-	Na	78	219—222	—
2,3,4,6-Tetrachloro-	Ag	80	213—235	—
Pentachloro-	Ag	73	192—194	1500
Pentabromo-	Na	63	300—310	—

The free-radical mechanism of the condensation of halogenated phenols to meso(phenylene oxides) has been proved by work on the oxidation of these phenols by aryloxy-radicals[168], benzoyl peroxide[169-171], lead tetraacetate or dioxide[172], or copper(II) acylates[173], in which trichloro-, tribromo-, tri-iodo-, and pentabromo-phenols gave meso(phenylene oxides) having molecular weights of 2000–5000, melting points from 165° to 265°C, and cyclohexadienone terminal groups; potassium pentafluorophenoxide in the presence of copper(II) oxide yielded the corresponding polymer of molecular weight 1700–4300.[174]

The formation of meso(phenylene oxides) from *m*-halogenophenols has been investigated by Brown and his coworkers[175-180]. They find that the Ullmann polycondensation of *m*-bromophenol takes place at 150–220°C to give the corresponding meso(phenylene oxide). Catalysis by copper salts results in branched products. In the presence of polar solvents secondary reactions involving C–C coupling predominate. The exothermic character of the reaction results in cross-linked products when the process is accomplished in the mass. Optimum results are obtained in a system formally analogous to suspension polymerisation, with high-boiling aliphatic hydrocarbons used as reaction medium. With appropriate preparation and purification of the catalyst (metallic copper) it is possible to obtain by this method meso(phenylene oxides) having molecular weights from 4000 to 10 000 in the form of solid powders suitable for the production of filled plastics which are thermostable up to 500°C.[175,176].

2. Synthesis of Meso(phenylene Oxides) by the Decomposition of 4-Diazocyclohexadienones

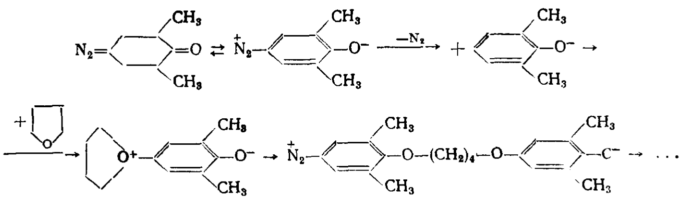
The second general method used in attempts to synthesise meso(phenylene oxides) was the decomposition of "*p*-benzenediazo-oxides" [4-diazocyclohexadienones]. It was assumed that such decomposition would involve the intermediate formation of a biradical , which would probably polymerise to a poly(phenylene oxide). Süs and his coworkers[181] studied the decomposition of 4-diazocyclohexadienone in various solvents under the influence of ultraviolet radiation. In all cases products containing solvent molecules were obtained. Similar results have been found by Wang[182]. In methanolic solution the main product was *p*-methoxyphenol. In boiling benzene *p*-phenylphenol was formed in almost theoretical yield. At room temperature a small quantity of a phenolic resin melting at 300°C could be isolated together with a phenylphenol from benzene solution.

An elastomer having good thermal stability could be obtained by decomposing a fluorinated "diazo-oxide"[183].

Dewar[184] investigated the thermal decomposition of 2,6-dibromo-4-diazocyclohexadienone in chlorobenzene. He hoped that blocking the oxygen by means of adjacent bromine atoms would diminish secondary reactions, including those in the *ortho*-position relative to the oxygen. This method yielded only polymers of low molecular weight (1600–6600) soluble in chloroform, with softening points of 200–220°C. Elementary analysis showed that the polymer contained chlorine as well as bromine, indicating that the solvent had taken part in the reaction. Conducting the same reaction in chlorobenzene containing 1% of methanol or water diminishes the yield of polymer, several benzene derivatives of low molecular weight being formed. The author regards these results as confirming the intermediate formation of a biradical similar to the above.

Kunitake and Price[185] studied the decomposition of 4-diazo-2,6-dimethylcyclohexadienone in a series of solvents under the influence of heating and ultraviolet irradiation. The diazonium salt, prepared by the usual method, was extracted from aqueous solution in an organic solvent, in which it was then decomposed. In benzene solution only 2,6-dimethyl-4-phenylphenol is formed by the action of light and heat. From chlorobenzene solution unchanged diazonium salt and *o*- and *p*-chlorohydroxybiphenyls were isolated, which was taken as evidence that an intermediate biradical was involved in the reaction.

The heating or ultraviolet irradiation of 4-diazocyclohexadienone in oxolan or dioxan yields semi-solid products of molecular weight 1400 or a powder of melting point 60–70°C. The ratio of the areas of the peaks for aliphatic and aromatic protons in the nuclear magnetic resonance spectrum of these products indicates a structure in which the ratio of tetramethylene oxide and phenylene oxide units is about 1 : 1. This is supported by elementary analysis. The facts that the polymers have the same composition independently of the conditions of this reaction and that some of the polymers are shown by X-ray diffraction to be crystalline indicate a structure with a regular alternation of aliphatic and aromatic units. The mechanism suggested for the reaction is



It is interesting that the "diazo-oxide" reacts to form either a biradical or an ionic intermediate compound depending on the solvent.

A similar formation of alternant copolymers has been observed by Stille et al.[186] when diazocyclohexadienone reacts with 1,4-epoxycyclohexane or with 2,2-bischloromethyloxetan. No copolymer could be obtained with methyloxiran[187].

Dimerisation and ring-closure have also been observed in several experiments on the decomposition of 4-diazocyclohexadienones.

With the exception of the work of Wall[183], in which the intermediate biradical may have been stabilised by the electron-acceptor effect of fluorine, and work by Price and Stille on copolymers, the use of diazo-compounds to prepare poly(phenylene oxides) has proved to be on the whole unsuccessful.

3. Other Methods for the Synthesis of Meso(phenylene Oxides)

Several other routes to the synthesis of meso(phenylene oxides) have been tried by various workers. Golden[165] and Briner[188] were unsuccessful in attempting to synthesise poly(phenylene oxides) by the dehydration of polyhydric phenols. Paushkin and his coworkers[189,190] conducted this reaction in the presence of zinc chloride at 200°C, but obtained only oligomers of molecular weight exceeding 1000 and softening points of 310–330°C. Treatment of phenols with iron(III) chloride gave similar results[191]. Although a polyphenylene structure was attributed to the products, their properties, especially the infrared spectra, were closer to those of known meso(phenylene oxides), not those of polyphenylenes.

Price[192] prepared a cross-linked polymer, in the form of a powder containing 12% of a soluble oligomeric fraction, by the decomposition of 4-acetoxymercuri-2,6-dimethylphenol.

An interesting method for synthesising a polymer containing alternating poly-*p*-phenylene and poly-(*p*-phenylene oxide) units was found by Stille and his coworkers[25], who accomplished a Diels–Alder polycondensation between 3,3-(oxydi-*p*-phenylene)-2,4-bistriphenylcyclopentadienone and *m*- and *p*-diethynylbenzene in toluene solution at 200°C.

A series of meso(phenylene oxides) were synthesised as insoluble, infusible powders of molecular weight 4000–7000 (from end-group analysis) or soluble resins of molecular weight 1000–2000 by Cox et al.[193], who subjected alkali-metal halogenophenoxides to thermal decomposition in the absence of a catalyst.

Meso(phenylene oxides) have been prepared also by the radiolysis of diphenyl ether[81] and by the Williamson polycondensation of dihydric phenols with bis-*p*-chloromethylphenyl ether[23,194,195]. In neither case was the structure of the products proved, and the molecular weight did not exceed 2000. Molecular weights up to 2300 have been obtained[196] by the condensation of oligo(phenylene oxides) with arenedisulphonyl chlorides. Several meso(phenylene oxides) have been synthesised by the oxidative polycoupling of phenols. Since this reaction is discussed in the following Section, information on these compounds will be given there.

Almost all meso(phenylene oxides) are dark coloured, friable powders which, although exhibiting certain properties characteristic of polymers, have not yet found practical application.

IV. POLY(PHENYLENE OXIDES)

As has been indicated in the preceding Section, the history of the synthesis of poly(phenylene oxides) of high molecular weight has been characterised by perennial unsuccessful attempts. The best results were obtained when the intermediate formation of radicals of phenoxyl type was possible under the conditions of polycondensation of halogenated phenols. The approach to catalysts for the process was therefore reviewed: metallic copper was replaced by oxides and complex salts of the metal, as a result of which polymers of high molecular weight could be obtained in good yield not only from halogenated phenols but also from phenols containing no *ortho*- or *para*-substituents.

The early failures are explained by the inadequate mobility of the halogen in these monomers, as is confirmed by the relatively easy preparation of polymers containing arylene oxide units by the polycondensation of diphenoxides with aromatic dihalides activated by a strongly electron-acceptor nuclear substituent, such as sulphonyl, nitro, or fluorine. For example, a polymer prepared from the disodium salt of bisphenol A and bis-*p*-chlorophenyl sulphone has already become available commercially[19,197,198]. This reaction is accomplished in a dipolar aprotic solvent by heating in the absence of oxygen and moisture at 130–140°C for 4–5 h. Several polymers of this type are listed in Table 3.

Table 3. Poly(arylene oxides) synthesised by nucleophilic substitution of halogen.

Diol	Dihalide	Glass point T_{gl}, °C
2,2-Diphenylpropane-*pp*′-diol	di-*p*-chlorophenyl sulphone	19
1,1-Diphenylethane-*pp*′-diol	ditto	200
Diphenylmethane-*pp*′-diol	"	180
Quinol	"	1
1,3-Diphenylethylcyclohexane-*pp*′-diol	"	230
1,1-Diphenylisopropylethane-*pp*′-diol	"	200
pp′-Dihydroxybenzophenone	"	205
Tetraphenylmethane-*pp*′-diol	"	230
Di-*p*-hydroxyphenyl sulphone	"	*
Di-*p*-hydroxyphenyl ether	"	180
2,2-Diphenylpropane-*pp*′-diol	*pp*′-difluorobenzophenone	155
2,2-Diphenylpropane-*pp*′-diol	2,4-dichloronitrobenzene	150
2,2-Diphenylhexafluoropropane-*pp*′-diol	di-*p*-fluorophenyl sulphone	205
2,2-Diphenylhexafluoropropane-*pp*′-diol	*pp*′-difluorobenzophenone	175

* Softening point 310°C.

A similar result is obtained by treating pentafluorophenol with caustic soda in pyridine[199]:

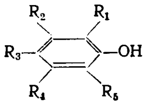
$$C_6F_6 + NaOH \rightarrow C_6F_5ONa \rightarrow [-C_6F_4O-]_n \ .$$

Heterolytic nucleophilic substitution is usually difficult in the aromatic series. Poly(phenylene oxides) can be successfully synthesised probably only by homolytic substitution of halogen, as is confirmed both by the coloration noted by Hunter and by Blanchard and by the sequence of activity of the halogens—I > Br > Cl—observed by Hunter, for the opposite sequence—F > Cl > Br > I—is found with heterolytic substitution[200].

An unexpected result has been found by Bolton and his coworkers[201,202], who have obtained insoluble films of poly(phenylene oxides) by the prolonged heating of *p*-phenoxyphenols in air at 330°C. This method of synthesis is an example of oxidative coupling.

During the past 10–15 years, in the course of work on the oxidation of phenols under various conditions, in particular in the synthesis of biphenylquinones by this method, formation of a certain amount of an amorphous polymeric byproduct has been observed[203-207]. More careful study and development of this line of research led Hay[208] and Price[192] to the almost simultaneous discovery in 1959–1960 of a new method of synthesising poly(phenylene oxides) of high molecular weight by the oxidative polycoupling of phenols and halogenated phenols. Poly-(2,6-dimethyl-1,4-phenylene oxide) was synthesised from 2,6-xylenol by the action of oxygen in the presence of a copper–pyridine catalyst or interfacially from 4-bromo-2,6-xylenol in the presence of potassium hexacyanoferrate(III) in the benzene–aqueous alkali system. Poly(phenylene oxides) have since been obtained by the same and similar methods from several dozen other phenols.

Table 4. Poly(phenylene oxides) obtained by oxidative coupling of phenols of the type.

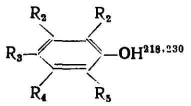


Substituents					Yield,%	Intrinsic viscosity, dl g^{-1}	Mol. wt.	Ref.
R_1	R_2	R_3	R_4	R_5				
Me	H	H	H	Me	85	0.72	31000	213
Me	H	H	H	Et	82	0.40	25400	213
Me	H	H	H	OMe	60	0.27	13000	213
Me	H	H	H	Pr^i	62	0.24	15350	213
Me	H	H	H	Ph	60	oil	—	213
Ph	H	H	H	Ph	46	0.05	—	213
Et	H	H	H	Et	81	0.53	32000	213
Me	H	H	H	All	—	oil	—	213
All	H	H	H	All	—	oil	—	213
OMe	H	H	H	OMe	30	—	2450	214
Me	H	H	H	H	22	oil	—	218
Me	H	H	H	H	82	—	15000	219
H	Me	H	H	H	35	—	800	220
H	Me	H	Me	H	10	—	1000	220
Me	H	Me	H	Me	79	—	1800	221
Me	Me	H (Br)	Me	Me	0	—	—	192
Me	H	H	H	Cl	88	0.47	71000	213
Me	H	H	H	Br	18	0.03	—	213
Cl	H	H	H	Cl	70	0.16	4000	222
Br	H	H	H	Br	—	—	3800	223
Cl	H	H	H	H	30	—	4750	224
Br	H	H	H	H	60	—	5500	224
Me	H	Cl	H	Me	92	1.20	65000	224
Me	H	Br	H	Me	85	0.40	14000	225
Cl	H	Cl	H	Cl	75	—	13000	226
Br	H	Cl	H	Br	—	0.01	—	225
Cl	H	Br	H	Cl	90	0.07	11000	225
Br	H	Br	H	Br	90	0.02	2300	225
Cl	Cl	Cl	Cl	Cl	87	0.02	—	225
Br	Br	Br	Br	Br	0	—	—	192
H	Cl	H	Cl	H	20	—	1900	227
OR	H	H	H	H	34	0.26	—	228
Me	H	H	H	Ph	55	0.88	—	229
Ph	H	H	H	Ph	75	0.80	—	229

The results are summarised in Tables 4–6. An emulsion method of synthesis has been patented[209]. Complex compounds of almost all metals of variable valency were used as catalysts. Electrochemical synthesis has also been tried[210-212]. Replacement of pyridine by its derivatives and the introduction of platinum black into the system have enabled the poly(phenylene oxides) to be obtained from phenols which do not polymerise under ordinary conditions (Table 5).

Only the two original methods of synthesising poly(phenylene oxides)—the hexacyanoferrate(III) and copper—amine processes—have been investigated in any detail. Though sharing many common features, they have several individual characteristics, and will therefore be discussed separately.

Table 5. Synthesis of poly(phenylene oxides), on an activated copper–amine catalyst, from phenols of the type.



Substituents					Intrinsic viscosity, dl g^{-1}	Cocatalyst
R_1	R_2	R_3	R_4	R_5		
CH_3	H	H	H	H	0.10	2-benzylpyridine
H	H	H	H	H	0.20	2-methyl-6-undecylpyridine
CH_3	H	H	H	H	0.39	2-ion-5′-ylpyridine
C_6H_5	H	H	H	H	0.11	2-benzylpyridine
H	C_6H_5	H	H	H	0.66	2,4,6-trimethylpyridine
CH_3	CH_3	H	CH_3	CH_3	0.92	platinum on carbon

1. Polymerisation initiated by Potassium Hexacyanoferrate(III)

Staffin and Price[192] found that poly(phenylene oxides) of molecular weight 4000–7000 are formed from 4-bromo-2,6-dimethylphenol in the presence of oxidants of the type potassium hexacyanoferrate(III), lead dioxide, etc. The reaction is initiated by ultraviolet irradiation, iodine, and phenoxy-radicals. The correctness of the 1,4-chain structure was confirmed by the nuclear magnetic resonance, infrared, and ultraviolet spectra. When polymerisation is initiated by phenoxy-radicals, excess of alkali is required: otherwise the polymerisation slows down[231,232]. This suggests that initiation consists in oxidation of the phenoxide anion to the phenoxy-radical.

Since the bromide ion is quantitatively precipitated during the process, chain growth may be supposed to occur by replacement of the *para*-bromine atom, probably with the formation of some intermediate state, i.e. that on the whole the process is a classic case of oxidative coupling. In an inert atmosphere polymerisation ceases soon after introduction of the catalyst, and the "frozen" process is revived by a fresh portion of catalyst; the molecular weight of the poly(phenylene oxide) does not exceed 10 000.[233] In air polymerisation continues until the monomer is completely converted, and the molecular weight reaches 40 000–50 000. In neither case is a direct relation between molecular weight and degree of conversion observed. The authors therefore regard this process as similar to the free-radical polymerisation of vinyl monomers. The mechanism of the action of oxygen consists in chain transfer by means of the hydroperoxy-radical.

End-group analysis combined with osmometry showed that 0.1 phenolic hydroxyl and 4 bromine atoms were associated with each macromolecule. This was explained either by the formation of ethers of quinol similar to those obtained by Dimroth[234] or by branching of the polymer chain resulting from attack by a phenoxylic macroradical at the middle of a neighbouring chain.

Considerable attention has been paid to the effect of substituents in the phenols. In the view of Staffin and Price[192] 4-bromodurenol and pentabromophenol do not polymerise because of steric hindrance to the approach of a phenoxy-radical to a bromine atom. Poly(phenylene oxides) from 2,6-disubstituted 4-bromophenols are listed in Table 6.[235,236]

Table 6. Effect of substituents on the polymerisation of 2,6-disubstituted 4-bromophenols[235,236].

R_2	R_6	Intrinsic viscosity	Product
$-CH_3$	n-C_3H_7	0.15	polymer
$-CH_3$	$-CH_2CH=CH_2$	0.17	polymer
$-CH_2CH=CH_2$	$-CH_2CH=CH_2$	0.15	polymer
n-C_3H_7	$-CH_2CH=CH_2$	0.11	polymer
n-C_3H_7	$-C_6H_5$	0.10	polymer
$-CH_2CH=CH_2$	$-C_6H_5$	0.11	polymer
$-H$	$-H$	—	biphenylquinone and oligomers
$-CH_3$	$-COOCH_3$	—	polymer
$-CH_3$	F	—	minute amounts of semi-solid products
t-C_4H_9	t-C_4H_9	—	no polymer

Table 6 shows that introducing a phenyl, allyl, or n-propyl group into an *ortho*-position yields poly(phenylene oxides) of low molecular weight. The allylic double bond is then inactive towards the growing radical and the catalyst: such great liability of phenolic hydroxyl to oxidation in comparison with an ethylenic double bond has been observed previously[237]. An attempt to polymerise 4-bromo-2-vinylphenol by this method resulted in an amorphous powder containing 80–90% of bromine based on the amount calculated for the monomer, probably as a consequence of a complicated growth reaction involving the double bond.

Polymerisation does not take place with bulky substituents such as t-butyl or strong electron acceptors such as $COOCH_3$ or fluorine.

A polymer containing reactive groups in its framework is interesting as a basis for several polymerlike reactions. Allylphenols themselves do not polymerise readily, but with xylenol they give various copolymers having molecular weights up to 50 000.[238–241]

2. Polymerisation initiated by Amine Complexes of Copper Salts

Although the interfacial polycondensation of halogenated phenols does enable copolymers to be obtained, the low molecular weight of the poly(phenylene oxides), the complicated technology, and the use of expensive monomers restrict its application. The homogeneous oxidative coupling of phenols is free from these defects and permits delicate control of the activity of the catalyst (Table 5). The use of a copper–amine catalyst for synthesising poly(phenylene oxides) from *p*-halogenophenols in the absence of oxygen revealed the necessity of using stoichiometric or even greater quantities of catalyst relative to the monomer[219], which is consistent with results for the catalytic activity of basic copper salts alone[242,243]. 4-Bromo-2,6-dinitrophenol and 4-bromo-2,6-dichlorophenol did not yield polymers by this method, and only an oil of low molecular weight was obtained from a 2-aryl-4-bromo-6-methylphenol.

The secondary formation of biphenylquinones during the synthesis of poly(phenylene oxides) had already been noticed in Hay's early work[213]. Further investigations established that polymerisation (C–O coupling) and the formation of the quinones (C–C coupling) are competitive reactions, depending on the substituents and the amine : copper (N/Cu) ratio. The larger the substituent the more readily is a biphenylquinone formed (Table 7).

Table 7. Formation of biphenylquinones.

R_2	R_6	Yield, %	M.p., °C
$-CH_3$	t-C_4H_9	45	217
t-C_4H_9	t-C_4H_9	97	246
n-C_3H_7	n-C_3H_7	53	255
$-OCH_3$	$-OCH_3$	74	>300

Interesting results have been obtained for the oxidation of 2,6-xylenol. The highest rate of absorption of oxygen by the reaction mixture was observed at a ratio $N/Cu \simeq 100$, whereas formation of biphenylquinones was noted only at $N/Cu < 10$.[244] The specific rates of C–O and C–C coupling were calculated by means of the equations

$$R_{C-O} = f_P \cdot R; \quad R_{C-C} = f_Q \cdot \frac{R}{2}$$

where f_P and f_Q are the yields of poly(phenylene oxides) and biphenylquinones respectively, while R is the actual rate of absorption of oxygen. Table 8 shows that both R_{C-O} and R_{C-C} increase with increase in N/Cu, with the former increasing more rapidly, so that polymerisation predominates.

Table 8. Specific rates of C–C and C–O coupling of 2,6-dimethylphenol under the influence of oxygen on a copper–pyridine catalyst.

N/Cu	$10^3 \cdot R_{C-O}$	$10^3 \cdot R_{C-C}$
0.67	0.0065	0.0256
1.0	0.0338	0.0505
2.0	0.267	0.112
3.0	0.639	0.162
10.0	3.90	0.270

Later Blanchard et al.[245,246] have shown that the polymers and the quinones are formed on catalysts differing in structure, which are present together in the reaction system.

A study of the relation between degree of conversion (from the absorption of oxygen) and the molecular weight of the poly(phenylene oxide) established[244] that the latter was not very high up to 80–90% of the theoretical absorption of oxygen, but increased rapidly as the stoichiometric quantity was approached. In view of this it was at first assumed that this was a process of step-by-step increase in molecular weight, akin to polycondensation, as was supported indirectly by the ability of dimers and trimers to give a polymer identical with that obtained from the monomer. Since neutral oligo(phenylene oxides) are inert solvents for the process [247,248], a mechanism was suggested in which oxidation of an oligomeric phenoxide anion to the phenoxy-radical is followed by migration of the unpaired electron along the polymer chain from its "tail" to its "head", so that the "head" again becomes anionic, and the "tail" a radical-ion. Addition of the radical "head" of a monomer or an oligomer to such a "tail" makes the number of electrons in the system even, after which the process is repeated [249]. An alternative mechanism was proposed by Cooper, who used trimethylchlorosilane to terminate the polymerisation of dimers at an early stage, and observed considerable quantities of monomer and trimer among the products [55-57]. On the basis of these results a new scheme—of quinol ether equilibrium disproportionation—was set up. The use of labelled atoms [250,251] revealed that exchange of protons in *meta*- and *para*-positions occurred during polymerisation, which was explained by a fresh scheme involving a phenonium intermediate compound (Scheme 2). It was suggested that the hexacyanoferrate(III) and copper–amine methods of synthesising poly(phenylene oxides) occurred by different mechanisms. It was found, however, that the dimeric 4-(4-bromo-2,6-dimethylphenoxy)-2,6-dimethylphenol polymerised in the same way by both methods [252], which could be explained only by the same mechanism—quinol ether equilibrium disproportionation—operating in both cases.

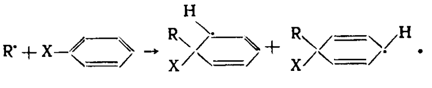
Taking this into account, McNelis [268] represented his own and published experimental results by a fundamentally different general scheme of oxidative polycoupling of phenols to form poly(phenylene oxides) and biphenylquinones (Scheme 1). Analysis of this scheme reveals several defects:

1. The formation of biphenyldiols (VIII) and biphenylquinones (IX) is in no way related to the composition or the structure of the catalyst.

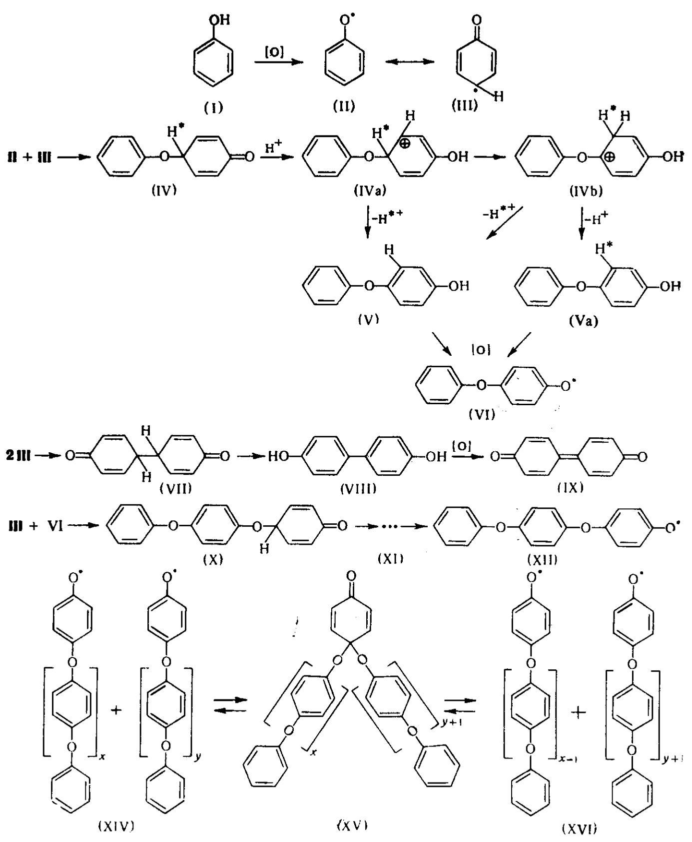
2. The scheme is applicable only to phenols in which the *para*-position is unsubstituted.

3. The stage of conversion of quinol ether (IV) into aryloxyphenol (V) and aryloxyphenoxyl (VI) involves hydrogen ions and should depend on the pH of the medium. In practice, however, replacement of pyridine by trihexylamine and other amines has hardly any effect on the results [24], and the acceleration of the reaction in the presence of caustic alkalis [269-271] is inconsistent with such a mechanism.

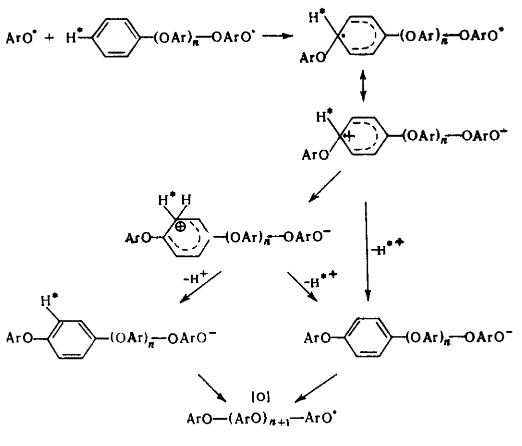
4. Coupling of the isomeric radicals (II) and (III) was presented as probability processes. According to this scheme no biphenylquinone is formed if the system contains very little or no radical (III), but in such case nor could a polymer be formed. Moreover, this scheme takes no account of the work of Milyutinskaya [272], de Tar [273], or Grashey [274], who showed that the addition of free radicals to a benzene ring resembles their addition at a C=C bond:



Scheme 1 (Ref.268)



Scheme 2

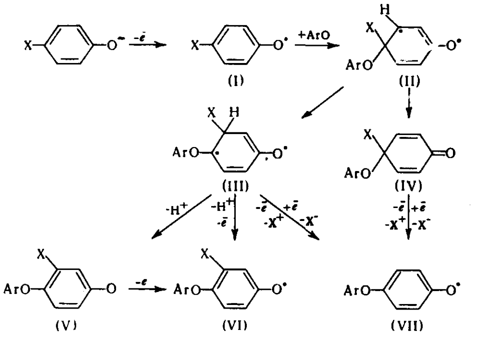


(where H* = H, D, T).

Kopylov and Pravednikov [275] were the first to show experimentally that the synthesis of poly(phenylene oxides) by this method involves free radicals of phenoxyl type, and this was soon confirmed by Waters [276]. Conversion of the monomer, formation of the polymer, and the variation in content of e.p.r. detectable species in the reaction system were used to investigate the kinetics of the process, and a new generalised scheme was suggested [277] in which the process consisted of a series of consecutive reactions of the first order with respect to the monomer and having activation energies of 16–17 kcal mole^{-1} (Scheme 3). On the whole the mechanism of the oxidative polycoupling of phenols to poly(phenylene oxides) is ambiguous, being determined by the oxidisability of the phenol and the nature of the *para*-substituents and also by the oxidant used. The former group of factors can be assessed quantitatively from the distribution of electron density in the phenoxyl radical, which can be estimated from the critical oxidation potentials, the pK of the phenols, or the Hammett constants.

Only certain empirical rules can be derived for the latter group of factors. The catalysts used for the synthesis of poly(phenylene oxides) have been various salts and complex compounds of silver[268,278], cupric and cuprous copper[252-267], and lead[208,214-216], oxides, chelates, and halides of cobalt and manganese[279-285], manganese dioxide[217,221], potassium permanganate[286], nickel peroxide[287,288], iron complexes[192], persulphates[289], organic and inorganic peroxides[169-171], compounds of mercury[290], chromium, iodine, and many compounds of Groups IV – VI elements[291,292], and tri-t-butylphenoxyl radicals[293]. It has also been shown that poly(phenylene oxides) are formed by the oxidation of *p*-phenoxyphenols by air in the absence of a catalyst[201], by their oxidation with chlorine in the presence of copper salts[294], and by the electrolytic oxidation of phenols[211].

Scheme 3



and then as XIV-XV-XVI in Scheme 1, where X = H, D, T, Hal, etc.

It was found here that phenols of low pK yield a polymer only when catalysts of high oxidation potential are used, and conversely. Furthermore, it was definitely established that the activity of the catalyst could be controlled by varying the coordinated ligands. Thus poly(phenylene oxides) of high molecular weights are obtained by the polycondensation of sodium *p*-halogenophenoxides in the presence of complexes of copper(I) chloride with organic compounds containing a tertiary nitrogen atom. The yield and the molecular weight of the polymer vary with the ligand used[295,296]. A similar rule has been noted in the oxidative coupling of amines to give azo-polymers[297].

3. Secondary Processes

Besides the formation of biphenylquinones, several other secondary processes, especially oxidation of the skeleton, complicate the oxidative polycoupling of phenols to form poly(phenylene oxides). Many workers have noted that the resulting polymer is yellowish or reddish, the colour not being removed or even weakened by repeated reprecipitation or purification by Soxhlet extraction. The presence of an absorption band in the region of 1660 cm^{-1} in the infrared spectra of such polymers and the weakening of the colour under the influence of reducing agents indicate that the colour is due to quinonoid groups entering the polymer chain[298]. Peroxy- and hydroperoxy-groups are probably present in poly(phenylene oxides)[192,299-301]. Up to one carboxyl per twenty chain units has been found in the polymer[219,298], its formation being explained by the presence of peroxides in the reaction system. In several cases cross-linked, insoluble, or thermosetting polymers are formed during the synthesis, which can be explained by the production and interaction of functional groups in the skeleton of the polymer chain. The occurrence of such "defects" is due to replacement of the catalyst—of copper halides by acylates—or to a rise in the temperature of the synthesis above a critical value.

When 2,6-xylenol is polymerised in a mixture of chlorobenzene and methanol, the molecular weight of the resulting poly(phenylene oxide) is inversely proportional to the mole fraction of methanol, this being due to precipitation of the polymer when it reaches a certain molecular weight[302].

4. Properties of Poly(phenylene Oxides)

Published information on the properties of poly(phenylene oxides) is extensive and varied—from advertising matter to special reviews and references in textbooks and monographs[303-310]. Only general technical and working properties will be discussed here: questions of the mechanism of synthesis and thermal degradation are discussed elsewhere.

At the present time only poly-(2,6-dimethyl-1,4-phenylene oxide) (2,6-p.ph.o.) is produced on an industrial scale, being manufactured by the General Electric Company in the USA, by A. K. U. in Holland, and by Hodgson-Thomson [*sic*] in France. It is a thermoplastic, non-crystalline linear polyether. The material can be welded by means of ultrasonic vibrations and cemented with organic solvents. Injection moulding and extrusion are effected in standard equipment at 288 – 343°C, the duration of the casting cycle being 15 – 30 s and the pressure employed 850 – 1400 atm. The mould should first have been heated to 120 – 150°C to improve filling; the mould is emptied at 190°C. Preliminary mastication on worm machines is recommended to shorten the casting cycle. This process is used to make tubes, profiled articles, rods, insulation for wire, parts for mechanical and electrical equipment, wood screws, etc. The resistance to heat and moisture and their great chemical stability enable 2,6-p.ph.o. to compete with alloy steel and fluorinated plastics for operation in corrosive media at high temperatures. The high resistance to arcing and the low dielectric loss angle of 2,6-p.ph.o. enable it to be used for the manufacture of parts for electronic equipment. The good dielectric properties permit the employment of this polymer for the electrical insulation of high-voltage lines.

Two brands of 2,6-p.ph.o. —C-1001 pure polymer and Noryl modified polymer—are manufactured on an industrial scale. Furthermore, foam plastics are also obtained from C-1001.[311,312].

The chief characteristics of these materials are listed in Table 9. Goods made of C-1001 withstand 200 treatments in a sterilisation autoclave without change in appearance or mechanical properties. The polymer resists the action of mineral acids and alkalis, salt solutions, organic acids, and aliphatic hydrocarbons and alcohols, swells slightly in ketones, and dissolves in aromatic hydrocarbons, halogenated hydrocarbons, and certain cyclic ethers. Although 2,6-p.ph.o. is usually amorphous, it crystallises on the prolonged heating of a 2-pinene solution[313]. The parameters of the unit cell are $a = 8.45$ Å, $b = 6.02$ Å, and $\gamma = 91°1'$. The dielectric characteristics of the polymer do not vary by more than 20% over the temperature range from −80° to +160°C and the frequency range 10–10^8 c/s.[314] The dependence of certain properties of 2,6-p.ph.o. on molecular weight is given in Table 10.

Such almost unique combination of properties with simplicity of production and processing ensure for 2,6-p.ph.o. wide practical applications—from high-frequency insulation to parts of chemical equipment, from surgical instruments to units in the construction of sputniks. Information is available on the production from it of films and fibres by spinning from solutions and melts[315-317].

Table 9. General characteristics of poly(phenylene oxides).

Property	Units	C-1001	Noryl
Tensile strength at 23°C	kgf cm^{-2}	750	675
Tensile strength at 125°C	ditto	420	—
Modulus of elasticity at 23°C	»	26000	24500
Modulus of elasticity at 125°C	»	23000	—
Relative extension on rupture at 23°C	%	80	20
Residual extension at 23°C	%	9	8
Cold flow at 23°C under 200 kgf load after 300 h	%	0.75	—
Bending strength at 23°C	kgf cm^{-2}	1000	—
Impact strength	kgf cm cm^{-2}	750—970	—
Rockwell hardness	—	118	119
Abrasion	g/1000 rev	0.017	—
Coefficient of friction to rotation on the material	—	0.18—0.23	—
Colour	—	beige	black
Density	g cm^{-3}	1.06	—
Optical properties	—	opal	opaque
Odour	—	none	none
Absorption of moisture at 23°C during 7 days	%	0.1	—
Absorption of moisture at 100°C during 7 days	%	0.3	—
Coefficient of linear expansion	10^{-5}/°C	5.2	6.7
Moulding shrinkage	%	0.8	0.5—0.7
Deformation temperature under 19 kgf cm^{-2} load	°C	191	—
Rate of burning	—	—	self-extinguished
Temperature of loss of flexibility	°C	—170	—
Breakdown voltage	V mm^{-1}	16000—20000	—
Volume resistivity	ohm cm	10^{17}	—
Dielectric constant at 60 c/s	—	2.58	—
Dispersion factor at 60 c/s	—	0.00035	—
Dispersion factor at 10^6 c/s	—	0.00090	—

The characteristics of poly(phenylene oxides) obtained by other methods or having a different structure from 2,6-p.ph.o. can be briefly summarised as follows: (1) all poly(phenylene oxides) possess high thermal stability (this will be discussed in greater detail in the following subsection); (2) all poly(phenylene oxides) possess good hydrolytic and chemical stability and good electrical properties; and (3) various polymers having specific properties can be prepared from poly(phenylene oxides) by various polymerlike transformations.

A base for high-temperature adhesives has been obtained by the epoxidation of copolymers of 2,6-xylenol and 2-allyl-6-methylphenol[240].

A series of papers has been published on the preparation of ion-exchange resins having a poly(phenylene oxide) matrix. An anion-exchange resin has been prepared by the dimethylamination of chloromethylated 2,6-p.ph.o. [318-321]. Treatment of 2,6-p.ph.o. or chlorinated 2,6-p.ph.o. with chlorosulphuric acid, oleum, trialkyl phosphites, potassium cyanide, and other reagents followed by hydrolysis or reduction gives cation exchangers and anion exchangers based on poly(phenylene oxides) and having exchange capacities up to 4.0 m-equiv. g^{-1}.[322-339] Most of these ion exchangers are soluble in organic solvents, and from the solutions yield durable elastic films of electrical resistance 4 ohm cm and above, which can be used as membranes in fuel cells and for other purposes. The conductivity of these membranes is determined by the degree of sulphonation, which depends on the reaction conditions[335]. Electron-exchange resins and semiconductors have been based on poly(phenylene oxides)[324]. The ion-exchange resins are used for the coagulation of photographic emulsions[339], for the production of antistatic coatings[329,331], etc. The action of *N*-bromosuccinimide on 2,6-p. ph.o. in the presence of benzoyl peroxide results in bromination of the methyl groups. By choosing different catalysts it is possible to control the chlorination of 2,6-p.ph.o. to produce substitution in the benzene ring or in the methyl groups[319,321]. As analogue of benzyl halides the products are highly reactive, are easily hydrolysed, form quaternary ammonium salts with amines[318,329], and can be reduced to the original polymer[340].

Table 10. Properties of poly-(2,6-dimethylphenylene oxides) of different molecular weights.

Property	Units	Specimens		
		No. 1	No. 2	No. 3
Intrinsic viscosity $[\eta]$	dl g^{-1}	0.635	0.780	0.920
Dispersion factor tan δ	–	0.00245	0.00200	0.00146
Dielectric constant ϵ	–	2.54	2.2—2.4	2.50
Volume resistivity $10^{-16}\rho_V$	ohms	7.41	2.8—3.8	—
Tensile strength σ	kgf cm^{-2}	—	775.4	705
Relative extension ϵ	%	—	8.3	8.7
Vicat thermal stability	°C	225	222	—
Vickers hardness	–	18.9	17.2	—
Dinstat impact resistance	–	—	7.7	—

Under mild conditions poly-(2,6-diallylphenylene oxide) is oxidised to the corresponding carboxylic acid, with incidental degradation of the polymer chain and considerable decrease in the molecular weight[235].

The infrared spectra of poly-(2,6-dimethylphenylene oxides) have been investigated in some detail. All authors agree in asigning the absorption bands at 835 and 855 cm^{-1} to a tetrasubstituted benzene ring, at 1180–1190 cm^{-1} to an ether bond, at 1232 cm^{-1} to a *para*-substituted benzene ring, at 1300 and 1380 cm^{-1} to aliphatic C–H bonds, and at 1490 and 1600 cm^{-1} to C=C bonds in the benzene ring. Some divergence appears in the asignment of bands at 3400–3500 cm^{-1}, in the region of vibrations of the hydroxy-group. Hay[213] considers this band as due to the presence of traces of water. Endres[244] explains it as originating in terminal phenolic hydroxyls, the content of which per macromolecule is calculated as 1.5 group. Laborie-Gardaix[223] also attributes this band to hydroxy-groups in the polymer, without specifying their position. Kopylov and Pravednikov regard this band as due to the presence of carboxy-groups in the polymer[298]. The most debatable are the bands at 1660, 1690, and 1720 cm^{-1}, which have been ascribed to residual catalyst[213], overtones of out-of-plane C–H vibrations[213], a C=O group of undefined position[135], a tetrasubstituted benzene ring[224], and a carboxylic or quinonoid C=O group[219,220,298].

The molecular weight of the poly(phenylene oxides) also proved to be a quite complicated problem, since large discrepancies were observed depending on the method of determination. From an analysis of end-groups Price[192] derived for 2,6-p.ph.o. the equation

$$[\eta] = 8.7 \cdot 10^{-8} M^{0.876}$$

linking the intrinsic viscosity in benzene at 30°C with the molecular weight. Tsou[238] compared viscometric and osmometric data in benzene at 25°C, and suggested the equation

$$[\eta] = 1.5 \cdot 10^{-7} M^{1.44} \quad .$$

Hay and his coworkers[341,342] determined the molecular weights of a series of poly(phenylene oxides) by osmometry and light scattering, and obtained the values given in Table 11. A systematic investigation of the viscosity, osmotic pressure, and light scattering of dilute solutions of fractionally precipitated 2,6-p.ph.o. led Pepper et al.[343,344] to establish the following formulae at 25°C:

$$\text{in toluene} \quad [\eta] = 2.85 \cdot 10^{-4} M^{0.68 \pm 0.02} \quad ,$$
$$\text{in chlorobenzene} \quad [\eta] = 3.78 \cdot 10^{-4} M^{0.66 \pm 0.02} \quad ,$$
$$\text{in chloroform} \quad [\eta] = 4.83 \cdot 10^{-4} M^{0.64 \pm 0.02} \quad .$$

Table 11. Viscosity and molecular weight of some poly(phenylene oxides) obtained by the oxidative polycoupling of phenols.

Monomer	$[\eta]$ in $CHCl_3$ at 25°C, dl g^{-1}	Mol. wt. of polymer from	
		osmometry	light scattering
Phenol	0.070	18500	66000
	0.085	28000	—
	0.095	41000	710000
	0.115	58000	—
	0.200	80000	6100000
o-Cresol	0.190	44000	382000
2,6-Xylenol	0.450	63000	2150000
	0.185	16500	114000
	2.140	165000	6780000
o-Phenylphenol	0.150	47700	1220000
o-Chlorophenol	0.240	82000	5400000

The size of the undisturbed molecular tangle in the same solvents was calculated as (883 ± 10), (830 ± 5), and (845 ± 20) $\times 10^{-11}$ cm mole$^{0.5}$ g$^{-0.5}$ respectively.

5. Thermal Properties of Poly(phenylene Oxides)

Two aspects of the thermal degradation of aromatic polyethers must be distinguished. The degradation of the phenylene oxide chain itself has been studied in sufficient detail on oligo(phenylene oxides). This case is hardly ever met in poly(phenylene oxides) of high molecular weight, since these polyethers begin to break down at lower temperatures under the influence of end-groups, chain defects, and functional groups in the framework. The phenylene oxide chain itself is stable in an inert atmosphere and in air at least up to 500°C, as Stille and his coworkers[25] showed, for example for poly(penta-*p*-phenylene oxide) prepared by Diels–Alder condensation. It was also shown that the thermal stability of polymers containing aromatic hydrocarbon or heterocyclic rings joined by carbonyl, sulphonyl, and/or oxygen bridges equals or exceeds that of polyphenylenes[345]. It was found that, in the case of poly-(*p*-phenyleneethylene-*p*′-phenylene oxide) in air for 2 h, loss in weight, beginning at 375°, reaches 50% by 425° and 80% at 450°C, the activation energy of this process being 40 kcal mole^{-1}. The polymer specimen investigated had a molecular weight of 5000 and a softening point of 150°C, and was soluble in chloroform. Neither the mechanism of degradation nor the composition of the products was examined.

Cox and his coworkers[193] made a kinetic study of the thermal degradation of a large number of poly(arylene oxides) prepared by the polycondensation of halogenated phenols and containing 3–70 monomer units in the polymer chain. The structure of these units and the properties of some of the polymers are given in Table 12.

Table 12. Properties of some poly(phenylene oxides) obtained by polycondensation[193].

Polymeric	Mol. wt.	Solubility	Softening temp.	$T_{50\%}$*
m-Phenylene oxide	1800/A	—	465	610 (40%)
o-Chloro-*p*-phenyl oxide	—	+	270	590
p-Phenylene oxide (I)	7700/A	—	315	515 (31%)
p-Bromo-*o*-phenylene oxide–*p*′-phenylene oxide	4000	—	500	550
2,6-Dichloro-1,4-phenylene oxide	9600/B	+	190	480
p-Phenylene oxide (II)	2800/B	+	285	480
o-Bromo-*p*-phenylene oxide	—	+	240	510
2-Bromo-6-*p*- chlorophenyl-1,4-phenylene oxide	—	+	310	470
2,6-Dibromo-1,4-phenylene oxide	3150/B	+	240	445
pp′-Biphenylylene oxide	2000	+	155	470 (48%)
o-Fluoro-*p*-phenylene oxide–*p*′-phenylene oxide	4200	+	210	445
2,3,6-Trichloro-1,4-phenylene oxide	—	+	210	425
6-Bromo-4-phenyl-1,2-phenylene oxide	1400/B	+	265	445
2,6-Dibromo-1,4-phenylene oxide–4,6-dibromo-1,2-phenylene oxide	2800/B	+	210	425
2,3,5,6-Tetrabromo-1,4-phenylene oxide	—	+	300	380
2,3,5,6-Tetrachloro-1,4-phenylene oxide	1450/B	+	195	370
2,5-Dichloro-1,4-phenylene oxide	—	+	215	135

Notes: A = analysis of end-groups; B = cryoscopic measurements. Solubility in organic solvents in the cold and on heating.

* Temperature at which 50% loss in weight is achieved in 2 h. In the second column a minus sign means insoluble, and a plus sign soluble.

It was established that degradation of most of the polymers investigated took place in two stages. There was a considerable loss in weight during the first stage. After this, the losses diminished sharply, owing to stabilisation of the polymer probably caused by the formation of a system of fused aromatic rings after the loss of substituents, X-ray examination showed that, at a pyrolysis temperature of 400°C, the non-volatile residue was almost identical with the initial polymer. With a pyrolysis temperature of 600°C the rings were randomly arranged in the residue, and after 1000°C the residue contained structures comprising 3–4 fused rings. After degradation at 400°C the elementary composition of the residue was close to that of the original polymer, but at higher temperatures the carbon content of the residue increased, and the hydrogen content decreased.

The relative stability of the polymers investigated was expressed in terms of the temperature at which heating the polymer for 2 h results in half-decomposition (50% loss in weight). These values are also included in Table 12. With increase in the number of substituents in the aromatic ring the thermal stability diminishes. The anomaly observed with poly-(2,5-dichlorophenylene oxide) is probably due to 2,3,7,8-tetrachlorodibenzo-*p*-dioxan structures, either present in the specimen or formed during degradation. With the exception of the tetra-substituted poly(phenylene oxides), the chlorinated polymers are more stable than the brominated derivatives. Polymers in which rotation about the oxygen atom is difficult are the least stable. Poly(phenylene oxides) having the same structure but obtained by different methods differ in thermal stability. The rate constants of the initial stage of degradation can be represented by the equations $k = 10^{12} \exp(-52\,000/RT)$ and $k = 10^{10} \exp(-43\,000/RT)$ for poly-(2,3,6-trichloro-1,4-phenylene oxide) and poly-(2,3,5,6-tetrabromo-1,4-phenylene oxide) respectively.

Most of the degradation products of poly(phenylene oxides) consisted of compounds which were volatile at the pyrolysis temperature but not volatile at room temperature. Compounds volatile at room temperature constituted not more than 4% of the total products. An attempt at a mass-spectroscopic analysis of the composition of the thermal degradation products was unsuccessful because of the complexity of the mass spectra, and therefore the authors refrained from expressing any ideas on the mechanism of degradation.

Thermogravimetric data indicate that the degradation of 2,6-p.ph.o of molecular weight ~10 000 begins in an atmosphere of nitrogen at 350°, goes most rapidly at about 400°, reaching 65% in extent, and then slows down markedly, the loss in weight reaching 70% by 900°C.[240] Other results indicate weight losses of 1%, 13%, and 69% at 320°, 370°, and 420°C.[192] After degradation at 320° and 370°C no products which condense out in a liquid nitrogen trap are observed, and after degradation at 420°C most of the products condense out at room temperature.

Heating 2,6-p.ph.o. with an equimolecular amount of phenol in the presence of a free-radical type of catalyst at 150–250°C results in the formation of 4-aryloxy-2,6-dimethylphenols and the corresponding trimers[42]. In the electrolytic oxidation of 2,6-p.ph.o. of molecular weight 20 000 at potentials up to 1.6 V only a portion of the polymer is converted into 2,6-dimethylbenzoquinone and 3,3′,5,5′-tetramethylbiphenylquinone; the unoxidised residue was not investigated[346].

Investigation of the thermal properties of 2,6-p.ph.o. of molecular weight about 40 000 in a differential adiabatic calorimeter showed[347] that its melting point was 267°C (540°K), its glass point 221°C (498°K), and its specific heat of fusion 16.4 J g^{-1}. The abnormally high T_{gl}/T_m ratio was attributed to the residual entropy of the amorphous polymer. Degradation of the polymer in an atmosphere of nitrogen began at about 460°C with a strongly exothermic process. The discrepancy in the temperature at which degradation begins, in comparison with the results of other workers, was explained by differences in the molecular weight and the method of preparation of the polymer.

Petris used a thermomechanical method and obtained different values for the glass point[348]. He found temperatures of 600°, 480°, and 400°K respectively for poly-(1,4-phenylene oxide), poly-(2,6-dimethylphenylene oxide), and poly(diphenylenepropane–diphenylene sulphone oxide).

The thermo-oxidative degradation of poly-(2,6-dimethylphenylene oxide) of molecular weight 40 000 and of the corresponding 2-isopropyl-6-methyl polymer of molecular weight 10 000 was investigated at temperatures up to 500°C by Conley and Alvino[349]. In an inert atmosphere thermogravimetric results were consistent with those of other investigators, but in air loss in weight began at 150°C with the dimethyl polymer, some increase was then observed at about 250°C, after which degradation rapidly reached 100% by 400°C. In argon the isopropyl methyl polymer behaved in the same way as the dimethyl polymer, but this behaviour did not change in air. Differential thermal analysis of the dimethyl polymer showed a strong exothermic effect at 210°C, overlapped by a still stronger endothermic effect in the range 250–270°C. Infrared spectroscopy indicated the appearance and increase in intensity of absorption bands in the range 1660–1720 cm^{-1}, which were attributed to a carboxy-group and to quinonoid structures. The mass spectra of the volatile degradation products were too complicated to be deciphered; with the dimethyl polymer the mass spectra were almost identical for degradation in inert and oxidising atmospheres. In both cases chromatography showed the presence of sixteen products, three of which, constituting up to 40% of the total quantity, could be identified as substituted phenols and quinones. With the isopropyl polymer the main products were water and acetone. No viscometric results could be obtained for the residues because of gel formation.

The scheme suggested for degradation of the isopropyl polymer involves attack on a tertiary hydrogen atom by oxygen followed by the cumene hydroperoxide type of decomposition into acetone and phenol with further cross-linking of the polymer of the ether, dioxan, or biphenyl type.

Oxidation of the methyl group is assumed to involve the successive formation of CH_2OOH, CH_2OH, CHO, and COOH groups with decarboxylation of this last group and parallel processes of cross-linking of the polymer by interaction of the groups. In both cases cleavage of the polymer chain was probably due to attack by aryloxy-radicals, but the mechanism was not specified. Kelleher and his coworkers[299-301] have studied the oxidative degradation, initiated by heat and by light, of poly-(2,6-dimethylphenylene oxide) at 100° and 125°C. The experiments were made on films of the polymer 0.025 and 0.15 mm thick, of intrinsic viscosity 0.32. The films were heated in air in the dark or in ultraviolet radiation for up to 10 000 h. Elementary analysis of the initial polymer indicated excess of oxygen—13.51% in comparison with 13.32% calculated for the formula C_8H_8O—and traces (0.14%) of nitrogen, which was regarded as indicating some oxidation of the polymer even during preparation and contamination by the catalyst. However, an alternative interpretation can be given for this fact, for the experiment was made on industrial specimens of the polymer which had been carefully purified, so that the retention of traces of catalyst in the polymer was doubtful. On the other hand, picric acid is a good initiator for synthesis of this polymer[341], and calculation based on Pepper's formula[343] gives a value of 55 000 for the molecular weight of the polymer. Accepting a bimolecular mechanism of termination during polymerisation, i.e. assuming the macromolecule to contain two $C_6H_2(NO_2)_3O$ end-groups, we obtain calculated oxygen and nitrogen contents of 13.67% and 0.153%.

As the polymer specimens aged under the above conditions their oxygen content increased from 13.51% to 17.95%. At the same time the intensity of absorption increased in the region of the hydroxy-group and at 1695 cm^{-1} (carboxyl C=O group), while a weak absorption band appeared at 1660 cm^{-1}. The mass spectrum of the volatile degradation products shows the formation of carbon dioxide and traces of hydrogen. Losses in weight reached 2% during the first 200–500 h, and increased to 4% by 10 000 h. Up to 10% of a gel fraction was formed on ultraviolet irradiation, and up to 80% in the dark. The intrinsic viscosity of the soluble fraction fell to 0.49, compared with an initial value of 0.52. The authors regard this as indicating that the molecular weight of the polymer does not change, which can hardly be correct, for the appearance of a large quantity of functional groups in the framework should result in a change in the rigidity of the macromolecule and a decrease in the viscosity of the solution. The maintenance of the viscosity in this case indicates an increase in the molecular weight of the polymer, i.e. the first stage of cross-linking. The 0.15-mm film after exposure in air to ultraviolet radiation for 2 min gives an electron spin resonance signal with $g = 2.0065$, probably due to radicals of phenoxyl type; exposure in a vacuum doubles the intensity of the signal.

The mechanism suggested for the process involves formation of phenoxy-radicals in the polymer as the first stage. There are three sources—decomposition of hydroperoxides present in the initial polymer, photolysis of an Ar–O–Ar bond, or breakdown of hydroperoxides formed during the experiment—for such radicals. The radical chain grows by the attack of an aryloxy-radical on the methyl groups, formation of phenol and a benzyl radical following addition of oxygen, etc. by a branching kinetic chain, terminated by cross-linking of the polymer or the formation of hydroxymethyl, oxomethyl, carboxyl, and other groups in the framework.

A systematic study of the thermal degradation of a series of poly(phenylene oxides) made by Kopylov and Pravednikov[350,351] established the following generalisations:

1. At 175–300°C quinol ether groups in the polymer dissociate by a first-order reaction having an activation energy of 22–23 kcal $mole^{-1}$, with the formation of terminal radicals of phenoxyl type.
2. At 350–450°C these radicals initiate degradation of the polymer chain, which under their influence undergoes random breakdown into a mixture of fragments, mainly hexamers of phenylene oxide structure containing hydroxy- and oxo-groups.
3. Increasing the molecular weight of the poly(phenylene oxide) and blocking the end-groups tends to improve the thermal stability of the polymer and increase the activation energy of degradation from 15–20 to 30–40 kcal $mole^{-1}$.

These authors suggested a general scheme for the thermal degradation of alkylated poly(phenylene oxides) involving radicals of phenyl, phenoxyl, and benzyl types as well as quinone methides. The conclusions reached in this work are confirmed by the effective stabilisation of poly(phenylene oxides) by blocking their end-groups by arylation, alkylation, alkoxylation, acylation, or the action of isocyanates, thiols[352-359], phosphites, or borates[360,361].

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Oligo-, meso-, and poly-(phenylene oxides) constitute a separate class of organic compounds. They exhibit several identical chemical properties—high resistance to acid and alkaline hydrolysis, stability towards oxidants, ability to form complexes, and readiness to undergo substitution rather than addition and cleavage—besides having the same chemical structure. On the other hand, all these compounds are equally inclined to interact with free-radical species, which results in breakdown of the phenylene oxide chain, except in rare cases of self-stabilisation. With regard to practical application phenylene oxides are of greatest value as materials stable to heat and radiation and as a durable basis for several polymerlike transformations.

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Karpov Physicochemical Institute,
Moscow

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Recent Advances in Ion-exchange Catalysis

N.G.Polyanskii

Since the last review article on this topic was published by the writer seven years ago, a great deal of experimental information on the use of ion-exchange resins as organic reaction catalysts has become available, the range of techniques for ion-exchange catalysis has been extended, new types of resin have been examined, and some important theoretical generalisations have been formulated. Reviews by Andreas[2], Sugihara[3], Kaldor[4], and Mulder[5] have dealt with various aspects of the problem: the most extensive of these[3] gives 136 references, mainly up to 1960. The present article discusses some theoretical problems in ion-exchange catalysis, and the use of ion-exchange resins as catalysts in the hydration, dehydration, hydrolysis, esterification, alkylation, polymerisation, isomerisation, and condensation of organic compounds. 254 references.

CONTENTS

I. THEORETICAL PROBLEMS IN ION-EXCHANGE CATALYSIS

Helfferich[6] has defined the effectiveness q^1 of an ion-exchange resin, and has related it to the distribution coefficient λ of the reactants between the catalyst phase and the solution phase. He treats the liquid surrounding the resin particles as an inert medium whose only function is to contain and supply the reactants. This outer solution is in equilibrium with an immobile liquid phase in contact with the resin, which is considered to be the true seat of the reaction. Since the immobile liquid is not separated from the active centres of the resin by an interface, Helfferich[6] treats ion-exchange catalysis as a special case of homogeneous catalysis, whilst recognising that (as in the case of heterogeneous catalysis) rate limitation may be associated with inner diffusion effects.

Combining the concept of resin effectiveness with the hypothesis of a quasi-homogeneous reaction, Helfferich[6] examined the relationship between the former quantity and the distribution coefficient of the reactants between the phases.

Defining the distribution coefficient as the ratio of the molalities of the reactant in the resin phase ($\bar{m}_{AB}$) and in the solution phase (m_{AB}), we have

$$\bar{m}_{AB}/m_{AB} = \lambda. \tag{1}$$

Hence, the reaction rate in the presence of the resin can be written

$$v_r = k_r\bar{m}_{AB} = k_r m_{AB}\lambda , \tag{2}$$

whereas under homogeneous conditions the rate is

$$v_h = k_h m_{AB}. \tag{3}$$

Assuming that both rate constants are proportional to the concentration of catalytically active ions (m_{cat}), which are present in equivalent numbers, we have

$$k_r = k'_r m_{cat} \tag{4}$$

$$k_h = k'_h m_{cat}. \tag{5}$$

Substituting the values of k_r and k_h from (4) and (5) into (2) and (3), we finally arrive at

$$q = (k'_r/k'_h)\lambda. \tag{6}$$

Eqn. (6) describes the main specific feature of ion-exchange catalysis, and underlines the possibility of differences in the composition of the reacting system as between the resin phase and the bulk of the solution.

The experimental determination of the distribution coefficient presents some difficulties[7], which were ingeniously overcome by Tartarelli in his work on the application of Eqn. (6) to the hydrolysis of a series of aliphatic carbonate esters[7]. Relatively little work of this type has been published so far, but it has already made a significant contribution to our understanding of the influence upon ion-exchange catalysis of the factors which control the distribution coefficient (nature of the solvent, size of the reactant molecules, structure of the resin network).

The stability of the resin in operation is of the utmost importance to the theory and practice of ion-exchange catalysis. The commonly observed loss of catalytic activity of the resin during a reaction is frequently due to a gradual decrease in the number of catalytically active ions. The detailed mechanism of structural changes of this type within cation- and anion-exchange resins has been studied by the writer and his coworkers. A relationship has been established[8,9] between the thermal stability and the catalytic activity of ion-exchange media towards the polymerisation of tertiary pentenes, and the correctness of this approach has been confirmed in a study[10] of the racemisation kinetics of $d(+)$-α-isobutyldesoxybenzoin.

However, it would be wrong to ascribe all changes in activity to desulphonation, deamination, or degradation effects. In some reactions which take place under particularly mild conditions, such as the hydration of propylene oxide[11] and the decomposition of ethyl diazoacetate[12,13], the activity of sulphonated resins is found to decrease quite rapidly although desulphonation under the experimental conditions seems unlikely. It was found that in these systems the pores of the resin particles are blocked by reaction products, and reactant molecules are therefore unable to reach the active sites. The steric hindrance opposing access to some of the counterions present in the resin has been shown[12] to be high enough to prevent alkalimetric titration[14] of these ions at room temperature. The number of hydrogen ions corresponding to the initial exchange capacity can be set free only by boiling the treated resin with an aqueous solution of sodium sulphate. Gaseous nitrogen (produced by the decomposition of the diazoacetate and responsible for the loss of catalytic activity) is released at the same time.

As a result of this blocking effect, the rate constant for the reaction falls quite quickly to some limiting value, whose level is lower, the greater the degree of cross-linking of the resin catalyst. The changes in catalytic activity can be accompanied by changes in the kinetic order of the reaction[13].

In the present case, the change in catalytic activity is described by the equation

$$H=(H_A-H_R)e^{-\frac{\alpha u}{H_0}}+H_R, \qquad (7)$$

where H is the activity at the instant when the extent of reaction is u, H_A and H_R are the initial and the final residual activity respectively, H_0 is the ideal activity of the catalyst in the absence of diffusional limitations, α is the activity decrease coefficient (a measure of the probability of retention of gaseous nitrogen in the resin), and e is the base of natural logarithms. Eqn. (7) can be treated as a general equation for the change in activity of a resin under the influence of blocking by any reaction product.

Frisch[15] has discussed the mechanism of the loss of activity of macroporous resins and some special aspects of the kinetics of catalytic reactions in the presence of these resins. A useful attempt is made in that work to identify the optimum catalyst porosity (corresponding to maximum activity).

Saito[16] has produced a mathematical theory of the reaction rate in ion-exchange catalysis, with allowance for the influence of particle size, the degree of cross-linking, and the distribution coefficient of the reactants.

Thus, some attempts at generalising the results of experiments on ion-exchange catalysis have been made during the period covered by the present review. The ultimate objective of the present stage is the development of a full, quantitative theory of reactions proceeding in the presence of ion-exchange resins.

II. ION-EXCHANGE CATALYSIS IN ORGANIC SYNTHESIS

1. Hydrolytic Reactions

Because hydrolytic reactions are reversible, they are seldom carried out (at least for preparative purposes) as batchwise processes[17,18]. The reactor is usually a three-necked flask fitted with stirrer, reflux condenser, and thermometer, held in a thermostat bath. The catalyst is added to the reaction mixture when the desired temperature has been reached. A nitrogen atmosphere is used when the reactants are sensitive to atmospheric oxygen[17].

The static method is useful for determining the distribution coefficient of the reactants and solvents between the resin and the solution phase. The measurement is made rapidly, without allowing the reactant concentrations in the bulk of the solution and in the resin to change[6]. If the cation exchange resin is used in the sodium rather than in the hydrogen forms[7], the risk of hydrolysis during analysis is eliminated.

The static method has occasionally been used to study the kinetics of hydrolysis[19] by keeping the reaction mixture and the catalyst for a known time in sealed tubes in a temperature-controlled centrifuge, quenching the reaction by cooling, and analysing the mixture.

Dynamic methods require more complicated apparatus, but they have been widely used in preparative work[20-22] as well as in kinetic studies of hydrolysis[7,23-25]. The reactor usually consists of a column, packed with a layer of the resin, and carrying a continuous flow of the reaction mixture. The equilibrium can be strongly displaced towards hydrolysis by distilling off the volatile reaction products[20] or by extraction[21]. In this way the efficiency of the apparatus and the yield of the desired product can be made very high[27], and energy losses can be minimised[21]. Some reactions (e.g. the hydrolysis of pentaerythritol trichlorohydrin monobutyrate[22]) can only be exploited under dynamic conditions. Spes[21] has described a rational continuous process which offers quantitative hydrolysis yields with minimum consumption of energy.

The best hydrodynamic flow conditions are obtained with a column packing of sulphonated polystyrene catalyst rings[22] or of ion-exchange resins mixed with porous polyethylene[21].

The following compounds have been hydrolysed with ion-exchange catalysts†: ethyl acetate[27] (KU-1), methyl acetate[28], methyl lactate[29] (Duolite-C25), allyl acetate[30] (Amberlite-IR 120), ethyl malonate[31] (Dowex-50 W), esters of dicarboxylic acids[32] (KU-2), simple vinyl esters of aliphatic and aromatic alcohols[20] (KU-2 and SG-50), saccharose (Amberlite-IR 120 + Amberlite-IRA 410)[33], starch[34] (sulphonated coal), protein fractions of molecular weight 600–2000[35] (KMT), phenylalanine peptides[17] (Amberlite-IR 113), and ethyl iodide[19] (various anion exchange resins). In the latter case the resin plays the part of a reactant, by taking up acidic products and thus displacing the equilibrium in the desired sense.

The most typical saponification catalysts for esters are cation exchange resins in the hydrogen form, occasionally promoted by Ag ions[30,36] or by Group IVB and VB elements of the Periodic Table[29]. In all reactions so far examined, sulphonated resins have been more effective than carboxylic acid resins. Some reactions (e.g. the hydrolytic cleavage of vinyl phenyl ether) occur only on sulphonated resins.

The efficiency of cation exchange resins towards hydrolytic reactions depends not only on the nature of the active groups but also on the structure of the polymer network. Thus, the hydrolysis of Sarin [isopropylmethylphosphonofluoridate (Ed. of Translation)] is hardly catalysed by a sulphonated phenol–formaldehyde cation exchange resin, but it is quite fast in the presence of the sulphonated styrene–divinylbenzene copolymer[37].

Hydrolytic reactions are usually carried out at relatively low temperatures, where the stability of cation exchange resins is fairly high. Hence there is no reason to doubt the good operating lives of cation-exchange catalysts reported in the literature. According to a group of Soviet workers[22], a granular sulphonated styrene–divinylbenzene copolymer, operated intermittently during 3 years for hydrolysis and esterification reactions, has retained its activity for 500 h without regeneration. Mixed resins, containing 50 wt.% of Amberlite-IR 120 in a matrix of polyethylene, showed no detectable change after 5000 h operation[21]. On the other hand, Dowex-50w X 8 cation exchange resin suffered blocking effects, particularly at elevated temperatures, when used as an inversion catalyst for concentrated saccharose solutions[38].

The kinetic aspects of ion exchange catalysis have been investigated in the fullest detail for the case of hydrolytic reactions.

As in homogeneous acid-base catalysis, the rate of hydrolysis in the presence of resins increases (other things being equal) with the number of catalytically active ions. In some reactions (e.g. the hydrolysis of Sarin in aqueous solutions with a sulphonated resin catalyst)[37] the reaction rate is a linear function of the quantity of catalyst added. The specific rate constant of these reactions, referred to 1 g of resin or to 1 mg-equiv. of sulphonic acid groups, is independent of the amount of catalyst. However, these

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† Throughout this paper the grade of resin is shown in brackets.

relationships become more complicated when diffusional limitations are involved. The specific rate constant for the inversion of saccharose in aqueous solution[39] decreases continuously from 4.63×10^{-6} to 3.96×10^{-6} s^{-1} mg-equiv.$^{-1}$ on increasing the amount of KPS-200 resin catalyst from 1.16 to 6.87 g. The specific rate constants for the hydrolysis of the diesters of dicarboxylic acids in water–dioxan solutions remain constant as the proportion of KU-2 resin is increased up to 25%,[40] but they begin to fall off at higher concentrations, which the authors ascribe to diffusion-limited access to some of the H^+ ions in the sulphonic acid groups.

As in the case of homogeneous acid–base catalysis, the rate of hydrolysis in the presence of ion-exchange resins is influenced by the strength of the bond being attacked (i.e. by the chemical nature of the compound). However, and in contrast to homogeneous catalysis, the steric factor (defined as the ratio of the size of the reactant molecules to the distance between the counterions of the nearest active groups in the catalyst) plays an important role in ion-exchange catalysis. This effect accounts for the often reported influence of molecular size on reaction rate. Ordyan and coworkers[41] found that methyl acetate is hydrolysed 5 times faster than butyl acetate, and the latter only 1.2 times faster than methyl valerate. The ratio of the rate constants for the esters of the C_5 acids (valeric, trimethylacetic, and isovaleric) is 3.29 : 1.31 : 1, indicating that the reaction is retarded by branched chains: similar effects have also been observed[7] with n- and isopropyl acetate.

It is important, however, not to overestimate steric conditions as a kinetic factor in ion-exchange catalysis. Thus, disaccharides show widely different rates of hydrolysis despite the fact that the geometrical conditions of the reaction are practically identical in all cases. Saccharose, in which the C–O–C bond joining the monosaccharide residues is less stable than in its isomers, is hydrolysed 100 times faster than maltose and cellobiose on KPS-200 resin[13].

Inert solvents can have a profound effect on the rate of hydrolysis. The rate constants for the hydrolysis of ethyl acetate[27] and acetanilide[42] in aqueous acetone solutions decrease as the mole fraction of acetone increases. We must assume that the inhibition of the reaction by increased concentration of organic solvent is due not only to the lowering in dielectric constant but also to the different distribution of reactant molecules between the solid and the liquid phase. As the concentration of acetone increases, the relative amount of water absorbed by the resin also increases, and this effect hinders the penetration of relatively insoluble compounds into the resin. Bolton and Henshall[42] conclude, from their experimental results, that sparingly soluble compounds are most efficiently hydrolysed in the presence of the minimum amount of organic solvent required for their dissolution. The relationship between the reaction rate and the dielectric properties of the medium is not always unequivocal. For example, the rate of hydrolysis of dimethyl sebacate in water–dioxan and water–acetone solutions in the presence of KU-2 cation exchange resin goes through a maximum on varying the ratio of water to organic solvent[32].

The influence of the organic solvent on the efficiency (as defined by Hammett) of the resin catalyst was discussed at length in our previous review[1]. In aqueous solutions the efficiency of resins with an intermediate degree of cross-linking towards the hydrolysis of acetates[7] and of ethyl acetoacetate[31] is in excess of unity. The efficiency of a strongly cross-linked cation exchange resin[22] towards the hydrolysis of methyl acetate is well below unity, probably as a result of diffusional limitations.

Reactants having large molecules are particularly sensitive to changes in the content of bridging component. The hydrolysis of Sarin[37] was used to demonstrate the rapid increase in rate constant accompanying a decrease in the divinylbenzene content of the resin from 8 to 1%. It was shown that the catalytic activity of the weakly cross-linked cation exchange resin is comparable to that of soluble acids.

Many workers have examined the influence of the resin particle size on the reaction kinetics in order to throw light on the role of diffusional limitation. The hydrolysis rate constants of ethyl acetate[25] and acetamide[43] are practically independent of particle size over quite a wide range: the rate-limiting step in these reactions is the chemical act itself.

Kinetic effects arising from inner diffusion are very clearly observed when the reactant molecules are very large or branched. Hydrolysis of saccharose under static[18] or dynamic[23,38] conditions is much faster when smaller resin particles are used: Reed and Dranoff[23] have observed a linear relationship between the rate constant and the catalyst particle size. In the hydrolysis of Sarin[37] the kinetic curves become steeper as the diameter of the catalyst particles decreases and as the temperature increases.

The calculated activation energy for the hydrolysis of Sarin on Amberlite-IR 100 is relatively low (5500 cal mole^{-1}). This is additional evidence in favour of rate limitation by inner diffusion. However, the same reaction in the presence of Dowex-50, which has a more open three-dimensional network, gave an activation energy of 11200 cal mole^{-1}, and closely similar values were obtained for the hydrolysis of ethyl acetate[27] and dimethyl sebacate[32].

The rate of hydrolysis of Sarin[37] on Dowex-50 cation exchange resin is insensitive to stirring rate. On the other hand, with a more active catalyst (Amberlite-IRA 400) the rate constant at 20° was 5.3, 7.5, and 8.5 h^{-1} at 60, 800, and 1000 revolutions min^{-1} respectively, suggesting that film diffusion was the rate-limiting step.

Thus, the mechanism of the rate-limiting step depends on the nature of the catalyst.

2. Hydration Reactions

The hydration of organic compounds has been investigated, like their hydrolysis, under static conditions[44] or in a flow system[45].

The hydration of unsaturated hydrocarbons, which gives rise to a system of immiscible liquids, presents some practical difficulties. Effective contact between the reactants and the catalyst is obtained by specially pretreating the cation exchange resin[54] or by homogenising the liquid phase with a suitable solvent or emulsifier[46-48]. Much better yields are obtained in the conversion of hydrocarbons into alcohols by using mixed gas–liquid processes, in which the reaction takes place in a thin layer of water surrounding the resin particles, whilst the reaction products are continuously removed by an excess of water[45].

The writer and Kozlova[44] have increased the equilibrium conversion of tertiary pentenes in the hydration of the pentane–pentene fraction by using a large excess of water and keeping the catalyst (KU-2 cation exchange resin) at the boundary between the liquid phases in a hydrophobic state, obtained by replacing part of the hydrogen counterions by trioctylamine[49]. The reactor was of stainless steel, and fitted with a stirrer. It is interesting to note that the achievement of equilibrium was accelerated by the addition of anion exchangers: the mechanism was probably analogous to that of the hydrolysis of saccharose[33]. The use of a hydrophobic cation exchanger raised the conversion of tertiary pentenes from 2.7 to 13% (as compared with the previously recommended method[50]).

In the development of apparatus for the continuous production of tertiary butanol by the conversion of isobutene in high yields it has been necessary to abandon the countercurrent principle[51]. It is stated that the best contact between the reactants and the most complete conversion are obtained by a downward flow of water and isobutene through a layer of resin.

Ion exchange resins have been used for the hydration of the following compounds: tertiary pentenes[44,46] (KU-1, KU-2), 2-methylpent-1-ene[46] (KU-1), 2-dioxymethylnorbornene-5[52] (Dowex-50), acetylene[53] (KU-2), hydrocarbons with double and triple bonds[54] (Allasion CS), propene oxide[11] (KU-2. phosphate resins), and hydrocarbons with lactone rings[55] (Amberlite-IRA 400).

Hydration in the presence of a cation exchanger in the hydrogen form is believed to involve the formation of an intermediate carbonium ion[1]. Sulphonated resins are almost invariably chosen, but phosphate and even carboxylate resins can be used for the hydration of reactive materials[11] such as propene oxide. Cation exchange resins in the Hg form are used as catalysts for the Kucherov reaction[53,54]. In view of the conditions used in their preparation, these catalysts are likely to contain H^+ counterions; hence, it is interesting to examine the effect of various counterions on the catalytic activity of the resin. A group of Roumanian workers has shown that in the presence of CS-1 resin in the Cu, Zn, or Cd form acetylene undergoes polymerisation rather than hydration[56].

Cation exchange resins suffer changes of various types when used in practice as hydration catalysts. Firstly, changes in the degree of swelling under the influence of the reactants or of the heat of reaction can lead to disintegration of the particles[1]. An interesting way of guarding against these effects is to use coarsely granular[57] or two-phase[21] cation exchange resins. Secondly, blocking of the active groups in the resin may occur as a result of the incorporation of reactant[58] or product[11] molecules. Thirdly, irreversible chemical reactions (e.g. desulphonation) can proceed within the resin at high temperatures. The writer and Tulupov have shown[58-60] that this reaction can be vigorous in aqueous, alcoholic, and other media, particularly at high temperatures and when the heat of reaction is large. Thermal desulphonation and other forms of ageing of the resin lower the yield of hydration products[45].

The thermal stability and catalytic activity of sulphonated cation exchange resins in hydration reactions depend on the structure of the polymer network. In many reactions the presence of sulphonic acid groups is a necessary but not always sufficient condition for catalytic activity. For example, the hydration of acetylene proceeds smoothly in the presence of the sulphonated cation exchange resin KU-2, but it is not catalysed by the sulphonated phenol–formaldehyde KU-1 resin[53]. Sulphonated asphaltene deposited on silica gel does not catalyse the hydration of tertiary pentenes[61].

The water uptake of the catalyst plays an important role in determining the effectiveness of the catalyst, and sometimes even the course of the main reaction. It has been shown[8] that a KU-2 resin containing $<$ 24% of water catalyses only the polymerisation of tertiary pentenes. At higher water concentrations the strength of the bond between water molecules and the sulphonic acid groups decreases, and addition of water to the double bond of the hydrocarbon becomes easier. In the presence of a large excess of water the hydration of pentenes is practically quantitative, with a negligible amount of polymerisation[44].

Tertiary pentenes form carbonium ions more readily than other C_5 alkenes: in practice, therefore, they alone can add on water in the presence of KU-2. Normal pentenes, and 3-methylbut-1-ene, remain unchanged[62] even after lengthy treatment at high temperature (75°) with hydrated KU-2 resin. A process for the selective removal of tertiary pentenes from complex mixtures[62] can be based on these properties.

The rate of hydration of alkenes and other sparingly water-soluble compounds can be increased by adding indifferent organic solvents to improve the contact between catalyst and reactants. This principle has been successfully applied in practice[46], but a quantitative relationship between the reaction rate and the nature of the solvent has not yet been derived.

The hydration of alkenes is often accompanied by polymerisation and isomerisation side reactions, also involving a carbonium ion mechanism. Polymer formation has been observed in the hydration of propene[45], isobutene[51], and tertiary pentenes. These side reactions can become predominant under the appropriate experimental conditions[63].

3. Dehydration Reactions

For preparative purposes, dehydration is often carried out as a batch process. When an azeotrope-forming solvent[64] is used, the reactor includes a reflux condenser fitted with a water-separation trap, and the reaction is allowed to continue until the stoichiometric amount of water has been collected. In some cases the organic dehydration product is steam-distilled, thus ensuring that the water content of the resin remains constant and providing relatively mild conditions[65].

Under industrial conditions, dehydration is usually carried out as a continuous process. Soviet workers[66,67] have described a rational pilot-scale process for the production of isobutene which relies on a reactor without heat exchangers in order to minimise energy consumption. Free transport of the materials and a high throughput (1300–1400 kg h^{-1}) were achieved by locating the KU-1 cation exchange resin in the upper part of the reactor[68].

A flow apparatus for studying dehydration kinetics has been described[69]. It includes a continuous sampling facility (a microsyringe for removing samples of the product through a silicone rubber cap).

Resins have been used to dehydrate the following compounds: pentan-1-ol[64] (KU-2), cyclohexanol[70] (KU-2), cyclohexylethanol[71] (KU-2), menthol[72] (sulphonated polyphenyl resin), terpin hydrate[65] (KU-2), dimethylvinylethynyl carbinol[74] (KU-1), methylphenylethanol[73] (KU-2, phosphate exchangers), symmetric alkyne glycols[75] (KU-1), and castor oil[76]. All the cation exchangers were used in their hydrogen form.

There can be no doubt that the use of cheap sulphonated phenol–formaldehyde resins is fully justified, since these materials can extract water from alcohols at temperatures $<$ 100°. Under these conditions the exchange capacity and other physicochemical properties of the resin do not change appreciably[60]. At higher temperatures, on the other hand, the loss of capacity of these resins in aqueous[60], alcoholic[60], and hydrocarbon[8] media can be serious.

Thus, the claim by some French workers[77] that sulphonated phenol–formaldehyde resins can be used up to 210° is unacceptable. The KU-2 resin is appreciably more stable[60]: it can be used as a dehydration catalyst up to 150°, or up to 200° if used once only. If the experimental conditions require a reaction temperature in excess of 200°, the recently developed[72] sulphonated polyphenyl cation exchange resins, which have a high thermal stability, should be tried.

Since the catalytically active form of the cation exchange resins is the hydrogen form, the effectiveness of these catalysts is determined primarily by their acidic properties. The writer has shown[78] that the carboxylic acid resin SG-1 does not catalyse the dehydration of t-pentanol. The more acidic, phosphorus-containing RF cation exchanger accelerates this reaction, but the achievement of equilibrium is even faster in the presence of the KU-2 cation exchange resin. The relative activity of the sulphonate and phosphate exchanger was later confirmed[73], and it was shown that in the latter the kinetics of methylphenylethanol dehydration are affected by the structure of the polymer network. Zirconium phosphate was found to be the least active of the phosphorus-containing exchangers.

Water content has a large effect on the activity of cation exchangers. It would appear from the available experimental data that water absorption lowers the catalytic activity of cation exchangers towards the dehydration of compounds with a relatively low molecular weight (e.g. ethanol[69] and t-butanol[79]). In the dehydration of compounds with large or branched molecules, such as terpene alcohols[80], trapped water loosens the three-dimensional network of the cation exchanger and decreases the steric barriers to the formation of carbonium ions, thus leading to faster reaction.

An important controlling factor in dehydration reactions at cation exchangers, which allows control over the nature and yield of the products, is the composition of the medium and in particular the addition of indifferent solvents. Karpov and coworkers[81], who published the only noteworthy data on this subject, stress the importance of careful choice of solvent. Thus, addition of high-boiling hydrocarbon solvents in the preparation of dipentyl ether affects neither the yield nor the rate of the reaction, but if the reaction is carried out in a *p*-xylene medium the yield of ether drops by 17% owing to alkylation of the solvent by the alcohol. For the same reason, addition of xylene is undesirable in the preparation of di-n-octyl ether. On the other hand, addition of n-nonane prevents the complete dehydration of octanol on KU-2 and raises the yield of octyl ether by 29%.

The reaction temperature has a profound effect on the nature of the dehydration products. Shuikin and coworkers[82] have shown, in their study of the dehydration of primary alcohols, that the reaction on KU-2 gives mainly ethers at 135° in 5 h. On raising the temperature and the contact time, the proportion of alkenes in the reaction products increases.

As in the case of homogeneous acid–base catalysis, the rate of dehydration on ion exchangers increases with the concentration of catalytically active ions. The dehydration of t-butanol is faster in the presence of KU-1 resin[83] than in the presence of an equivalent amount of sulphuric acid. According to Helfferich's theory[6], the greater efficiency of the ion exchanger is due to selective absorption of alcohol molecules by the cation exchanger rather than to any difference in catalytic activity between hydrogen ions under homogeneous catalysis and ion-exchange catalysis conditions respectively. Unfortunately, no data are given[83] on the distribution of the alcohol between the liquid phase and the catalyst.

Soviet workers have shown that the catalytic activity of sulphuric acid and of sulphonated polystyrene resin towards the dehydration of tetracycline is determined only by value of the Hammett acidity function and is independent (within the range explored) of the concentration of water, divinylbenzene, and third component (Na^+ ions) in the resin[84]. As Fig. 1 shows, all the points in the experimental plot of the logarithm of the rate constant for this reaction against the acidity function lie on the same straight line. This is evidence that the catalytic activity of the H^+ ions is the same in the resin and in the acid phase. It would be interesting to extend these results[84] to reactions whose kinetics depend on the distribution of reactants between the liquid phase and the cation exchanger.

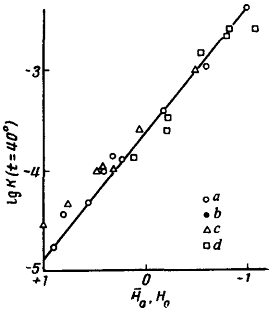

Figure 1. Logarithm of the rate constant for the dehydration of tetracycline plotted against the acidity function in the presence of: *a*) H_2SO_4; *b*) ion exchanger in the mixed Na–H–T form; *c*) ion exchanger in the T–H form; *d*) ion exchanger in the T–H form, dried to a known water content (T = tetracycline)

Detailed kinetic studies of the dehydration of tetracycline[85], ethanol[69], and dimethylethanol[79,83] have been published.

4. Synthesis of Esters

Esters are prepared mostly by esterification and ester interchange (transesterification) reactions. In order to avoid the formation of water and thus to raise the yield of esters, anhydrides are sometimes added with the alcohol[86,87], and alkenes[88], ethylene oxide[89], or ethylene carbonate[90] with the acid.

Like the reactions discussed above, esterification can be carried out as a batch process or as a continuous process. A simple version of the laboratory apparatus for the continuous production of ethyl octanoate[91] is shown in Fig. 2. The mixture of reactants in a known molar ratio, and containing hydroquinone as a polymerisation inhibitor, is supplied by the metering pump *2* to the bottom of a temperature-controlled glass reactor *4* of the "double tube" type, packed with KU-1 resin swelled in the reaction mixture. The vapours of ethyl octanoate, ethanol, and water, formed in the reactor at the boiling point of the reaction mixture, are continuously condensed (*6*) and collected in the receiver *7*.

Trofimov and Isagulyants[92] have described a relatively simple, high-capacity reactor for the continuous production on an industrial scale of n-nonyl methacrylate by the transesterification of methyl methacrylate.

Ion exchangers have been used to esterify formic acid with ethanol[93] (KU-2), acetic acid with ethanol[94] (KU-2), butanol[95] (KU-2), isobutanol[95] (KU-2), and pentanol[96] (KU-2), acrylic acid with ethanol[91], methacrylic acid with C_5–C_{10} aliphatic alcohols (KU-2) and ethanediol[98] (SBS, SDV-3), naphthenic acids with ethanediol[99] (KU-2), adipic acid with methanol[100] (KU-2) and higher aliphatic alcohols[101] (KU-2) as well as ethanediol[86] (silicone cation exchange resin), sebacic acid with allyl alcohol[102] (KU-2), benzoic acid with ethanediol[103] (KU-1), salicylic acid with aliphatic alcohols[104] (KU-2), maleic acid with allyl alcohol[102] (KU-2), terephthalic acid with methanol[105] (Wofatit KPS-200), and sorbic acid with aliphatic alcohols[106] (KU-2). Furthermore, esters have been prepared by the reaction between maleic anhydride and butanol[107] (KU-2), phthalic anhydride and glycerol[86] (silicone cation exchange resin), and methyl methacrylate and n-nonanol[92] (KU-2).

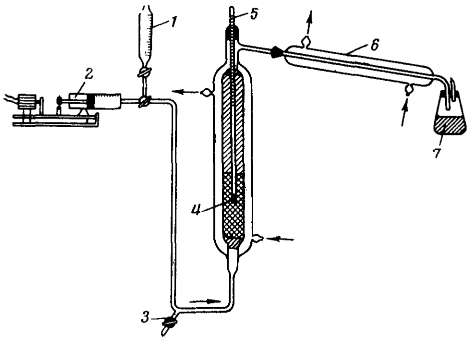

Figure 2. Laboratory apparatus for the continuous esterification of acrylic acid with ethanol

Since many of these esters are produced on an industrial scale, the use of ion-exchange catalysis should now be regarded not merely as an elegant preparative technique but also as a potential method in modern chemical technology, combining simplicity in the design and operation of the plant with high yields of valuable products.

In addition to the traditional hydrogen form, salt forms of sulphonated cation exchangers[108,109], which behave as Lewis acids, are used in the catalytic synthesis of esters. Because of their high thermal stability in the salt form[110], these resins can be used to accelerate reactions taking place at temperatures of 200° or higher. Sulphonated cation exchangers in the hydrogen form on a silicone substrate are also interesting in this respect[86]. Macroporous cation exchangers—about whose catalytic activity very little is yet known—offer the prospect of accelerating esterification reactions involving large molecules.

It should be noted that the nature of the polymer network of the resin has practically no effect on the yield of the ester[107] or on the kinetics of the reaction between low-molecular-weight acids and alcohols[16]. However, if one of the reactants has a high molecular weight the structure of the three-dimensional network becomes an important kinetic factor: some interesting comparisons have been reported[111,112] of various sulphonated cation exchangers as catalysts for the synthesis of butyl oleate and polyesters. Cation exchangers containing carboxyl groups are said[111] to have little effect on the rate of these esterifications.

On increasing the amount of cation exchanger the yield of ester, as a rule, increases to a limiting value and thereafter remains constant[96,104,113]. However, in the esterification of methacrylic acid with higher alcohols[114] the yield of ester goes through a maximum at 10 wt.% of catalyst. Unfortunately, the results of different authors are often difficult to compare because different units are used to define the amount of catalyst added. The writer suggests the adoption of mg-equiv. of active groups per g-equiv. of acid or alcohol as a universal scale: these units are particularly useful in kinetic studies.

Rate constants referred to 1 mg-equiv. of active groups give a clear indication of the specific features of the catalyst and are to be preferred to the traditional quantities used in formal kinetics. The rate constants for the esterification of glycerol by acetic acid, referred to 1 g of KU-1 and KU-2 resins, have been reported[115] as 1.65×10^{-4} and 4.29×10^{-4} min^{-1} respectively. When referred to 1 mg-equiv. of active groups these constants become practically indistinguishable (4.0×10^{-4} and 3.9×10^{-4} min^{-1}), which is consistent with the lack of a specific effect of the network structure under these particular conditions.

Table 1. Influence of particle size and cross-linking of KU-2 ion exchanger on the rate of esterification of acetic acid by ethanol

Particle size, mm	Reaction rate, $\frac{g\ CH_3COOH}{s \cdot g\ KU\text{-}2} \times 10^4$			
	1% devinylbenzene		20% divinylbenzene	
	liquid-phase reaction	vapour-phase reaction	liquid-phase reaction	vapour-phase reaction
0.5—1.0	53	16.2	11	9.8
0.1—0.25	58	34.5	—	13.7
0.01—0.10	67	85.8	18	20.5

If the rate of esterification is limited only by the reaction itself, and diffusional limitations are negligible, the reaction rate is independent of the stirring rate[116,117] and of the size of the resin particles[116–118]. As inner diffusion effects become predominant, the size of the catalyst particles begins to influence the rate of esterification. Table 1 shows the effect of this factor and of the degree of cross-linking of the KU-2 exchanger on the rate of esterification of acetic acid by ethanol in the liquid[94] and the vapour[119] phase (for 15–20% conversion).

It is evident from Table 1 that the influence of particle size on the rate of esterification of acetic acid by ethanol is appreciable even in the liquid phase. In the vapour phase the effect is more marked because the swelling of the catalyst is minimal. As expected, the reaction is faster on the strongly swelled KU-2 cation exchanger containing 1% of divinylbenzene than on the resin with 20% of cross-linking agent. Very large reactant molecules can interact by topochemical reactions: in this case the effect of particle size is even more marked[1]. In a very few cases (e.g. the esterification of glycerol by phthalic anhydride and talloleic acid[86]) the cation exchanger does not accelerate the reaction, evidently because of inactivation of the exchanger by alkyd resins.

The rate of esterification decreases substantially when the chain length of the aliphatic radical in the alcohol[104] or the acid[120] is increased: the analogous relationship for homogeneous acid–base catalysis was established by Menshutkin[121] at the end of the last century. The influence of this factor on the esterification kinetics is less marked at elevated temperatures[122].

The yield of esters is a function of the structure of the reactants. Normal alcohols give esters in higher yields than their isomers. The accurate correlation between the yield of ester and the molecular weight of the alcohol, which had been established[123] for homogeneous reactions at equilibrium, does not hold in the presence of ion exchange catalysts[97]. On raising the molecular weight of aliphatic acids up to C_5 the yield of isopentyl esters remains constant[120], but with still larger acid molecules the yield begins to decrease. This effect is probably associated with side reactions, or with the preparative difficulty of isolating the esters of higher acids, rather than with any thermodynamic feature of the esterification reaction.

Some workers[96] lower the temperature of the reaction mixture by adding low-boiling solvents in order to minimise side reactions. However, this expedient also lowers the rate of the main reaction, and it is necessary to reach a compromise and accept solvents of relatively high boiling point. In particular, the esterification of ethanediol by naphthenic acids and of pentanol by salicylic acid gives higher yields[99,104] in boiling xylene than if toluene is used to remove the water azeotropically.

The yield of esters[124] and the reaction kinetics[120,122] are very sensitive to the molar ratio of alcohol to acid. Esterification in the presence of an excess of alcohol produces conditions leading to resin swelling, which accelerate the reaction[120,122]. On the other hand, in the presence of an excess of carboxylic acids the resins do not swell appreciably and the reaction is slower than when the reactants are taken in equimolecular proportions.

It does not follow, however, that a chemical reaction is invariably accelerated by increasing the degree of swelling of the resin. The water evolved in the liquid-phase esterification of acetic acid by ethanol accentuates the swelling of the cation exchanger, but the rate constant of the reaction falls off[94]. In the esterification of salicylic acid by methanol, increased water concentration in the reaction mixture tends to inhibit the reaction[117]: the author[117] correctly ascribes this effect to partial deactivation of the protons in the sulphonic acid groups by hydration, as a result of which the formation of active intermediate complexes is sterically hindered.

Esterification is often accompanied by side reactions which (like the main reaction) involve the participation of a carbonium ion: dehydration of the alcohol[104,120] and polymerisation of the resulting alkenes[120], alkylation of the solvent[104], and dehydration of the ester[122].

The adoption of ion-exchange catalysis in industrial synthesis is economically justified[96]. According to Chashchin and coworkers[124], a saving of 10–20 roubles per tonne of butyl acetate could be made by replacing the soluble catalysts by ion exchangers.

5. Alkylation

Like the reactions already discussed, alkylation can be carried out as a batch process or as a continuous process. The use of a fluidised bed of catalyst by Belov and Isagulyants[125] is particularly interesting.

Ion exchangers have been used as catalysts for the alkylation of *p*-xylene by propene[126], *o*-xylene by isobutanol[127] (KU-2), phenol by propene[128] (KU-2), isobutene[129], and pentenes[130] (Ku-2), and by 2-ethylhex-1-ene[131] (SDV-3), propene trimer[132] (Amberlist-15), isoprene[133] (KU-2), monoarylacetylenes[134] (sulphonated cation exchanger), α-pinene[135] (KU-2), isobutanol[136], higher aliphatic alcohols[137] (KU-2), and benzyl alcohol[138] (KU-2); also for the alkylation of *p*-cresol by isobutene[139] (KU-2), cyclohexene[140] (KU-2), styrene[141] (KU-2), octanol[142] (KU-2), and cyclohexanol[140] (KU-2), for the alkylation of *o*-xylenol by hex-2-ene[143] (KU-2), cyclohexene[143] (KU-2), and styrene[144] (KU-2) of β-naphthol by isobutanol and butanol[145] (KU-2), of pyrocatechol by but-1-ene[146] «Allasion CS» and isobutene[147] (KU-2), of hydroquinone by isobutene[148] (KU-2), of guaiacol by hex-1-ene[149] (KU-2), and of *p*-methoxyphenol by alkenes[150] (KU-2).

The main reaction in the alkylation of phenols is direct replacement of hydrogen in the benzene nucleus, leading in most cases to the formation of monoalkylphenols: the substitution occurs mostly in the *p*-position to the phenolic hydroxyl, or (if this position is occupied) in the *o*-position[142]. Dialkyl phenols are sometimes formed in addition to the monosubstituted phenols. In the presence of a large excess of alkylating agent the disubstituted phenol may account for most of the yield[143,144]. Some workers have observed the formation of alkyl phenyl ethers, which usually[140,151] but not invariably[140] undergo regrouping into alkylphenols. Some reactions are complicated by the disproportionation of the alkylphenols[152], the replacement of one alkyl radical by another[152], the degradation of branching side-chains[153], and polymerisation of the hydrocarbons[144,152]. The yield of dialkyl substituted phenols decreases as the molar ratio of phenol to alkylating agent increases[125,138,148,154,155] and also if the reaction time is extended[155]. Other conditions being the same, the yield of dialkylphenols on cation exchangers is less than in the presence of soluble acids[155], which suggests selective sorption of the phenols from the reaction mixture[154].

The nature of the reactants has a considerable influence on the total yield of alkylation products. Increasing the number of substituents in the nucleus of the compound to be alkylated, and branching of the hydrocarbon chain of the alkylating agent, produce a lower yield of alkylphenols[153]. Soviet workers[153] have convincingly demonstrated, by studying the alkylation of the cresol and xylenol isomers, steric hindrance to the entry of a tertiary radical in the *o*-position to the methyl or hydroxyl group of a phenol. This *ortho*-effect is most marked in symm.*o*-xylenol, which is not alkylated by di-isobutene: the t-octyl radical (6.18 Å in diameter) cannot be located between two methyl groups or between a methyl and a hydroxyl group, whose separation is 5.24 and 5.17 Å respectively[157].

Information on the influence of the cation exchanger on alkylation reactions is mostly qualitative[141], and is so scanty that useful generalisations cannot be made.

More definite conclusions are possible on the effect of water content of the catalyst on the yield of alkylation products. The yield of alkylphenol on KU-1 resin containing 20–30% of water is 50% lower than on the same resin dried to constant weight[158]. Alkylation of phenol on SDMS resin prepared by sulphonation of shredded rubber[159] and having a water content of 20% gave a 69% yield of octylphenol. On decreasing the water content to 9% the yield rose to 75%, and on a dry resin the yield reached 80%. The highest yield of bis-phenols by the reaction of phenol with diarylalkynes[134] was obtained at 2% water content of the cation exchanger. From these results, pre-drying of ion-exchange alkylation catalysts in an air oven at 110–120° is recommended. Alternatively, the resin may be dried in a vacuum or by refluxing with an azeotropic solvent (e.g. benzene).

If the alkylation involves not only the surface but also the bulk of the resin particles, smaller particle size raises the yield of dialkyl derivatives. Soviet workers have given a convincing explanation of this effect[154] by pointing out that the molar ratio of phenol to alkylating agent is greater in the cation exchanger than in the bulk of the solution: this favours the formation of monoalkyl derivatives. When the particle size of the resin is decreased the relative importance of the reaction taking place at the surface (and therefore at the same molar ratio of components as in the reaction mixture) increases, and so also does the yield of dialkylphenol.

In some cases it is useful (or even necessary) to operate at elevated temperatures in order to increase the rate of diffusion of reactants within the resin particles and the mobility of the counterions of the active groups as well as accelerating the reaction itself. However, an excessive rise in temperature may cause dealkylation and favour side reactions as well as irreversible changes in the catalyst. Thus, on raising the temperature of the alkylation of phenol by di-isobutene in the presence of the cation exchanger SDMS the yield of alkylphenol increases up to 100°, remains constant in the range 100–115°, and falls off above 120° due to the onset of dealkylation[159]. When phenol is alkylated with high-molecular-weight alkenes, the total yield of alkylphenol rises from 64 to 81% as the temperature is increased from 150 to 160°. [160]However, whereas at 130° only monoalkylphenols are formed, the product obtained at 150° appears to contain (judging by its boiling range) di- and even polyalkylphenols.

Special caution is necessary when using sulphonated phenol–formaldehyde cation exchangers at high temperatures. The KU-1 resin is so unstable towards heat that the yield of useful product decreases by a factor of two[141] when the resin has been used three times as a catalyst for the aryl-alkylation of *p*-cresol at 110°. Under the same conditions the KU-2 resin retains its catalytic properties unchanged for at least 12 consecutive operations, and has been used for 500–600 h without regeneration[153] in the continuous alkylation of phenols at 120°. Under the more stringent conditions of the alkylation of asymm.*o*-xylenol by alkenes[143], the exchange capacity of KU-2 fell from 4.9 to 2.3 mg-equiv. g^{-1} after 13 reaction cycles.

The catalytic properties and technological potential of cation exchangers in alkylation reactions are affected not only by changes in exchange capacity but also by the extent of swelling in the reaction medium[161], resinification of the surface[161,162], and breaking up of the particles[163]. Resinification of the surface can be avoided by adding indifferent solvents, and its effects can be cured by regenerating the cation exchanger. Regeneration can be achieved in the cold or by refluxing with resin solvents such as acetone[143], ethanol[154], benzene[161], or an alcohol–benzene mixture[153]. Some authors recommend successive treatment of the resin in alkali and hydrochloric acid[143] (or 10% sulphuric acid[135]) after the treatment with organic solvents.

The mechanism of the reaction is generally considered to be a nucleophilic addition through a reactive intermediate state (π-complex or carbonium ion[136,164,165]).

This mechanism has recently been confirmed by Soviet workers[153] by measurements of the electrical conductivity of mixtures of phenol, KU-2 resin, and the trimer of propene.

6. Polymerisation and Isomerisation Reactions

These reactions can be carried out as batch processes at high pressure in stirred autoclaves[166], but semi-continuous[167] or continuous[168] methods are usually employed. The continuous method sometimes offers higher yields[167] as well as the other advantages of continuous operation.

Ion-exchange resins have been used as catalysts for the dimerisation and trimerisation of alkenes[166,168] and acetaldehyde[167] (KU-2), and also for the polymerisation of vinylbenzene[169], isobutyl vinyl ether[170], and acetaldehyde[171] (various sulphonated resins). Ion exchangers have also been used as catalysts for the isomerisation of alkenes[62,72,172,173] (sulphonated cation exchangers), unsaturated alcohols[54] ("Allasion CS"), hydrocarbons (Wofatit L-150)[174], phenol esters[175] (KU-2), cyclohexanoneoxime[176] and phenylhydrazones[3] (resins of the KU-2 type).

Often polymerisation, isomerisation, and cracking occur together, and the reaction product is complex and variable in composition. In most cases these reactions are accelerated by cation exchangers in the H form, but a resin containing mercury counterions has been used[54] for the isomerisation of propynols. The isomerisation of glucose is accelerated by anion exchangers in the OH form[174].

In the low-temperature polymerisation of oxygen-containing compounds the main factor leading to loss of catalytic activity is the blocking of reactive sites by the reaction products, which hinders the contact between the counterions and reactant molecules[170]. Impurities in the monomer contribute to the deactivation of the catalyst: hence, special attention must be devoted to the purification of the raw materials.

If the isomerisation can proceed at temperatures up to 80–90°, sulphonated phenol–formaldehyde cation exchangers can be used without serious loss of catalytic activity. Thus, after 99, 477, and 1600 h operation at 75–80°, samples of KU-1 gave 83, 78, and 76% conversion of 2-methylpent-1-ene and 2-methylpent-2-ene, the selectivity remaining constant[168]. A cation exchanger of higher thermal stability (e.g. KU-2) must be used for the di- and trimerisation of alkenes, which usually require temperatures in excess of 100°.

The effect of temperature on the yield of polymerisation and isomerisation products depends on the nature of the reactants, on the reversibility of the reaction, on the reaction time, and on the moisture content of the resin[177–180].

The possibility of a reaction is often determined by the nature of the active groups and by the geometry of the three-dimensional network of the resin. For example, it is well known that carboxylate and phosphate cation exchangers do not catalyse the polymerisation of isobutene[177]. Sulphonated polyphenyl cation exchangers[72] are efficient catalysts for the isomerisation of but-1-ene to but-2-ene, and for the same reason a phosphoric acid polyelectrolyte has a negligible effect on the rate of this reaction. The KU-2 resin is a more effective catalyst than hydrochloric acid for the pinacoline rearrangement[181], and the polymeric carboxylate cation exchanger KB-4P-2 does not affect the rate of isomerisation.

However, these reactions are not accelerated by any sulphonated cation exchanger in any physical state. For example, a technical mixture of KU-1 and another sulphonated phenol–formaldehyde cation exchanger does not catalyse the polymerisation of tertiary pentenes[182] and isobutene[177]. Within limits, the activity of a cation exchanger can be altered by modifying the state of the resin. Thus, by finely dividing the dried KU-1 resin or by loosening its network with water or methanol it is possible to bring about a very significant increase in its catalytic activity towards the polymerisation of tertiary pentenes. However, if the finely divided exchanger is heated in the air or in nitrogen atmosphere it ceases to be a catalyst for this reaction[182]. The more ordered network of the polymeric KU-2 catalyst is sufficiently open even under dry conditions to permit diffusion of low-molecular-weight alkenes such as isobutene[170], tertiary pentenes[178], and α-methylstyrene[73]. In this case the polymerisation proceeds faster on the dried than on the hydrated resin. The KU-2 catalyst is more active towards the formation of high polymers when in the hydrated state[80], since a very open three-dimensional network is needed to allow the interlinking of a large number of monomer units.

The step which controls the reaction kinetics depends on the water content of the cation exchanger. In the pinacoline rearrangement, carried out in the presence of KU-2 resin swelled to the limit, the rate-limiting step is the chemical reaction itself[181], because the diffusion of pinacone is unhindered when the resin particle is swelled by water. Diffusional limitation begins to be appreciable in the polymerisation of t-pentenes on dried KU-2 resin, and therefore the rate of this reaction decreases as the size of the catalyst particles increases. Fang[10] obtained a similar somewhat unexpected result in his work on the kinetics of isomerisation of (*d*+)-α-isobutyldesoxybenzoin on a macroporous cation exchanger in which practically all the sulphonic acid groups of its enormous internal surface were available for the formation of carbonium ions.

Fang[10] used the change in the rate constant for the racemisation of (*d*+)-α-isobutyldesoxybenzoin as a measure of the stability of the catalyst (Amberlist-15) towards heating in an inert medium at 100–165°. This is the first example of the use of a kinetic quantity to characterise the thermal stability of a resin. These results are shown in Table 2 as rate constants referred to 1 g of catalyst (k_1) or 1 mg-equiv. of active groups (k_2).

Table 2. Influence of heat treatment on the catalytic activity of Amberlist-15

Temp. of heat treatment, °C	Exchange capacity of resin, mg-equiv. g^{-1}	Rate constants, min^{-1}	
		$k_1 \times 10^4$	$k_2 \times 10^4$
100	4.61	5.33	1.16
110	4.55	5.07	1.11
120	4.55	5.00	1.10
130	4.48	5.09	1.14
140	4.30	4.81	1.12
150	4.07	3.53	0.87
165	4.36	3.42	1.02

It can be seen from Table 2 that heat treatment of the cation exchanger at temperatures up to 140° leads to partial desulphonation with a corresponding decrease in k_1, whilst k_2 remains approximately constant. At still higher temperatures both rate constants decrease, since the access of ketone molecules to the active centres is hindered by the shrinkage of the three-dimensional network of the resin. These views have long been held by the present writer in connection with the thermal stability of ion exchangers[183]: their relevance to ion-exchange catalysis is now beginning to be appreciated.

As in the case of other Brønsted acids[184], polymerisation in the presence of ion exchangers occurs by a cationic mechanism[185]. Intermediate formation of a carbonium ion is suggested during the isomerisation of *l*-menthene[72], and this mechanism has been proved beyond doubt for the transformation of but-1-ene into but-2-ene (which was investigated by the isotope exchange method[24]).

7. Condensation Reactions

Additional evidence of the advantages of ion exchange catalysis over the classical methods relying on soluble acids or alkalis has become available as a result of the current interest in condensation reactions brought about by ion-exchange resins.

Many reactions take place under milder conditions in the presence of ion exchangers, giving a higher grade of product[186,187] in better yields[188]. Because of the improved quality of the technical products obtained by ion-exchange catalysis, some purification stages can be omitted (for example, extraction in the preparation of polyhydric alcohols[187] or neutralisation in the preparation of diacetone alcohol[189]), and therefore the process can be speeded up on the industrial as well as on the laboratory scale. Thus, the preparation of diacetone alcohol by the condensation of acetone in the presence of barium hydroxide requires 120 h as compared with 8–10 h if an anion exchanger is used[189].

In some cases the use of ion exchangers offers new possibilities in organic synthesis. A striking example of this is the cyanoethylation of water in the presence of AV-16 anion exchanger, achieved by Mekhtiev and coworkers[190], which is impossible under homogeneous acid–base catalysis conditions.

The advantages of ion-exchange catalysis have led many authors[187,191–193] to suggest the use of ion exchangers as condensation catalysts on a pilot-plant scale and even on a full industrial scale.

Like the reactions already discussed, condensation can be carried out as a batch process or a continuous process. However, a combined approach is used for the synthesis of trimethoxypropane because the reaction mixture tends to separate into layers in the continuous reactor, causing low yield[187].

Most of the recent work in this field has been concerned with the use of ion exchangers as catalysts for cyanoethylation[4,194–197] (anion exchangers), aldol condensation[103,187,189,198,199] (anion exchangers, and occasionally cation exchangers), the Prince reaction[192,200–203] (cation exchangers), and the reaction between aldehydes and alcohols[103,204–208]. Some papers have dealt with the Knoevenagel condensation[209] (Dowex-3) and the reactions of phenol with acetone[191] and acetylene[210] (cation exchangers), the reactions of nitromethane with furfural[211] and paraformaldehyde[212] (anion exchangers), of acetic anhydride with hydrogen sulphide[193] and sugars[213], of cyclohexene with hydrogen peroxide[214] (KU-2), of various phenols with 1,3-cyclohexadiene[215] (Dowex-50), of oleic acid with diethylenetriamine[216]. Among the areas where further research is needed we could mention hydroxylation reactions[214], the synthesis of nitro derivatives[217,218] and the hitherto unpromising condensation of ketones with alcohols to give the corresponding acetals[206].

Although ion-exchange catalysts in general offer a higher selectivity than soluble acids and alkalis, this feature should not be overstated[187,195,219,220]. Very careful selection of the optimum conditions is necessary to minimise side reactions. Parameters such as reaction temperature, contact time, and molar ratios of components must be varied, as well as the water content, amount, and nature of the resin (ionic strength of the active groups, structure of polymer network, degree of cross-linking). As an illustration, the effect of various parameters on the yield of the cyanoethylation of ethanethiol[221] is shown in Fig. 3. It is evident that the yield of β-(ethylmercapto)propionitrile, calculated on the basis of acrylonitrile consumed, is not a sensitive function of the reaction conditions. On the other hand, the yield calculated on the basis of added acrylonitrile varies widely with the conditions of the reaction, and this behaviour must be taken into account in optimising the process.

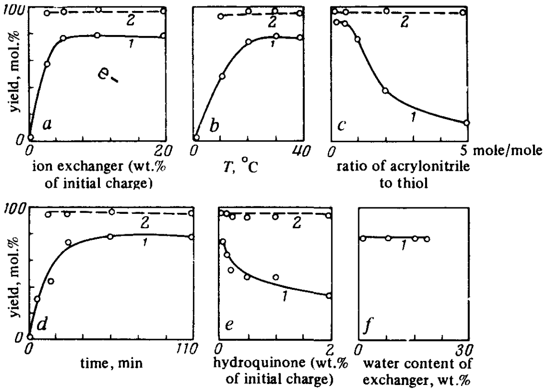

Figure 3. Effect of various parameters on the yield of the cyanoethylation of ethanethiol, expressed in terms of acrylonitrile (AN) added (*1*) and consumed (*2*): *a*) amount of AV-16 anion exchanger; *b*) temperature; *c*) AN : thiol molar ratio; *d*) time of experiment; *e*) amount of hydroquinone added; *f*) water content of resin

With the exception of the condensation of phenol with acetylene[210], catalysed by a resin in the Hg form, cation exchangers are commonly used as catalysts in the H form, and anion exchangers in the OH form, though an anion exchanger in the acetate form has been used[209] in the Knoevenagel condensation. The activity of the cation exchangers towards the condensation of phenol with acetone[191,222] can be increased by the addition of promoters: thioglycollic acid, ethanethiol, and others. A very ingenious method has been devised[222] to improve the quality of the diphenylolpropane obtained catalytically: 3–20% of the sulphonate groups in the cation exchanger are esterified with thiols instead of adding promoters to the reaction mixture.

The effectiveness of anion exchangers increases with their basicity, and improved yields can sometimes be obtained in this way. In some cases, however, weakly basic anion exchangers give better results (e.g. in the synthesis of thioglycollic acid[193]), and in some reactions (aldol condensation of acetaldehyde[1]) their use is mandatory.

Sulphonated cation exchangers are most frequently used in reactions which occur through the formation of an intermediate complex cation. In some reactions[197], adequate activity is obtained with phosphate or carboxylate resins, the latter being the more active.

Several examples have been reported[191,208,223] of the superiority of sulphonated polystyrene cation exchangers as compared with various sulphonated phenol–formaldehyde resins, all of which have a more compact three-dimensional network. Some compounds, such as diphenylolpropane, are formed only on KU-2 cation exchanger: the KU-1 resin merely absorbs phenol and acetone in molar proportions without inducing condensation.

In the presence of water, the activity of the catalyst can remain unchanged[198], it can increase[205], or it can even decrease[191]. Hence, the exchanger may have to be hydrated, or it may have to be dried, before the reaction.

Dehydration, like other forms of heat treatment, is relatively safe with cation exchangers of the sulphonated polystyrene type. Thus, KU-2 cation exchanger can be used for 1200 h without regeneration[222] in the synthesis of diphenylolpropane at 75°. Its analogue (Dowex-50) remained active for several years[206] under milder conditions in the condensation of acetone with alcohols.

Strongly basic anion exchangers in the OH form are sensitive to heat, and their exchange capacity rapidly decreases[224] on drying the resins even at ordinary temperature. Hence, the deactivation of the AV-17 anion exchanger towards condensation reactions reported by Isagulyants and coworkers[217,225] is not surprising. The relationship between the thermal stability and the catalytic activity of anion exchangers has not so far been investigated.

Published work on the condensation kinetics has dealt with the effect on the reaction rate of indifferent solvents[226], of the particle size[227], and degree of cross-linking of the resin[191], and of the nature of the active groups[228]. The activation energy[195,221,227,229] and the kinetic order of some condensation reactions have been reported[195,200,209,221,230]. An anomalously low activation energy has been observed[229] in the aldol condensation of acetone (4.5 kcal mole^{-1}), pointing to inner diffusion as the rate-limiting step. The kinetic order of the reaction on ion exchangers may not be the same as in homogeneous acid–base catalysis[200]; in the condensation of chloroacetaldehyde with polyhydric alcohols[230] the kinetic order depends on the amount of KU-1 present and on the molar ratio of the reactants. This fact underlines the specific features of ion-exchange catalysis, which goes beyond the simple idea of "a homogeneous phase in which the reaction can take place".[6]

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The period in the development of ion-exchange catalysis which we have discussed is qualitatively different from the previous stage. Between 1961 and 1968, satisfactory theoretical foundations were developed and new ideas were put forward (for example, on the blocking of ion exchangers) in the form of precise quantitative relationships. Kinetic studies have attracted much more attention than during the previous stage, and have helped to reveal the specific features of ion-exchange catalysis. Considerable progress has been made in the synthesis and exploitation of new (thermally stable, macroporous, and mixed) ion-exchange catalysts which enable many of the defects of the older ion-exchange materials to be overcome or at least mitigated. The relationship between thermal stability and catalytic activity has been formulated in principle; these basic ideas are of the utmost importance for the optimisation of the reaction condition in ion-exchange catalysis.

Future work on ion-exchange catalysis should aim to remedy the shortcomings of some of the researches of the current period. Firstly, the criteria for the choice of catalyst should be further refined, making allowance for the electrochemical properties of the active groups, the exchange capacity, the degree of cross-linking, the structure of the polymer network, the pore characteristics (for macroporous exchangers), and the thermal stability, using mathematical expressions for these properties. Secondly, our understanding of the role of indifferent solvents in ion-exchange catalysis must be extended in breadth and in depth, taking account of their influence on the distribution of reactants between the catalyst and the reaction medium. Thirdly, it is important to intensify the study of reaction kinetics and mechanisms, with special emphasis on the exact kinetic description of the properties of the catalysts. Fourthly, the thermal stability of the catalysts must be investigated, and means must be found to prevent ageing of the catalysts under practical conditions. Lastly, work on the synthesis of new ion exchangers with desirable thermal and mechanical properties must continue. Advances in all these directions will help to shorten the gap between the theoretical studies of the methods of ion-exchange catalysis and their general exploitation in the chemical industry.

While this article was in press, new papers have been published on the hydrolysis[231], hydration[232], dehydration[233–235], decomposition[236,237], esterification[238–243], ester interchange[244], alkylation[245–248], isomerisation[249], and condensation[250–252] of organic compounds in the presence of ion-exchange resins as catalysts. A special review of the dehydration of various compounds (mainly alcohols) has appeared[253]. The writer's thesis[254] presents a general discussion of ion-exchange catalysis.

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Tambov Institute of Chemical Plant
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RUSSIAN
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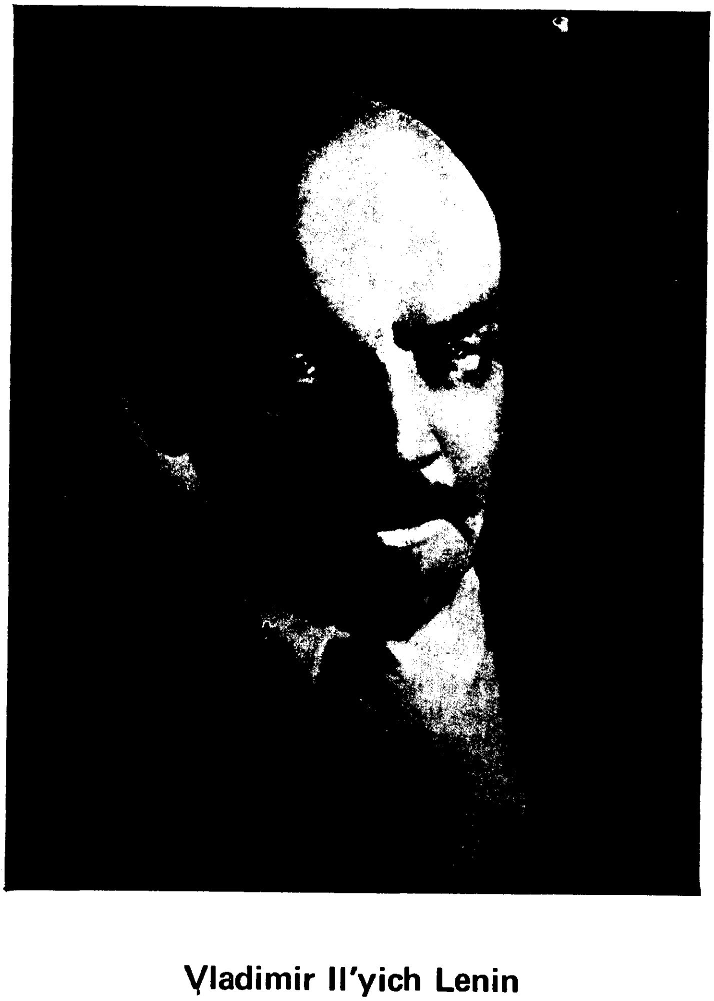


Vladimir Il'yich Lenin

U.D.C. 62.09

Fulfilling V.I.Lenin's outline for the development of Soviet chemistry

V.I.Spitsyn

All progressive mankind marks the centenary of the birth of Vladimir Il'yich Lenin, founder of the Communist Party of the Soviet Union and of the first Socialist State, and one of the greatest scientists of our time.

Lenin was the first political figure of world calibre to consider science to be enormously important and to base his concepts of Party and State on thoroughly scientific foundations. It is well known that Lenin's philosophical works—"Materialism and Empirical Criticism", "Philosophical Notebooks" and others—played a very important part in the period between the two Russian revolutions. In these works Lenin also touched on questions of modern science—among them the depth of our knowledge of the outside world, the inter-relation of matter and energy, the transformation of chemical elements.

Lenin paid much attention to the problems of chemistry. Whilst writing his "Materialism and Empirical Criticism", he studied the work of the chemists Ostwald and Liebig, and those philosophers and physicists who had exerted much influence on the development of chemistry—Falaise, Democritus, Gassendi, Newton, Faraday, Helmholtz, and Thomson. In the Sorbonne and Berne libraries Lenin studied the works of Abderhalden, the organic chemist, and Meyer. He was interested in radioactivity, agricultural chemistry, coal chemistry, petrochemistry and geochemistry. He read carefully the works of the gifted agricultural chemist and publicist, Engelhardt, as well as those of Vernadskii, who was one of the founders of geochemistry; he read Planck's "The Principle of the Conservation of Energy", and Boltzmann's papers in the "Vienna Scientific Treatises". The V. I. Lenin Library in the Kremlin contains, besides works on philosophy, history, the law, and economics, many special works dealing with various problems of chemistry and other related sciences: works by Lomonosov, Timiryazev, Vernadskii, Fersman and others.

Lenin also made a study in depth of the problems of the development of the chemical industry. In his work "The Development of Capitalism in Russia" he noted that "chemical production is of the utmost importance for economic development and the growth of the country's productive power" (Complete Works, Vol. 3, p. 476). Subterranean gasification of coal, suggested by Mendeleev and then by the English chemist Ramsey, constituted, in Lenin's view, a gigantic technological revolution which, under Socialism, would help in electrifying factories and railways (Vol. 23, p. 93).

After the October victory Lenin embarked on a scientific plan for the building of a new society. He believed that the country had sufficient natural resources and manpower, and the necessary scope was given to "the national endeavour by the great Revolution—in order to create a truly mighty and prosperous Russia" (Vol. 36, p. 80). Lenin gave an important role to the chemical industry in creating the material and technological basis for Socialism. He wrote: "Increased efficiency of labour requires first of all a proper material basis for heavy industry: increased production of fuel and steel, growth of mechanical engineering and the chemical industry" (Vol. 36, p. 188). Lenin considered Karabugaz, a bay in the Caspian Sea, as the richest source of raw materials for the chemical industry.

On Lenin's initiative, the Supreme Economic Council created a Department of Chemical Industry as early as December 1917. In 1918 Lenin signed the decree prepared by this Department concerning the transfer of a number of chemical and chemico-pharmaceutical enterprises to the ownership of the Russian Republic. Several months later the Council of People's Commissars adopted the decree which nationalised all chemical enterprises. Despite the great hardships besetting the young Republic, considerable sums were assigned in that year for completing the building of the "Provodnik" rubber goods factory in Moscow, for prospecting for phosphorites in the Volga-Kama region and near Aktyubinsk, and for the rebuilding of a number of chemical plants. The Supreme Economic Council did much to assist the Department of Chemical Industry in acquiring raw materials and equipment for chemical laboratories.

In the second half of April 1918 Lenin composed his famous outline plan for scientific and technological progess. This arose as the result of an approach made to the Soviet Government by the Academy of Sciences in March 1918, suggesting that scientists should be drawn into a survey of the country's natural resources. This proposal by the Academy was discussed at a meeting of the Council of People's Commissars on 12 April 1918. The resolution adopted stressed the aim of a "systematic solution of the problems of proper distribution of industry in the country and the most effective utilisation of its economic forces".

In his outline scientific and technological plan, Lenin recommended that the Academy of Sciences be asked to form a series of Commissions of experts in order to work out with all possible speed a plan for reorganising industry and bringing about economic recovery and progress in Russia. This plan had to include a rational siting of industry in relation to accessibility of raw materials and minimising the labour involved in their processing; provision of all the main types of raw materials and industries for the Soviet Russian Republic; special emphasis on the electrification of industry, transport and agriculture; utilisation of inferior types of fuel for producing electric power; and the use of water power and wind-driven motors generally and in agriculture.

Scientists and highly qualified engineers were needed to solve these problems. There were eminent individual scientists in pre-Revolutionary Russia who were working chiefly in academic institutions. Among the chemists there were N. S. Kurnakov, L. A. Chugaev, and I. A. Kablukov (Inorganic Chemistry), D. P. Konovalov, V. A. Kistyakovskii, and E. I. Shpital'skii (Physical Chemistry), N. D. Zelinskii, A. E. Favorskii, and A. E. Chichibabin (Organic Chemistry), N. A. Tananaev, and K. A. Nenadkevich (Analytical Chemistry), V. I. Vernadskii and A. E. Fersman (Geochemistry), D. N. Pryanishnikov (Agricultural Chemistry), V. S. Gulevich (Biochemistry), V. E. Tishchenko and A. A. Yakovkin (Chemical Technology), and V. G. Khlopin (Radiochemistry). These scientists had only a few colleagues, teaching in the various Departments. The material and technological basis for developing research inherited from Tsarist Russia was totally inadequate and became still worse as the result of wartime destruction. This, and the poorly developed network of centres of higher learning prevented the development of large schools of scientific research in pre-Revolutionary Russia at a time when these were already flourishing abroad.

On Lenin's initiative, and with the active participation of leading Russian scientists, specialised research Institutes, including chemical ones, began to be created from the first months of Soviet power. Among the first ones to be created in 1918 in Petrograd were the Institute of Platinum and Other Noble Metals (Director—L. A. Chugaev) and the Institute of Physico-Chemical Analysis (Director—N. S. Kurnakov) In Moscow the Central Chemical Laboratory was organised under the aegis of the Supreme Economic Council; it subsequently became the L. Ya. Karpov Physico-Chemical Institute. A number of other Institutes followed, including the State Institute of Applied Chemistry, the State Institute of High Pressures, the Scientific-Research Institute of Pure Chemical Reagents, the Institute of Fertilisers.

The VIII Congress of the Russian Communist Party which took place in Moscow in March 1919, included the following in the Party programme: "The Soviet Government has already taken a number of measures designed to advance science and strengthen its links with industry by creating a network of new Institutes of Applied Science, laboratories, experimental stations, pilot plants for testing new technological methods, improvements and inventions, and by registering and organising all available scientific manpower and resources. The Russian Communist Party supports all these measures and aims at their further development and the creation of the most favourable conditions for scientific work relevant to improving the productive forces of the country".

The plan of the State Commission on the Electrification of the Republic was based on Lenin's ideas concerning the material and technological foundations of a Socialist society; this was the first long-term plan for the economic development of the Soviet Republic put forward in 1920 and calculated for 10—15 years. It was devoted mainly to the problem of electrification of Soviet Russia, but it also dealt with the means of developing the principal branches of the country's economy. In particular, it outlined an accelerated growth of the chemical industry. Its production was to show a 2.5-fold increase compared with 1913. At that time it was a gigantic task.

It is well known that before the Revolution the Russian chemical industry was technologically backward, despite the eminence of individual Russian chemists. It was characterised by small-scale production, factories limited to several areas in the European part of the country, absence of a well developed base for raw materials, and shortage of qualified personnel. The chemical industry was immensely dependent on foreign capital. Tsarist Russia, possessing vast deposits of mineral raw material was forced to import pyrites, phosphorites, sulphur, potassium salts and saltpetre. One-third of valuable chemical products and 80% of mineral fertilisers were also imported from abroad. The country had no chemical engineering and not a single college specialising in chemical technology. Suffice it to say that in 1913 there was one graduate chemist per 340,000 population!

The Communist Party and the Soviet Government began in the first years of Soviet power to carry out Lenin's indications for the extensive use of chemistry in the national economy. With the liberation of territories captured by the Whites, measures were taken to restart and reconstruct the oil industry in Baku and the coal chemistry industry in the Donbass, as well as to restore and reorganise the existing basic chemical works.

Besides being concerned about the preservation and utilisation of already existing chemical plants, Lenin gave much attention to new lines of technological development. In 1918 he ordered the evacuation of uranium ore stocks from Petrograd to the Urals. In July 1918 the Council of People's Commissars adopted a resolution on starting a pilot radium plant. The telegram sent to the Urals Economic Council, signed by Lenin, read: "Work on the radium plant must begin forthwith". The first preparation of Soviet radium was obtained in 1921, under the direction of V.G. Khlopin and I. Ya. Bashilov. The problem which had baffled the shareholders of the "Ferganskii Rare Metals Company" before the Revolution was solved. The isolation of radium and the training of highly qualified specialists able to handle highly radioactive substances played an important part twenty years later in organising the atomic industry in the USSR.

In that early period the Council of People's Commissars was much concerned with the production of synthetic materials. It initiated a competition for developing a method of preparation of synthetic rubber. This problem was solved in 1932, when the technique of synthetic rubber production, developed under the direction of S. V. Lebedev, was adopted.

Research into the use of oil shales as chemical raw material for the production of primary shale tar and the preparation of valuable chemicals from it was begun in 1918 on Lenin's personal instigation.

At the same time, on Lenin's instructions, new centres for tertiary education were being established. In the three years from 1918 to 1920 the following institutions came into being: Universities in Tbilissi, the Urals (Sverdlovsk), Erevan and Central Asia (Tashkent), and the Moscow Mining Academy, with increased admissions to already existing tertiary schools. Chemical specialties were extended and chemical Faculties created at the Moscow, Petrograd and other Universities. The training of qualified chemists was extended in Technical Colleges (the Moscow Technical College and the Technological Institute in Petrograd, among others). In 1920 the first specialised Chemical Technological College—the D. I. Mendeleev Institute of Chemical Technology—was opened in Moscow.

These measures made it possible to train in a few years many researchers and chemical engineers for research Institutes, laboratories and industrial concerns. Whereas in early 1925 there were 2750 engineers working in the chemical industries, two years later their number had risen to 4000.

The establishment of new scientific Institutes continued throughout the Civil War and after its end. These included the Radium Institute, the Institute of Applied Mineralogy and Non-Ferrous Metallurgy, the State Institute of Rare Metals, and many other chemically-oriented Institutes. There was considerable expansion of research in the Chemistry Departments of Colleges. A start was made on the organisation of Applied Research and Designing Institutes geared to various branches of industry. Among the first of these were the Urals Chemical Research Institute, the Mining Chemical Institute, the Scientific-Research Institute of Basic Chemical Industry in Kharkov, the Glass Institute, the State Institute of the Nitrogen Industry, the GIPROKHIM Design Institute, and others.

In the not quite seven years during which Lenin led the Soviet State the development of science in our country, and chemistry in particular, received a great stimulus. Lenin's genius and creative initiative played a vital role in this respect. As N. P. Gorbunov, Secretary of the

Council of People's Commissars, wrote subsequently in his memoirs, there is hardly a scientific or technological undertaking in the Soviet Union which has not been associated with Lenin's name.

After Lenin's death, science and industry in the USSR continued to advance along the lines laid down by him. An important step in the advance of science in our country was the transfer in 1934 of the Academy of Sciences of the USSR from Leningrad to Moscow, which led to an expansion of a network of new academic Institutes. The Institute of General and Inorganic Chemistry came into being through the merging of the Institute of Platinum and other Noble Metals with the Institute of Physico-Chemical Analysis and the Chemical Laboratory of the Academy of Sciences. The Institute was subsequently named after N.S.Kurnakov. It became an important centre for advances in Soviet inorganic chemistry. Other Institutes which were created included the Institute of Organic Chemistry, and the Institute of Colloidal and Electro-Chemistry which subsequently became the Institute of Physical Chemistry from which, in turn, the Institute of Electrochemistry split off later. The Institute of Chemical Physics came into the structure of the Academy. Academy bases and branches were being organised; many of these became, in time, Academies of Science of the Republics. At the same time stronger links were being forged between the work of the Academy and practical needs, in accordance with Lenin's testament. In 1938 the Council of the People's Commissars of the USSR proposed that the Academy of Sciences concentrate its attention on the main scientific problems dictated by the development of the Socialist economy and culture.

The development of Soviet chemistry had leaned on the continuously growing might of our chemical industry, mechanical engineering and the national economy as a whole. The State Plan for the Electrification of the Republic was fulfilled ahead of schedule. By 1926 chemical production had reached again the 1913 level. New workshops and factories began to be built for the production of synthetic ammonia, various acids and salts, artifical fertilisers, intermediate products of aniline dye-stuffs industry, etc.

In 1929 the Central Committee of the All-Union Communist Party published its resolution concerning the work of the Northern Chemical Trust, which stressed the importance of further acceleration in the development of the chemical industry. During the First Five-Year Plan (1929-1932) chemical production increased 3.2-fold, outstripping other industries in growth. The development of Soviet chemistry during that period was greatly helped by a national movement in support of a chemical orientation of the national economy which was headed by a number of eminent scientists and resulted in the appointment by the Government of a Committee for promoting this orientation at the Council of People's Commissars of the USSR (1928).

The resolution of the XVII Congress of the All-Union Communist Party put forward the following aim for the Second Five-Year Plan (1933-1937): "To achieve decisive advances in the development of the chemical industry, ensuring an extensive chemical basis for all branches of the national economy and strengthening the country's defences". The resolution urged the adoption by the chemical industry of the newest technological methods (electrolysis, electrothermy, gaseous phase reactions), the use of new raw materials, the creation of a series of new enterprises and further steps in combining the chemical industry with other branches of the national economy. The Second Five-Year Plan achieved a 3-fold increase in chemical production compared with 1932.

A still more extensive programme for the growth of the chemical industry was envisaged in the Third Five-Year Plan, which was interrupted by the treacherous invasion of the Soviet Union by Fascist Germany. Nevertheless, our country had achieved considerable success in the development of the chemical industry during the pre-war Five-Year Plans. Over one hundred large chemical plants were built to produce synthetic ammonia, nitric acid and nitrogeneous fertilisers, sulphuric acid, synthetic rubber, synthetic fibres, potassium and phosphorus fertilisers, aluminium and magnesium compounds for smelting appropriate metals, rare element compounds and many rare metals. The creation of an organic chemical industry was a great achievement. By 1941 the chemical production output had exceeded the 1931 level by a factor of over 20. This proved to be one of the decisive factors in ensuring that the Army and the rear were supplied with all the necessary chemical materials. Soviet chemistry made an important contribution towards the defeat of Germany Fascism and the victory in the Great Patriotic War.

The chemical industry, like other branches of our national economy, suffered greatly from Hitler's invasion. The heroic efforts of the Soviet people during the post-war period made it possible rapidly to restore destroyed factories and build new plants. By 1948 the industry as a whole had returned to the 1940 level and continued to advance. The establishment of new Institutes and research centres continued. In 1957 the Siberian Branch of the Academy of Sciences of the USSR was organised, together with a number of Chemical Institutes. Later, a Research Centre of the Ukrainian Academy of Sciences was created in Donetsk.

As a result of the successful fulfilment and over-fulfilment of four Five-Year Plans (the Fourth, 1946-1950; Fifth, 1951-1955; Sixth, 1956-1960 and Seventh, 1961-1965) the level of chemical production in 1965 had risen 300-fold compared to 1913. The Eighth Five-Year Plan (1966-1970) will see at least a further 1.5-fold increase in chemical production.

Against this background of rapid growth of the chemical industry and allied branches of the national economy there has been an intense development of Soviet chemical science in all directions, many of which had been indicated by Lenin in his time. In a short article one can only mention the most important achievements.

Important discoveries have been made in the field of organic catalysis by N.D. Zelinskii and other outstanding scientists. It became possible to effect various previously unknown transformations of hydrocarbons with the help of specially selected catalysts. Many of these reactions found practical applications in the production of high-quality liquid fuels from oil (catalytic cracking), and served to advance petrochemistry. The multiplet theory of catalysis, put forward by A.A. Balandin, has thrown light on the mechanism of catalytic processes, especially for complex organic reactions.

The growing amount of work on petrochemistry and the processes of oil refining has been accompanied by the establishment of special Research Institutes—the Institute of Petrochemical Synthesis of the Academy of Sciences of the USSR, The Institute of Petrochemical Processes of the Academy of Sciences of the Azerbaidzhan SSR, and others. The achievements of petrochemistry have justified in full the help which Lenin extended to the oil industry in the early period of Soviet power.

A. E. Favorskii and his students, who investigated isomerisation and polymerisation of unsaturated hydrocarbons, did much to fulfill the demands for new synthetic materials made by Lenin and the Council of People's Commissars. This school of scientists developed methods of producing synthetic rubber from divinyl and acetylene, and plastics and adhesives from vinyl acetylene, vinyl esters and other acetylene derivatives. Our chemistry of organic polymers has continued to advance further; its achievements and targets were discussed at the May Plenary Session of the Central Committee of the Communist Party of the Soviet Union in 1957.

The stimulus given to the development of Soviet Organic chemistry after the Great October Socialist Revolution has led to the appearance of new branches of this science. Among these one must mention the chemistry of organoelemental compounds, based on the work of P. P. Shorygin, A. E. Arbuzov and other outstanding Soviet chemists. Organic silicon compounds found extensive application in the preparation of new polymers, lubricating substances and other products. Organic compounds containing atoms of tin, lead, antimony and other metallic elements are used as antiseptics, catalysts and other valuable materials. They have also played an important part in evolving a theory of the structure of organic substances.

In his outline plan for science and technology, Lenin stressed that the young Soviet Republic must aim at being able to provide its own most important raw materials. This aim was pursued on a wide front by large groups of researchers over a period of years. Geological prospecting for the necessary mineral raw materials was associated with experimental work on their technology.

One must mention the work associated with the preparation of aluminium oxide from Tikhvin bauxites which made it possible to organise the production of aluminium by the first Soviet aluminium enterprises—the Volkhovskii and the Dneprov plants. The studies carried out by A. A. Yakovkin on the technology of the production of alumina and by P. F. Antipin on its electrolysis played a very important part in this. Similar work was done on the production of magnesium from carnallite.

In 1922 V. I. Spitsyn and colleagues, working in the Laboratory of Inorganic Chemistry of the Moscow State University, began the study of the chemistry of high-melting rare metals—molybdenum and tungsten. The technology of these metals was studied on samples of native ores and these processes were then translated to an industrial scale at the Baskakov Cable Works in Moscow. In 1925, under the direction of T. M. Aleksenko-Serbin, the country obtained home-produced molybdenum and tungsten wire for the manufacture of electric bulbs and other electrical equipment.

In order to coordinate research into the geology, mineralogy, chemical technology and metallurgy of rare elements, as well as the economic problems associated with these, the Scientific and Technological Section of the Supreme Economic Council established, in 1922, a Bureau to deal with the study and industrial application of rare elements. This Bureau organised the first studies of the chemistry and technology of beryllium, tantalum and the rare earth elements. Later all these resulted in the establishment of industries which had not previously existed in our country. The Bureau's supervisory work passed to the State Institute of Rare Metals when it was established in 1931. Within the latter's walls were developed the scientific foundations for many rare element industries. Among these were the studies directed by M. N. Sobolev on the extraction of vanadium from wastes obtained in the processing of the Urals titanium-magnetite ores. The production of ferrovanadium, established before the start of the Great Patriotic War, ensured the production of high-quality steel alloys for the war effort.

The Institute of Rare Metals organised the production of metallic beryllium, lithium, many rare earth elements, very pure antimony, titanium, germanium and other rare metals. Research into the chemistry of rare elements was also carried out in many scientific Institutes with other designations and in Academic departments. N. P. Sazhin deserves special mention for his contribution to the development of research into the technology of many rare elements.

Platinum metals occupy a special place among the rare elements. Before the Revolution crude platinum was mined in large amounts in Russia, but methods of its refining were not known and it was exported abroad. From there pure platinum and other platinum metals were reimported at great cost. As already mentioned, one of the first Soviet Institutes to be established in 1918 was that for the development of research into the chemistry and technology of platinum and other precious metals. The Institute carried out successfully the targets set by the Soviet Government. Here, under the direction of L. A. Chugaev and I. I. Chernyaev, were begun the investigations which subsequently formed the basis for an original method of platinum refining, which was finally developed at the Institute of General and Inorganic Chemistry of the Academy of Sciences of the USSR. Our country obtained all the platinum metals separately, and in a very pure state.

Rare elements present a particularly good example of the way in which the problem of satisfying all the requirements of our Socialist country in terms of raw materials and manufactured products was taken up by Soviet scientists as a patriotic duty and solved by them. At present the Soviet Union has all the chemical elements which have a practical application.

The Institute of Physico-Chemical Analysis, created under Lenin, carried out under N. S. Kurnakov's direction, an immense task of national importance in studying the salt deposits of our country and the methods of utilising these. Solikamsk, Kara-Bogaz-gol, the soda lakes of Siberia—these are but a few of the subjects studied by researchers at the Institute and later in the Institute of General and Inorganic Chemistry. One must also mention a different line of physico-chemical analysis followed by G. G. Urazov and other colleagues at the Institute. This was the study of metallic systems, which formed the basis for producing high-quality Soviet alloys for aviation and other technological needs. Furthermore, the creative development of methods of physico-chemical analysis which took place in our country after 1917 made an immense contribution to world science.

The part played by Lenin in establishing radium production in Soviet Russia has already been mentioned. The outstanding work directed by V. G. Khlopin put the separation of radium and barium by fractional crystallisation on a scientific basis. The Law of co-crystallisation of micro-admixtures and carriers, discovered by them, threw a new light on the phenomena of isomorphism, and made it possible to use co-precipitation for determining the valency states of elements in unstable compounds and for determining the composition of substances present in minute amounts. At the same time the country was also being provided with radium for medical and research purposes.

The accumulated experience of working with radioactive substances proved later to be extremely important when the problem of organising an atomic industry and preparing pure fissile materials arose in the early Forties. Now the Soviet Union is fully provided with all radioactive elements. Methods have been devised for isolating individual fragment elements used as sources of energy particles (conversion of the heat of radioactive decomposition into electrical energy by means of thermoelectric transducer), in electric charge neutralisers for the textile industry (for neutralising the charges which arise on the thread during spinning) and in other spheres. Industrial production of radioactive isotopes for use in technology and in research has been going on in the Soviet Union for over 20 years.

It would not, of course, be proper to limit this review only to those lines of development in Soviet chemical science which had been directly initiated or supported by Lenin. The Great October Socialist Revolution which took place under Lenin's inspired leadership, brought out new ranks of scientists and engineers from the people and opened before them a wide path of creative activity. They responded to all the new challenges presented by the rapid developments in science and technology. They shared the will to realise Lenin's vision of close ties between science and the practical demands of the national economy.

It has not therefore been an accident that our country became, under the Soviet Government, one of the most important centres of research into the chemistry of complex compounds (I. I. Chernyaev, A. A. Grinberg, and others). Some of the achievements of Soviet chemists include: detailed unravelling of the theory of chain reactions which makes it possible to control the kinetics of chemical processes; creation of an important new aspect of physical chemistry—physico-chemical mechanics with its numerous practical applications; elaboration of the theory of surface phenomena in electrode processes, which is of the utmost importance in clarifying the mechanism of reactions occurring in chemical sources of current; the work of V. A. Kistyakovskii, G. V. Akimov and their students which laid the foundations for the theory of corrosion processes in metals and developed effective anti-corrosion measures; study of adsorption, begun during the First World War by N. D. Zelinskii and N. A. Shilov which led to the discovery of important laws recently used in the synthesis and rational application of new types of sorbents, which have become very important in modern technology (molecular sieves).

The scientific and technological revolution in our country has followed Lenin's outline and brought about a rapid growth in culture and technical education of the population unmatched elsewhere. In 1917 the Russian Physico-Chemical Society had 565 members. At present the D. I. Mendeleev All-Union Chemical Society has a membership of 180 000, and the total number of scientsts and chemical engineers far exceeds this number. Before the Revolution the number of scientists in Russia, Doctors and Masters of Chemical Science did not exceed a few score. Now the Soviet Union has over 1100 Doctors and about 11,000 Candidates of Chemical Science.

It can be said without exaggeration that at present Soviet scientists and engineers, workers and technicians in our chemical industry are able to solve the most complicated problems that the Soviet State may place before them. Our people have achieved these successes by their persistent endeavours under the guidance of the Communist Party. But we shall never forget that it was Lenin who set the course for the development of science and technology in the first Socialist State.

U. D. C. 547.311 : 547.422.22 – 31 : 547.71

Cyclisation Reactions with Participation of Epoxy-compounds

V.N.Yandovskii, V.S.Karavan, and T.I.Temnikova

The review deals with reactions of epoxy-compounds in which they are involved in the formation of cyclic structures. Intramolecular rearrangements with participation of epoxy-compounds can lead to alicyclic and heterocyclic compounds. Intermolecular condensations of epoxy-compounds with various reagents give rise to heterocyclic structures.
The bibliography comprises 307 references.

CONTENTS

I. INTRODUCTION

The continuing interest of chemists in epoxy-compounds is due to unusual reactions undergone by compounds of this class. The interest in them increased especially when their significant role in biological processes, where epoxy-compounds are involved as intermediates in the fixation of oxygen by the ethylene bond yielding numerous derivatives in subsequent reactions, became recognised. Many natural products containing the epoxy-ring have been isolated and their number is continually increasing[1].

In recent years a number of reviews dealing with reactions of epoxy-compounds have been published[2-4]. However, the treatment of processes in which epoxy-compounds take part in the formation of cyclic products has been clearly inadequate.

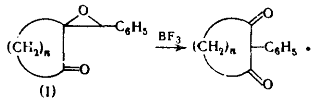
The primary aim of the present review has been to give a systematic account of reactions of this type and to classify them in accordance with common cyclisation mechanisms.

II. INTRAMOLECULAR CYCLISATIONS

1. SYNTHESIS OF CARBOCYCLIC COMPOUNDS

a. Rearrangement on Displacement of an sp^3-hybridised atom

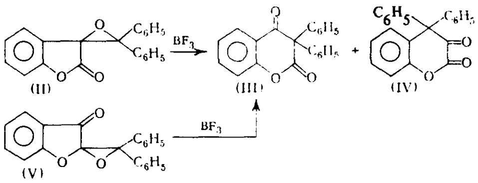
Rearrangements with participation of a carbonium ion. Epoxy-compounds are known to isomerise to the corresponding carbonyl compounds in the presence of acids. The process is accompanied by the migration of the group adjacent to the electron-deficient carbon atom, produced on opening of the ring. In the special case where the epoxy-derivatives of cycloalkenes with an *endo*- or *exo*-double bond are isomerised, the migration of an alkyl group leads to the contraction or expansion of the ring respectively. For example, the epoxy-derivatives obtained from methylenecyclopropane and methylenecyclobutane isomerise to cyclobutanone[5] and cyclopentanone[6] respectively, while the epoxy-derivative of methoxybenzylidenecyclohexane gives 2-anisylcycloheptanone[7]. House and Wasson converted the epoxy-compounds (I) into β-diketones under the action of boron trifluoride in benzene[8]:



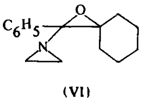
(I)

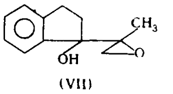
(n = 3 4,5)

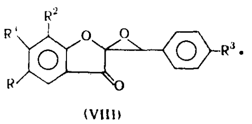
Schönberg and Junghans[9] also observed cases of ring expansion in the isomerisation of epoxy-compounds: the epoxy-compound (II) gave a mixture of products (III) and (IV), the former being obtained also in the isomerisation of the epoxy-compound (V):



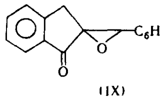
Another example is the conversion of epoxyamines (VI) into cycloheptanone derivatives[10], the conversion of *threo*- and *erythro*-1-(2-hydroxyindolyl)-1-methyloxirans (VII) into a mixture of α- and β-tetralones[11] and also the conversion of the epoxy-compound (VIII) into 4-hydroxycoumarin derivatives[12]:

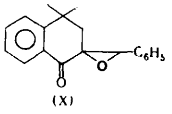

(VI)


(VII)


(VIII)

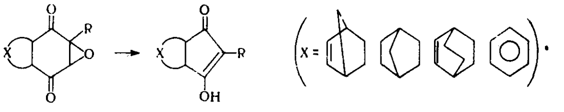
Certain other spirocyclic epoxy-compounds, for example (IX) and (X), undergo similar isomerisation with ring expansion under the action of boron trifluoride[13,14]:


(IX)


(X)

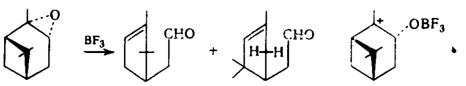
The isomerisation of alicyclic epoxy-compounds with ring contraction is observed much more frequently. Thus magnesium bromide causes the rearrangement of epoxycyclohexane to formylcyclopentane[15-18], of 1,2-epoxycyclohex-3-ene and 1,2-epoxycyclohex-4-ene to 2- and 3-formylcyclopentenes respectively[19], and of 1,2-epoxy-1-methylcyclohexane to acetylcyclopentane[18]. Under analogous conditions, 4-acetoxy-1,2-epoxy-1-methylcyclohexane rearranges to 1-acetoxy-3-formyl-3-methylcyclopentane[20] and the epoxy-derivative of dihydronaphthalene rearranges to 2-formylindane[21]. The isomerisation of 2,3-epoxycyclohexanone catalysed by boron trifluoride-ether yields 2-formylcyclopentanone[22], and 2-formyl-2-phenylcyclopentanone was obtained by the isomerisation of 2,3-epoxy-3-phenylcyclohexanone[22].

The reaction of epoxycyclohexane with methyl-[23,24], ethyl-[24], cyclohexyl-[25], β-phenylethyl-[26], and phenylmagnesium bromides[27,28] gives alkylcyclopentylmethanols, since the formylcyclopentane formed initially reacts further with the Grignard reagent. Similarly the reduction of 1-methylepoxycyclohexane with the mixed aluminium hydride $AlH_3.2AlCl_3$ yields 1-hydroxymethyl-1-methylcyclopentane[29]. The epoxy-compounds (XI) are isomerised by acid catalysts (BF_3, H_2SO_4) to compounds (XII) as a result of ring contraction and subsequent deformylation[30]:



(XI) (XII)

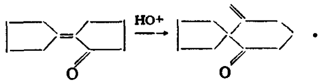
The reactions of epoxy-compounds under acid conditions may be accompanied sometimes by very pronounced changes in the carbon skeleton. Thus the epoxy-derivative of *trans*-cyclo-octene is isomerised by formic acid to hexahydro-*o*-toluic aldehyde[31] and the epoxy-derivative of α-pinene forms campholenic aldehyde under the action of Lewis acids[32-35]. Moreover, apart from campholenic aldehyde (XIII), the mixture contained a certain amount of the aldehyde (XIV), the formation of which can be understood only as a result of non-concerted C-7 and C-2 migration in the carbonium ion (XV)[34]:



(XIII) (XIV) (XV)

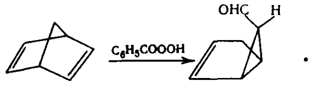
The reactions of the epoxy-derivatives of α- and β-pinenes has been reviewed[36]. The isomerisation of the 3,4-epoxycarane system also provides examples of profound changes in the carbon skeleton[37-39]; the reactions of certain sesquiterpenes[40] and also rearrangements in the steroid series[41-45] catalysed by boron trifluoride-ether have been described.

The oxonium ion formed on co-ordination of the oxygen atom of the epoxy-ring to acids resembles in many respects the structures formed on halogenation and protonation of the ethylene bond; the subsequent rearrangements of this ion with migration of the adjacent group resemble the isomerisation reactions which accompany, for example, the halogenation of a double bond at a quaternary carbon atom[46]. The conversion of a double bond into an epoxy-derivative also includes the formation of an oxonium complex as one of the stages; there are examples of 1,2-alkyl migration in the oxidation of olefins by peracids. In special cases this can cause the contraction or expansion of the carbon ring. The conversion of an exocyclic double bond into an epoxy-group leads to ring expansion[7,47], for example the reaction of a mixture of trifluoroperacetic acid and boron trifluoride with (XVI) yields (XVII):



(XVI) (XVII)

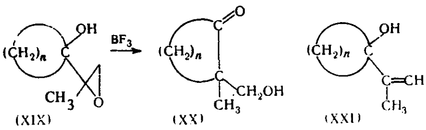
The conversion of an endocyclic double bond into an epoxy-group results in ring contractions: oxidation of norbornadiene with perbenzoic acid gives the aldehyde (XVIII)[48]:



(XVIII)

Certain other examples concerning steroids have been quoted[49].

In the halogenation of a double bond and its conversion into an epoxy-group and in the co-ordination of epoxy-compounds to acids the positive charges at the carbon atoms in the transition states are in general different. This can lead to different final products when account is taken of the possibility of the following competing reactions: (1) internal nucleophilic (in the limit) attack by the oxygen atom in the conversion to an epoxy-group leads to the closure of the epoxy-ring; (2) the migration of the adjacent group yields isomerisation products; (3) the anchimeric assistance of an adjacent group with electron-donating properties (when such is present) can result in the formation of cyclic structures; (4) external nucleophilic attack leads to addition products. In connection with the above, we may note that the epoxy-compounds (XIX) are isomerised by boron trifluoride to the ketones (XX) with ring expansion[50], the reaction of the hydrocarbons (XXI) with hypohalous acids also gives the ketones (XX) while their conversion into epoxy-derivatives yields only compounds (XIX):



(XIX) (XX) (XXI)

All the cases quoted so far included the formation of a new C–C bond as a result of the migration of an alkyl group to a carbonium ion generated on opening of the epoxy-ring or on its formation. Considerably much less attention has so far been devoted to the reactions of epoxy-compounds with bases. Most of the examples studied included an investigation of the addition of various basic reagents in proton-donating solvents (alcohol, water, dilute acids). However, the latest studies of Cope, Crandall, and Temnikova and coworkers led to the discovery of new interesting reactions of epoxy-compounds in the presence of strong bases.

Anionoid rearrangements. Crandall and coworkers[5] reported certain reactions of epoxy-compounds in the presence of strong bases (R_2NLi, BuLi). A proton may be eliminated from the α- or β-position in the epoxy-compound molecule.† Elimination from the α-position yields a carbene, which can be subsequently inserted intramolecularly in a C–H bond or can add to a C=C bond.

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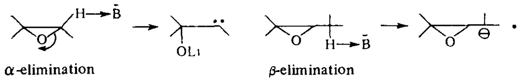
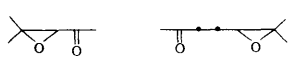
† Here and henceforth Crandall's terminology is used[51].

β-Elimination yields a carbanion, the rearrangement of which leads to the isomerisation of the epoxy-compound to an allyl alcohol[51-55]:

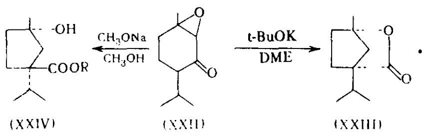


The contributions of α- and β-elimination are determined by the presence of a proton in the appropriate positions and the ease of its elimination[51].

Evidently Crandall's mechanism can be supplemented by certain specific cases. Thus, when the molecule of the epoxy-compound contains a powerful electron-accepting group (for example a carbonyl group), elimination of a proton from other positions in the substrate becomes possible and therefore one can speak of γ-elimination, δ-elimination, etc. The most interesting examples of γ-elimination are the rearrangements of αβ-epoxy- and γδ-epoxy-ketones into cyclopropane derivatives:

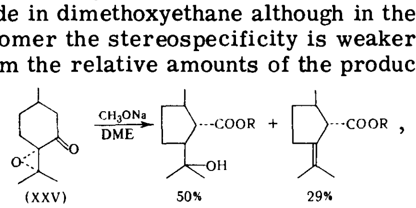


The close analogy between αβ-epoxyketones and α-halogenoketones is quite evident; it is confirmed also by the very similar behaviour of these bifunctional substrates in the Favorskii rearrangement. The intermediate formation of cyclopropanone as a result of a co-ordinated S_Ni attack by the carbanion on the α-carbon atom takes place similarly in both cases. The subsequent cleavage of cyclopropanone under the reaction conditions takes place stereospecifically in non-polar solvents (for example dimethoxyethane) or non-stereospecifically‡ (water, alcohol) and leads to hydroxyacids or lactones. The isomerisation of the epoxy-derivative of piperitone (XXII) yields (XXIII) as a result of a stereospecific Favorskii rearrangement in dimethoxyethane (DME), while in methanol (XXIV) is formed non-stereospecifically[56]:

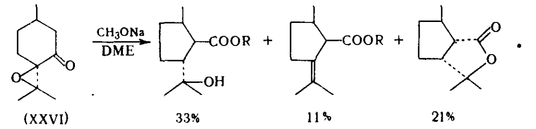


(XXIV) (XXII) (XXIII)

The *cis*-epoxy-derivative (XXV) and *trans*-epoxy-derivative (XXVI) of pulegone undergo preferential stereospecific rearrangement in the presence of sodium methoxide in dimethoxyethane although in the case of the *trans*-isomer the stereospecificity is weaker[57], as can be seen from the relative amounts of the products:



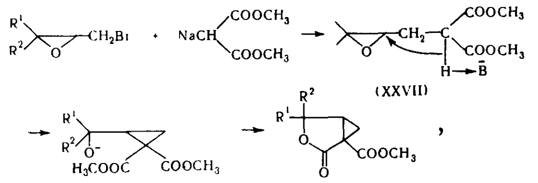
(XXV) 50% 29%



(XXVI) 33% 11% 21%

The study of the reactions of the same epoxy-compounds with sodium methoxide in ethanol or with sodium hydroxide in aqueous ethanol and water showed that in such cases the reaction is stereospecific[61,62]. The Favorskii rearrangement of the epoxy-derivative of isophorone[56] and of αβ-epoxyketones of the steroid series[57] also involves the contraction of a six- to a five-membered ring.

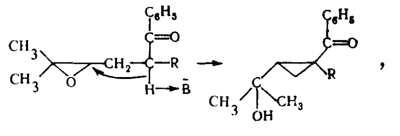
Other interesting examples involving the formation of the cyclopropane ring are provided by the rearrangement of γδ-epoxyketones. Thus the alkylation of dimethyl sodiomalonate with α-bromo-derivatives of epoxypropane, 1,2-epoxy-2-methylpropane, 1,2-epoxybutane, 2,3-epoxybutane, and 2,3-epoxy-2-methylbutane gave the γ-lactone of 1-hydroxymethyl-2-methoxycarbonylcyclopropane-2-carboxylic acid and its homologues according to the following mechanism[63,64]:



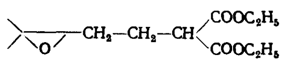
(XXVII) (XXVIII)

where R¹ = H and R² = H or CH_3 or R¹ = CH_3 and R² = CH_3.

The mechanism is confirmed by the finding that the epoxy-compound (XXVII) obtained in a different way isomerises to (XXVIII)[64]. The products of the alkylation of the sodio-derivatives of acetophenone and benzyl methyl ketone with 1-bromo-2,3-epoxy-3-methylbutane in toluene undergo a similar rearrangement[65,66]. The epoxyketones formed in the first stage isomerise in an alkaline medium to cyclopropane structures via the intramolecular attack by the nucleophilic carbon atom of the epoxy-ring according to the mechanism[66]

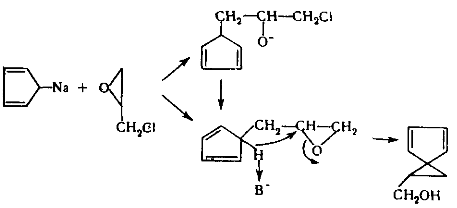


where R = H or C_6H_5. We may note that the epoxy-compound (XXIX) (synthesised by an independent method), the chain of which contains one carbon atom more than in (XXVII), is not converted into the corresponding cyclobutane[67]:



(XXIX)

The interaction of epichlorohydrin with cyclopentadienylsodium leads to the formation of cyclopropane as a result of the attack by the carbanion on the epoxy-ring according to the mechanism[68]



The authors do not state which pathway is actually followed. For information about the preparation of cyclopropane by the rearrangement of 1,2-dicyano-oxiran, see Ershov et al.[69]

b. Reactions with Participations of a Carbene

The elimination by strong bases of a proton from epoxy-compounds without electron-accepting functional

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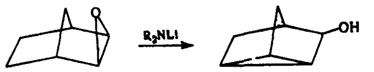
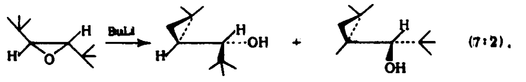
‡ For a discussion of this problem, see Refs. 56–60.

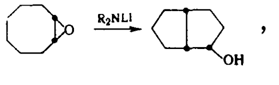
groups involves, as already stated, competition between α- and β-elimination. In the vast majority of cases β-elimination is observed[51]. There are, however, cases, where the formation of a carbene predominates or constitutes the sole reaction of epoxy-compounds in the presence of bases. For instance, epoxynorbornane rearranges to a nortricyclanol via the intermediate formation of a carbene, because the elimination of a proton from the β-position is impossible[70]:

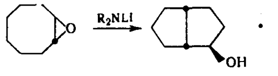


1,2-Di-t-butylepoxyethane yields two products of the insertion of a carbene in the C–H bond[71]:

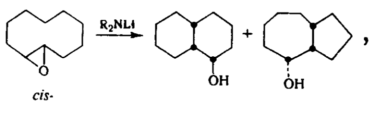


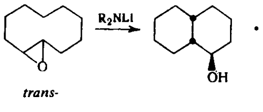
The formation of a considerable amount of the second isomer is evidence of the incomplete stereospecificity of the insertion reaction and can probably be accounted for by the existence of the carbene as a discrete entity. On the other hand, the configurational mobility of the carbon chain leads to a mixture of products. In contrast to aliphatic epoxy-compounds, the epoxy-derivatives of cycloalkanes (n = 7, 8, or 10) undergo stereospecific *trans*-annular insertion of the carbene. The closeness of the atoms in medium rings leads to the preferential interaction of the carbenes with the C–H bond at the opposite end of the molecule. The epoxy-compounds derived from *cis*- and *trans*-cyclo-octenes undergo a stereospecific rearrangement to the corresponding bicyclo-octanols[72,73]:



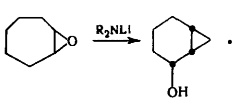


The epoxy-compounds derived from *cis*- and *trans*-cyclodecenes are converted into bicyclodecanols also as a result of a stereospecific *trans*-annular insertion of the carbene in a C–H bond[73,74]:

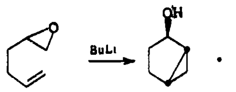




The rearrangement of epoxy-cycloheptane takes place similarly[51]:

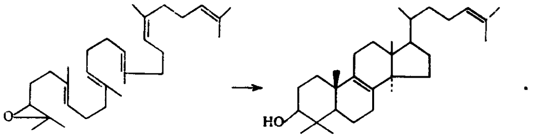


The stereospecificity of reactions involving the *trans*-annular insertion of carbenes into medium rings and also the predominance of α-elimination in such cases have been explained[51,71,75]. We shall only note an interesting example of intramolecular addition of a carbene to a double bond in the rearrangement of the monoepoxy-compound derived from diallyl[71]:

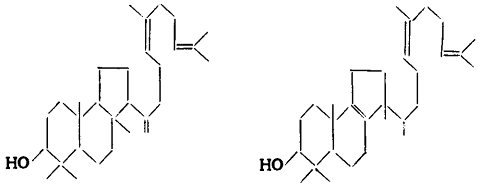


c. Nucleophilic Participation of the C=C bond in the Rearrangement of Epoxy-Compounds

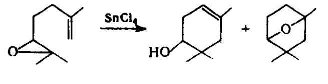
A study of the rearrangement of the electron-deficient carbon atom in the opening of the epoxy-ring gives rise to the following natural question: whether the alkyl group migrates synchronously as the charge of the carbon atom in the oxonium complex increases or whether the coordination of the epoxy-compound molecule to acids with subsequent ring opening involves a discrete carbonium ion. Probably this question can be solved in a concrete form as a function of the reaction conditions and the object investigated[76,77]. In particular, there are a number of examples where the rupture of the C–O bond in the epoxy-ring takes place synchronously with formation of the new bond, with the adjacent group playing the role of a donor. This leads ultimately to cyclic products. This process can be aided by the nucleophilic effect of a hetero-atom (O, N, etc) or groups with a relatively high electron content, for example, a multiple bond. The nucleophilic involvement of the C=C bond in enzyme- and acid-catalysed reactions of epoxyolefin systems attracted very considerable attention in recent years as a model of the biosynthesis of natural products (terpenes, steroids). The most interesting example of this kind is the conversion of squalene-2,3-oxide into lanosterol steroids, which has been achieved enzymically under laboratory conditions[78-81]:



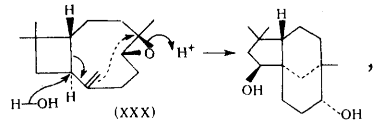
Certain homologues of squalene-2,3-oxide and its derivatives have also been converted into lanosterols[82-86]; by varying the enzymes, it proved possible to obtain under laboratory conditions fusidic acid[87] and pentacyclic products: β-amyrin[88] and cycloartenol[89]. Non-enzymic cyclisation of 2,3-oxidosqualene with stannic chloride yielded only tricyclic products[90]:

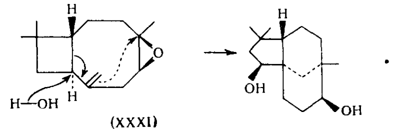


One of the first studies in this series involved an investigation of the cyclisation of the monoepoxy-derivative of geraniolene as a model compound in the synthesis of 3-hydroxy-derivatives of polycyclic systems (steroids, terpenes)[91]:

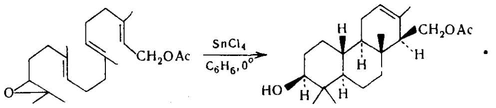


The yield of these cyclic products in the presence of boron trifluoride as a catalyst (both in benzene and in ether)[92] was smaller than in the presence of $SnCl_4$. Pyrethrosin undergoes a cyclisation of a similar type yielding a tricyclic product[93]. The epoxy-compounds derived from caryophyllene (XXX) and isocaryophyllene (XXXI) cyclise[94,95] to the corresponding glycols by the mechanisms

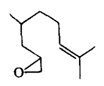

(XXX)

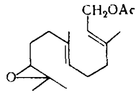

(XXXI)

A similar process takes place when geranylgeranyl acetate is treated with stannic chloride[96]:



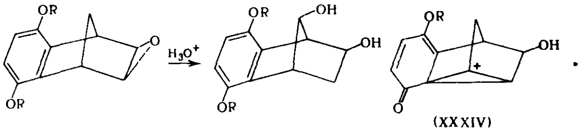
Goldsmith et al.[97] studied the reaction of stereoisomeric epoxy-derivatives of citronellal (XXXII), and the stereochemistry of the cyclisation of the epoxy-derivatives of farnesyl acetate (XXXIII) has been discussed by van Tamelen and coworkers[98,99]:


(XXXII)


(XXXIII)

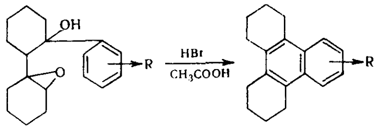
The conversion of certain epoxyolefins into carbocyclic compounds has also been described[100-102].

The involvement of a double bond, formerly included in a benzene ring, in the acid-catalysed hydrolysis of epoxy-groups in the benzonorbornene series yields anomalous water addition products. The formation of a new C–C bond in the intermediate structure (XXXIV) is postulated, as shown in the mechanism below[103-105]:



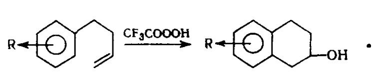
(XXXIV)

The epoxy-compound (XXXV) reacts similarly; under these conditions, the cyclic product is dehydrated[106]:



(XXXV)

An unusual example of the involvement of the C=C bond is quoted by Davidson and Norman[76]. The conversion of butenylbenzenes (XXXVI) into epoxy-derivatives with trifluoroperacetic acid leads to 1,2,3,4-tetrahydronaphthols in yields of 7% (R = H) and 25% (R = OCH_3):



(XXXVI)

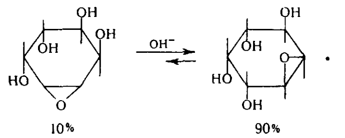
It is surprising that in the presence of boron trifluoride epoxy-compounds derived from unsaturated hydrocarbons do not yield naphthols.

2. SYNTHESIS OF HETEROCYCLIC COMPOUNDS

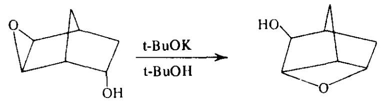
The previous section quoted certain examples of the reactions of epoxyolefins with the nucleophilic participation of the carbon–carbon double bond and formation of carbocyclic products. In this section we shall discuss cases of the formation of heterocyclic compounds such as the intramolecular nucleophilic involvement of the heteroatom in the base- and acid-catalysed rearrangements of epoxy-compounds with functional groups.

a. Attack by the Heteroatom on the Epoxy-ring without Incorporation of the Oxygen Atom into the Cyclic System

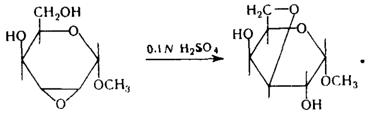
The simplest example of processes of this kind is the so called migration of the epoxy-group, which in the case of sugars, for example, can lead to an equilibrium mixture of isomers[107]:



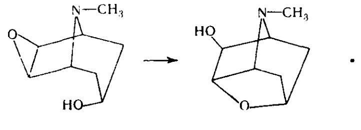
Some examples of reactions of this type have been reviewed by Newth[108] and Lemieux[109]. Similar cases of migration of the epoxy-group have been observed by Payne[110] for epoxyalcohols[110] and Akhrem and coworkers for steroids[111,112]. All these reactions take place under mild alkaline conditions involving the formation of an oxy-anion. The participation of such anions can lead to a strained oxacyclobutane system[113]:



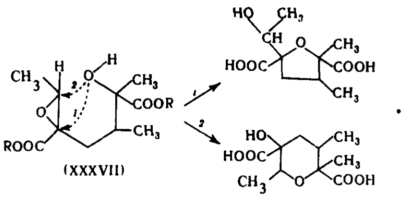
If, owing to steric factors, the participation of an O^- or OH group is impossible, then furans and pyrans are readily formed when the epoxy-ring is opened. The acid hydrolysis of methyl-2,3-anhydro-D-hexopyranosides leads to 3,6-anhydropyranosides[114]:



This cyclisation, which takes place most readily under mild alkaline conditions, has been described in the literature for 2,3-anhydro-derivatives[114-118] and 5,6-anhydro-derivatives[119]. Reactions of a similar kind are encountered among alkaloids: for example, scopine is converted into scopoline[120]:



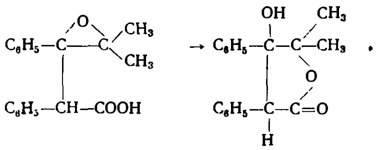
The alkaloid jacobine (XXXVII) is converted into a mixture of substituted tetrahydrofuran and tetrahydropyran derivatives[121] (in the formulae below R = R = H or R = R = retronecine residue):



(XXXVII)

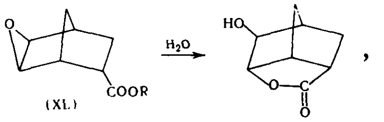
Many other examples of O-5 and O-6-involvement of the hydroxy-group in acid- and base-catalysed reactions of epoxy-derivatives of the terpene series, leading to the formation of furan and pyran derivatives, have been found in recent years[122-126].

Examples of the nucleophilic involvement of the carboxy-group in the isomerisation of epoxyacids are rarely encountered in a pure form. In particular, we may note that the $\beta\gamma$-epoxyacid (XXXVIII) is readily converted into the lactone (XXXIX) in the presence of *p*-toluenesulphonic acid[127]:



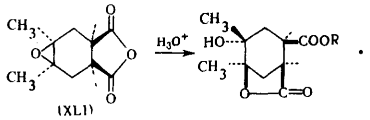
(XXXVIII) (XXXIX)

In most cases it is difficult to decide, because of a deficiency of data, whether the epoxy-ring opens with participation of the adjacent group or whether the epoxy-group is first hydrolysed to a glycol and the lactone is formed as a result of the interaction between the hydroxy- and carboxy-groups. This is illustrated by the conversion of the epoxyester (XL) into a hydroxylactone[113]:



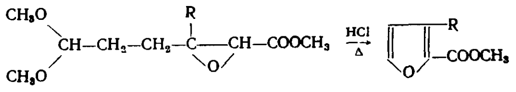
(XL)

or the conversion of the epoxyanhydride (XLI) into a hydroxylactone on hydrolysis[128]:

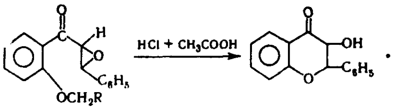


(XLI)

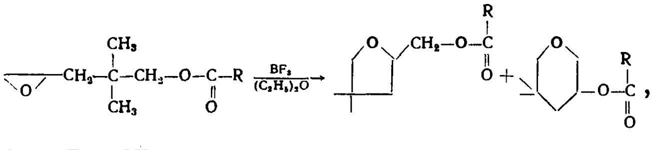
Excellent examples of translactonisation occurring on opening of the epoxy-ring in epoxylactones subjected to hydrolysis or reduction with lithium aluminium hydride have been given by Conroy[129,130] and Nazarov et al.[131] Cases of the participation of the oxygen atom in ether, ester, and epoxy-groups following the opening of the epoxy-ring in the corresponding epoxy-compounds under acid conditions are very numerous. In particular, the cyclisation of δ-acetals of glycidic esters leads to 3-substituted furans[132]:



and epoxy-derivatives of 2′-hydroxychalcone yield 3-hydroxyflavanone[133]:



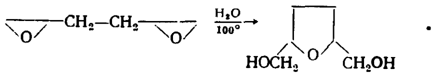
The rearrangement of 4,5-epoxy-2,2-dimethylpentyl acetate catalysed by boron trifluoride gave a mixture of furan and pyran derivatives[134]:



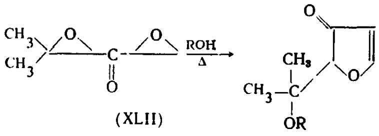
where R = CH_3.

Only the furan derivative was isolated after the reaction of 4,5-epoxy-2,2,4-trimethylpentyl isobutyrate[134].

The nucleophilic co-operation with the epoxy-oxygen atom in the opening of the second epoxy-ring in diepoxy-compounds is also well known. For example, the diepoxy-compound derived from hexa-1,5-diene forms a tetrahydrofuran derivative in the presence of acids[135]:

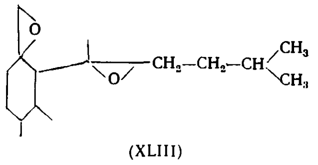


On heating in the presence of alcohol, the epoxy-compound (XLII) isomerises to dihydrofuranone[136]:



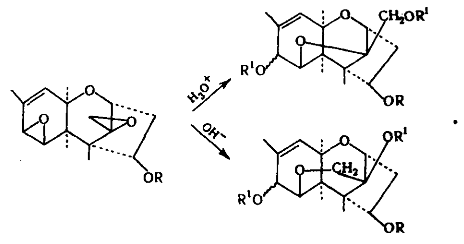
(XLII)

Klein and coworkers[137,138] described the conversion of diepoxy-derivatives of geraniol, nerol, and linalo-ol into furan and pyran derivatives under mild alkaline conditions. In the course of experiments designed to elucidate the structure of fumagillin (XLIII), Tarbell[139] observed various reactions of this compound due to the presence of two epoxy-groups:



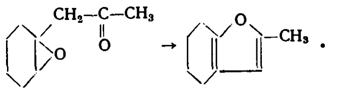
(XLIII)

Crotocin, an antimildew antibiotic, also contains two epoxy-groups, the interaction of which is different under acid and alkaline conditions[140], leading to furan or pyran derivatives:



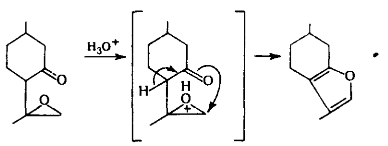
Similar reactions have been described also for certain other diepoxy-compounds[126,141].

The intramolecular interaction of carbonyl and epoxy-groups can take place in two different ways. Under alkaline conditions, there is a possibility of the formation of a mesomeric enolate anion, the intramolecular interaction of which with the epoxy-ring leads to carbocyclic products (cyclopropanes, cyclobutanes, etc) in the case of C-alkylation or to oxiran (oxetan, tetrahydrofuran, etc.) derivatives in the case of O-alkylation. In an acid medium the epoxy-group activated by co-ordination to the catalyst can cause a displacement via a field effect of the electrons from the carbonyl group (or the hydroxy-group of the enol if such is formed), which leads to the formation of cyclic products, as in O-alkylation in an alkaline medium. For example, the ketoepoxy-compound (XLIV) is cyclised by dilute sulphuric acid to furan[142]:

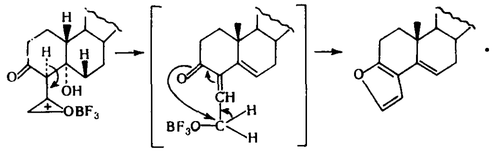


(XLIV)

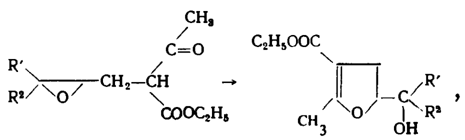
The epoxy-derivative of isopulegone undergoes a similar reaction, menthofuran being formed under very mild conditions, close to those obtaining in biological systems[143]:



Epoxyketols of the cholestane series also tend to undergo similar reactions; the reaction is catalysed by boron trifluoride which behaves at the same time as a dehydrating agent[144,145]:



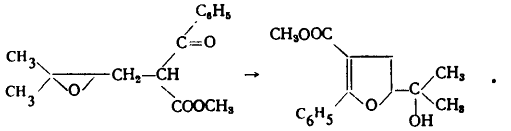
Much attention has been devoted to the problem of the biosynthesis of furans from natural products, in particular from epoxy-derivatives[144,146]. Interesting results were obtained in the alkylation of metal derivatives of carbonyl compounds by α- and β-bromoepoxy-compounds. In most cases the alkylation products formed initially undergo a rearrangement as a result of attack by the enolate anion on the epoxy-ring. In the interaction of sodioacetoacetic ester with 1-bromo-2,3-epoxybutane and 1-bromo-2,3-epoxy-3-methylbutane, compound (XLV), formed as an intermediate, rearranges to dihydrofuran[147,148]:



(XLV)

where $R^1 = R^2 = CH_3$ or $R^1 = H$ and $R^2 = CH_3$.

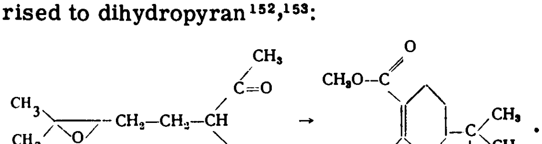
Similarly, compound (XLVI), formed as an intermediate in the reaction of methyl benzoylacetate with 1-bromo-2,3-epoxy-3-methylbutane in methanol also yields a dihydrofuran[149]:



(XLVI)

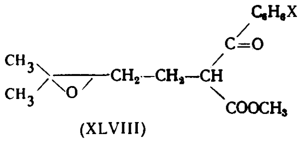
Dihydrofurans have also been obtained in the alkylation of the sodio-derivatives of benzyl phenyl ketone, benzoylacetone, and acetylacetone with 1-bromo-2,3-epoxybutane as a result of rearrangement under the reaction conditions of the γδ-epoxyketones formed[150,151].

In the alkylation of methyl acetoacetate with 1-bromo-3,4-epoxy-4-methylpentane the intermediate (LVII) isomerised to dihydropyran[152,153]:



(XLVII)

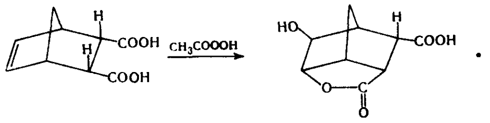
The epoxy-compounds (XLVIII) synthesised by an independent procedure are also converted into dihydropyran in the presence of bases[154]:



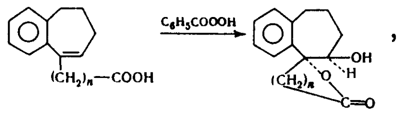
(XLVIII)

where $X = p\text{-}CH_3O$, $p\text{-}CH_3$, H, or $p\text{-}NO_2$.

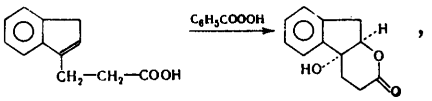
The nucleophilic involvement of an oxygen atom may be reflected not only in the opening of the epoxy-ring but also in its formation. Thus in the conversion into epoxy-derivatives of unsaturated compounds containing hydroxy-, carboxy-, ester, ether, or epoxy-groups the reaction is anomalous. The reaction of peracetic acid with 2,3-di-*endo*-carboxybicyclo[2,2,1]hept-5-ene gives a lactone[155]:



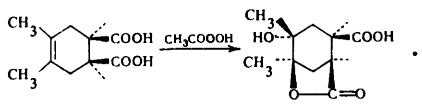
Lactones are formed similarly from the derivatives of benzocycloheptene[156]:



indene[157]:

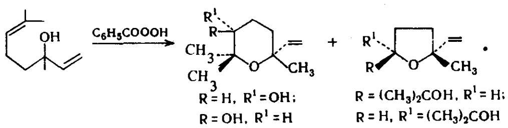


and 4,5-dimethyl-Δ^4-cyclohexene-*cis*-1,2-dicarboxylic acid[128]:



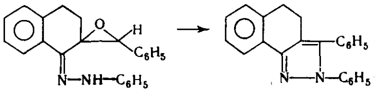
Interesting examples of the formation of a mixture of γ- and δ-lactones in the oxidation of *trans*- and *cis*-*o*-carboxystilbenes with perbenzoic acid have been quoted by Berti and Bottari[158-160] (see also Nazarov et al.[131] and Mousseron et al.[161]).

The most numerous examples of the participation of the hydroxy-group have been found in the Prilezhaev oxidation of hydroxyolefins with formation of furans and pyrans. For example, the conversion of 2-allylphenols into epoxy-derivatives leads to benzofurans[162,163]. Benzofurans have also been obtained by the oxidation of 2-propenylcresols[164]. The conversion of linalo-ol into an epoxy-derivative over phthalic acid yields a mixture of stereoisomeric tetrahydropyrans[165,166]:

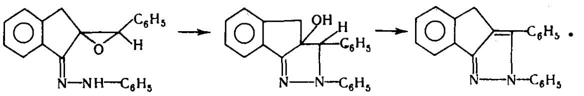


More detailed studies showed that the mixture contained also stereoisomeric tetrahydrofurans[125,167]. The formation of furan and pyran derivatives in the conversion to epoxy-derivatives of diallyl[168], octadeca-9,10-trienecarboxylic, octadeca-11,12-trienecarboxylic, and octadeca-13,14-trienecarboxylic acids[169], and other compounds[170,171] has been described.

Few data have been published on the intramolecular cyclisation of epoxy-compounds with participation of a nitrogen atom, probably owing to the difficulty of the synthesis of such bifunctional compounds. Cromwell showed that epoxyphenylhydrazones of type (XLIX) and (L), which are formed in the reaction between the corresponding $\alpha\beta$-epoxyketones with phenylhydrazine, are readily converted into pyrazoles[13,172]:

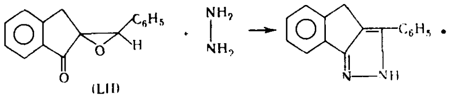


(XLIX)



(L) (LI)

Since the rates of cyclisation of epoxyphenylhydrazone (L) into pyrazoline (LI) and its subsequent dehydration are comparable, it proved possible to isolate all three products. The interaction of the epoxy-compound (LII) with hydrazine leads directly to a pyrazole[13]:

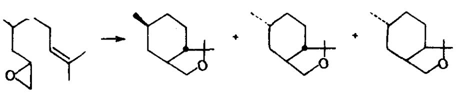


(LII)

Certain other examples of the formation of pyrazoles in the interaction of $\alpha\beta$-epoxyketones with hydrazine have been described[173-176].

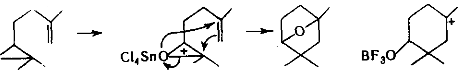
b. Cyclisation with Incorporation of the Oxygen Atom of the Epoxy-compound into the Cyclic System

Most of the examples considered above involved an intramolecular nucleophilic attack on the epoxy-ring with inversion at the carbon atom attacked. In reactions in an alkaline medium the group eliminated (the oxy-anion) was stabilised by abstracting a proton from the medium. In acid-catalysed processes the oxygen atom of the epoxy-group was bound to a proton or a Lewis acid. The molecule was then stabilised either by splitting off the catalyst and forming a carbonyl compound or by the fixation of the oxygen atom as a hydroxy-group as a result of hydrolysis by the reaction medium. It is quite evident that this mechanism is oversimplified. Indeed, if the molecule is fairly complex, in the rearrangement in the presence of bases the liberated oxy-anion may attack any other electrophilic centre in the same molecule (if allowed by the geometry). Such a case has already been mentioned (p. 267). Another example is provided by acid-catalysed rearrangements of epoxyolefins. The isomerisation of the epoxy-derivative obtained from citronellal leads to bicyclic products[97]:



The cyclisation of the mono-epoxyderivative obtained from geraniolene (p. 268) and the epoxy-derivative from geranylgeranyl acetate takes place similarly[96]:

The fact that the yield of the cyclic products was higher in the catalysis by $SnCl_4$ than in the catalysis by BF_3 is striking[91,92]. As a catalyst, $SnCl_4$ is a weaker Lewis acid than BF_3 and the rupture of the C–O bond of the epoxy-ring requires a higher degree of nucleophilic co-operation by an adjacent (geometrically suitable) C=C bond. Consequently in this case the cyclisation process is more synchronous. As the C–O bond is broken, the interaction of the π electrons of the double bond with the positive charge generated at one of the carbon atoms of the epoxy-ring becomes intensified simultaneously with the intensification of the nucleophilic interaction between the oxygen atom and the carbon of the multiple bond. The entire process may be represented by the following mechanism:-

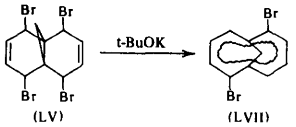


(LIII) (LIV)

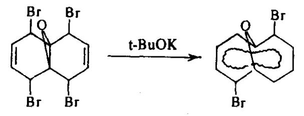
In the presence of boron trifluoride the carbonium cation structure of the transition state in the opening of the epoxy-ring is more pronounced and therefore the process is less synchronous and the yield of the cyclohexane derivative is lower. The bicyclic product (LIII) is also formed in a small amount, because the significant weakening of the nucleophilicity of the oxygen atom increases the probability of a competing process—the stabilisation of (LIV) by the elimination of a proton. We believe that the greater resemblance to a carbonium cation of the transition state in the BF_3-catalysed reaction of epoxy-compounds is indicated by the formation of fluorohydrins in this reaction, which has been known for a long time. On the other hand, in the reaction catalysed by $SnCl_4$ the formation of chlorohydrins has not been observed.

c. Valence Tautomerism of Epoxy-compounds

The valence tautomerism of acyclic and alicyclic dienes and their cyclopropyl analogues, involving 1,5-dienyl or homodienyl migration of hydrogen, has been described fairly adequately[177]. A certain similarity in the state of the bonds in the cyclopropane and oxiran rings is reflected in a number of rearrangements of vinyl-substituted cyclopropanes and oxirans. For example, dehydrobromination of (LV) and (LVI) with potassium t-butoxide in ether at 10°C leads to (LVII) and (LVIII) respectively[178]:

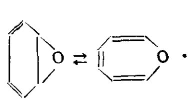


(LV) (LVII)

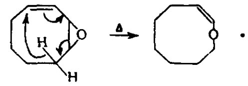


(LVI) (LVIII)

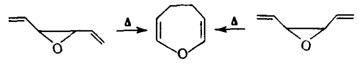
The monoepoxy-derivative of benzene is in equilibrium with its monocyclic tautomer—oxepin; in iso-octane their ratio is 3 : 7, while in aqueous methanol epoxycyclohexadiene predominates[179]:



Crandall and Watkins reported 1,5-migration of hydrogen in epoxycycloalkenes[180]:



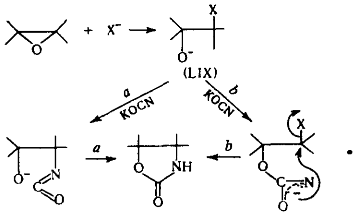
This rearrangement has also been observed in the acyclic series. When the epoxy-derivatives obtained from *cis*- and *trans*-1,2-divinylethylenes are heated, 4,5-dihydro-oxepin is formed. The *trans*-isomer of the epoxy-compound reacts under more severe conditions and is usually present in a mixture with 4,5-dihydro-oxepin[181,182]:



Certain other examples have also been described[183-185].

III. INTERMOLECULAR CYCLISATIONS

All the cases of the formation of cyclic products in the condensation of epoxy-compounds with various reagents described below involve the formation of five-membered rings. Huisgen[186] suggested that these reactions of epoxy-compounds can be classified as 1,3-dipolar addition processes in which the molecule of the epoxy-compound in the transition state is regarded as a 1,3-dipole, (i.e. $^{-}O-C-C^{+}$). The expansion of the oxiran ring in the presence of bases evidently does not include such a dipolar structure, since in the first stage the nucleophilic agent attacks the least substituted carbon atom with formation of an intermediate oxy-anion, the existence of which has been demonstrated in many cases[187]. The interaction of the oxy-anion with the electrophilic agent completes the cyclisation when the electrophilic centre is also part of the attacking agent. Epoxy-compounds react in this way with carbanions. The reactions of epoxy-compounds with molecules having multiple bonds (cyanates, isocyanates, isothiocyanates, etc.) probably involve a different mechanism. As will be shown below, in all cases a catalyst must be present (metal and ammonium halides and certain others). The role of the catalyst reduces to the formation of the oxy-anion (LIX), the interaction of which with the condensing agent can occur via two pathways:



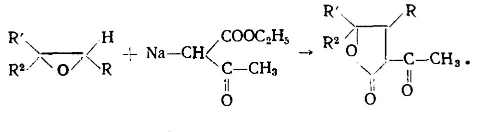
The kinetic data for reactions of epoxyalkanes with carbon dioxide catalysed by potassium, sodium, and ammonium halides support pathway *b*[188,189]; the alternative pathway *a* has been considered by Dyen and Swern[190]. The acid-catalysed condensation of epoxy-compounds with compounds having multiple bonds has been investigated purely empirically. Here the role of the acid probably reduces to the activation of the epoxy-ring (the formation of an oxonium complex) and, on the other hand, to the activation of the multiple bond, which becomes polarised as a result of co-ordination to the catalyst.

For a number of reasons, it is difficult to classify the intermolecular reactions. For example, pyridine, tribenzylamine, $ZnCl_2$, $FeCl_3$, LiCl, alkalis, etc. have been suggested as catalysts for the reactions of epoxy-compounds with isocyanates[191-193]. The site of the opening of the epoxy-ring is known to depend also on the presence of even traces of acids and therefore it is evident that pyridine and zinc chloride catalysts will lead to different reaction products. Moreover, the primary condensation products sometimes undergo pronounced changes under the reaction conditions, which also hinders the classification. Nevertheless, we believe it useful to consider separately reactions occurring in the presence of acids and bases. To simplify the task, the interaction of epoxy-compounds with the simplest inorganic molecules (CO_2, CS_2, COS, SO_2) will not be considered; this problem is discussed in detail in a recent review[4].

1. CONDENSATIONS IN THE PRESENCE OF BASES

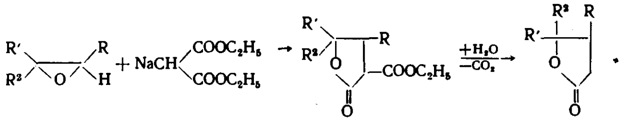
a. Attack of the Epoxy-ring by Carbanions

The most numerous examples of this type of interaction are the reactions of epoxy-compounds with *α*-dicarbonyl compounds, which lead to *γ*-lactones. The latter are formed, for example, in the reaction of sodioacetoacetic ester with epoxyethane[194], epoxypropane, epoxyethylbenzene[195], epichlorohydrin[196,197], the propyl, isopropyl[198], ethyl, and phenyl[199] ethers of glycidol, and *ββ*-dimethyl- and *α*-phenyl-glycidic esters[200], the epoxy-ring being opened on the side of the least substituted carbon atom in all the cases enumerated:



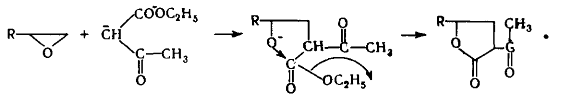
1,2-Epoxybut-3-ene[195], 2,3-epoxypent-4-ene[201], and 1,2-epoxypent-3-ene[201] form a mixture of lactones, the products obtained as a result of the attack by the nucleophilic agent on the unsubstituted carbon atom predominating. Two lactones were isolated also in the interaction of sodioacetoacetic ester with 3-chloro-1,2-epoxybutene[202], the product ratio (4 : 1) illustrating the preferential ring opening in accordance with Krasusskii's rule. The reaction of epoxyethane[203] and epichlorohydrin[196,203] with methylsodioacetoacetic ester also leads to the corresponding lactones; epoxyethane reacts similarly also with benzoylacetic ester[204].

The least substituted carbon atom is also attacked in the reaction between sodiomalonic ester and epichlorohydrin[205], epoxyethylbenzene[206-208], 2,3-epoxybutene[206], epoxycyclohexane[209,210], epoxymethylcyclohexane, the epoxy-derivative from menthene[209], *ββ*-dimethyl-[200,211], *ββ*-dialkyl-[212], and *β*-phenyl-glycidic esters[213], the ethyl and phenyl ethers of glycidol[199], and 3-dialkylamino-1,2-epoxypropanes[214], as a result of which γ-lactones are again formed:



It has been shown recently that sodiomalonic ester reacts with epoxyethylbenzene attacking the rings at two different carbon atoms[215] and not exclusively at the primary carbon atom, as was claimed in early investigations[206,207]. Cristol and Osman[216] also confirmed that epoxyethylbenzene is attacked preferentially and *p*-(epoxyethyl)nitrobenzene entirely at the secondary carbon atom. Similar results were obtained by de Puy et al.[217], who established that epoxyethylbenzene is attacked to the extent of 60% at the secondary carbon atom and to the extent of 40% at the primary carbon atom.

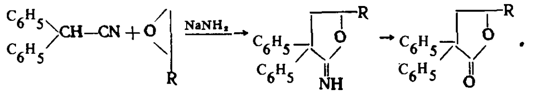
Lactones were also obtained in the reaction of sodiomalonic ester with the epoxy-derivative of dihydronaphthalene[209] and in the reactions of sodioethylmalonic ester with the ethyl and phenyl ethers of glycidol[199] and of methylsodiomalonic ester with 1,2-epoxy-3,4-dihydronaphthalene[218]. The mechanism of the above condensations was examined in the reaction with sodioacetoacetic ester by Adams and Vander-Werf[195] (see also Chelintsev[219]):



The condensation of epoxy-compounds with sodioacetoacetic and sodiomalonic esters takes place with high yields and can be used for preparative purposes[3,220].

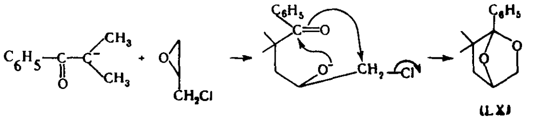
γ-Lactones are formed also in the reaction of epoxy-compounds with sodiocyanoacetic ester. In the presence of sodamide epoxyethylbenzene and 2,3-epoxybutene[221] give rise to stereoisomers of α-cyano-γ-lactones; under these conditions, as in the interaction between sodiocyanoacetic ester with ethyl and phenyl ethers of glycidol[199], the unsubstituted carbon atom of the epoxy-compound is attacked. Glickman and Cope[222] showed that epoxyethane reacts similarly, forming α-cyano-γ-butyrolactone[222].

Imidolactones, which are subsequently readily hydrolysed to γ-lactones, were obtained in the reaction of diphenylacetonitrile with a number of epoxy-compounds in the presence of sodamide[223,224]:



Under these conditions too, the carbanion attacks the primary carbon atom (see also Temnikova and Kovalevskaya[225]).

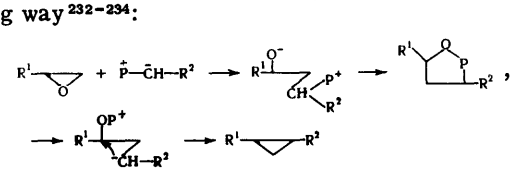
The interaction of epoxy-compounds with Ivanov's reagent also leads to γ-lactones[226-228]. The reaction of the sodio-derivative of isobutyrophenone with epichlorohydrin takes place in an interesting way[229]:



(LX)

The bicyclic product (LX) had been isolated earlier but its structure had not been demonstrated[230].

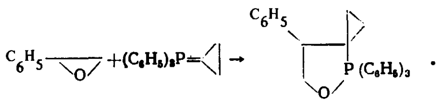
The interaction of epoxy-compounds with phosphorus ylides takes place in an unusual manner[231]. The reaction mechanism probably involves substitution in the epoxy-ring with subsequent rotation about the C–C bond and the closure of a five-membered ring, the subsequent rupture of which leads to the formation of cyclopropane in the following way[232-234]:



(LXI)

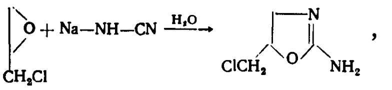
where R^1 = H or alkyl, P = Ph_3P, $(RO)_2PO$, or R_2PO, and R^2 = CN or COOR.

The formation of cyclopropanes by the above mechanism takes place only with reagents of the type $P^+-C^-H-R^2$, where R^2 is an electronegative group (CN, $COOC_2H_5$). The stabilisation of the carbanion (LXI) by these reagents favours the rupture of the intermediate five-membered ring[232-236]. The interaction of cyclopropylidenetriphenylphosphorane with certain epoxy-compounds gives rise to stable ring compounds[237], for example:

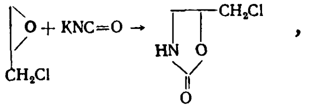


b. Attack of the Epoxy-ring by a Nitrogen Atom

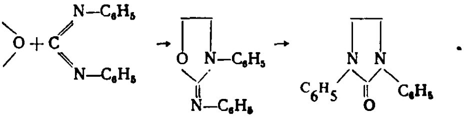
Epichlorohydrin and sodiocyanamide react in the cold in aqueous solution to form 2-amino-5-chloromethyloxazoline[238-239]:



while potassium isocyanate and epichlorohydrin give 5-chloromethyl-2-oxazolidinone[240]:

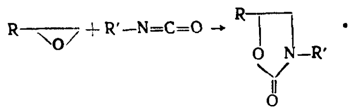


i.e. in such cases the primary carbon atom of the epoxy-ring is attacked. Pyridine, triethylamine, and lithium chloride catalyse the reaction of epoxyethane with carbodi-imides. The imino-oxazolidine formed initially rearranges under reaction conditions to 1,3-diphenyl-2-imidazolidinone[223]:

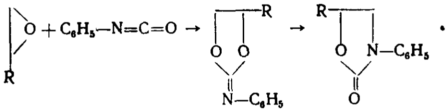


The interaction of epoxyethane, epoxypropane, epoxydodecane with phenyl and ethyl isocyanates in dioxan, dimethylformamide, and acetonitrile at 160–200°C [catalyst $(C_2H_5)_4NBr$ and KBr] leads to 2-oxazolidinones.

In this case the reaction involves the unsubstituted carbon atom[241]:



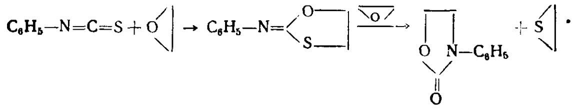
Dimethylbenzylamine catalyses the condensation of benzylepoxyethane and the phenyl ether of glycidol with phenyl isocyanate to the corresponding 2-oxazolidinones in yields up to 45%[242]. Pyridine, tribenzylamine, metal (zinc, lithium, and iron) chlorides, alkalis, etc. were used as catalysts for the reaction of aliphatic, aliphatic-aromatic, and alicyclic epoxy-compounds with phenyl isocyanate[191-193]. 2-Oxazolidinones were also obtained in the absence of a solvent at 180–200°C. Gulbins and Hamann[223,243] suggested that the initial products of this reaction are 2-phenylimino-1,3-dioxolans which isomerise to 2-oxazolidinones under the reaction conditions:



The occurrence of such isomerisation has been demonstrated by the conversion of 2-imino-1,3-dioxolans into 2-oxazolidinones at 200°C in the presence of lithium chloride (under conditions identical to those indicated above). However, this does not mean that dioxolans must necessarily be the primary products in all cases. Their formation is more evident under conditions of acid catalysis when the secondary carbon atom of the epoxy-ring in the oxonium complex is attacked and the nucleophilic centre in the phenyl isocyanate molecule is the oxygen atom. In the presence of basic catalysts, normal ring opening takes place and 2-oxazolidinones may be formed directly. Numerous examples of the synthesis of 2-oxazolidinones by the condensation of epoxy-compounds with cyanates, cyanuric acid, organic isocyanates, and urea and its derivatives, have been discussed in detail by Dyer and Swern[190,244].

c. Cyclisation with Participation of a Sulphur Atom

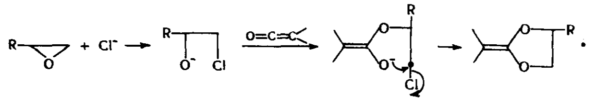
The interaction of epoxy-compounds with isothiocyanates takes place in a more complex manner than with isocyanates and is accompanied by various side processes: for example, epoxyethane and phenyl isothiocyanate give 2-oxazolidinone according to the mechanism[245]



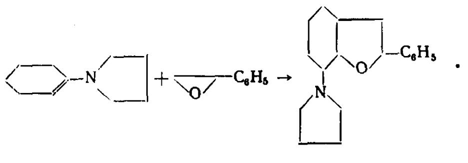
The reaction with alkyl isothiocyanates is even more complex. Without considering this process in detail, which is analysed in the review by Grobov et al.[4], we shall only mention that the epoxy-ring is attacked by the more highly polarised sulphur atom with subsequent S → O migrations[246].

d. Certain Other Cases

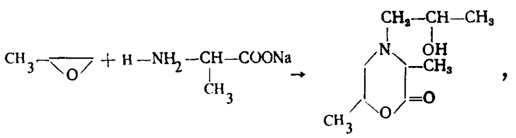
There are no data on the base-catalysed condensations of epoxy-compounds with carbonyl components. The formation of ketals in the interaction between epoxy-compounds and diphenylketen is noteworthy[223] and may be explained by the following mechanism:



The interaction of epoxyethylbenzene with enamines leads to cyclic products[247]:



Morpholone derivatives are obtained in the interaction between epoxypropane and certain aminoacids[248]:

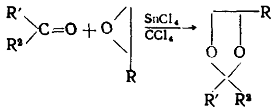


2. CONDENSATIONS IN THE PRESENCE OF ACIDS

The interaction of the epoxy-ring with polar groups having multiple bonds (carbonyl, cyano-, azomethine, etc.) might constitute a good method for the synthesis of new heterocyclic compounds. However, the small number of experimental data and almost total absence of any attempt to discover the laws governing these processes preclude for the moment the use of this method on an adequate scale.

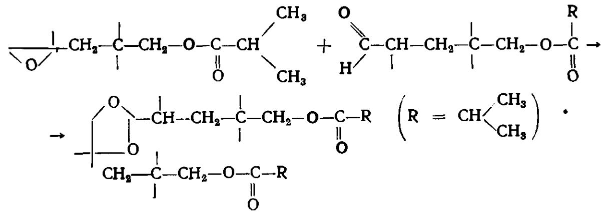
a. Synthesis of 1,3-Dioxolans

In 1861 Wurtz attempted for the first time to prepare 1,3-dioxolan by the direct condensation of epoxyethane with acetaldehyde[249]. The formation of 1,3-dioxolan as a side product was observed in 1906 in the catalytic synthesis of dioxan from epoxyethane[250]. It was suggested that the acetal is formed from epoxyethane and acetaldehyde formed by the isomerisation of the epoxy-compound. This was confirmed by the work of Bogert and Roblin[251], who obtained 1,3-dioxolans by the condensation of epoxyethane and epoxypropane with a number of aldehydes and ketones (benzaldehyde, hexanal, hexyl ethyl ketone, acetophenone):



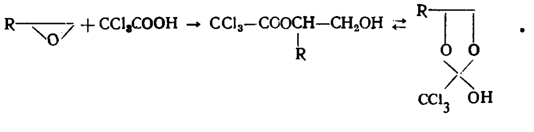
$SnCl_4$, $SnCl_4.4H_2O$, $ZnCl_2$, $FeCl_3$, $SbCl_3$, $AlCl_3$, and $CaCl_2$, as well as HCl, H_2SO_4, and $POCl_3$ were chosen as catalysts. Best results were obtained with $SnCl_4$. In recent years the reaction of carbonyl compounds with epoxy-compounds has been applied to some extent in the synthesis of new 1,3-dioxolans. The interaction of epichlorohydrin and epibromohydrin with aliphatic aldehydes (acetaldehyde, propionaldehyde, butyraldehyde, crotonaldehyde, chloral) and also with ketones (diethyl ketones, cyclopentadecanone, bromoacetophenone, benzophenone[252,253]), of epoxyethane, epoxypropane, epoxybutane, and epoxy-derivatives obtained from pseudo- and iso-butenes with a wide variety of aldehydes and ketones[254,255], and of glycidol ethers, 2,3-epoxybutene, and epoxyethylbenzene with acetone[256,257] has been investigated. Certain 1,3-dioxolans have been obtained as intermediates in the synthesis of antispasmodic compounds by the condensation of epichlorohydrin and epibromohydrin with various aromatic ketones[258,259]. The interaction of acetylenic epoxy-compounds with acetone, ethyl methyl ketone[260], cyclopentanone, and cyclohexanone[261] has been described.

1,3-Dioxolans may be formed also as side products in the intramolecular reactions of epoxy-compounds. House observed their formation in a study of the isomerisation of *cis*- and *trans*-2,3-epoxybutanes in the presence of $MgBr_2$ and BF_3.[262] The isomerisation of 4,5-epoxy-2,2,4-trimethylpentyl isobutyrate to a tetrahydrofuran derivative under the influence of boron trifluoride-ether is accompanied by the formation of dioxolan, which is probably obtained as a result of the interaction between the initial epoxy-compound and an aldehyde[134]; the formation of the latter under the reaction conditions has been demonstrated:



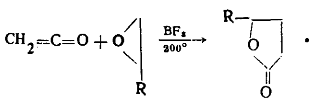
In the presence of inorganic acids (HCl, H_2SO_4) benzoin reacts with epichlorohydrin, and epoxyethane and epoxypropane react with formaldehyde, yielding 1,3-dioxolans[263,264]. The preparation of certain ketals containing a silicon atom or a triple bond in the 4-position of the ring has been described[265-267].

Aldehydes and ketones are usually employed as the carbonyl components in the synthesis of acetals and ketals, but Hibbert[268,269] and Meerwein[270,271] attempted to extend the applications of this reaction. In Meerwein's report on the preparation of 2-hydroxy-1,3-dioxolans by the condensation of di- and tri-chloroacetic acids with epoxyethane, epichlorohydrin, and glycidic ester at room temperature, it is stated that the reaction product can exist as a tautomeric mixture of cyclic and linear compounds. The cyclic structure is indicated by the stability of the product in the presence of alkalis and the ease with which it is hydrolysed by acids, which is typical for a ketal:

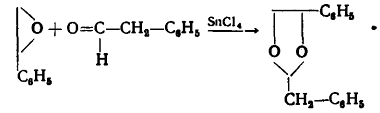


Under the same conditions, monochloroacetic and acetic acids yield the half-esters, e.g. $CH_2Cl-COOCH_2CH_2OH$.

The possibility of using ketens for the synthesis of 2-methylene-1,3-dioxolans appears to be attractive but only one such example is described in the literature. Diphenylketen was allowed to react in a sealed tube with epoxyethane at 200°C for 4–5 h, forming a dioxolan (catalyst LiCl).[223] The interaction of keten with epoxyethane, epoxypropane, and epichlorohydrin under acid conditions (BF_3) leads to the corresponding γ-lactones[272]:

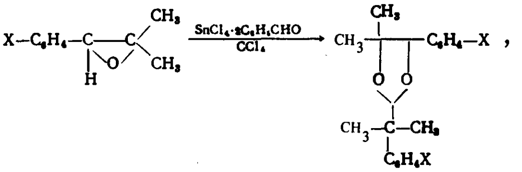


The behaviour of epoxy-derivatives obtained from substituted styrenes is striking. The attempt to condense epoxyethylbenzene with acetophenone did not give the desired results even in the presence of a large excess of epoxy-compound: the main reaction product was 2-benzyl-4-phenyl-1,3-dioxolan[273,274], probably formed as a result of the interaction between the epoxy-compound and phenylacetaldehyde (an isomerisation product of the epoxy-compound):



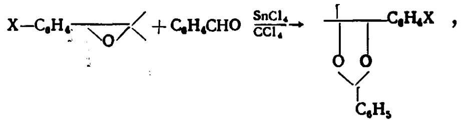
2-Benzyl-4-phenyl-1,3-dioxolan formally corresponds to the dimer of epoxyethylbenzene; previously the structure of 1,4-dioxan was attributed to the dimer, which is formed from the epoxy-compound[275] or the corresponding glycol[276,277] under acid conditions.

The behaviour of the epoxy-derivatives obtained from *para*-substituted ββ-dimethylstyrenes in the condensation with benzaldehyde in the presence of $SnCl_4$ was investigated[278]. It was found that, for epoxy-compound : benzaldehyde : catalyst ratios of 2 : 2 : 1 (under these conditions, the benzaldehyde is fully bound in a complex with $SnCl_4$), only the so called "dimers" of epoxy-compounds—2-benzyl-1,3-dioxolans—are formed:



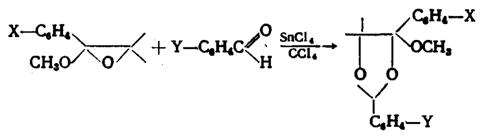
where X = Cl, H, or CH_3.

In the presence of an excess of the carbonyl compound (aromatic aldehyde) normal products are formed:



where X = Cl, H, or CH_3.

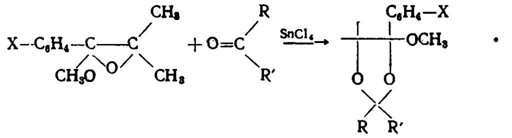
However, the epoxy-derivatives obtained from α-methoxy-ββ-dimethylstyrenes condense with aromatic aldehydes regardless of whether the aldehyde is bound in a complex with $SnCl_4$ or not[279]:



where X = Cl, H, CH_3, or CH_3O and Y = Cl, H, or CH_3.

The very sharp difference between the behaviour of the epoxy-compounds can be accounted for by the different stabilities of the carbonium ions generated on opening of the ring.

Temnikova and Gontarev obtained a large amount of 4-methoxy-1,3-dioxolans by the condensation of methoxy-derivatives of epoxy-compounds with various aldehydes and ketones[280-283]:

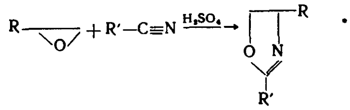


The presence in the products obtained of a system of acetal bonds may prove to be of significant interest.

An adequate mechanism has not been proposed[251,252,278] for the condensation of epoxy-compounds with carbonyl compounds.

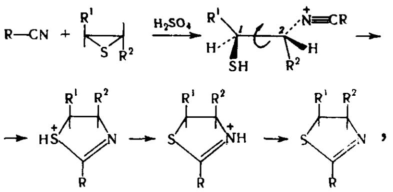
b. Synthesis of 2-Oxazolines and 2-Oxazolidines

Oda et al.[284] were the first to isolate 2-oxazolines by condensing epoxyethane, epoxypropane, and epichlorohydrin with acetonitrile, phenylacetonitrile, benzonitrile, and isobutyronitrile in concentrated sulphuric acid:



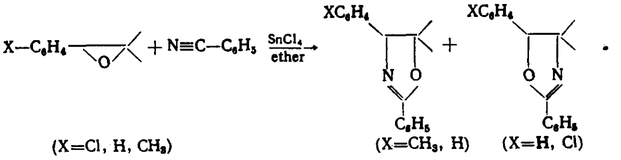
After the interaction of epoxypropane and acetonitrile, they succeeded in isolating two oxazolines: 2,2-dimethyl- and 2,5-dimethyl-Δ^2-oxazolines in proportions of 7 : 3, i.e. the opening of the epoxy-ring at the secondary carbon atom predominates. Unfortunately, the systems investigated do not allow an interpretation of the stereochemistry of the reaction.

The interaction of episulphides, which are very close in their properties to epoxy-compounds, with nitrile in concentrated sulphuric acid takes place according to the mechanism[285,286]



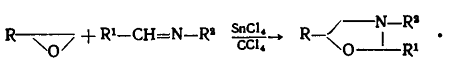
i.e. involves nucleophilic attack from the rear with formation of a nitrilium salt and subsequent rotation of the C^1-C^2 bond and ring closure. The validity of extending this mechanism to epoxy-compounds has not yet been proved.

Temnikova and Zhesko were the first to isolate a 4-methoxy-Δ^2-oxazoline by the reaction of 1,2-epoxy-1-methoxy-2-methyl-1-phenylpropane with benzonitrile in the presence of $SnCl_4$ in carbon tetrachloride[287]. They suggested the structure of 4-methoxy-Δ^2-oxazoline for this product in accordance with the usual rule governing the rupture of the epoxy-ring in methoxy-derivatives of epoxy-compounds under acid conditions. The epoxy-derivatives obtained from *para*-substituted $\beta\beta$-dimethylstyrenes did not yield appreciable amounts of oxazolines in the condensation with benzonitrile under these conditions[288]. When carbon tetrachloride was replaced by butyl ether, the desired products were obtained, the *para*-substituents in the molecule of the epoxy-compound having a decisive influence on the mode of attack on the epoxy-ring by the nitrile. The mechanism below shows that, with X = Cl, benzonitrile attacks the tertiary carbon atom and, with X = CH_3, the secondary carbon atom:



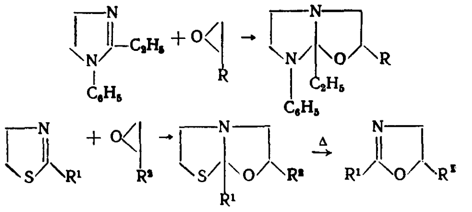
The unsubstituted epoxy-compound gives two products.

The condensation of Schiff bases with epoxyethane, epoxypropane, and epichlorohydrin in the presence of $SnCl_4$ leads to oxazolidines[289]. The reaction is carried out in carbon tetrachloride at 10–20°C. The yield of the final product greatly depends on the structure of the substrate and as a rule decreases when BF_3 is employed instead of $SnCl_4$:



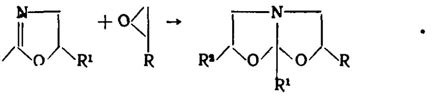
The interaction with t-butylazomethine does not require a catalyst, the introduction of which only reduces the yield.

The condensation of epoxy-compounds with certain imidazolines and thiazolines with C=N bonds in the ring gives rise to bicyclic products[290,291]:

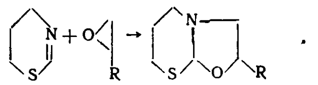


(LXII)

In the case of thiazolines the product (LXII) is unstable under the reaction conditions and is converted into oxazoline, which reacts with a further molecule of the epoxy-compound:

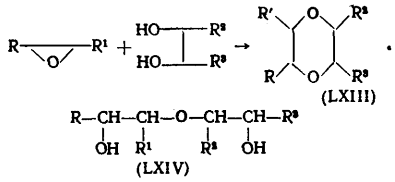


This mechanism is confirmed by the isolation of stable bicyclic products in the condensation of epoxy-compounds with thiazines[290]:



c. Certain Special Cases

The interaction of epoxyalkanes with glycols[292-294] yields dioxans (LXIII). The reaction proceeds via the intermediate formation of (LXIV), further reaction of which giving rise to dioxan:

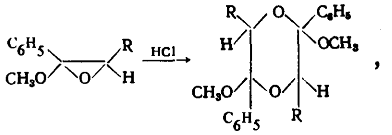


(LXIII)

(LXIV)

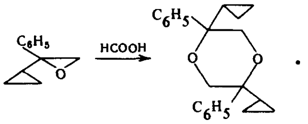
3. DIMERISATION AND n-CYCLOMERISATION OF EPOXY-COMPOUNDS

Numerous data have been published on the formation from epoxy-compounds of dimeric products to which the structure of 1,4-dioxans has been attributed. The industrial manufacture of 1,4-dioxan from epoxyethane is generally known; epoxypropane gives dimethyldioxan[295]. More detailed studies of the polymerisation products of epoxypropane, 1,2-epoxybutane, and epichlorohydrin initiated by BF_3, $SnCl_4$, and triethyloxonium fluoroborate showed that the low-molecular-weight products obtained from epoxy-propane, for example, consist of a mixture of dimers (*cis-* and *trans-*isomers of 2,5- and 2,6-dimethyl-1,4-dioxans), tetramers, pentamers, and hexamers[296,297]. It appears likely that the dimers are formed from methoxy-derivatives of the epoxy-compounds in acid media by the mechanism[298-300]:

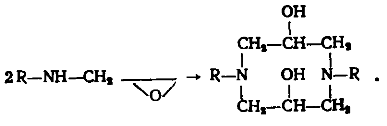


where R = CH_3, C_2H_5, or C_6H_5.

The reactions of epoxyethylbenzene in the presence of acids are usually accompanied by the formation of a high-boiling product to which the structure of 1,4-dioxan was attributed initially[275]. Summerbell and coworkers[273,274] showed that the main product of the reaction of epoxyethylbenzene in the presence of $SnCl_4$ is 2-benzyl-4-phenyl-1,3-dioxolan with only a slight admixture (up to 5%) of the isomeric 2,5-diphenyl-1,4-dioxans (see also Pasika[301]). Tiffeneau and Levy[302,303] proposed the 1,4-dioxan structure also for the dimerisation product of epoxy-$\beta\beta$-dimethylethylbenzene, but the latter proved to be in fact a derivative of 2-benzyl-1,3-dioxolan[278]. Of the other examples available, mention may be made of the dimerisation of epoxy-α-methylethylbenzene to 2,5-dimethyl-2,5-diphenyl-1,4-dioxan[304] and of the work of Oda and coworkers on the synthesis of 1,4-dioxan by the cleavage of 1-cyclopropyl-1,2-epoxyethylbenzene with formic acid[305]:



Alkyl-2,3-epoxypropylamines are converted into cyclic dimers—1,5-dialkyl-1,5-diazacyclo-octane-3,7-diols[306,307]:



Mixed condensation of two glycidylamines is also known to occur.

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Leningrad State University

U. D. C. 547.556.7

The Current State of the Problem of the Structure and Reactivity of Aromatic Diazo-compounds

B.A.Porai-Koshits (deceased)

The author, one of the leading investigators of the chemistry of diazo-compounds, describes in this article his views on the structure and reactivity of aromatic diazo-compounds. In the usual sense of the of the word, this is not a complete review of studies on diazo-compounds; it does not reflect all the numerous data published recently and does not contain a critical analysis of new results obtained in the last decade. The review describes the author's views based on the experimental data from his laboratory. The bibliography comprises 32 references.

The Editors

CONTENTS

1. THE DIAZOTISATION REACTION

The study of the detailed structure of aromatic diazo-compounds is at present impossible without establishing the relations governing their formation. Therefore, before considering the structure, it is necessary to describe at least briefly the modern views on the preparation of aromatic diazo-compounds.

Without exaggeration one can say that the diazotisation reaction, as well as the structure of the diazo-compounds formed, is one of the most interesting and at the same time the most complex problems of organic chemistry. The experimental difficulty consists in the extreme instability and variability of diazo-compounds, which makes it difficult to isolate the individual substances.

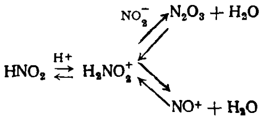
The simplest and the most widely used method for diazotisation consists in treating the amine dissolved in an aqueous inorganic acid, with alkali metal nitrites. An acid medium during the diazotisation reaction is essential, on the one hand in order to prevent the shift of the ammonium ion ⇌ amine equilibrium to the right (although, as we shall see below, the free amine is in fact diazotised and not its salt), which makes the amine insoluble, and, on the other hand in order to form the most active species participating in the reaction with the amine during its diazotisation. Finally a distinctly acid medium in the diazotisation process prevents the formation of certain side products.

Alkali metal nitrites are used in strictly stoichiometric amounts. An excess as well as a deficiency have an unfavourable effect on the stability of the diazo-compound formed. With decrease of the basicity of the amine diazotised, it is difficult to carry out the reaction in dilute aqueous solutions. In such cases concentrated acids (usually sulphuric) are used as solvents together with dry alkali metal nitrites[1]. Apart from these main diazotisation methods, there exist also certain others, the discussion of which would not throw any fundamentally new light on the problem.

The occurrence of the diazotisation reaction in an acid medium is as it were evidence that not the free amine but the salt is diazotised. However, if we remember that in a fairly concentrated acid there is always an equilibrium between the arylammonium ion and the free amine base and also that aromatic amines are fairly weak bases, the hypothesis that even in a strong acid medium the free amine is converted into the nitroso-derivative is not unexpected. Various workers arrived at this conclusion independently[2-6] and its validity was proved in 1958 by Hughes et al using kinetic methods[7]. However. recently publications have appeared where the possibility of diazotisation of certain arylammonium salts, probably by a synchronous mechanism, is postulated[8]. In either case, the first stage in the diazotisation process is the introduction of a nitroso-group into the amino-group. In principle, this reaction does not differ from the nitrosation of secondary aliphatic aromatic amines and is one of the amine acylation reactions.

In accordance with the electrophilic mechanism of the substitution of a hydrogen atom in acylation, it was to be expected that the nitrosating species would carry a positive charge or would exhibit a strong tendency to acquire such a charge.

The nitrous acid formed in the first instant of the reaction between alkali metal nitrites and the inorganic acid also reacts with the inorganic acid, giving rise to a number of equilibria which can be represented as follows:

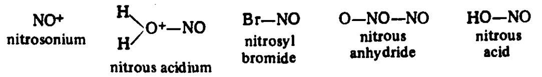


,

and in the presence of hydrogen halides:

$$HNO_2 \rightleftarrows H_2NO_2^+ \xrightleftharpoons{Hal^-} HalNO + H_2O.$$

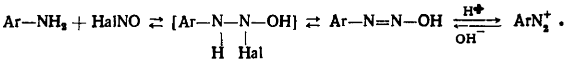
These mechanisms show that in sulphuric acid a powerful nitrosating species is formed and readily gives rise to the nitrosonium cation, which is the essential electrophilic agent. In the presence of hydrogen halides nitrosyl halide with a highly polarised nitrogen–oxygen bond is formed, which also leads to the presence in the medium of an electrophilic species. Bearing in mind the above equilibria in the nitrous acid–inorganic acid system, all possible nitrosating agents can be arranged in the following sequence with respect to their effectiveness:



Nitrosyl halide HalN=O, which adjoins nitrous acidium as regards its activity but is formed only in hydrogen halide solutions, stands somewhat in isolation in the above series. Experimental proof of the validity of this sequence of nitrosating species in terms of their activity was found by Hammett, Ingold, and others[9,10].

It appeared that the interaction of the nitrosonium ion with the free base of an aromatic amine should give rise to a nitrosammonium ion. Therefore the nitrosamine should be at least slightly basic. In one of the present author's studies[11] it was shown that the basic properties of nitrosamine are extremely weak. Thus even if the nitrosammonium ion is formed (this is the view of, for example, Zollinger[12]), it must be rapidly hydrolysed under the reaction conditions. Consequently its formation should be regarded as a quasi-steady-state intermediate reaction stage. Another mechanism of the nitrosation reaction, in which the interaction of the nitrosonium ion with the amine and the elimination of a proton take place synchronously, is extremely probable. The difference between the both mechanisms is minimal.

In diazotisation in hydrogen halide solutions the first reaction product is a complex formed by the addition of the amine to nitrosyl halide, which is subsequently converted into a diazonium salt:



$$\mathrm{Ar{-}NH_2 + HalNO} \rightleftarrows [\mathrm{Ar}{-}\underset{\mathrm{H}}{\mathrm{N}}{-}\underset{\mathrm{Hal}}{\mathrm{N}}{-}\mathrm{OH}] \rightleftarrows \mathrm{Ar{-}N{=}N{-}OH} \underset{\mathrm{OH^-}}{\overset{\mathrm{H^+}}{\rightleftarrows}} \mathrm{ArN_2^+}\,.$$

The conversion of nitrosamine into a diazonium salt is fairly clear in broad outline. Since the nitrosamine is in tautomeric equilibrium with the amphoteric diazohydroxide, in an acid medium the latter reacts instantaneously with the inorganic acid and is converted into the diazonium salt:

$$\mathrm{Ar{-}NH{-}NO} \rightleftarrows \mathrm{Ar{-}N{=}N{-}OH} \xrightarrow[-\mathrm{H_2O}]{+\mathrm{H^+}} \mathrm{Ar{-}N_2^+}$$

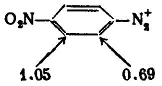
2. THE STRUCTURE AND REACTIVITY OF DIAZO-COMPOUNDS

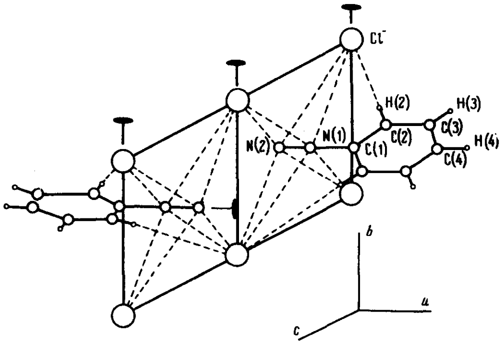
X-Ray diffraction analysis of diazonium salt crystals showed[13] that the anion is at a distance of 3.5 Å from the diazonium group and slightly closer to the extreme nitrogen atom. This is evidence that both nitrogen atoms have positive charges, which is extremely important for the understanding of the structure and reactivity of the diazonium cation.

The effective radii of the anion and the nitrogen atoms overlap, albeit to only a slight extent, but probably enough for the bond between the anion and cation to vary somewhat in type, while remaining ionic, depending on the properties of the anion. This is probably the cause of the differences between the properties of various salts of the same diazonium cation.

The above X-ray diffraction analysis shows that the diazonium cation is a planar system with nitrogen atoms linearly distributed in the plane of the aromatic ring; the the nitrogen atoms are thus *sp*-hybridised. The anion is located on one side of the plane of the organic ion. The Figure gives a clear representation of the steric structure of benzenediazonium chloride.

As a substituent of the aromatic ring, the diazonium group is strongly electronegative. Its electronegativity is approximately twice as pronounced as that of the nitro-group[14-16], which means that, in relation to the diazonium group, the aromatic ring is an electron donor even when it includes an electron-accepting substituent such as the nitro-group. This is demonstrated by the degrees of electron shielding characterising the depletion of the electron cloud and determined by NMR method, resulting from the electron-withdrawing effect of the nitro- and diazonium groups in the *para*-positions relative to one another: they are 1.05 and 0.69. This can be illustrated by the following scheme:





Schematic representation of a benzenediazonium chloride crystal according to X-ray diffraction data.

In the unsubstituted benzene ring the above numbers are 2.72.

It has been firmly established that the bond between the nitrogen atoms approaches the triple bond type[17,18]. This is illustrated in the Table, where the first column lists the substituents in the phenyldiazonium ring and the remaining columns give the absorption frequencies of the triple bond in liquid paraffin and in water together with the multiplicities of the bond between the nitrogen atoms.

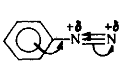
It is clear from the Table that the bond multiplicity varies between 2.645 and 2.850. Calculation of electron density by the MO method in the Hückel approximation carried out by Schuster and Polansky[19,20] led to similar conclusions. The triple bond character of the link between the nitrogen atoms contradicts to some extent the X-ray diffraction data, according to which a greater part of the positive charge is concentrated on the outer nitrogen atom, since a triple bond implies the presence of only one positively charged nitrogen atom (linked directly to the ring).

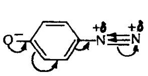
The following considerations may be adduced to eliminate these conditions. Of the three bonds between the *sp*-hybridised nitrogen atoms only one π bond, the plane of the electronic vibrations of which coincides with the π-electron plane of the aromatic ring, is capable of transmitting conjugation. As a result of the presence of this bond, the aromatic ring is conjugated with all its substituents and the extreme nitrogen atom. Infrared spectroscopic data show that this conuugation may influence to some extent the link between the two nitrogen atoms causing its approach to or departure from the "pure" triple bond.

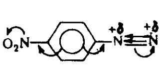
Frequencies and multiplicities of the nitrogen–nitrogen bonds in various benzenediazonium compounds.

Substituent	In liquid paraffin		In water	
	V	*P*	*V*	*P*
p-NO_2	2304	2.850	insol.	—
m-NO_2	2302	2.847	ditto	—
p-SO_2NH_2	2290	2.830	2296	2.837
p-$COOCH_3$	2299	2.843	2292	2.834
m-Cl	2306	2.853	insol.	—
m-$COOCH_3$	2298	2.841	2290	2.830
p-$COOC_2H_5$	2300	2.845	2288	2.827
p-SO_3^-	2284	2.821	2286	2.824
m-SO_3^-	2284	2.821	2288	2.827
p-I	2282	2.818	2278	2.812
p-Br	2286	2.824	2280	2.815
p-Cl	2290	2.830	2282	2.813
p-F	2294	2.836	2288	2.826
m-OCH_3	2298	2.841	decomp.	—
H	2296	2.837	2284	2.821
m-CH_3	2296	2.837	decomp.	—
p-CH_3	2286	2.824	2276	2.809
p-OCH_3	2252	2.773	2250	2.771
p-$NHCOCH_3$	2252	2.773	2252	2.773
p-OH	2242	2.756	2236	2.750
p-NH_2	2183	2.673	—	—
p-$N(CH_3)_2$	2166	2.649	2164	2.645

The second π bond, which is not in the plane of the π-electron cloud over the aromatic ring, and the third σ bond can transmit only the inductive effect of the positively charged nitrogen atom to the extreme nitrogen atom, which also carries in consequence a permanent positive charge, this being confirmed by X-ray diffraction data. It appears that the following formulae of the most typical diazonium cations reflect to some extent all that has been said about their structure:







The Reactivity of Diazonium Salts

The most important reaction of which aromatic diazo-compounds are capable is azo-coupling. Therefore, when speaking of the reactivity of diazo-compounds, one usually has in mind their reactivity in the azo-coupling reaction. Since various investigators have established rigorously that only the diazonium cation enters into the azo-coupling reaction, the reactivity in this reaction is usually attributed to the diazonium cation.

Since within the framework of a short article it is impossible to consider all the reactions of which aromatic diazo-compounds are capable, here too only the azo-coupling reaction, interpreted, however, in a somewhat extended sense, will be dealt with.

From the above considerations, it follows inevitably that the reactivity of the diazonium cation is linked to the electrophilic properties of the extreme nitrogen atom or, in a more restricted sense, the Lewis acid strength of the diazonium cation.

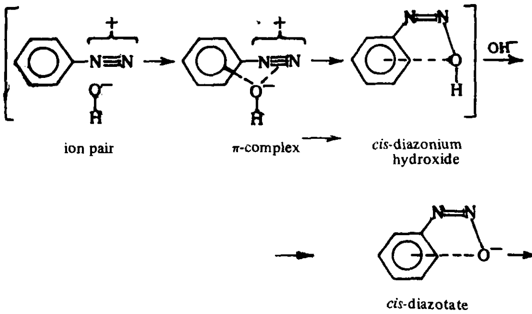
Bearing in mind that the aromatic ring with any of the usual substituents is always an electron donor in relation to the diazonium group and therefore always neutralises to a greater or lesser extent the positive charge of the extreme nitrogen atom, the problem of the reactivity reduces to the degree of neutralisation of the charge by various substituents. From this point of view, *p*-nitrobenzene diazonium for example, should be much more reactive than *p*-dimethylaminobenzenediazonium.

At the same time the first of the above substances is a stronger Lewis acid than the second. Evidently the strength of the Lewis acid and its reactivity in the azo-coupling reaction should be correlated, since acidity constitutes a special case of electrophilicity. Therefore the reactivity of the diazonium cation is initially most conveniently investigated in its reaction with a hydroxide ion. As will be shown below, despite its apparent simplicity, this reaction has certain features which permit it to be treated as a model for more complex cases.

The reaction between a hydroxide ion and a diazonium cation begins with the formation of an ion pair. The ion pair should be fairly stable, since the hydroxide ion is oriented by the π-electron system of the aromatic ring and the diazonium group. The gradual conversion of this ion pair into a π complex takes place in such a way that the bond between the hydroxyl and the π-electron system of the ring is maintained, which predetermines the steric configuration of the diazohydroxide formed subsequently. In the π complex the nitrogen atom linked to the ring is in a state of *sp*-hybridisation and therefore the structure of this complex is still linear.

In the next, slowest reaction stage the π complex is converted into diazohydroxide in which both nitrogen atoms are now in a state of sp^2-hybridisation as a result of which the molecule becomes bent. Since the hydroxyl probably remains linked to the aromatic ring, both residues must occupy *cis*-positions in relation to the double bond of diazohydroxide. Suhr and coworkers[21] found on the basis of a study of PMR spectra of aromatic diazotates that not all the ring hydrogen atoms are equivalent. From this, he concluded that there is a bond between the oxygen of the diazotate ion and the carbon atom in the *ortho*-position, which is also evidence in favour of the *cis*-configuration.

The reaction of the diazonium cation with the hydroxide ion is shown schematically below:



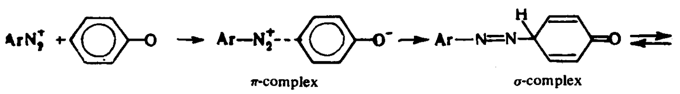
Usually diazohydroxide is not regarded as the final reaction product, since no representative of this series has so far been isolated. It is regarded either as "an intermediate product in a quasi-steady state" or as a σ complex. The present author believes it more logical to regard the *cis*-(or *syn*-) diazohydroxide as the final compound which has, however, unusual properties enabling it to undergo further reactions under the given conditions. One of the most important properties of diazohydroxide is its amphoteric nature which leads to its rapid acid or base ionisation. The diazotate ion in which the multiplicity of the bond between the nitrogen atoms is 1.4 according to calculations[22], formed on acid ionisation of diazohydroxide, is also capable of *cis–trans* isomerism and in an alkaline medium comparatively readily undergoes a stereochemical transformation, forming the *trans*-(*anti*-) isomer, which is extremely stable.

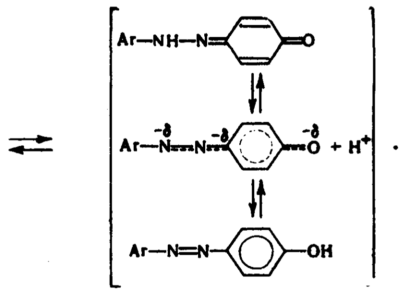
However, the reactions which follow the formation of the *cis*-diazohydroxide should not be included, according to the present author, with the nucleophilic attack proper by the hydroxide ion on the diazonium cation.

Thus one may assume that the reaction between the diazonium cation and the hydroxide anion has an S_N2 mechanism. The substrate (diazonium cation) undergoes the most pronounced changes in this process: the state of hybridisation of the nitrogen atoms changes, the previously non-existent capacity for stereoisomerism appears, etc. It is scarcely possible to regard the hydroxide anion as the substrate in this reaction and the diazonium cation as the reagent. It would then be necessary to assume that the hydrogen atom in the hydroxide ion is substituted. The azo-coupling reaction, which takes place in exactly the same way, is then assumed to have an S_E2 mechanism with a quasi-steady-state intermediate stage. The diazonium cation is regarded as an electrophilic reagent, similar, for example, to the nitronium cation, the chlorine cation, the carbonium cation, and other positive species. "The quasi-steady-state intermediate product" (or σ complex) differs from the final compound by the position of the proton, which is removed from the molecule by any base present in the medium during the second, faster reaction stage.

The present author believes that there is no fundamental difference between the interaction of the diazonium cation with the hydroxide anion and with the azo-component. In both cases the diazonium cation undergoes the same, much more significant changes than the reagent—the hydroxide anion or the azo-component. Also in both cases a covalent bond is formed between the extreme nitrogen atom and the atom of the attacking species. In the first case this atom is the oxygen of the hydroxide anion and consequently one may speak of the acidity of the diazonium cation. In the second case it is a carbon atom, the electrophilic properties of which may be assessed.

On the other hand, analysis of the structure of the so called σ complex ("the quasi-steady-state intermediate product"), formed in the azo-coupling reaction shows that it is none other than the final product in one of its possible tautomeric forms. Its further conversion into another tautomeric form, the azo- or quinohydrazo-form, usually does occur but under certain conditions may not. Therefore in the scheme representing the stages in the azo-coupling reaction—the ion pair, the complex, and one of the possible steric isomers of the azo-compound—the stage in which the tautomer formed is converted into another form, which may involve the inversion of the configuration, is separate from the azo-coupling reaction proper:





Indirect confirmation of the validity of the separation of further reactions of the product from the azo-coupling reaction proper is provided by the wide variety of views concerning the presence or absence of a kinetic isotope effect in the azo-doupling reaction[23]. In some cases it is absent, while in others it is observed. This is probably associated with the different rates of tautomeric transformations of the so called σ complex. The changes in the hybridisation of the carbon atom linked to the extreme nitrogen atom of the diazonium cation are of the usual type accompanying any tautomeric transformation.

Thus it is possible to postulate that the azo-coupling reaction also has an S_N2 mechanism, i.e. the reagent (the azo-component) adds to the triple bond of the substrate (the diazonium cation).

This new approach to the azo-coupling reaction will make it possible to treat from the same standpoint reactions which are at first sight quite different and to combine them in a single system.

The present author has in mind (apart from the azo-coupling proper) the reactions of the diazonium cation with amines leading to the formation of diazoamino-compounds, with alcohols leading to ethers, and with nucleophilic reagents such as the sulphite ion, the nitrilium ion, etc. — in other words all the reactions of the diazonium cation resulting in the formation of a covalent bond between the terminal nitrogen atom and any other atom in a nucleophilic species (base). There is a possibility now of determining the causes of the stereoisomerism, the reactivities of various nucleophilic agents, etc.

It must be emphasised yet again that the properties of the product of the addition of the nucleophilic agent to the triple bond determine its subsequent fate. If this is a product resulting from the attack by an azo-component, then, as stated above, it may undergo tautomeric transformations; if it is a result of reaction with amines, there is a possibility of a rearrangement of the diazoamino-compound formed into an aminoazo-compound; if it is a product of the addition of a hydroxide ion, it undergoes acid ionisation with further stereochemical transformations; if it is a product of the reaction of hydrocyanic acid with the diazonium cation, it undergoes only stereochemical changes; finally, if it is a compound formed as a result of nucleophilic attack on the diazonium cation by any alkoxide, the reaction terminates at this point, etc.

It is interesting to note that in all these cases the sequence of cations arranged in order of increasing or decreasing reactivity is maintained. It is possible to estimate the reactivities of various nucleophilic agents as a function of their structure, and the possibility of further reactions of the primary product of addition to the triple bond.

The capacity of certain diazo-compounds for decomposition on irradiation with ultraviolet light is widely used in engineering. Diazo-compounds with electron-donating hydroxy-, dialkylamino-, arylamino-, sulphide, etc. groups in the *para-* or *ortho*-positions in relation to the diazonium-group are particularly light sensitive. As a result of the presence of these groups, the neutralisation of the positive charge of the extreme nitrogen atom is considerable. However, infrared spectrophotometric data and calculations by the molecular orbital method in the Hückel approximation suggest that the bond between the nitrogen atoms is much closer to a triple than to a double bond. This is true also in those cases where the *para-* (or *ortho-*) position in relation to the diazonium group contains a readily ionisable hydroxy- or acid imino-group. Therefore the "quinodiazide" structure proposed for these compounds, like the name itself, is hardly accurate. The "quinodiazide" formula must be regarded only as one of the extreme resonance structures, invariably associated with another formula, whereby these substances are represented as inner salts and which makes a much greater contribution.

In accordance with the above considerations, the electrophilic reactivity of diazonium salts with powerful electron-donating substituents in the *para-*(or *ortho*)-position in relation to the diazonium group is reduced, although they, including the so called "quinodiazides", retain their capacity for azo-coupling. On the other hand, their light sensitivity and thermal stability are enhanced[24-26]. The latter is important for applications in engineering.

3. DIAZOHYDROXIDES AND NITROSAMINES

When diazonium salts are treated with alkalis one might expect that the neutralisation of one equivalent of acid would convert the substance into diazohydroxide (as shown above, *syn*-diazohydroxide). However, because of the amphoteric properties of diazonium hydroxide and the high rate of its reaction with the second equivalent of hydroxide ions leading to the formation of the final product (*syn*-diazotate), diazohydroxide is not formed. As shown by Bryuske[27], the theoretical explanation of this is that in an aqueous medium the diazohydroxide is fully ionised. Therefore the attempt to isolate representatives of this class of compound were in vain. The interaction of alkali with diazonium salts leads to the formation of a mixture of diazonium cations and diazotate anions and not diazohydroxide. The amphoteric properties of the latter and the fact that the reaction with the second equivalent of hydroxide ions is faster than with the first constitutes the foundations of all modern hypotheses concerning the structure of aromatic diazo-compounds. These properties of diazohydroxides suggest that, if they are ever isolated, it will be from non-aqueous solutions and even then under non-equilibrium conditions. However, there is no doubt about the existence of diazohydroxides as a necessary logical and chemical stage in the neutralisation of diazonium cations by alkalis. The well known curves obtained by the potentiometric titration of various diazonium cations with alkalis confirm this[28]. As regards *anti*-diazohydroxides, we may note that this structure has been sometimes attributed to the product of the acidification of *anti*-diazotates. However, in a recent study Eiges[29] showed by infrared spectrophotometry, dipole moment measurements, and molecular orbital calculations that in those cases where the product of the acidification of the *anti*-diazotate can be isolated from solutions (and this has been achieved for diazo-compounds with electron-accepting groups in the *para*-position with respect to the diazo-group) it has the structure of a primary nitrosamine. At one time Hantzsch suggested that the nitrosamine and *anti*-diazohydroxide are in equilibrium. This view should evidently be accepted but in a modern sense: the two compounds are in tautomeric equilibrium and the *anti*-diazohydroxide does not exist in aqueous solutions because of its amphoteric properties.

4. DIAZOTATES

Syn- (or *cis-*) diazotates, obtained by the interaction of alkalis with diazonium salts, can be isolated as precipitates, although this operation requires a considerable skill of the experimenter. On heating in concentrated alkalis, these diazotates are converted into stable readily isolated *anti-*(*trans-*)diazotates, which, in contrast to *syn*-isomers capable of undergoing instantaneous coupling with the azo-component, are capable of this reaction only after relatively prolonged treatment with inorganic acids. It will be seen later that this is because the equilibrium in aqueous solutions between the *syn*-diazotate and the diazonium cation is established instantaneously, while that between the *anti*-diazotate and the diazonium cation is attained slowly. There is at present no doubt that both diazotates are stereoisomers. However, it must be emphasised that the modern view differs somewhat from the Hantzsch hypothesis which postulates the stereoisomerism of covalent diazo-compounds (for example, diazohydroxides assuming them to be unionised), while modern chemists postulate the stereoisomerism of the ions (diazotates).

The present author and Shaburov[30] not only succeeded in demonstrating this but also showed the presence of the *syn*-diazotate in solution for the *p*-nitrobenzenediazo-compound, the existence of the *syn*-diazotate of which had not been proved previously. The converse transition of the *anti*-diazotate into the *syn*-diazotate has been demonstated in only a few cases. It occurs when the *anti*-diazotate is irradiated with solar ultraviolet light.

5. EQUILIBRIUM BETWEEN DIFFERENT FORMS OF DIAZO-COMPOUNDS

Various forms of diazo-compounds were mentioned above. We have seen that these include diazonium salts, diazohydroxides, nitrosamines, and diazotates. A mechanism for the interconversions of these forms of diazo-compounds was put forward for the first time by Hantzsch but this now requires some modernisation, revision, and correction. All the forms are present in equilibrium in aqueous solution. The position of this equilibrium depends on the pH of the medium and in some cases may be displaced to a limit where a particular form of the diazo-compound can be isolated and investigated in detail. There are protolytic and tautomeric equilibria. The stereoisomeric transformations do not give rise to equilibria and are rarely reversible.

We shall first attempt to examine special equilibrium systems, included in the general reaction mechanism; purely protolytic equilibria will be artificially separated from tautomeric and stereochemical transformations.

The behaviour of the diazonium cation is typical for dibasic Lewis acid. When acted upon by alkali, it reacts in succession first with one and then with another hydroxide ion and is converted into a diazotate anion. To some extent this occurs also in the absence of alkali: one can then speak of the hydrolysis of the Lewis acid. This acid–base equilibrium has been well investigated. It is established extremely rapidly and has many characteristic features.

The first stage in the interaction of the diazonium cation with the hydroxide ion is, as stated above, the formation of a covalent *cis*-diazohydroxide, while the second, faster stage is the ionisation of the diazohydroxide and the formation of *cis*-(*syn*-) diazotate:

$$\mathrm{Ar{-}N_2^+} \underset{\mathrm{H^+}}{\overset{\mathrm{OH^-}}{\rightleftharpoons}} \mathrm{Ar{-}N{=}N{-}OH} \underset{\mathrm{H^+}}{\overset{\mathrm{OH^-}}{\rightleftharpoons}} \mathrm{Ar{-}N{=}N{-}O^-}(syn)\,.$$

The neutralisation curves obtained by potentiometric titration do not show a jump in potential after the addition of the first equivalent of alkali as happens in the titration of the usual dibasic acids. This form of neutralisation curve implies that the equilibrium constant for the first reaction stage is much lower than for the second stage[31]:

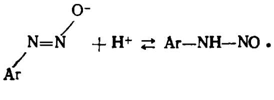
$$K_1 = \frac{[\mathrm{Ar{-}N_2OH}][\mathrm{H^+}]}{[\mathrm{Ar{-}N_2^+}]}\,;\quad K_2 = \frac{[\mathrm{Ar{-}N_2O^-}][\mathrm{H^+}]}{[\mathrm{Ar{-}N_2OH}]}\,;\quad K_2 \gg K_1\,.$$

The condition $K_2 \gg K_1$ means that, when exactly one equivalent of alkali is added to the solution of the diazonium salt, the product is not diazohydroxide as indicated in the above equation, but a 1 : 1 mixture of diazotate anions and diazonium cations. Thus a kind of salt—diazonium diazotate—is formed. This interesting phenomenon is based on the amphoteric properties of diazohydroxide mentioned above. The high rate of equilibration between the diazonium cation and *syn*-diazotate, to which Littler first drew attention[32], gives rise to the apparent capacity of the diazotate for azo-coupling. After a time, the *syn*-diazotate rearranges to the *anti*-isomer under the action of alkalis or heat. Since the basicity of the *anti*-diazotate is lower, this rearrangement involves a spontaneous decrease of the pH of the medium. The stronger is the Lewis acid (diazonium cation) from which the *syn*-diazotate has been obtained the easier is the stereoisomeric rearrangement.

The rearrangement of the diazo-compound from *p*-nitroaniline is so fast that the intermediate formation of the *syn*-diazotate can be observed only by special methods[30]. On the other hand, the more basic the amine from which the diazo-compound has been prepared the more severe conditions are required for the rearrangement: for example, the rearrangement of the diazo-compound obtained from aniline requires treatment with concentrated alkali at 130–150°C.

The converse transformation of the *anti*-diazotate to the *syn*-isomer takes place, as stated above, only in certain cases on irradiation with ultraviolet light[33]. Therefore the stereoisomeric transformation cannot be regarded as reversible. The acidification of *anti* -diazotate solutions never regenerates the *syn*-isomers, other reactions taking place.

When a proton adds to the *anti*-diazotate, an acid is formed, which, as stated above, in those cases where it could be isolated proved to have the structure of a nitrosamine:



$$\mathrm{Ar{-}N{=}N{-}O^-} + \mathrm{H^+} \rightleftarrows \mathrm{Ar{-}NH{-}NO}\,.$$

The interaction of the nitrosamine with an acid medium leads to a gradual formation of the diazonium cation.

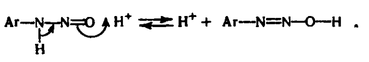
We may recall that an obligatory stage involving the formation of a nitrosamine with its subsequent conversion into the diazonium cation is also postulated for diazotisation, which is carried out in an acid medium. The mechanism of the transformation in an acid medium of the nitrosamine (which had acid properties) into the diazonium cation has not as yet been investigated, but kinetic methods will probably assist in its determination. However, one can now postulate that it consists in a tautomeric rearrangement of the nitrosamine into diazohydroxide, which instantaneously ionises to form the diazonium cation. We may recall that Hantzsch adhered to exactly the opposite view. He suggested that the acidification of the *anti*-diazotate yields the *anti*-diazohydroxide, which is in equilibrium with the nitrosamine. The latter rearranges via an unknown mechanism to the diazonium salt. On the other hand, one cannot postulate the preliminary formation of the *anti*-diazohydroxide in diazotisation, since the formation of the nitrosamine constitutes the first diazotisation stage.

Conversely the transformation of the nitrosamine into the diazonium cation cannot be logically imagined without the diazonium hydroxide stage, of whatever steric configuration, since on formation it should instantaneously (particularly in an acid medium) decompose into the diazonium cation.

The transformation of the nitrosamine into diazohydroxide takes place under the influence of protons. The tautomeric rearrangement presupposes the formation of an ion common to both tautomers. Thus, as stated previously, one must either postulate that the nitrosamine has minimal basic properties or that its transformation into diazohydroxide takes place by a push-pull (synchronous) mechanism. Then attack by the proton is directed to the most nucleophilic oxygen atom. The mechanism of the transformation of the nitrosamine into diazohydroxide can be represented as follows under these conditions:

$$\mathrm{Ar{-}NH{-}NO} + \mathrm{H^+} \rightleftharpoons [\mathrm{Ar{-}NH{-}N{=}\overset{+}{O}{-}H} \leftrightarrow \mathrm{Ar{-}\overset{+}{N}H{=}N{-}O{-}H}] \rightleftharpoons \mathrm{Ar{-}N{=}N{-}OH} + \mathrm{H^+}$$

or



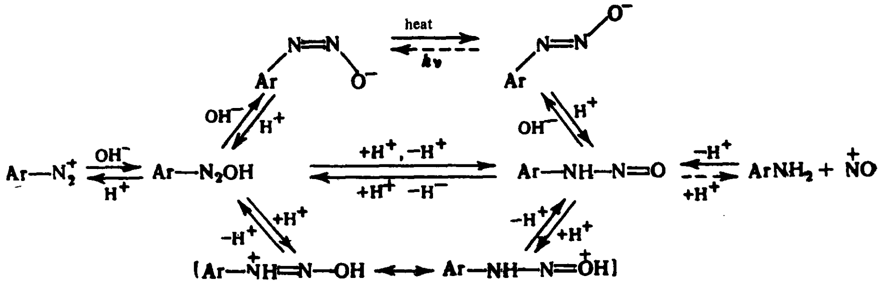
$$\mathrm{Ar{-}N(H){-}N{=}O\ H^+} \rightleftharpoons \mathrm{H^+} + \mathrm{Ar{-}N{=}N{-}O{-}H}\,.$$

Regardless of its steric structure, the diazohydroxide form is instantaneously converted into the diazonium cation:

$$\mathrm{Ar{-}N{=}N{-}OH} + \mathrm{H^+} \rightarrow \mathrm{H_2O} + \mathrm{Ar{-}N_2^+}\,.$$

Summarising all the above considerations, one may postulate the following "cycle of transformations" of the diazo-compounds in the equilibrium systems formed in aqueous solutions of diazonium salts and by the action of alkalis on diazonium salts followed by treatment with acids.

The suggested mechanism involves protolytic, tautomeric, and stereochemical transformations, i.e. transformations of the type investigated and discussed in modern theoretical organic chemistry. It is not therefore surprising that the data collected in the study of aromatic diazo-compounds are frequently extended to other classes of organic compounds and the conclusions drawn from them are of great importance for theoretical organic chemistry.



In conclusion the author would like to deal with a minor terminological problem. Above, diazo-compounds, including in this term diazonium salts, diazohydroxides, diazotates, and nitrosamines, were considered. At the same time all these compounds differ markedly from one another in their structure: diazonium salts are indeed "diazo-compounds" since in them two nitrogen atoms replace a hydrogen atom of the aromatic ring; nitrosamines and diazohydroxide contain, in addition to the two nitrogen atoms replacing hydrogen, also an oxygen and a hydrogen atom. Diazotates contain an additional oxygen atom. Many investigators include among diazo-compounds substances in which there is a covalent bond between the terminal nitrogen atom and occasionally a very complex residue (for example diazonium sulphonates, diazonium cyanides, etc.) but do not include among them diazoamino-compounds or azo-dyes.

To eliminate these logical contradictions, the present author believes it correct to name as diazo-compounds only substances which in aqueous or other media are involved in simple or complex equilibria with diazonium cations.

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Lensovet Leningrad
Technological Institute

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Fluorine-containing Aminoacids

F.Weygand (deceased) and W.Oettmeier

CONTENTS

I. INTRODUCTION

Organofluorine compounds are important not only because they have unusual chemical properties and applications in engineering but also because some of them prove to be physiologically active. The fluorides of dialkylphosphoric acids and derivatives of monofluoroacetic acid are highly toxic, 5-fluorouracil and fluoro-orotic acid are tumour inhibitors, and the replacement of hydrogen by fluorine in certain steroid hormones greatly increases their biological activity.

The reason for the physiological activity of fluorine compounds probably consists in the fact that the cell cannot distinguish fluorinated and non-fluorinated compounds and makes use of them equally because the dimensions of the hydrogen and fluorine atoms are similar (covalent radii: H 0.35 Å, F 0.64 Å; van der Waals radii: H 1.20 Å, F 1.55 Å). However, the replacement of hydrogen by very electronegative fluorine creates a centre with an enhanced electron density and the powerful hydrogen bonds formed by this component of the molecule with enzymes can prevent the formation of normal enzyme–substrate complexes[1,2].

Since aminoacids play an important role in metabolism, the effects of fluorinated aminoacids on the organism is particularly interesting. This review deals with the synthesis and properties of fluorinated aminoacids and also their biological activity (in those cases where it is has been investigated). The review is restricted mainly to carboxylic 2-aminoacids (apart from fluorinated 3-aminopropionic acids).

II. THE SCOPE OF THE SYNTHESIS OF FLUORINE-CONTAINING AMINOACIDS

The syntheses of fluorinated aminoacids achieved hitherto can be divided into three general groups.

1. It is possible to use the classical syntheses for aminoacids from fluorinated starting materials, for example Erlenmeyer's azlactone synthesis, syntheses with acylmalonic esters, ammonolysis of carboxylic 2-halogenoacids, and Strecker's cyanohydrin synthesis. However, the replacement of hydrogen by fluorine in the starting compound can lead to complications. Because of the powerful *I*-effects of the fluoroalkyl and fluoroaryl groups, the substitution and addition reactions in the course of the synthesis may be hindered, facilitated, or take place in a different way. Finally, decomposition reactions, in particular the elimination of fluorine, may occur.

2. Another possibility is to introduce fluorine into existing aminoacids, their derivatives, or intermediate products by exchanging hydrogen, another halogen, or a hydroxyl for fluorine.

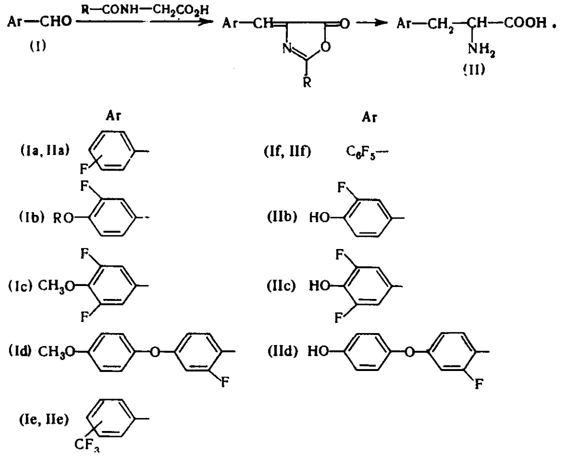
3. Special methods have also been developed (particularly for the synthesis of polyfluorinated aminoacids), which have no analogy in the chemistry of non-fluorinated aminoacids.

III. PREPARATION OF FLUORINE-CONTAINING AMINOACIDS BY CLASSICAL METHODS FOR AMINOACID SYNTHESIS

1. Fluorinated Aromatic Aminoacids

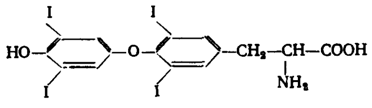
Fluorine-substituted aromatic compounds are readily obtained by the decomposition of aromatic diazonium fluoroborates and can be used for the synthesis of fluorinated aromatic aminoacids. Thus as early as 1932 Schiemann and Roselius succeeded in obtaining three isomeric fluorinated derivatives of phenylalanine (IIa) by the condensation of *o*-, *m*-, or *p*-fluorobenzaldehyde (Ia) with hippuric acid and subsequent hydrolysis and reduction[3] (see Scheme 1).

Scheme 1



It proved possible to obtain 3-fluorotyrosine (IIb) by this method using as starting materials 3-fluoro-4-methoxy- or 4-ethoxy-3-fluoro-benzaldehyde (Ib, R = CH_3 or C_2H_5) as starting materials. This compound can be also synthesised from *m*-fluorophenylalanine by nitration, reduction, and decomposition of the corresponding diazo-compounds on refluxing[4,5]. 3,5-Difluorotyrosine (IIc) was obtained similarly[6].

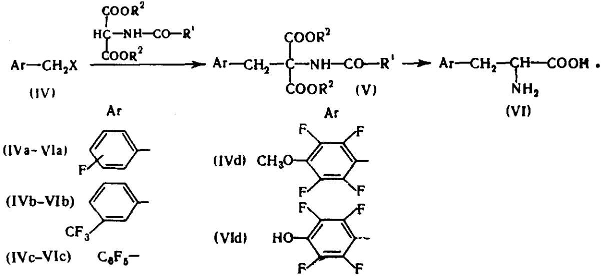
Thyronine, a compound related to tyrosine, is the non-iodinated analogue of the thyroid hormone—thyroxine (III):



Schiemann and coworkers succeeded in synthesising 2-fluorothyronine (IId) using a fluoroaldehyde (Id)[4,5]. In connection with their possible application in therapy, subsequently a series of similar fluoro-derivatives of thyronine were obtained: 3′-fluorothyronine, 3′-fluoro-3,5-di-iodothyronine, 3′-fluoro-3,5,5′-tri-iodothyronine, 3′,5′-difluorothyronine, and 3′,5′-difluoro-3,5-di-iodothyronine[7,8].

Three isomeric fluorophenylalanines were obtained in high yields by the condensation of the corresponding fluorine-substituted benzyl chlorides (IVa, X = Cl) with acetamidomalonic ester and subsequent hydrolysis of the acylamino esters formed (V, $R^1 = CH_3$, $R^2 = C_2H_5$) (see Scheme 2).

Scheme 2



The racemate produced can be separated into optical isomers by synthesising enzymically in the presence of papain the phenylhydrazides of the *N*-acylaminoacids, only the L-aminoacids reacting[9]. Similar resolution of racemates is possible also for 3-fluorotyrosine[10].

All the above aminoacids proved to be biologically active. Thus a number of studies have been published on the biological activity of fluorotyrosine and *p*-fluorophenylalanine. Only a few examples illustrating the importance of these antimetabolites were selected arbitrarily and are described below.

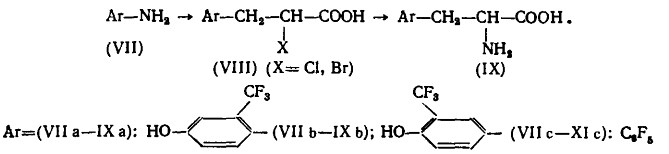
3-Fluorotyrosine is much more toxic than sodium fluoride: the lethal dose is about 12 mg kg^{-1} (for white mice)[11]. The lethal dose is independent of whether the D-isomer, the L-isomer, or the racemate is employed (experiments on rats)[10]. The Gudernatsch test on tadpoles (their growth is greatly accelerated by the addition of thyroxine) showed that fluorotyrosine may counteract the effect of thyroxine[12]. For this reason, fluorotyrosine is used in medicine in the treatment of goitre ("Pardinon") produced by the Bayer Company)[13]. It also inhibits the growth of tumours in rats and mice[14].

Fluorophenylalanines also inhibit the growth of *Neurospora crassa*[15] and are toxic to rats[16]. The addition of *p*-fluorophenylalanine to cultures of *E. coli* retards their growth, but at a certain phase in the development of *p*-fluorophenylalanine is incorporated in the proteins[17-19]. It is also possible to grow strains which are stable in relation to *p*-fluorophenylalanine[20]. These stable strains contain a phenylalanine-RNA synthetase, which no longer activates *p*-fluorophenylalanine[21,22].

A number of trifluoromethylphenylalanines and trifluoromethyltyrosines were obtained by Filler and coworkers. While *m*-trifluoromethylphenylalanine (VIb) is readily obtained from *m*-trifluoromethylbenzyl bromide (VIb, X = Br) and dibenzyl *N*-benzylyxycarbonylaminomalonate ($R^1 = C_6H_5CH_2O$, $R^2 = C_6H_5CH_2$; Scheme 2), the synthesis is unsuitable for the *o*- and *p*-isomers. However, all three isomers of trifluoromethylphenylalanine (IIe) can be readily obtained by azlactone synthesis (Scheme 1) from trifluoromethyl-substituted benzaldehydes (Ie) and aceturic acid (R = CH_3) (the benzamido-group is eliminated only with difficulty after the synthesis)[23].

Meerwein arylation was chosen for the synthesis of 2- and 3-trifluoromethyltyrosines (IXa, b):

Scheme 3



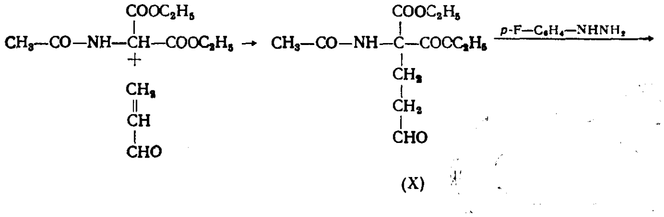
The diazonium chloride obtained from the aromatic amine (VII) is converted under the action of copper(I) chloride and acrylic acid into 3-aryl-2-chloropropionic acid (VIII), which yields the aminoacid after ammonolysis[24,25].

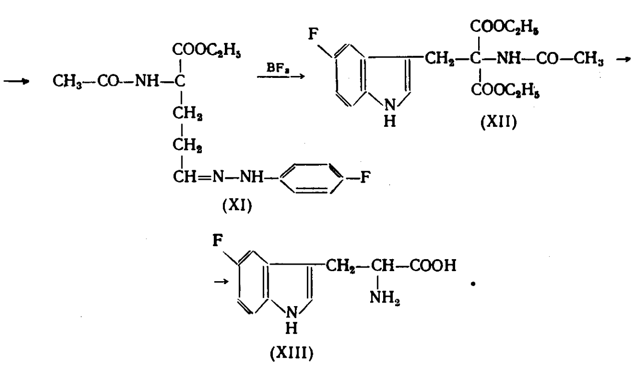
The corresponding aminoacids were obtained from the available polyfluorinated aromatic compounds. Pentafluorophenylalanine was synthesised by all three methods: azlactone synthesis (Scheme 1) with pentafluorobenzaldehyde (If)[26,27,30], synthesis with acetamidomalonic ester (Scheme 2) using pentafluorobenzyl bromide (IVc, X = Br)[28,30], and finally Meerwein arylation (Scheme 3) starting with pentafluoroaniline (VIIc) via 3-aryl-2-halogenopropionic acid (VIIIc)[28,30]. In this case it is impossible to obtain the aminoacid (IXc) by treating the chloride or bromide (VIIIc) with ammonia, since elimination and substitution reactions result in the formation of *trans*-4-amino-2,3,5,6-tetrafluorocinnamic acid. It is necessary to employ the azide and hydrogenate it catalytically. Pentafluorophenylalanine proved to be biologically inactive[28,30].

Finally, tetrafluorotyrosine (VId) was also obtained according to Scheme 2.[29,30]

The next aromatic acid for which fluoro-derivatives are known is tryptophan. Rinderkneche and Niemann[31] synthesised a fluoro-derivative using the method for the synthesis of tryptophan developed by Warner and Moe[32,33].

The addition of acetamidomalonic ester to acrolein by the Michael reaction gives 4-acetamido-4,4-diethoxycarbonylbutyraldehyde (X), the *p*-fluorophenylhydrazone (XI) of which can be cyclised by the Fischer method to an indole derivative (XII) and 5-fluorotryptophan (XIII) may be obtained by subsequent hydrolysis:





Hoffmann et al. prepared the same compound by the usual method of synthesis via gramine starting with 5-fluoroindole[34]. 5- and 6-Fluorotryptophans proved to be just as interesting key compounds for biochemical studies as fluorophenylalanine and fluorotyrosine. Only a few examples will be quoted: fluorotryptophan is toxic to mice[35], inhibits the tryptophan hydroxylase of rat brain[36], and inhibits the growth of a wild strain of *E. coli*. However, a mutant of *E. coli* incapable of synthesising tryptophan incorporates fluorotryptophan in its proteins[37].

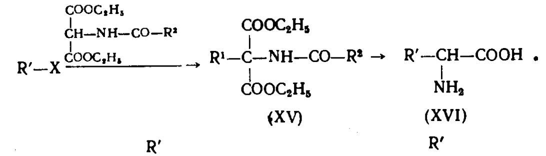
2. Fluorinated Aliphatic Monoaminoacids

After the reason for the toxicity of monofluoroacetic acid became known, the attention of biochemists was drawn to other aliphatic monofluoro-compounds. Monofluoroacetic acid takes part in the citric acid cycle, like acetic acid. The condensation of fluoroacetate with oxalylacetate is irreversible and aconitase cannot propagate the cycle in the usual way.

It was found that unbranched carboxylic ω-fluoroacids with an even number of carbon atoms are just as toxic as monofluoroacetic acid, since on β-oxidation in the living organisms they are converted into monofluoroacetic acid.

Aliphatic monofluoro-substituted aminoacids were synthesised for further investigation. Using an acylaminomalonic ester, Raasch and Lontz obtained 2-amino-4-fluorobutyric acid (XVIa), 5-fluoronorvaline (XVIb), and 6-fluoronorleucine (XVIc).

Scheme 4



$$R'{-}X \xrightarrow{CH(COOC_2H_5)_2{-}NH{-}CO{-}R^2} R^1{-}C(COOC_2H_5)_2{-}NH{-}CO{-}R^2 \rightarrow R'{-}CH(NH_2){-}COOH\,.$$

(XV) (XVI)

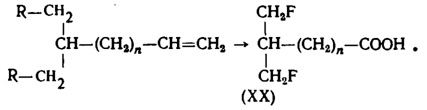
R′
(XIV a — XVI a) $F(CH_2)_2—$
(XIV b — XVI b) $F(CH_2)_3—$
(XIV c — XVI c) $F(CH_2)_4—$

R′
(XIV d — XVI d) $CH_3—CHF—(CH_2)_2—$
(XIV e — XVI e) $CF_3—(CH_2)_3—$
(XIV f — XVI f) $CF_3—CH(CH_3)—(CH_2)_2—$

The fluorine atom in the ω-position is very sensitive to hydrolysis; for example, the hydrolysis of the derivative (XVa) of acetamidomalonic ester with dilute sulphuric acid yields, together with the fluorine-containing aminoacid, an equal amount of 2-amino-4-hydroxybutyric acid. Therefore compounds (XVb) and (XVc) were hydrolysed with 48% hydrofluoric acid to prevent this exchange reaction[38,39]. Hudlický obtained by the same method 5-fluoronorleucine (XVId) from 4-bromo-2-fluorobutane (XIVd). In this case too the fluorine atom is readily substituted; more prolonged heating with dilute inorganic acids yields almost exclusively 5-hydroxynorleucine[40,41].

As was to be expected from the above, 5-fluoronorvaline proved to be very toxic (actually 10 times more toxic than sodium monofluoroacetate), while 6-fluoronorleucine is almost non-toxic. In this connection it is interesting to note that 3-fluoropyruvic acid (the product of the transamination of 3-fluoroalanine, the synthesis of which will be discussed below) is non-toxic and is not converted into monofluoroacetic acid in the rat organism[39].

Lettré and Wolcke[42] obtained a number of mono- and di-fluoro-substituted aminoacids starting with carboxylic fluoroacids[42]. When the latter were not known, the authors developed a new method of synthesis. Toluene-*p*-sulphonates (XVIII) obtained from the unsaturated diols (XVII) were converted by the action of potassium fluoride in diethylene glycol into fluoro-olefins (XIX), the ozonolysis and oxidation of which gave the carboxylic acids (XX):



$$(R{-}CH_2)_2CH{-}(CH_2)_n{-}CH{=}CH_2 \rightarrow (CH_2F)_2CH{-}(CH_2)_n{-}COOH\,.$$

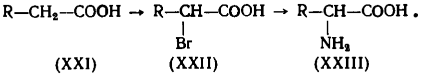
(XX)

(XVII) R=OH
(XVIII) R = OTs
(XIX) R=F

(n = 1 and 2)

The bromides of the fluoroacids (XXI) were brominated in the α-position and subsequently converted into aminoacids by the action of ammonia:

Scheme 5



$$R{-}CH_2{-}COOH \rightarrow R{-}CH(Br){-}COOH \rightarrow R{-}CH(NH_2){-}COOH\,.$$

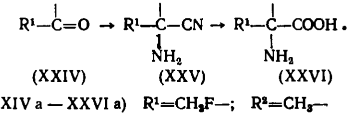
(XXI) (XXII) (XXIII)

(XXI a — XXIII a) $FCH_2—$
(XXI b — XXIII b) $F(CH_2)_2—$
(XXI c — XXIII c) $(FH_2C)_2CH—$
(XXI d — XXIII d) $(FH_2C)_2CH—CH_2—$
(XXI e — XXIII e) $CF_3—CF_2—CF_2—(CH_2)_2—$
(XXI f — XXIII f) $CF_3—CF_2—CF_2—(CH_2)_3—$

This method improved the synthesis of 3-fluoroalanine (XXIIIa) and 2-amino-4-fluorobutyric acid (XXIIIb) and made it possible to obtain for the first time 4,4′-difluorovaline (XXIIIc) and 5,5′-difluoroleucine (XXIIId). Attempts to prepare 4-fluoroleucine by this method had to be abandoned, because even the intermediate 3-fluoro-5-methylhex-1-ene splits off hydrogen fluoride at room temperature. The dipeptide DL-3-fluoroalanyl-L-leucine can be obtained from *N*-benzyloxycarbonyl-3-fluoroalanine and the trimethylsilyl ester of *N*-trimethylsilyl-L-leucine.

The Strecker method for the synthesis of aminoacids was also successfully employed to prepare mono- and di-fluoro-substituted aminoacids:

Scheme 6



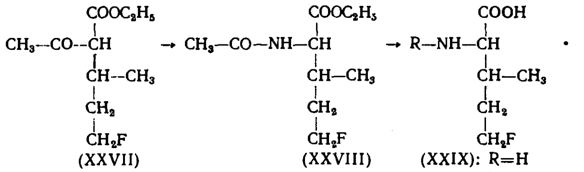
$$R^1{-}C(R^2){=}O \rightarrow R^1{-}C(R^2)(NH_2){-}CN \rightarrow R^1{-}C(R^2)(NH_2){-}COOH\,.$$

(XXIV) (XXV) (XXVI)

(XXIV a — XXVI a) $R^1=CH_2F—$; $R^2=CH_3—$
(XXIV b — XXVI b) $R^1=R^2=CH_2F—$
(XXIV c — XXVI c) $R^1=CF_3—CH_2—CH_2—$; $R^2=H—$
(XXIV d — XXVI d) $R^1=CF_3—$; $R^2=CH_3—$

However, here too side reactions play an appreciable role. Thus a mixture of 3-fluoro-2-hydroxyisobutyronitrile and 2-amino-3-fluoroisobutyronitrile (XXVa) was obtained by the reaction of fluoroacetone (XXIVa) with sodium cyanide and ammonium chloride; similarly, hydrolysis gives a mixture of 3-fluoro-2-hydroxyisobutyric acid and 2-amino-3-fluoroisobutyric acid (XXVIa)[43,44]. In the reaction of 1,6-difluoroacetone (XXIVb) 3,3′-difluoro-2-hydroxyisobutyronitrile formed as an intermediate is converted by the action of gaseous ammonia into 2-amino-3,3′-difluoroisobutyronitrile (XXVb), the hydrolysis of which gives 2-amino-3,3′-difluoroisobutyric acid (XXVIb)[43].

Hudlický chose a completely new method for the synthesis of monofluoro-derivatives of isoleucine[45]. Alkylation of acetoacetic ester with 3-bromo-1-fluorobutane gives the ethyl ester of 2-acetyl-5-fluoro-3-methylvaleric acid (XXVII). This acetyl derivative is converted by the Schmidt rearrangement into ethyl 2-acetamido-5-fluoro-3-methylvalerate (XXVIII):

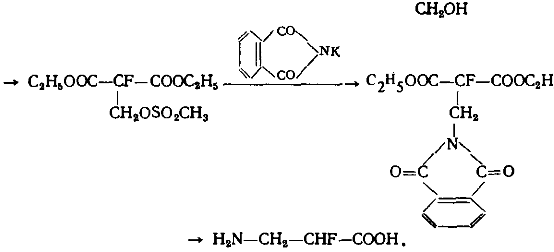


$$\underset{\text{(XXVII)}}{\begin{array}{c}\mathrm{COOC_2H_5}\\ |\\ \mathrm{CH_3{-}CO{-}CH}\\ |\\ \mathrm{CH{-}CH_3}\\ |\\ \mathrm{CH_2}\\ |\\ \mathrm{CH_2F}\end{array}} \rightarrow \underset{\text{(XXVIII)}}{\begin{array}{c}\mathrm{COOC_2H_5}\\ |\\ \mathrm{CH_3{-}CO{-}NH{-}CH}\\ |\\ \mathrm{CH{-}CH_3}\\ |\\ \mathrm{CH_2}\\ |\\ \mathrm{CH_2F}\end{array}} \rightarrow \begin{array}{c}\mathrm{COOH}\\ |\\ \mathrm{R{-}NH{-}CH}\\ |\\ \mathrm{CH{-}CH_3}\\ |\\ \mathrm{CH_2}\\ |\\ \mathrm{CH_2F}\end{array}\;.$$

(XXVII) (XXVIII) (XXIX): R=H
(XXX): R=CH₃—CO—

While acid hydrolysis gives DL-2-amino-5-fluoro-3-methylvaleric acid (XXIX), alkaline hydrolysis under mild conditions gives an *N*-acetyl derivative (XXX). To separate it into its optical isomers, this compound was acted upon by pig kidney acylase. However, instead of the expected L-aminoacid, its cyclisation product—*cis*-3-methyl-L-proline—was obtained together with D-2-acetamido-5-fluoro-3-methylvaleric acid. These results provide a key to the solution of the problem of the stereochemistry of the compounds. Since the *cis*-compound is obtained by the cyclisation of *threo*-2-amino-5-fluoro-3-methylvaleric acid, the product of the synthesis is evidently DL-5-fluoroalloisoleucine (XXIX). The *N*-acetyl derivative obtained by enzymic hydrolysis is thus (2S : 3R)-2-acetamido-5-fluoro-3-methylvaleric acid (XXX).

Here we should also mention the fluoro-derivative of 3-aminopropionic acid (β-alanine), although this is not an α-aminoacid. β-Alanine is one of the few β-aminoacids occurring in nature; it is a component of pantothenic acid. 3-Amino-2-fluoropropionic acid (XXXI) may be isolated as a decomposition product of 5-fluorouracil from the urine of mice, cats, or man after internal administration of 5-fluorouracil[46]. Bergmann and Cohen obtained α-fluoro-β-alanine (XXXI) in the following way[47]:



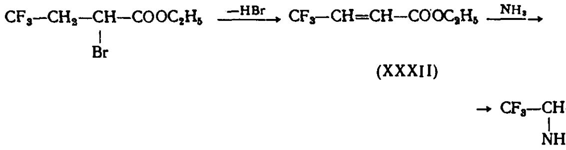
(XXXI)

A similar synthesis was developed by Tolman and Vereš on the basis of 2-fluoro-3-hydroxypropionic acid[48].

Bearing in mind the ease with which mono- and di-fluoro-substituted aminoacids lose fluorine, it is evident that the problem of whether the observed cytotoxic effect of the compound is determined by its properties as an antimetabolic or whether it is caused by the formation of fluoride ions remains open[42].

The stability of fluorine-containing aminoacids should increase following the introduction of a complete trifluoromethyl group or other perfluoroalkyl group at once instead of replacing one or two hydrogen atoms by fluorine.

Walborsky et al. synthesised 2-amino-4,4,4-trifluorobutyric acid (XXXVIa) from 4,4,4-trifluorobutyric acid. It is readily brominated in the α-position and is converted into ethyl 2-bromo-4,4,4-trifluorobutyrate. However, instead of the expected 2-amino-4,4,4-trifluorobutyramide ammonolysis yields the isomeric 3-amino-4,4,4-trifluorobutyramide (XXXIII)[49]:

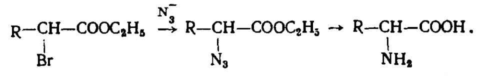


$$\mathrm{CF_3{-}CH_2{-}\underset{\underset{\mathrm{Br}}{|}}{CH}{-}COOC_2H_5} \xrightarrow{-\mathrm{HBr}} \underset{\text{(XXXII)}}{\mathrm{CF_3{-}CH{=}CH{-}COOC_2H_5}} \xrightarrow{\mathrm{NH_3}} \underset{\text{(XXXIII)}}{\mathrm{CF_3{-}\underset{\underset{\mathrm{NH_2}}{|}}{CH}{-}CH_2{-}CONH_2}}.$$

(XXXII)

(XXXIII)

As a result of the elimination of hydrogen bromide, ethyl trifluorocrotonate (XXXII) is formed initially, since the inductive effect of the trifluoromethyl group facilitates the elimination of a proton from the β-position. Subsequently ammonia adds in the usual way to the β-carbon atom. A less basic but more nucleophilic reagent (for example the azide ion) should drive the reaction towards normal substitution. Indeed, when the α-bromoester (XXXIVa) was treated with an azide with subsequent catalytic hydrogenation, 2-amino-4,4,4-trifluorobutyric acid (XXXVIa) was obtained[50]; 4,4,4-trifluorovaline (XXXVIb)[51] and 5,5,5,5′,5′,5′-hexafluoroleucine (XXXVIc)[52] were obtained similarly:



$$\underset{\text{(XXXIV)}}{\mathrm{R{-}\underset{\underset{\mathrm{Br}}{|}}{CH}{-}COOC_2H_5}} \xrightarrow{\mathrm{N_3^-}} \underset{\text{(XXXV)}}{\mathrm{R{-}\underset{\underset{\mathrm{N_3}}{|}}{CH}{-}COOC_2H_5}} \rightarrow \underset{\text{(XXXVI)}}{\mathrm{R{-}\underset{\underset{\mathrm{NH_2}}{|}}{CH}{-}COOH}}.$$

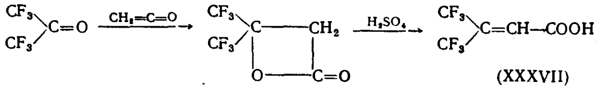
(XXXIV) (XXXV) (XXXVI)

(XXXIV a — XXXVI a) $\mathrm{CF_3{-}CH_2}$

(XXXIV b — XXXVI b) $\mathrm{CF_3{-}\underset{\underset{\mathrm{CH_3}}{|}}{CH}{-}}$

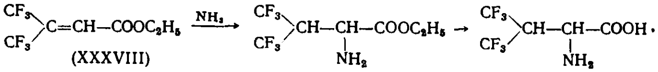
(XXXIV c — XXXVI c) $\mathrm{CF_3{-}\underset{\underset{\mathrm{CF_3}}{|}}{CH}{-}CH_2}$

Knunyants and Cheburkov showed that 3,3-bis(trifluoromethyl)acrylic acid (XXXVII), obtained from hexafluoroacetone and keten via a β-lactone[53],



(XXXVII)

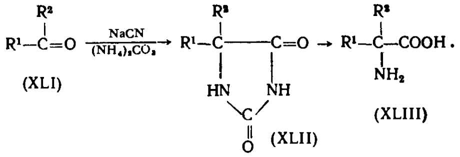
and also the ethyl ester of this acid (XXXVIII) do not behave like ethyl 4,4,4-trifluorocrotonate (XXXII). In the case of the ester (XXXII) the attack by ammonia is directed to the β-carbon atom and 3-amino-4,4,4-trifluorobutyramide (XXXIII) is formed; on the other hand, the ester (XXXVIII) combines with ammonia at the α-position. Free 4,4,4,4′,4′,4′-hexafluorovaline (XL) is then obtained from the aminoacid ester thus produced[54]:



(XXXVIII) (XXXIX) (XL)

A number of trifluoromethyl-substituted aminoacids have also been obtained in other ways. 6,6,6-Trifluoronorleucine (XVIe) and 6,6,6-trifluoro-5-methylnorleucine (XVIf) were synthesised with the aid of formamidomalonic ester (Scheme 4, $R^2 = H$)[49]; the starting materials were respectively 4,4,4-trifluorobutyl iodide (XIVe) or 4,4,4-trifluoro-2-methylbutyl iodide (XIVf), which may be obtained in several stages from 1,1,1-trifluoroacetone.

The Strecker synthesis (Scheme 6) was used successfully to prepare 5,5,5-trifluoronorvaline (XXVIc)[49] and 2-amino-3,3,3-trifluoroisobutyric acid (XXVId)[44]. However, while the yield of 5,5,5-trifluoronorvaline [(XXVIc) or (XLIIIa)] synthesised by the Strecker method is only 4.6%, synthesis via the hydantoin makes it possible to increase the yield to 30%:[49]

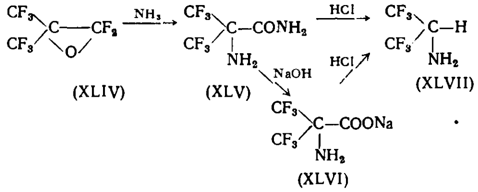


(XLI a — XLIII a) $R^1=CF_3-CH_2-CH_2-$; $R^2=H$

(XLI b — XLIII b) $R^1=CF_3-$; $R^2=CH_3-$

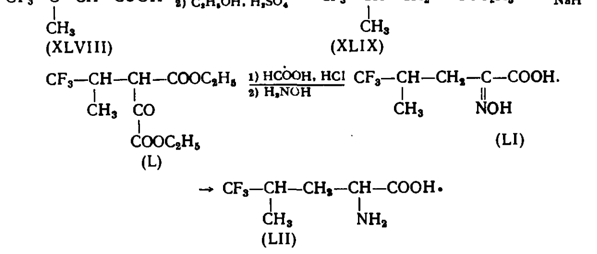
2-Amino-3,3,3-trifluorobutyric acid (XLIIIb) was also obtained via hydantoin[38].

In this connection it is interesting to note an observation by Knunyants and coworkers: it was found that the corresponding aminoacid derivative of hexafluoroacetone—2-amino-3,3,3,3′,3′,3′-hexafluoroisobutyric acid—is unstable. The interaction of epoxyperfluoroisobutane (XLIV) with ammonia at −10°C yields the amide of 2-amino-3,3,3,3′,3′,3′-hexafluoroisobutyric acid (XLV)[55]. Hydrolysis of this amide with dilute hydrochloric acid is accompanied by decarboxylation and gives hexafluoroisopropylamine (XLVII); although the sodium salt of the aminoacid (XLVI) can be obtained by alkaline hydrolysis, on acidification it too decarboxylates spontaneously[56]:



Yet another synthesis of 5,5,5-trifluoronorvaline and 4,4,4-trifluorovaline has so far been mentioned only in conference abstracts[57].

The synthesis of 5,5,5-trifluoroleucine (LII) should also be described. Rennert and Anker employed 4,4,4-trifluoro-3-methylcrotonic acid (XLVIII) as the starting material. Catalytic hydrogenation, esterification, and condensation with oxalate ester leads to compound (L). After hydrolysis and decarboxylation, the resulting 2-ketoacid is converted into the oxime (LI). Its catalytic hydrogenation yields the aminoacid (LII)[58]:



$$\underset{\substack{|\\CH_3\\(XLVIII)}}{CF_3-C}=CH-COOH \xrightarrow[2)\,C_2H_5OH,\,H_2SO_4]{1)\,H_2(Pt)} CF_3-\underset{\substack{|\\CH_3\\(XLIX)}}{CH}-CH_2-COOC_2H_5 \xrightarrow[NaH]{(COOC_2H_5)_2}$$

$$CF_3-\underset{\substack{|\\CH_3}}{CH}-\underset{\substack{|\\CO\\|\\COOC_2H_5\\(L)}}{CH}-COOC_2H_5 \xrightarrow[2)\,H_2NOH]{1)\,HCOOH,\,HCl} CF_3-\underset{\substack{|\\CH_3}}{CH}-CH_2-\underset{\substack{\|\\NOH\\(LI)}}{C}-COOH.$$

$$\rightarrow CF_3-\underset{\substack{|\\CH_3\\(LII)}}{CH}-CH_2-\underset{\substack{|\\NH_2}}{CH}-COOH.$$

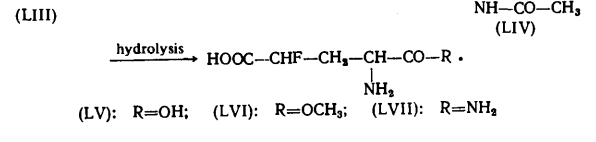
In view of their possible biochemical importance, Walborsky and Lang determined the pK's of a number of trifluoromethyl-substituted aminoacids and compared them with those of the corresponding non-fluorinated compounds[59]. As expected, pK_{COOH} and pK_{NH_2} decrease under the influence of electronegative trifluoromethyl groups and to a greater extent the closer the latter are to the dissociating groups. However, in biological tests the aminoacids obtained did not fulfil the expectations. 6,6,6-Trifluoronorleucine, 6,6,6-trifluoro-5-methylnorleucine, 4,4,4,4′,4′,4′-hexafluorovaline, 4,4,4-trifluorovaline, and 5,5,5,5′,5′,5′-hexafluoroleucine proved to be inactive in relation to *Saccharomyces cerevisiae* and *E. coli*; only 5,5,5-trifluoronorvaline inhibits the growth of *E. coli*[49,51,52]. On the other hand, the growth of HeLa cells ceases almost completely at a hexafluorovaline concentration as low as 7.2×10^{-4} M.[60]

An interesting effect was observed with 5,5,5-trifluoroleucine. Leucine dependent *E. coli* mutants continue to grow exponentially when trifluoroleucine is added to the nutrient medium. Inhibition is not observed until the concentration of trifluoroleucine exceeds by severalfold the concentration of leucine. When the trifluoroleucine : leucine ratio is 2, at least half of the leucine in the bacterial protein is replaced by trifluoroleucine. *E. coli* can actually become adapted to grow in a nutrient medium containing solely trifluoroleucine and the leucine in the protein is entirely replaced by trifluoroleucine. On the other hand, a wild strain of *E. coli* does not incorporate trifluoroleucine added to the nutrient medium[58].

Two perfluoroalkyl-substituted long-chain aminoacids, obtained by Brace[61] according to Scheme 4 from fluoroacids (XXIe) and (XXIf), namely 2-amino-5,5,6,6,7,7,7-heptafluoroheptanoic acid (XXIIIe) and 2-amino-6,6,7,7,8,8,8-heptafluorocaprylic acids (XXIIIf)[61], are not analogues of natural aminoacids.

3. Fluorinated Monofunctional Aliphatic Aminoacids

A monofluoro-derivative of glutamic acid has been obtained by several methods. 4-Fluoroglutamic acid (LV) was obtained for the first time by Hudlický[62,63] from ethyl α-fluoroacrylate (LIII). The Michael condensation of acetamidomalonic ester and subsequent hydrolysis of the addition product led to the aminoacid (LV):



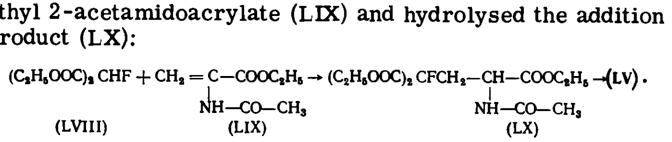
$$\underset{(LIII)}{C_2H_5OOC-CF=CH_2} \xrightarrow{CH_3CONHCH(COOC_2H_5)_2} C_2H_5OOC-CHF-CH_2-\underset{\substack{|\\NH-CO-CH_3\\(LIV)}}{C}(COOC_2H_5)_2 \rightarrow$$

$$\xrightarrow{hydrolysis} HOOC-CHF-CH_2-\underset{\substack{|\\NH_2}}{CH}-CO-R.$$

(LV): $R=OH$; (LVI): $R=OCH_3$; (LVII): $R=NH_2$

Tolman and Vereš[64] obtained 5-fluoroglutamine (LVII) by treating the γ-methyl ester of 4-fluoroglutamic acid (LVI) with ammonia; the amino-group was protected with carbon disulphide as the dithiocarbamate.

Independently of Hudlický, Buchanan et al. obtained 4-fluoroglutamic acid by this method. However, they described a second method as well, which is also based on the Michael addition but is otherwise the converse of the Hudlický method. They added diethyl fluoromalonate (LVIII) to ethyl 2-acetamidoacrylate (LIX) and hydrolysed the addition product (LX):



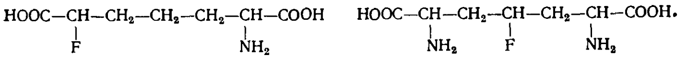
$$\underset{(LVIII)}{(C_2H_5OOC)_2CHF} + CH_2=\underset{\substack{|\\NH-CO-CH_3\\(LIX)}}{C}-COOC_2H_5 \rightarrow (C_2H_5OOC)_2CFCH_2-\underset{\substack{|\\NH-CO-CH_3\\(LX)}}{CH}-COOC_2H_5 \rightarrow (LV).$$

The yield was almost twice as high as in the previous synthesis. Biological tests showed that fluoroglutamic acid has virtually no activity.

Attempts to synthesise 3-fluoroaspartic acid proved to be unsuccessful[42,63].

2,6-Diaminopimelic acid is present in bacterial cell walls. Together with other aminoacids, it gives rise to the formation of cross-links between polysaccharide chains thereby imparting stability to the cell walls.

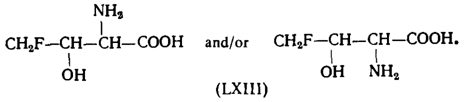
Cavalleri et al. synthesised as possible antimetabolites 2-amino-6-fluoropimelic acid (LXI) and 2,6-diamino-4-fluoropimelic acid (LXII) from the fluoropimelic acids by bromination in the α-position and replacement of bromine by the action of ammonia or potassium phthalimide[66]:



$$\mathrm{HOOC{-}\underset{F}{CH}{-}CH_2{-}CH_2{-}CH_2{-}\underset{NH_2}{CH}{-}COOH}\qquad \mathrm{HOOC{-}\underset{NH_2}{CH}{-}CH_2{-}\underset{F}{CH}{-}CH_2{-}\underset{NH_2}{CH}{-}COOH.}$$

(LXI) (LXII)

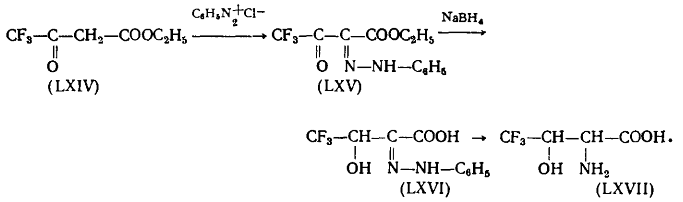
Furthermore, mention should also be made of 4-fluorothreonine (LXIII), a monofluorinated polyfunctional aminoacid. It was obtained by the addition of hypobromite to 4-fluorocrotonic acid with subsequent ammonolysis in liquid ammonia. So far it has not been determined whether this leads to the formation of DL-4-fluorothreonine or DL-4-fluoroallothreonine[42]:



$$\mathrm{CH_2F{-}\underset{OH}{CH}{-}\overset{NH_2}{CH}{-}COOH}\quad \text{and/or}\quad \mathrm{CH_2F{-}\underset{OH}{CH}{-}\underset{NH_2}{CH}{-}COOH.}$$

(LXIII)

Walborsky and Baum[67] proposed a synthesis of 4,4,4-trifluorothreonine (LXVII):



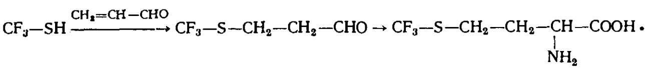
$$\mathrm{CF_3{-}\underset{\underset{O}{\|}}{C}{-}CH_2{-}COOC_2H_5}\xrightarrow{C_6H_5N_2^+Cl^-}\mathrm{CF_3{-}\underset{\underset{O}{\|}}{C}{-}\underset{\underset{N-NH-C_6H_5}{\|}}{C}{-}COOC_2H_5}\xrightarrow{NaBH_4}$$

$$\mathrm{CF_3{-}\underset{OH}{CH}{-}\underset{\underset{N-NH-C_6H_5}{\|}}{C}{-}COOH}\rightarrow\mathrm{CF_3{-}\underset{OH}{CH}{-}\underset{NH_2}{CH}{-}COOH.}$$

(LXIV) (LXV) (LXVI) (LXVII)

For this purpose, 4,4,4-trifluoroacetoacetic ester (LXIV) is treated with phenyldiazonium chloride (the Japp–Klingemann reaction), the keto-group is reduced to an alcoholic group with sodium borohydride, and the ester is hydrolysed. Finally, the phenylhydrazone (LXVI) is hydrogenated catalytically with formation of the aminoacid. Here too a mixture of trifluorothreonine and trifluoroallothreonine is probably formed. The attempts by the same authors to achieve the asymmetric synthesis of 4,4,4-trifluorothreonine will be described in Section V (subsection 1).

S-Adenosylmethionine is a transferring agent for the methyl group in biological methylation. Interesting results might have been expected on replacement of the methyl group by a trifluoromethyl group. Trifluoromethionine (or S-trifluoromethylhomocysteine) (LXX) was synthesised by Dannley and Taborsky[68] starting with trifluoromethanethiol (LXVIII), obtained by the fluorination of carbon disulphide with mercury fluoride. The mercaptan was added to acrolein and 3-trifluoromethylthiopropionaldehyde (LXIX) obtained in this way was converted into trifluoromethionine (LXX) by hydantoin synthesis:



$$\mathrm{CF_3{-}SH}\xrightarrow{CH_2=CH-CHO}\mathrm{CF_3{-}S{-}CH_2{-}CH_2{-}CHO}\rightarrow\mathrm{CF_3{-}S{-}CH_2{-}CH_2{-}\underset{NH_2}{CH}{-}COOH.}$$

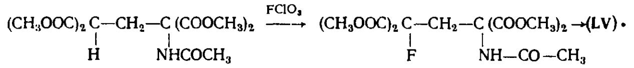
(LXVIII) (LXIX) (LXX)

The hopes concerning trifluoromethionine were indeed realised. It inhibits the growth of many micro-organisms[69] and forms an *S*-adenosyl derivative both *in vitro* and *in vivo*, competing thereby with methionine and preventing the demethylation of *S*-adenosylmethionine[70].

IV. SYNTHESES OF FLUORINE-CONTAINING AMINOACIDS BY THE INTRODUCTION OF FLUORINE INTO AMINOACIDS OR THEIR DERIVATIVES

1. Replacement of Hydrogen by Fluorine

4-Fluoroglutamic acid (LV) is not obtained solely by the two methods mentioned above. It is also possible to replace the hydrogen atom in the γ-position of the tetramethylester of 2-acetamido-2,4-dicarboxyglutaric acid (LXXI) by fluorine with the aid of perchloryl fluoride and then hydrolyse the fluorinated ester (LXXII)[71–73]:



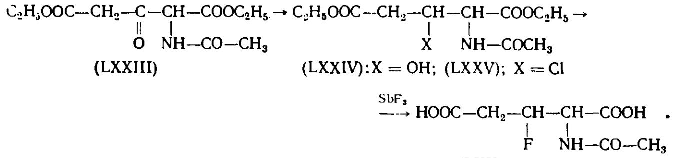
$$\mathrm{(CH_3OOC)_2\underset{H}{C}{-}CH_2{-}\underset{NHCOCH_3}{C}(COOCH_3)_2}\xrightarrow{FClO_3}\mathrm{(CH_3OOC)_2\underset{F}{C}{-}CH_2{-}\underset{NH-CO-CH_3}{C}(COOCH_3)_2}\rightarrow\mathrm{(LV)}.$$

(LXXI) (LXXII)

The diastereoisomers obtained could be separated[74].

2. Replacement of a Halogen by Fluorine

3-Fluoroglutamic acid, isomeric with 4-fluoroglutamic acid can be synthesised [as the *N*-acyl derivative of compound (LXXVI)] from the diethyl ester of 2-acetamidoacetonedicarboxylic acid (LXXIII)[75]. This ester is hydrogenated catalytically and the hydroxy-group in compound (LXXIV) thus formed is replaced by chlorine. The chlorine in the resulting chloro-derivative (LXXV) is replaced by fluorine by the action of antimony trifluoride and the ethoxycarbonyl group is then hydrolysed, which yields the *N*-acyl derivative of (LXXVI):



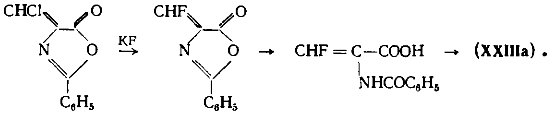
$$\mathrm{C_2H_5OOC{-}CH_2{-}\underset{\underset{O}{\|}}{C}{-}\underset{NH-CO-CH_3}{CH}{-}COOC_2H_5}\rightarrow\mathrm{C_2H_5OOC{-}CH_2{-}\underset{X}{CH}{-}\underset{NH-COCH_3}{CH}{-}COOC_2H_5}\rightarrow$$

(LXXIII) (LXXIV): X = OH; (LXXV); X = Cl

$$\xrightarrow{SbF_3}\mathrm{HOOC{-}CH_2{-}\underset{F}{CH}{-}\underset{NH-CO-CH_3}{CH}{-}COOH}\ .$$

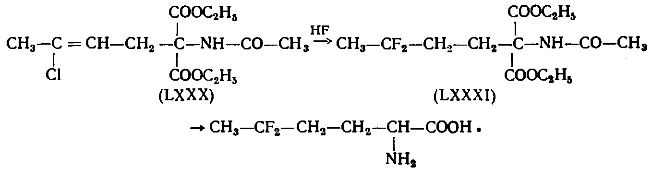
(LXXVI)

3-Fluoroalanine (XXIIIa) was obtained for the first time by a similar replacement of a halogen. 4-Chloromethylene-2-phenyl-5-oxazolone (LXXVII) is converted into the fluoro-derivative (LXXVIII) by the action of potassium fluoride in acetylacetone; the unsaturated *N*-benzamido-acid (LXXIX) obtained by hydrolysis is hydrogenated catalytically and finally the benzoyl group is eliminated[76]:



(LXXVII) (LXXVIII) (LXXIX)

In an attempt to replace chlorine by fluorine in a derivative of acetamidomalonic ester (LXXX) Hudlický[77] obtained immediately a difluoro-product (LXXXI), since hydrofluoric acid added simultaneously to the double bond. Hydrolysis gave 5,5-difluoronorleucine (LXXXII):

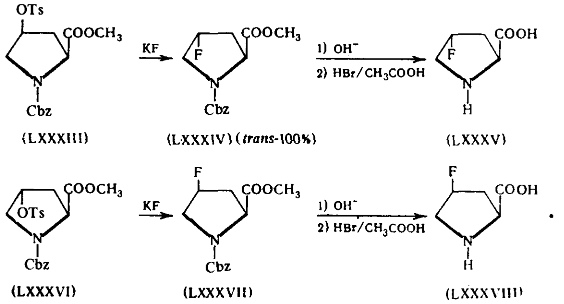


$$CH_3{-}\underset{Cl}{C}{=}CH{-}CH_2{-}\overset{COOC_2H_5}{\underset{COOC_2H_5}{C}}{-}NH{-}CO{-}CH_3 \xrightarrow{HF} CH_3{-}CF_2{-}CH_2{-}CH_2{-}\overset{COOC_2H_5}{\underset{COOC_2H_5}{C}}{-}NH{-}CO{-}CH_3 \rightarrow CH_3{-}CF_2{-}CH_2{-}CH_2{-}\underset{NH_2}{CH}{-}COOH.$$

(LXXX) (LXXXI) (LXXXII)

3. Replacement of a Hydroxy-group by Fluorine

Aminoacids containing hydroxy-groups are used in such syntheses. Witkop and coworkers achieved the stereospecific synthesis of *cis*- and *trans*-4-fluoro-L-proline (LXXXVIII) and (LXXXV) from L-hydroxyproline and L-hydroxyalloproline[78]:

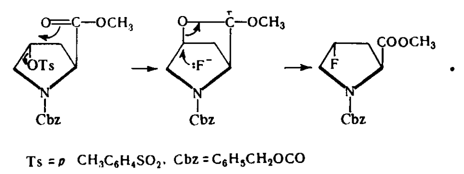


(LXXXIII) (LXXXIV) (*trans*-100%) (LXXXV)

(LXXXVI) (LXXXVII) (LXXXVIII)

OTs = p-$CH_3C_6H_4SO_2$
Cbz = $C_6H_5CH_2OCO$

When the methyl ester of *N*-benzyloxycarbonyl-*O*-tosyloxy-L-alloproline (LXXXIII) is heated with potassium fluoride in diethylene glycol, the *trans*-compound (LXXXIV) is obtained as a result of a stereospecific S_N2 reaction. Hydrolysis and elimination of the benzyloxycarbonyl group give *trans*-4-fluoro-L-proline (LXXXV). However, the fluorination of the methyl ester of *N*-benzyloxycarbonyl-*O*-tosyloxy-L-proline (LXXXVI) gives rise to a mixture of 83% of the *cis*-compound and 17% of the *trans*-compound. This can be explained by the intramolecular involvement of the ester carbonyl group in the substitution reaction:

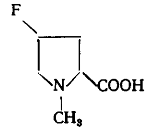


Ts = p $CH_3C_6H_4SO_2$, Cbz = $C_6H_5CH_2OCO$

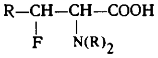
A somewhat modified synthesis was described by another group of investigators[79].

In tests on *E. coli* it was found that both isomers are incorporated in the protein but the *trans*-isomer is incorporated to a much greater extent. In contrast to the *cis*-isomer, *trans*-fluoroproline does not inhibit the growth of mice. On the other hand, in the presence of *cis*-fluoroproline the weight of mice is smaller approximately by one-quarter compared with the control experiment. When the animals were cut open, pathological changes were found, particularly in the liver. Therefore it is suggested that in the experiments with *E. coli* too *cis*-fluoroproline inhibits the biosynthesis of proteins[78,79]. In the case of collagens, which contain particularly large amounts of proline and hydroxyproline, the latter is obtained as a result of the replacement in the finished protein of a *trans*-hydrogen atom in the 4-position of proline by a hydroxy-group; hydroxyproline is not incorporated in proteins. Experiments with *trans*-fluoroproline labelled with tritium showed that fluorine can also be replaced enzymically by a hydroxy-group[78].

Cohen and Bergmann[80] attempted to use 2-chloro-1,1,2-trifluoroethyldiethylamine as a fluorinating agent for the replacement of a hydroxy-group by fluorine in the synthesis of monofluoro-substituted aminoacids from hydroxy-aminoacids. However, this method proved to be suitable only for aminoacids with alkylated amino- and carboxy-groups. 4-Fluoro-*N*-methylproline (LXXXIX) (from hydroxyproline), 3-fluoro-*NN*-dimethylalanine (XC) (from serine), 2-amino-3-fluoro-*NN*-dimethylbutyric acid (XCI) (from threonine), 3-fluoro-*NN*-dimethylphenylalanine (XCII) (from phenylserine), and *O*-ethoxycarbonyl-3-fluoro-*NN*-dimethyltyrosine (XCIII) (from hydroxyphenylserine) were obtained in this way; the last two compounds were prepared only as the methyl esters:

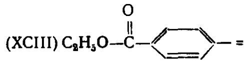


(LXXXIX)



$R{-}\underset{F}{CH}{-}\underset{N(R)_2}{CH}{-}COOH$

(XC) H— = R
(XCI) CH_3— = R
(XCII) C_6H_5— = R



(XCIII) $C_2H_5O{-}\overset{O}{\overset{\|}{C}}{-}C_6H_4{-}$ = R

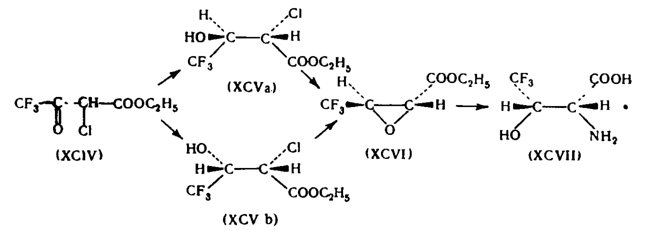
V. SPECIAL METHODS FOR THE SYNTHESIS OF FLUORINE-CONTAINING AMINOACIDS

This section deals mainly with the syntheses of highly fluorinated aminoacids, which are possible only due to the electronic influence of perfluoroalkyl groups. These syntheses are unsuitable for non-fluorinated compounds or they give rise to different products.

1. Opening of the Ring in Glycidic Esters

Apart from the synthesis of 4,4,4-trifluorothreonine already described, Walborsky and Baum attempted an asymmetric synthesis, which would not result in a mixture of 4,4,4-trifluorothreonine and 4,4,4-trifluoroallothreonine[67].

In the reduction with sodium borohydride of the ethyl ester of 2-chloro-4,4,4-trifluoro-3-oxobutyric acid (XCIV), which is readily obtained by the chlorination of 4,4,4-trifluoroacetoacetic ester, a mixture of both stereoisomers of ethyl 2-chloro-4,4,4-trifluoro-3-oxobutyrate [(XCVa) and (XCVb)] is formed:

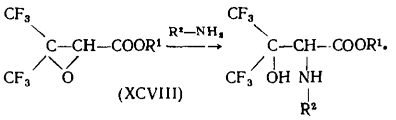


(XCIV) (XCVa) (XCV b) (XCVI) (XCVII)

The isomers may be separated by distillation; they are obtained in proportions of 7 : 4. According to Cram's rule, more of the *erythro*-compound (XCVb) than of the threo-isomer (XCVa) should be formed, so that the ester formed in a greater amount should be the *erythro*-isomer. However, ring closure in both isomers gave the same epoxy-compound (XCVI), to which Walborsky and Baum attributed the *trans*-configuration.

It was of interest to elucidate how the glycidic ester (XCVI) behaves when its ring is cleaved with ammonia; whether the attack is directed to the α-carbon atom with formation of a 2-amino-3-hydroxyacid or whether a 3-amino-2-hydroxy acid is formed as a result of attack on the β-carbon atom. Experiments showed that the ring is opened exclusively at the α-carbon atom, i.e. 4,4,4-trifluorothreonine or its amide is formed, depending on the conditions. Since ring opening is also a *trans*-reaction, the *erythro*-compound, i.e. 4,4,4-trifluoroallothreonine (XCVII), should be produced.

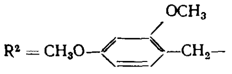
Knunyants and coworkers showed that diazoacetic ester reacts with hexafluoroacetone in an unusual manner with formation of bis(trifluoromethyl)glycidic ester (XCVIII)[81]. In this case too reaction with amines, for example, benzylamine or aniline, gives 2-amino-3-hydroxy-compounds (XCIX) or (C)[82]. When the amine employed is 2,4-dimethoxybenzylamine, the 2,4-dimethoxybenzyl group can be very readily eliminated from the resulting ethyl ester of 4,4,4,4′,4′,4′-hexafluoro-2-[*N*-(2,4-dimethoxybenzyl)-amino]-3-hydroxyisovaleric acid (CI) by means of a mixture of trifluoroacetic acid and its anhydride[83]. After hydrolysis, 2-amino-4,4,4,4′,4′,4′-hexafluoro-3-hydroxyisovaleric acid (CII) is obtained[84]:



(XCIX) $R^1 = C_2H_5—$; $R^2 = C_6H_5—CH_2—$

(C) $R^1 = C_2H_5—$; $R^2 = C_6H_5—$

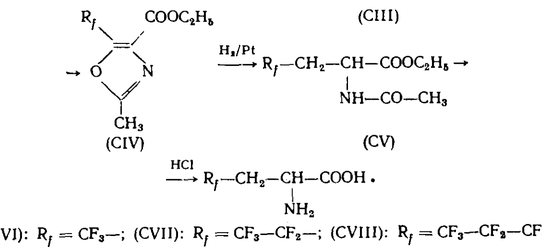
(CI) $R^1 = C_2H_5—$; $R^2 =$



(CII) R^1, $R^2 = H$

2. Opening of the Ring in Esters of 5-Perfluoroalkyl-2-methyloxazole-4-carboxylic Acids

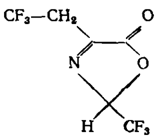
Steglich et al.[85] developed a general method for the synthesis of alanines with perfluoroalkyl substituents in the β-position. The starting materials were perfluoroacyldiazoacetic esters (CIII), which are readily obtained from the anhydrides of perfluoroacids and diazoacetic ester:



(CVI): $R_f = CF_3—$; (CVII): $R_f = CF_3—CF_2—$; (CVIII): $R_f = CF_3—CF_2—CF_2—$

When compounds CIII) are irradiated in acetonitrile, esters of 5-perfluoroalkyl-2-methyloxazole-4-carboxylic acids (CIV) are formed. Catalytic hydrogenation of the latter is accompanied by hydrogenolysis, which leads to the ethyl esters of *N*-acetyl-3-perfluoroalkylalanines (CV). Hydrolysis with concentrated hydrochloric acid gives, depending on the perfluoroalkyl group, 2-amino-4,4,4-trifluorobutyric acid (CVI), 4,4,5,5,5-pentafluoronorvaline (CVII), or 4,4,5,5,6,6,6-heptafluoronorleucine (CVIII). Measurements of the pK′s showed that, as expected, they are again lower compared with the non-fluorinated aminoacids[86].

DL-2-Amino-4,4,4-trifluorobutyric acid (CVI) can be converted into the L-form. The aminoacid is trifluoroacetylated and then cyclised by reaction with dicyclohexylcarbodi-imide to 4-(2,2,2-trifluoroethyl)-2-trifluoromethyl-Δ³-5-oxazolinone (CIX):

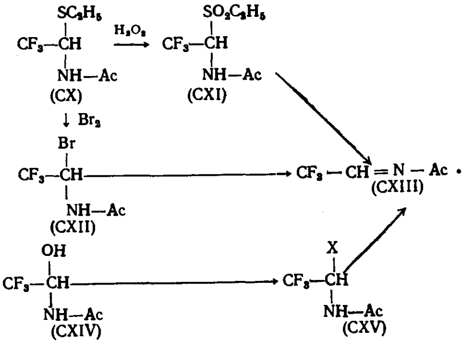


(CIX).

When the ring of this optically inactive Δ³-oxazoline derivative is opened by the action of the dimethyl ester of L-glutamic acid, the product is the dimethyl ester of *N*-trifluoroacetyl-(2-amino-4,4,4-trifluorobutyryl)-L-glutamic acid, which, as a result of optical induction, consists of 83% of the LL- and 17% of the DL-diastereoisomer (determined by gas–liquid chromatography). Repeated recrystallisation, hydrolysis, and elimination of L-glutamic acid gave pure L-2-amino-4,4,4-trifluorobutyric acid (CVI)[85]. L-4,4,5,5,5-pentafluoronorvaline (CVII) was obtained similarly[86].

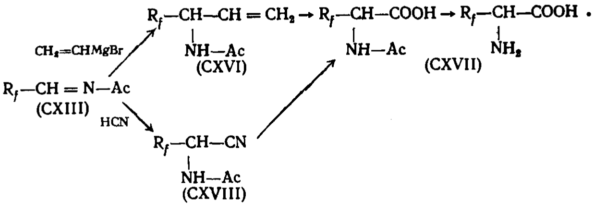
3. Reactions involving Addition to *N*-Acylimines of Perfluoroaldehydes and Perfluoroketones

Weygand, Steglich, and coworkers observed that the *N*-acylimines of trifluoroacetaldehyde (CXIII) are extremely reactive. *N*-Acyl-1-ethylthio-2,2,2-trifluoroethylamines (CX, Ac = CH_3CO, CF_3CO, C_6H_5CO, or $C_6H_5CH_2OCO$) are readily oxidised to sulphones (CXI) with hydrogen peroxide in glacial acetic acid[87]. It has been shown that the mechanism of reactions of the sulphones (CXI) with nucleophilic reagents involves elimination and addition; initially the sulphones are converted by bases into *N*-acyltrifluoroacetaldimines (CXIII), to which the nucleophilic agents were then added[87]. The bromination of the thioesters (CX) yields *N*-acyl-1-bromo-2,2,2-trifluoroethylamines (CXII) from which highly moisture-sensitive aldimines (CXIII) can be isolated in a pure form[88]. A simpler pathway to the aldimines (CXIII) involves the condensation of trifluoroacetaldehyde, trifluoroacetaldehyde hydrate, or hemiacetals of trifluoroacetaldehyde with acid amides; this results in the formation of *N*-acyl-2,2,2-trifluoro-1-hydroxyethylamines (CXIV), which can be readily converted into the chloro-derivatives (CXV, X = Cl) by the action of phosphorus pentachloride[88]; in the presence of acid-sensitive acyl groups such as the p-methoxybenzyloxycarbonyl or t-butoxycarbonyl groups, the hemiaminals (CXIV) can be converted into acyloxy-compounds (CXV, X = CR_3COO or CH_3COO)[89,90]:



As already stated, *N*-acyltrifluoroacetaldimines (CXIII) react with many nucleophilic reagents; there is then no necessity to isolate them in a pure form—one can start with their precursors[87–91].

The possibility of using these aldimines in the synthesis of fluorinated aminoacids is self-evident. For this purpose vinylmagnesium bromide was added to them initially[87]. The resulting 3-acylamino-4,4,4-trifluorobut-1-ene (CXVI) was oxidised with potassium permangate to 2-acylamino-3,3,3-trifluoropropionic acid (CXVII), Ac = C_6H_5CO or $C_6H_5CH_2OCO$)[87,92] and then the acyl residue was eliminated. 3,3,3-Trifluoroalanine (CXIX) was obtained in this way[92]:



(CXIX): $R_f = CF_3-$; (CXX) CF_3-CF_2-; (CXXI) $CF_3-CF_2-CF_2-$

This sequence of reactions is also applicable to other perfluoroalkyl residues and has led to the synthesis of 2-amino-3,3,4,4,4-pentafluorobutyric acid (CXX) and 3,3,4,4,5,5,5-heptafluoronorvaline (CXXI)[93].

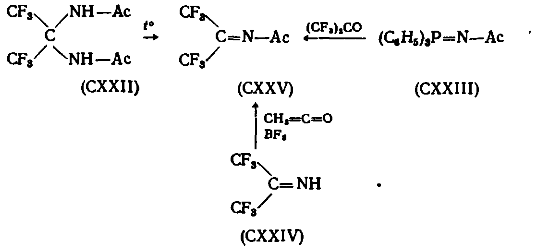
An attempt to use another method for the preparation of fluorinated aminoacids—by the interaction of the sulphone (CXI) with a cyanide—led only to the ethylene derivative as a result of the elimination of the fluoride ion[87].

However, the addition of anhydrous hydrocyanic acid to aldimines (CXIII) made it possible to develop yet another method for the synthesis of 3,3,3-trifluoroalanine. The resulting nitrile (CXVIII) is readily hydrolysed and the subsequent elimination of the acyl group gives the aminoacid (CXIX)[94].

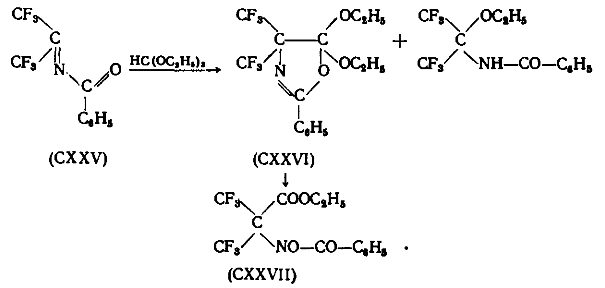
However, this synthesis is not suitable for higher α-perfluoroalkylglycines.

α-Perfluoroalkylglycines (CXIX–CXXI) have pronounced acid properties. pK_{NH_2} for trifluoroalanine (5.61) is much lower than for alanine itself (9.69). In contrast to the usual monocarboxylic 2-monoaminoacids, trifluoroalanine forms a crystalline dicyclohexylammonium salt. It may be acylated at the nitrogen atom and converted to the methyl ester with diazomethane[92,93].

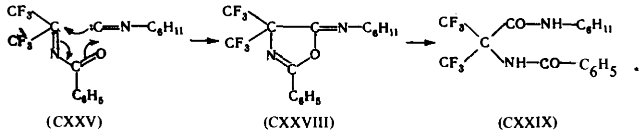
N-Acyl-1,1,1,3,3,3-hexafluoroisopropylideneimines (CXXV) are also very reactive in relation to nucleophilic agents. The acylimino-derivatives of hexafluoroacetone (CXXV) are obtained by the pyrolysis of bisbenzamido-compounds (CXXII, Ac = C_6H_5CO), by the reaction of hexafluoroacetone with triphenylphosphine-*N*-benzoylimine (CXXIII, Ac = C_6H_5CO)[95], and also by the acylation of the imino-derivative of hexafluoroacetone by the action of keten in the presence of boron trifluoride[96]:



The benzoylimino-derivative of hexafluoroacetone (CXXV, Ac = C_6H_5CO) enters into a 1,4-addition reaction with orthoformic ester, yielding 5,5-diethoxy-4,4,-di(trifluoromethyl)-2-phenyl-Δ^2-oxazoline (CXXVI), the hydrolysis of which gives the ethyl ester of 2-benzamido-3,3,3,3′,3′,3′-hexafluoroisobutyric acid (CXXVII)[97]. However, as stated above, the free acid is unstable[56]:

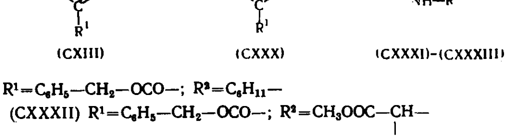


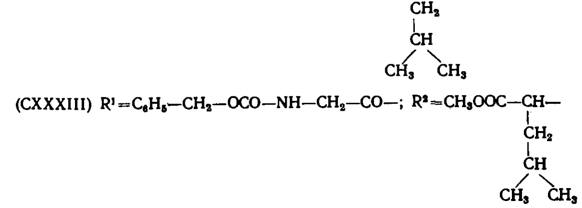
The addition of isonitriles to *N*-acylketimines (CXXV) is of great importance:



The resulting 5-cyclohexyl-4,4,-di(trifluoromethyl)-2-phenyl-Δ^2-oxazoline(CXXVIII) may be hydrolysed to the cyclohexylamide of 2-benzamido-3,3,3,3′,3′,3′-hexafluoroisobutyric acid (CXXIX)[98].

The application of this reaction to *N*-acyltrifluoroacetaldimines (CXIII) makes it possible to synthesise the cyclohexylamide of *N*-benzyloxycarbonyl-3,3,3-trifluoroalanine (CXXXI):





(CXXXI) $R^1=C_6H_5-CH_2-OCO-$; $R^2=C_6H_{11}-$

(CXXXII) $R^1=C_6H_5-CH_2-OCO-$; $R^2=CH_3OOC-CH(CH_2-CH(CH_3)_2)-$

(CXXXIII) $R^1=C_6H_5-CH_2-OCO-NH-CH_2-CO-$; $R^2=CH_3OOC-CH(CH_2-CH(CH_3)_2)-$

Trifluoroalanyl peptides can be obtained directly in this way by introducing into the reaction the isonitriles obtained from esters of *N*-formylaminoacids. The methyl ester of *N*-benzyloxycarbonyl-3,3,3-trifluoroalanyl-L-leucine (CXXXII) was obtained by this procedure. Additional possibilities are provided by the application of *N*-(*N*-benzyloxycarbonylaminoacyl)trifluoroacetaldimines. This results in the ester of the *N*-benzyloxycarbonyltripeptide with trifluoroalanine in the centre of the chain, for example the methyl ester of *N*-benzyloxycarbonylglycyl-3,3,3-trifluoroalanyl-L-leucine (CXXXIII)[92].

Peptides containing trifluoroalanine may be obtained also from *N*-benzyloxycarbonyl-3,3,3-trifluoroalanine by allowing it to react in the usual way with aminoacid esters in the presence of dicyclohexylcarbodi-imide. Trifluoroalanine can also be used in the form of the methyl or t-butyl ester as the ester component in peptide synthesis. However, while the benzyloxycarbonyl group is readily eliminated, it is impossible to hydrolyse the ester group by alkalis. It has been shown for the methyl ester of *N*-benzyloxycarbonyl-3,3,3-trifluoroalanine that the trifluoromethyl group is first hydrolysed to a carboxy-group[93]. Another possibility of synthesising peptides is provided by the sequence of reactions of compounds (CXIII)–(CXVII) using as the acyl residue an aminoacid residue with a protected amino-group[93].

According to the data on the biological activity obtained hitherto, the addition of trifluoroalanine inhibits many micro-organisms, albeit at relatively high concentrations[93]. L-Aminoacid oxidase does not act upon trifluoroalanine, but the addition of trifluoroalanine can prevent it from acting on other L-aminoacids[93].

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Institute of Organic Chemistry,
Higher Technical School, Munich,
German Federal Republic

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Steroids with a Heteroatom in the Nucleus or the Side Chain of the Molecule

G.I.Zhungietu, G.N.Dorofeenko, and B.M.Savin

CONTENTS

Methods for the synthesis of steroid compounds with N, O, and S atoms in the molecular side chain and steroid compounds containing an oxygen atom in the main steroid nucleus, obtained by the reaction of unsaturated steroids with ozone, are discussed. Methods for the preparation of steroids containing a nitrogen atom in the nucleus, synthesised by the reaction with ozone of unsaturated $\alpha\beta$-steroid ketones with subsequent heterocyclisation of the reaction products, are analysed. Methods are described for the total synthesis of steroid heteroanalogues from precursors of comparatively simple structure. Data are presented on the biological activity of the compounds.

The bibliography comprises 79 references.

I. INTRODUCTION

Compounds containing heterocyclic systems condensed with the main steroid nucleus have aroused considerable interest recently[1,2]. Several preparations isolated from them have found wide application in medical practice as anabolic agents[3].

In connection with the study of the physiological activity of modified steroid compounds and the problem of the regulation of cholesterol in the organism, studies have been made recently on the methods for the synthesis of heteroanalogues of steroid systems containing heteroatoms (oxygen, nitrogen, sulphur) in the cyclopentanoperhydrophenanthrene skeleton or in the molecular side chain.

One cannot exclude the possibility that these compounds will prove useful in the fight against various forms of neoplasms of a hormone-dependent type. They may also prove interesting as antihormonal preparations capable of reacting with the same receptor systems as steroids, and behave as antagonists of the latter.

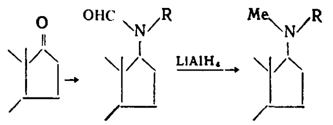
In the fight against the accumulation of cholesterol in the organism as the cause of the development of atherosclerosis, the idea of finding compounds which would be completely or at least partially free of oestrogenic properties appeared attractive. On the other hand, it was found that, when cholesterol is fed to animals, the rate of its synthesis in the liver diminishes[4,5]. The elucidation of the nature of this process might be of undoubted interest for the solution of the problem of cholesterol metabolism in the organism. With this aim in view, work has begun on the chemistry and pharmacology of heteroanalogues of natural steroids.

Although the number of such compounds increases every year, insufficient attention has been devoted to them in the literature, which makes it difficult to become familiar with the results achieved in this field.

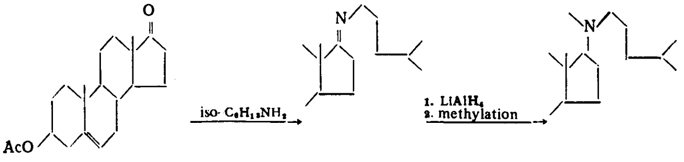
The desire to fill this gap to some extent led the authors to write this review. However, it must be remembered that this review deals very briefly only with compounds which are close analogues of steroids and does not include data on numerous heterocyclic homosteroids containing expanded rings A, B, C, and D.

II. COMPOUNDS WITH HETEROATOMS IN THE SIDE CHAIN

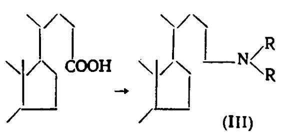
This group includes aza- and oxa-derivatives of steroids containing heteroatoms in the side chain and also compounds of type I with secondary amino-groups in rings A, B, and D and obtained by the Leuckart reaction[6]:



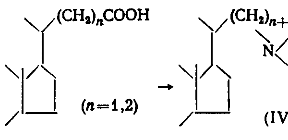
(I)



Lettré et al.[7] obtained 25-azacholesteryl acetate from the acetate of Δ^5-cholenic acid with subsequent reduction of its dimethylamide with $LiAlH_4$. This carefully developed method for the conversion of carboxylic acids via their chlorides and amides and the reduction of the latter with metal hydrides gives as a rule high yields of products and has been widely used by other investigators, in particular for the synthesis of a number of azacholestane derivatives of type (III)–(V)[8-10]:



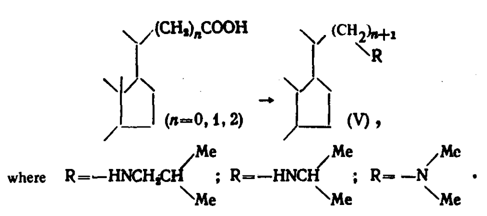
(III)



(n=1,2)

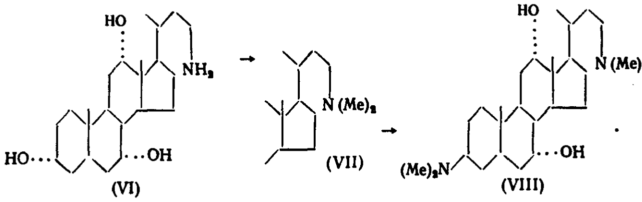
(R=H, Me, Et)

(IV)



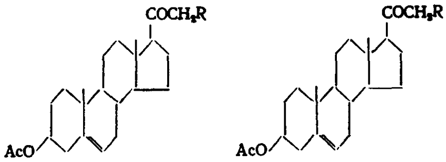
25-Azacoprostane was obtained in the same way from the corresponding cholane derivative[7].

Bisdimethylaminocholane (VIII) was synthesised from cholic acid azide, which was reduced to aminotrihydroxycholane and the amine was then methylated further to give (VII). Subsequent Oppenauer oxidation of (VII), reduction to the oxime, reduction of the oxime, and methylation of the resulting amine gave (VIII):



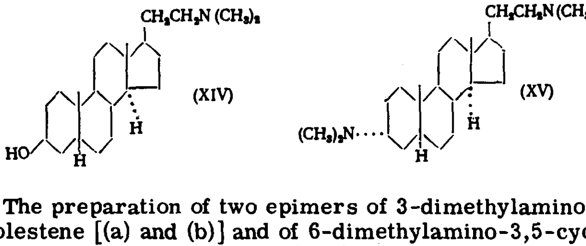
7α,12α-Dihydroxy-3-oxocholanic acid was converted in the same way into 3,17-bisdimethylaminoandrostane[7,11].

A series of 21-aminosteroids, obtained by the interaction of 21-iodo-derivatives (IX)[12] and (X)[13] with various secondary amines proved to be very interesting physiologically[14]:

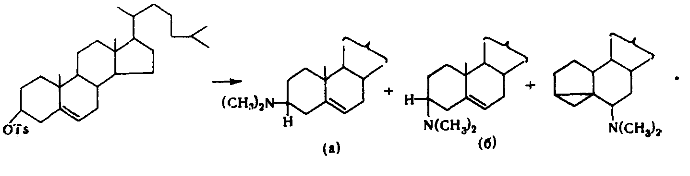


(X) R=I(Ref.13)
(XII) R=N(Me)$_2$ · HCl
(XIII) R=N-morpholino-HCl
(IX) R=I(Ref.12)
(XI) R=$\overset{+}{\text{N}}$(Me)$_3$I$^-$

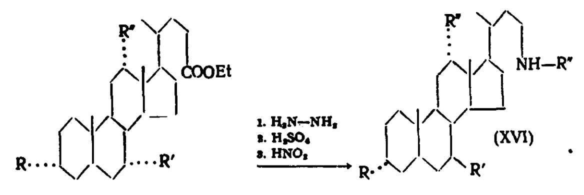
In the search for antibacterial agents 21-dimethylaminoallopregnan-3β-ol (XIV) and 3α,21-dimethylaminoallopregnane (XV) were synthesised[15]:



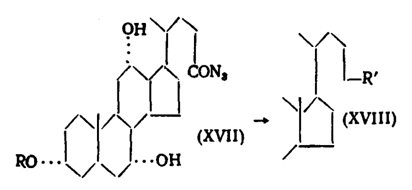
The preparation of two epimers of 3-dimethylaminocholestene [(a) and (b)] and of 6-dimethylamino-3,5-cyclocholest-5-ene by the action of $(CH_3)_2NH$ on 3β-tosyloxycholest-5-ene has also been described[16]. Hydrogenation of compounds (a) and (b) in acetic acid gave 3-dimethylaminocholestane, which was identified by synthesis—by the action of dimethylamine on 3α-tosyloxycholestane:



Certain 23-amino-derivatives (XVI) have been obtained by the Schmidt reaction from derivatives of cholanoic acid[17,18]:



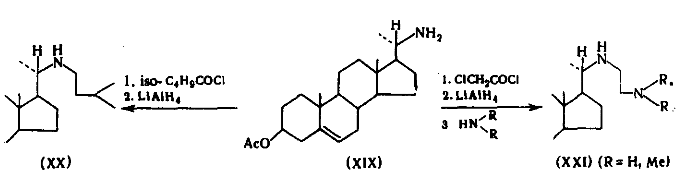
Certain amines (XVIII) were synthesised from cholic acid azide (XVII)[19]. The condensation of compound (XVII) with secondary amines gave the corresponding amides, which were then reduced to the tertiary amines (XVIII)[20]:



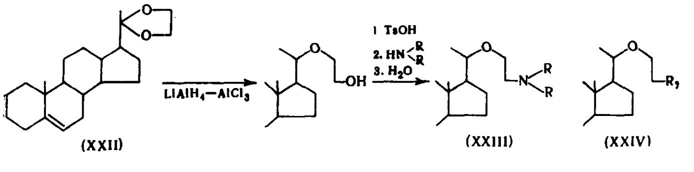
[R′ = piperidino, N-morpholino, N(Me)$_2$, N(Et)$_2$].

(R = Ac, COEt, or veratroyl)

The preparation of 22-azacholesterol (XX)[9] and 22,25-diazacholesterol (XXI)[22] from 20-amino-Δ^5-pregnen-3β-yl acetate (XIX) has been described[21]:

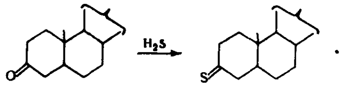


Crabbe and coworkers[23] obtained 25-aza-22-oxacholesterol (XXIII) and a number of its analogues (XXIV) from the ethyleneketal (XXII) by the following mechanism:



where R = CH_2-N-piperidine or CH_2I(F).

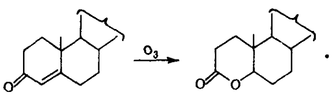
Of other studies in this field, mention should be made of the synthesis of steroids containing a sulphur atom. Thus Djerassi and coworkers synthesised[24] 21-thiolacetates—analogues of deoxycorticosterone, Reichstein's substance "S", and cortisone. These syntheses were achieved by the action of CH_3COSH on the corresponding diazoketones or by treating 21-hydroxy-20-ketones with p-toluenesulphonyl chloride and subsequent interaction with NaI and CH_3COSK. Thio-derivatives were obtained by the reaction of hydrogen sulphide with oxosteroids in the presence of $ZnCl_2$:[25]



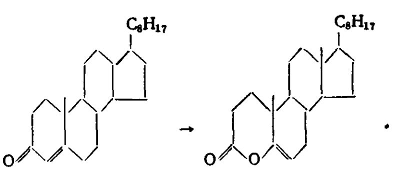
III. COMPOUNDS WITH HETEROATOMS IN THE STEROID NUCLEUS

1. Syntheses Based on Natural Compounds

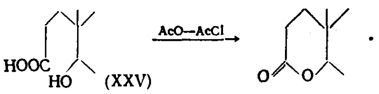
A large group of steroid oxygen-containing heterocyclic compounds were synthesised by the oxidation of Δ^4-3-oxosteroids with persulphuric acid or hydrogen peroxide[26]. However, best results were obtained by the reaction of oxosteroids with ozone in chloroform or acetic acid[27]:



The cleavage of ring A in steroids by the reverse Michael reaction has been described for cholest-4-en-3-one with the isolation of an enol lactone as an intermediate[28]:

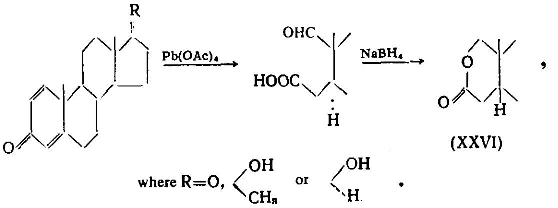


A number of 4-oxasteroids have been obtained[29] by the cyclisation of hydroxyacids (XXV):



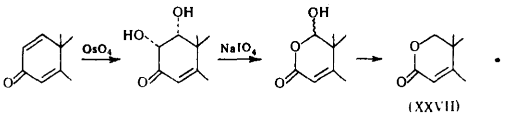
(XXV)

Interesting compounds were synthesised by replacing C_2 of the steroid ring by oxygen[30]:



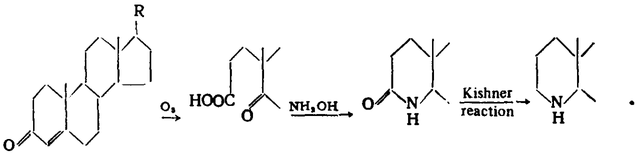
(XXVI)

The corresponding Δ^4-analogues are obtained with much greater difficulty and with much lower yields[30,31]:



(XXVII)

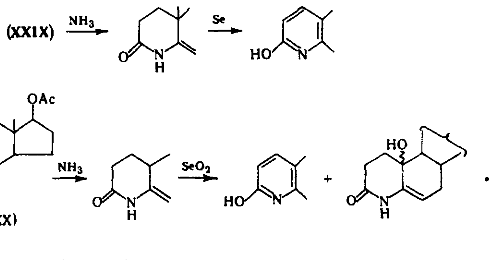
The main method for synthesising compounds containing a nitrogen atom in rings A and B consist in the reaction of ozone with $\alpha\beta$-unsaturated ketones and subsequent cyclisation of the oxidation products. This method was employed for the first time by Bolt as early as 1938[32]:



(XXVIII) (XXIX)

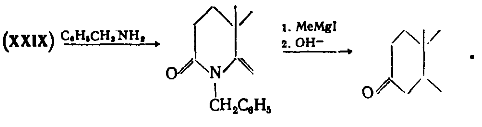
R = iso-C_8H_{17} or OAc.

For a long time this work was ignored until a more profound investigation of the synthetic heteroanalogues of steroids was begun. In 1959 a large series of 4-azasteroids was obtained by the reaction of the ketoacids (XXIX) and lactones of type (XXX) with ammonia in benzene according to the mechanism[33,34]:



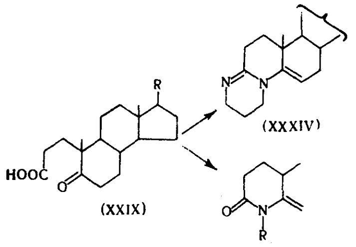
(XXX)

The reaction of (XXIX) with benzylamine gave a good yield of (XXXI), the α-piperidine ring of which is readily converted into ring A of the steroid to be synthesised[35]:



(XXXI) (XXXII)

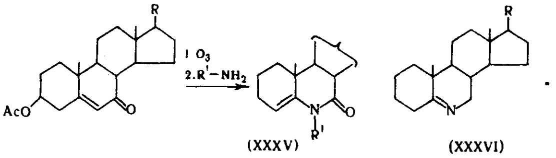
Many N-substituted natural compounds (XXXIII) were obtained by the reaction of the acid (XXIX) with various amines[27,36-39]. Treatment of (XXIX) with 1,3-diaminopropane gives the 4-aza-derivative (XXXIV):



(XXXIV) (XXIX) (XXXIII)

where R = methyl, benzyl, NH_2, OH, or CH_2CH_2OH.

6-Azasteroids containing a nitrogen atom in ring B [(XXXV) and (XXXVI)] were also obtained by reaction with ozone followed by heterocyclisation[30,31,40-44]:

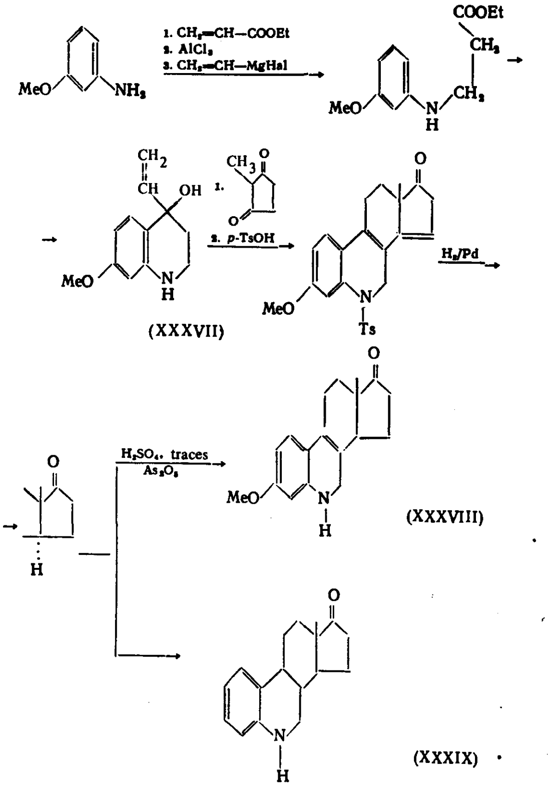


(XXXV) (XXXVI)

2. Total Synthesis of Steroid Heteroanalogues

The method of synthesis of oestrogens by the condensation of 6-methoxy-1-vinyl-1-tetralol with methylcyclopentanedione, extensively developed by Torgov in the Laboratory of Steroid Chemistry at the Institute of the Chemistry of Natural Compounds (IKhPS) of the USSR Academy of Sciences[45], proved to be suitable for the preparation of a wide variety of steroid heteroanalogues.

The tetrahydroquinolinone derivative (XXXVII)[46], obtained from m-anisidine, was used to synthesise the methyl esters of 1-azaequilenin (XXXVIII) and 6-azaoestrone (XXXIX)[46-53]:

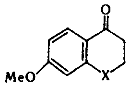


(XXXVII)

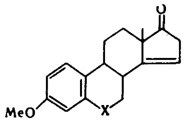
(XXXVIII)

(XXXIX)

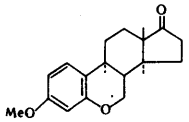
Chromanone (XL)[54] was converted by a similar mechanism into 6-oxaoestrone (XLI) and (XLIII) was obtained from 7-methoxythiachroman-4-one (XLII)[55]:



(XL) X=O
(XLII) X=S

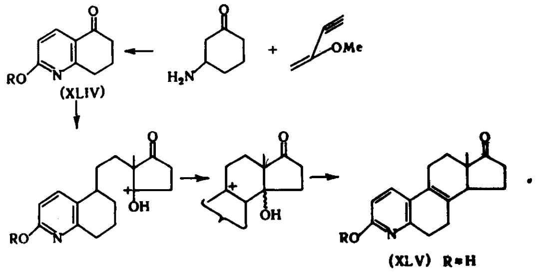


(XLIII)



(XLI)

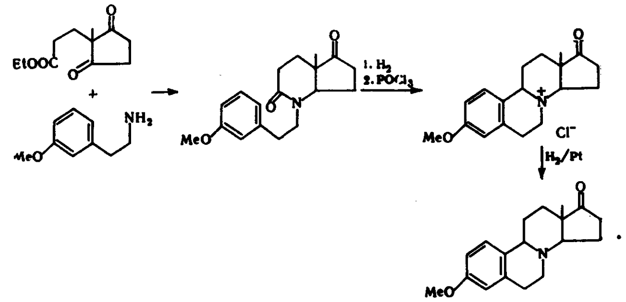
Meyers and coworkers described a three-stage synthesis of the methyl ether of *dl*-8-azaoestrone and its 14β-isomer from 1-(2-hydroxy ethyl)-2-methoxy-1,2,3,4-tetrahydroisoquinoline by condensation with 2-methylcyclopenta-1,3-dione[56]. 4-Aza-8,14-bisdehydrooestrone (XLV) was obtained similarly from pyridine (XLIV). The much greater difficulty of the reaction when R = H compared with the case where R = Et can be explained, according to the authors, by the preliminary rearrangement of the exocyclic double bond to an endocyclic double bond[57,58]:



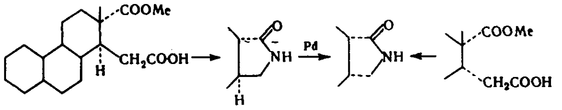
(XLIV)

(XLV) R=H
(XLVI) R=Et

Analogues of oestrone and D-homo-oestrone containing a nitrogen atom in the 8-position were obtained by the following mechanism[59,60]:

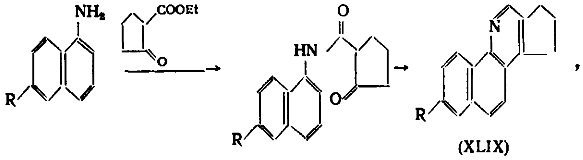


As early as 1950, in experiments designed to determine the configuration of the C–D junction in deoxy- and isodeoxy-equilenine, their 16-aza-analogues (XLVII) and (XLVIII) were obtained[61]:



(XLVII) (XLVIII)

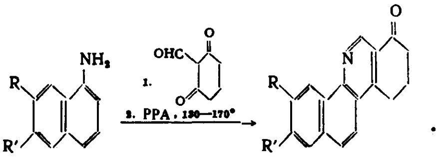
Other heterocyclic steroid analogues have also been described: 1-azachrysene[62] and 6-azachrysene, 1-azapyrene, and 3,4-benzo-5-azaphenanthrene[63], as well as the 11-aza-derivative (XLIX)[64]:



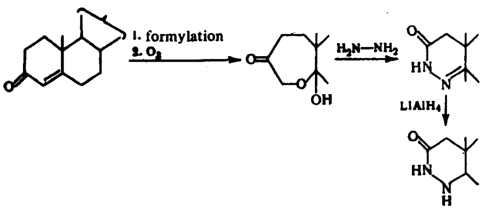
(XLIX)

where R = H or OMe.

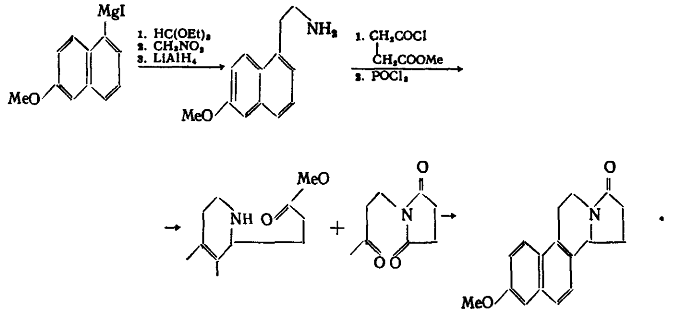
The attempts to introduce an oxo-group into (XLIX) by oxidation with SeO$_2$ and CrO$_3$ were unsuccessful. A compound of this type was obtained somewhat later in a different way[65]:



Tetrahydropyridazinone derivatives of steroids containing two nitrogen atoms in ring A have been described[66]:

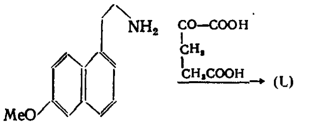


Recently the synthesis of a 13-aza-steroid analogue has been reported: the methyl ether of 13-aza-18-norequilenin (L) was obtained by the following mechanism[67]:



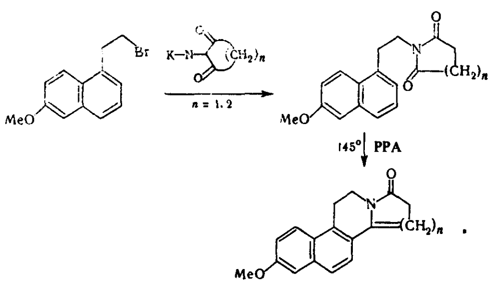
(L)

The same compound can also be prepared by the single-stage condensation of (LI) with α-oxoglutaric acid in boiling acetic acid but the yield is then much lower[68]:

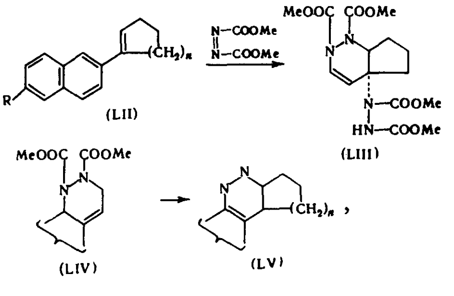


(LI)

A different synthesis has also been proposed for analogues of (L)[69]:

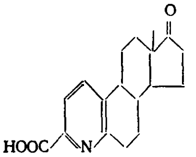


The addition of pseudodienes of type (LII)[70] [wrong reference (Ed. of Translation)] to the dimethyl azodicarboxylate leads to the formation of the adducts (LIII) and (LIV) which are converted by hydrolytic decarboxylation with hydrazine hydrate and oxidation with mercury(II) oxide into the 11,12-diaza-derivative (LV)[71]:



where R = H or MeO and n = 1 or 2. 7,8,9,10-Tetrahydronaphtho[1,2-*c*]cinnoline (LV, R = H) was obtained even earlier[72].

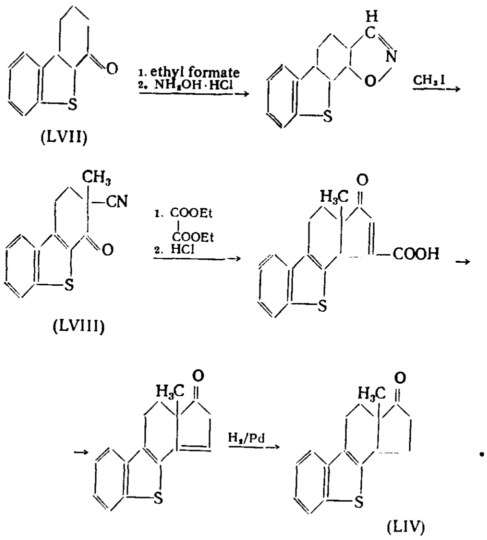
It is noteworthy that 17-oxo-4-azaoestrane-3-carboxylic acid (LVI) has been found among the products of the microbiological conversion of oestrone by *Nocardia sp.*[73]:



(LVI)

Steroid heteroanalogues containing a sulphur atom in their skeleton are of undoubted interest.

Collins and coworkers[74] obtained a thiophen analogue of 3-deoxyequilenin from 4-oxo-1,2,3,4-tetrahydrobenzothiophen (LVII), which is in turn obtained by succinylation of thianaphthene, the reduction of the resulting ketoacid, and its cyclisation to the ketone (LVII). The hydroxymethylation of (LVII) and cyclisation with hydroxylamine hydrochloride give rise to an isoxazole derivative, the reaction of which with CH$_3$I yields the methylketonitrile (LVIII). The latter reacts with ethyl succinate and after hydrolysis is converted into a ketoacid. The decarboxylation of this acid in pyridine and the reduction of the product with hydrogen over metallic palladium gave 3-deoxythiaequilenin (LIV):



In an assessment of the scope of the synthesis of steroids containing a heteroatom in the nucleus preference should probably be given to methods of total synthesis, taking into account the availability of the starting materials.

IV. BIOLOGICAL ACTIVITY

1. Steroids with a Heteroatom in the Side Chain

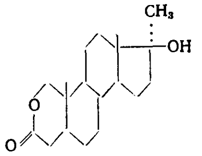
Among compounds containing an amino-group in the side chain, 21-aminosteroids proved to be physiologically active. Biological tests showed that some of them [(XI) and (XII)] fully inhibit the growth of *B. subtilis* and (XIII) inhibits the growth of *Aspergillus niger*. The hydrochlorides of 23-amino-3α-hydroxy- and 23-amino-3-oxocholanoic acids proved to be active against Gram-positive micro-organisms[17].

Certain oxa- and aza-derivatives of steroids were found to have marked cholesterolemic activity. Thus 20,25-diazacholesterol reduces the cholesterol content in blood by 30%[75]. Possibly it also acts on one of the receptors as a cholesterolmimetic agent[76]. 25-Aza-22-oxacholesterol reduces the cholesterol content in blood by 38% and 25-aza-21-nor-20-oxacholesterol reduces the cholesterol level by 47%[77].

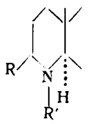
It is noteworthy that all these preparations interrupt the biosynthesis of cholesterol at the stage of its formation from desmosterol (24-dihydrocholesterol) and lead to the accumulation of the latter in the blood. As a result, the total amount of sterols is maintained at an approximately constant level[78,79].

2. Steroids with a Heteroatom in the Nucleus

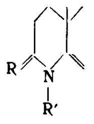
In general the biological activity of steroids containing an oxygen atom in ring A is comparable to that of the usual steroids[30]. Nevertheless (LV) proved to be a more effective anabolic agent than 17β-hydroxymethyl-17α-methylandrostan-3-one[3]:



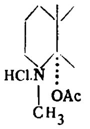
Of the compounds containing a nitrogen atom in ring A of the steroid skeleton, the following should be mentioned:



(LVI) $R=R'=CH_3$
(LVII) $R=Bz$, $R'=CH_3$
(LXI) $R=H$, $R'=Et$



(LVIII) $R=O$, $R'=\overset{+}{N}(CH_3)_3Et\ I^-$
(LX) $R=O$, $R'=Ph$.



(LXI)

Compounds (LVI)–(LIX) block the conversion of desmosterol into cholesterol, (LX) intensifies the synthesis of cholesterol, (LXI) has an antimicrobial activity, and (LXII) causes the expansion of coronary vessels.

Derivatives of 6-azasteroids containing a nitrogen atom in ring B also exhibit a physiological activity. Tests with 6-azacholesterol and 6-azacholestane revealed their intense cytotoxic activity[42]. The same compounds containing an acetate group at the 17-carbon atom have androgenic properties. They stimulate the activity of the hypophysis and exhibit antioestrogenic and antiprogestational activity[43]. Among compounds containing a sulphur atom in the nucleus, none have so far been found with appreciable physiological activity.

The data discussed show that many steroids containing heteroatoms in the nucleus or in the side chain exhibit physiological activity. There is no doubt that further progress in this very interesting branch of steroid chemistry will yield new important results and discoveries.

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Institute of Chemistry, Academy
of Sciences of the Moldavian SSR

Rostov-on-Don State University

Kharkov Endocrine Preparations
Factory

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Advances in the Polycondensation Methods for the Synthesis of Thermostable Polymers

S.V.Vinogradova and V.V.Korshak

The review deals with the properties and the methods of synthesis by non-equilibrium condensation of heat resistant and thermostable polymers which have found considerable practical application in various branches of engineering.
The bibliography includes 42 references.

The growing requirements for polymeric materials by many branches of modern engineering have, in the last decade, attracted much attention to polymers with enhanced heat resistant and thermostable properties. Heat resistance will be understood as the limiting temperature at which the polymer can retain a particular mechanical strength and thermal stability is defined as the limiting temperature which a given polymer can withstand without chemical change, mainly decomposition.

Classical examples of thermostable polymers known for a long time are, for example, polytetrafluoroethylene and organosilicon polymers of the polydimethylsiloxane type. However, despite their high thermal stability, they cannot be used successfully in many cases.

Recently it has become necessary to obtain new types of heat resistant materials which retain high strengths under load at elevated temperatures. Promising materials of this kind are polymers the macromolecules of which consist of aromatic or heterocyclic units. However, since the chains of such a structure are very rigid, many of these polymers cannot be used as starting materials for the preparation of films, fibres, and other articles for which a certain elasticity is needed. Therefore a natural solution of the problem was to synthesise polymers the macromolecules of which contain, in addition to the rigid phenylene and heterocyclic rings, more flexible bonds for example, esters and ether bonds.

The principal method for the synthesis of the majority of the known heat resistant and thermostable polymers is polycondensation, primarily non-equilibrium polycondensation. Until recently polycondensation methods, unlike polymerisation techniques, were not subdivided into various types. When fairly extensive experimental data on various polymerisation processes were accumulated and treated from a general standpoint, various types of the process became distinguishable, such as radical, cationic, anionic, and ionic–coordination polymerisation, each of which became established in polymer chemistry and occupies an honourable place among its techniques.

A similar development is being undergone by polycondensation reactions too. A general treatment of extensive experimental data on polycondensation makes it possible to subdivide polycondensation processes into at least two different types, namely equilibrium and non-equilibrium polycondensation processes which differ in the types of reaction occurring[1,2].

A principal feature of non-equilibrium polycondensation is the absence of degradation of the polymer by a low-molecular-weight polycondensation product and in most cases the absence from the polycondensation process also of other degradative exchange reactions.

Since the equilibrium constant for the process

$$A+B\underset{k_2}{\overset{k_1}{\rightleftarrows}}C+D$$

is defined by the equation

$$K=\frac{k_1}{k_2}=\frac{[C][D]}{[A][B]},$$

it follows that high equilibrium constants should be characteristic of irreversible processes and hence also of non-equilibrium polycondensation, i.e. $k_1 \ll k_2$, or $k_1 \to \infty$, or an infinitesimal value of k_2.

The absence from the polycondensation process of degradative exchange reactions, which is responsible for the irreversibility of the process, may be due to various causes: (a) owing to the occurrence of the process at fairly low temperatures where exchange reactions do not take place at all and the starting materials are sufficiently reactive to form the polymer under such conditions; (b) owing to the formation in the polycondensation process of a polymer with a chemical structure such that it is incapable of degradative reactions with a low-molecular-weight polycondensation product, with the starting materials, or with the growing or completed macromolecules.

In contrast to equilibrium polycondensation, which has been investigated fairly thoroughly, non-equilibrium polycondensation is a little known process. Reactions of this type have been investigated only in recent years. So far comparatively few cases of non-equilibrium polycondensation have been studied in detail and the main features of these processes are still not altogether clear, although a fairly large number of cases of non-equilibrium polycondensation are known. Table 1 presents a far from complete list of such reactions, many of which have been used successfully for the synthesis of heat resistant polymers. It is not possible to examine them all in detail in this review, but some of them will be considered.

One of the classes of heat resistant and thermostable polymers to which much attention has been drawn in the last decade are heterochain esters of dihydric phenols—polyarylates. Polyarylates of dicarboxylic aromatic acids have the most interesting properties[3]. Table 2 presents data on the softening temperatures and the thermal stability of some of these polymers, which show that these are highly heat resistant and thermostable macromolecular compounds[4-7].

Since in the synthesis of polyarylates one of the reaction components is a dihydric phenol the hydroxy-groups of which are less reactive to acids than those of aliphatic polyhydric alcohols, it proved useful to employ the chlorides of dicarboxylic acids as the acid reagents in the synthesis of polyarylates[3]. The use of acid reagents of this type made possible successful polycondensation in solution and at interfaces. In general the availability of these two methods of polycondensation is important for the synthesis of heat resistant high-melting polymers, since polycondensation can be continued to a high degree of completion of the process without decomposition of the polymer formed: because of the high melting point of many heat resistant polymers, including polyarylates, polycondensation in the melt would have to be carried out at 300–500°C and sometimes at even higher temperatures.

Thus the main method for the synthesis of heat resistant polyarylates is the reaction of dicarboxylic acid chlorides with dihydric phenols, which can be achieved in three versions.

(a) By the interaction of the dicarboxylic acid with the dihydric phenol in solution at an elevated temperature:

$$x\,ClOCRCOCl + x\,HOArOH \rightarrow [-OCRCOOArO-]_x + 2x\,HCl.$$

(b) By the interaction of the dicarboxylic acid with the dihydric phenol in solution at room or a relatively low temperature in the presence of a tertiary amine:

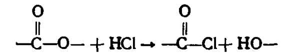
$$x\,ClOCRCOCl + x\,HOArOH \xrightarrow{NR'_3} [-OCRCOOArO-]_x + 2x\,NR'_3 \cdot HCl.$$

(c) By the interfacial polycondensation of the dicarboxylic acid chloride with the dihydric phenol:

$$x\,ClOCRCOCl + x\,HOArOH + 2x\,NaOH \rightarrow [-OCRCOOArO-]_x + 2x\,NaCl.$$

Until recently the polycondensation of dicarboxylic acid chlorides with dihydric phenols, carried out at high temperatures, was automatically classified as an equilibrium polycondensation process. However, studies in recent years at the Institute of Organic Derivatives of the Elements of the USSR Academy of Sciences in collaboration with the Laboratory of the Kinetics of Polymerisation Processes at the Institute of Chemical Physics of the USSR Academy of Sciences showed that this is not so.

The equilibrium in the reaction



$$-\overset{\overset{O}{\|}}{C}-O- + HCl \rightarrow -\overset{\overset{O}{\|}}{C}-Cl + HO-$$

was studied using as an example the interaction of hydrogen chloride with the polyarylate of terephthalic acid and 9,9-di-(4-hydroxyphenyl)fluorene and with model compounds such as 9,9-di-(4-benzoxyphenyl)fluorene and phenyl benzoate[8]. The reactions were carried out at 220°C in ditolylmethane in a stream of dry hydrogen chloride and also under pressure, which ensured the presence in the reaction mixture of a definite amount of hydrogen chloride.

Table 1. Examples of starting materials employed in non-equilibrium polycondensations and the types of polymers thus obtained

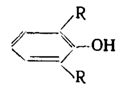
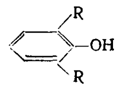
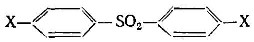
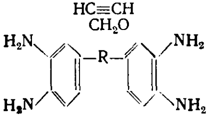
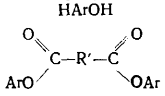
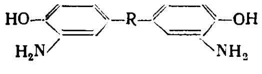
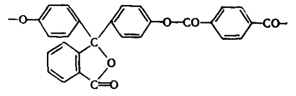
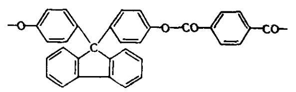
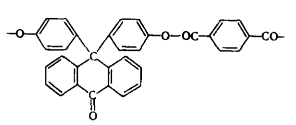
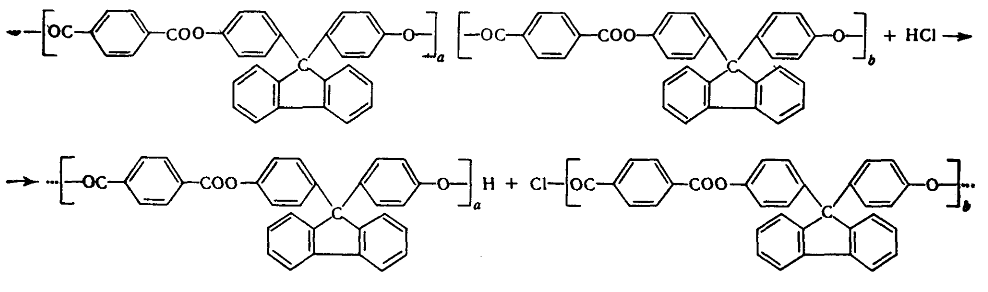
First component	Second component	Type of compound formed
$ClOCRCOCl$	$HOArOH$	polyarylate
ClO_2SRSO_2Cl	$HOArOH$	polysulphonate
$RPOCl_2$	$HOArOH$	polyphosphonate
$ClOCRCOCl$	$H_2NR'NH_2$	polyamide
ClO_2SRSO_2Cl	$H_2NR'NH_2$	polysulphonamide
$ClOCOROCOCl$	$H_2NR'NH_2$	polyurethane
$ClOCRCOCl$	$HOOCR'COOH$	polyanhydride
ClO_2SRSO_2Cl	$HArH$	poly(arylene sulphone)
$NaOArONa$	$XArX$	polyether
		polyether
$NaOArONa$		polyethersulphone
$HArH$	$ClRCl$	polyarylenealkane
C_6H_6	C_6H_6	polyphenylene
$HOOCRCOOH$	H_2NNH_2	polyaminotriazole
$HC{\equiv}CH$	$HC{\equiv}CH$	poly-yne (carbyne)
CH_2O	$HArOH$	polyphenol
		polybenzimidazole
	$ClOCR'COCl$	polybenzoxazole

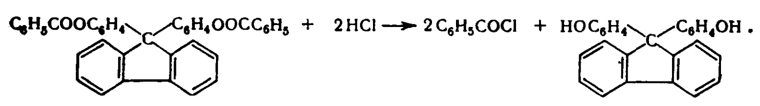
Table 2. Polyarylates

Repeating unit	Softening temp., °C (from thermomechanical curve)	Temp. of onset of decomposition, °C (inert medium)
	340	350—360
	350	350—360
	360	350—360

It was found that, on heating 1 M solutions of the polymer in an open system in a stream of dry hydrogen chloride for 5 h at 220°C, the molecular weight of the polymer remained unchanged. When phenyl benzoate and 9,9-di-(4-benzoxyphenyl)fluorene were heated under the same conditions, neither phenol nor benzoyl chloride were detected in the reaction mixture. This showed that the following reactions do not occur:



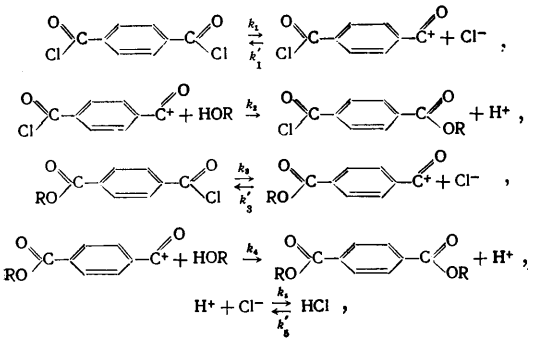
$$C_6H_5COOC_6H_5 + HCl \rightarrow C_6H_5COCl + C_6H_5OH;$$



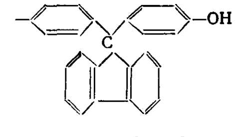
On the other hand, measurement of the equilibrium constant for the reaction of phenyl benzoate with hydrogen chloride in a closed system showed that at 40°C it is 2.35×10^{-4} and at 220°C 4.48×10^{-3}. Values of the same order of magnitude were also found by Polish investigators in a study of the equilibrium in the reaction of 2,2-di-(4-hydroxyphenyl)propane and its dichloroformate derivative in nitrobenzene at 60°, 80°, and 100°C.[9]

The equilibrium constants for equilibrium polycondensation processes are known to amount usually to several units. Thus the above data show that the equilibrium in the interaction of dicarboxylic acid chlorides with dihydric phenols is strongly displaced to the right. This suggests that the interaction is largely a non-equilibrium process for the low-molecular-weight polycondensation product.

More detailed studies were also made at the Institute of Organic Derivatives of the Elements and the Institute of Chemical Physics of the kinetics of the interaction of terephthalic acid chloride with 9,9-di-(4-hydroxyphenyl)fluorene under conditions typical for the synthesis of polyarylates by high-temperature condensation, namely in the temperature range 150–200°C using ditolylmethane, dowtherm†, and nitrobenzene as solvent[10]. It was found that the order of the reaction based on initial rates is 1.5: the reaction is first order with respect to the dihydric phenol and of order 0.5 with respect to the acid chloride. Analysis of the kinetic data and measurements of the conductivity of the system showed that the interaction has the following ionic mechanism:



where R =

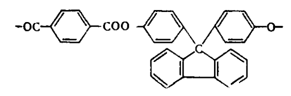


or the residue of the macromolecule.

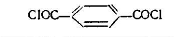
The first reaction stage is equilibrium ionisation of one of the acid chloride groups. The resulting acylium ion interacts with the phenol or recombines with a chloride anion. The second stage is the equilibrium ionisation of the acid chloride group in a mixed ester–acid chloride species and its further interaction with the phenol.

Despite the fact that the polycondensation of dicarboxylic acid chlorides with dihydric phenols is, as mentioned above, an irreversible process for the low-molecular-weight polycondensation product (hydrogen chloride), the chain propagation reaction is nevertheless accompanied also by various degradative exchange reactions between the polymer molecule formed and the starting materials and also between the macromolecules themselves, because the process is carried out at an elevated temperature. Owing to the higher stability of polyarylates to chemical processes as compared with other types of polyesters, these reactions take place to a lesser extent in the above series of polyesters but they do occur and must be taken into account in an examination of the general features of the formation of polyarylates by high-temperature polycondensation.

Table 3. Degradation of the polyarylate



by various reagents

Duration of degradation, h	η_{intr} in tricresol before and after degradation					
	hydroxyphenylfluorene				isophthalic acid	
	argon	HCl	argon	HCl	argon	HCl
0	0.80	0.8	0.80	0.80	0.80	0.80
2	0.74	0.60	0.77	0.74	0.80	0.72
4	0.71	0.50	0.75	0.65	0.73	0.67
10	0.58	0.40	0.69	0.46	0.65	0.59
20	0.49	—	0.63	—	0.64	—

* The degradation was carried out in a 10% solution of the polymer in ditolylmethane at 220°C.

Table 3 presents the results obtained for the degradation of poly[9,9-di-(4-hydroxyphenyl)fluorene terephthalate] by various chemical agents, from which it is clear that polyarylates do undergo exchange reactions[11]. It is interesting that the low-molecular-weight polycondensation product (hydrogen chloride) catalyses all types of degradative exchange processes in the synthesis of polyarylates by high-temperature polycondensation. It is also noteworthy that a tendency has been found for a narrowing of the molecular weight distribution of polyarylates (Table 4) as a result of degradative exchange reactions during polycondensation on heating[12].

Table 4. Variation of the coefficient of polydispersity (M_w/M_n) of the polyarylate as a result of degradation at 220°C

Degrading agent	Duration of reaction, h	Gas stream	M_ω/M_n
None	0		2.09
Hydroxyphenylfluorene	10	HCl	1.22
Hydroxyphenylfluorene	10	Ar	1.68
Hydroxyphenylfluorene	20	Ar	1.48
	20	Ar	1.45

Very interesting results were obtained at the Institute of Organic Derivatives of the Elements of the USSR Academy of Sciences in studies on the effect of the reaction medium on the synthesis of heat resistant polyarylates. In particular, it was established that the physicomechanical

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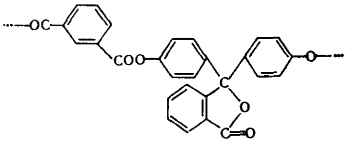
† A eutectic mixture of phenyl ether and biphenyl (Ed. of Translation).

properties of the polyarylate of isophthalic acid and phenolphthalein, the so called polyarylate F-1, depend appreciably on the solvent in which the polycondensation is carried out[13].

The chemical structure of the polyarylates of phenolphthalein and aromatic dicarboxylic acids is responsible for the high rigidity of the macromolecules:



Therefore in the synthesis of phenolphthalein polyarylate in ditolylmethane, which does not dissolve the polymer formed, the free energy of formation of coiled macromolecules should be lower than the free energy of formation of extended macromolecules (there are fewer points of contact between the coiled macromolecule and the insoluble polymer). This leads to preferential synthesis of the globular forms of the macromolecule, which is responsible for the globular type of the supermolecular structure of the phenolphthalein polyarylate synthesised in ditolylmethane. On the other hand, in the synthesis of phenolphthalein polyarylate in good solvents, for example, in 1-chloronaphthalene or nitrobenzene, extended macromolecules are formed preferentially. As a result packets of macromolecules and other fibrillar supermolecular structures arise. Polymers with this structure naturally possess better physicomechanical properties than the corresponding polymer with a globular supermolecular structure, as can be seen from the data presented in Table 5.[13]

Table 5. Properties of polyarylate F-1

Property	Medium in which polymer was obtained		
	ditolylmethane	1-chloronaphthalene	
Supermolecular structure	globular	fibrillar	
Molecular weight	28 000	28 000	48 000
Softening temperature, °C	270	290	300
Tensile strength, kgf cm^{-2}	640	740	780
Elongation on rupture, %	10—20	80	100
Specific impact strength, kg cm cm^{-2}	2—3	10	20

Thus in the synthesis of polymers with rigid macromolecular chains, which are, incidentally, typical for many heat resistant polymers, it is necessary to choose the correct reaction medium bearing in mind its effect on the selection of particular macromolecular conformations during the synthesis itself. In the synthesis of heat resistant polymers capable of crystallisation, the polycondensation conditions are sometimes very important. This will be illustrated by the synthesis of the crystallisable polyarylate of 9,9-di-(4-hydroxyphenyl)-10-anthrone and terephthalic acid[14]. Table 6 shows that, by varying the reaction temperature, it is possible to obtain either a crystalline or an amorphous polymer, which in turn affects its properties[14]. In the synthesis of crystallisable polymers it is necessary to take into account also other factors in the reaction conditions, such as the rate of heating and cooling of the reaction mass, the concentration of the reaction mixture, and methods for the isolation and purification of the polymer.

For polyarylate as an example, we considered one of the cases of non-equilibrium polycondensation which leads to heat resistant and thermostable polymers, the process involving heating in an organic solvent. Below we shall return to several cases of the synthesis of heat resistant polymers under such conditions.

In the last decade the synthesis of heat resistant polymers by non-equilibrium polycondensation under mild temperature conditions, virtually without heating, has attracted much attention. This process became possible owing to the discovery of methods for the synthesis of polymers such as interfacial polycondensation and low-temperature polycondensation in solution.

Table 6. Effect of the conditions of synthesis of the polyarylate obtained from hydroxyphenylanthrone and terephthalic acid on its properties and structure

Polycondensation conditions			η_{intr}, dl g^{-1} (Ph-TCE)*	Softening temp., °C (in a capillary)	Organic liquid dissolving the polymer	Structure
°C	duration, h	medium				
220	11—12	Sovol	0.42	does not melt, darkens at 450°	mixture of phenol and TCE	crystalline
220	10	1-chloronaphthalene	0.90	ditto	ditto	ditto
250	5	" "	1.70	380—400	tricresol, TCE, dichloroethane, $CHCl_3$, CH_2Cl_2, dioxan, cyclohexanone, etc.	amorphous structure predominates
320	1	Sovol	0.68	350—380	ditto	amorphous

* Ph = phenol and TCE = tetrachloroethane.

We shall not consider in detail interfacial polycondensation as a non-equilibrium polycondensation method since this has been extensively discussed in recent years[15,16]. We shall only note that its essential feature involves reaction between the starting materials when the solution of one of the active initial components (for example the dicarboxylic acid chloride) in an organic solvent is brought into contact with an aqueous (usually alkaline) solution of the second component (for example a diamine or a dihydric phenol). The reaction takes place at atmospheric pressure, at a low, usually room temperature and is very rapid. Under optimum conditions, the yield of polymers synthesised by this method is a rule high and so is the molecular weight. The range of heat resistant polymers synthesised by this method is fairly wide. These are heat resistant polyamides, polyarylates, polyanhydrides, polysulphonamides, polyamidoarylates, etc., based mainly on compounds with aromatic rings in the molecules:

$$x\,\mathrm{ClOCRCOCl} + x\,\mathrm{H_2NR'NH_2} \xrightarrow{\mathrm{NaCH}} [-\mathrm{OCRCONHR'NH}-]_x + 2x\,\mathrm{NaCl},$$

$$x\,\mathrm{ClSO_2RSO_2Cl} + x\,\mathrm{H_2NR'NH_2} \xrightarrow{\mathrm{NaOH}} [-\mathrm{SO_2RSO_2NHR'NH}-]_x + 2x\,\mathrm{NaCl},$$

$$x\,\mathrm{ClOCRCOCl} + x\,\mathrm{HOArOH} \xrightarrow{\mathrm{NaOH}} [-\mathrm{OCRCOOArO}-]_x + 2x\,\mathrm{NaCl},$$

$$x\,\mathrm{ClOCROOCl} + x\,\mathrm{HOOCRCOOH} \xrightarrow{\mathrm{NaOH}} [-\mathrm{OCRCOOOCRCOO}-]_x + 2x\,\mathrm{NaCl}.$$

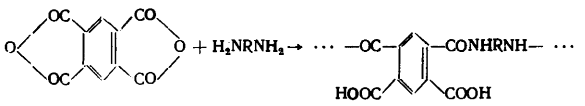
The method of the so called low-temperature polycondensation in solution is extremely interesting. One must stipulate immediately that, when non-equilibrium polycondensation including low-temperature polycondensation is carried out in an organic solvent, different versions are possible: (a) both the starting materials and the resulting polymer are readily soluble in the reaction medium and the polycondensation really takes place in solution; (b) the starting materials are soluble in the reaction medium, while the polymer is only partially soluble or altogether insoluble; (c) the starting materials are only partially soluble or completely insoluble in the reaction medium, while the polymer is soluble.

Despite the fact that in the last two cases the process takes place under heterogeneous conditions, nevertheless these methods are also known in the literature as polycondensation in solution, although it will of course be more correct to regard them as simply polycondensation in an organic solvent. The most favourable conditions for the synthesis of heat resistant high-melting polymers are, of course, usually those where the polymer is formed and is readily soluble in the reaction medium, since this makes it possible to manufacture articles from the polymer (films, fibres) directly from the reaction solution, omitting the preliminary isolation of the polymer itself.

Polycondensation in solution at low temperature (room temperature or slightly above) of the order of 50°C proved to be possible owing to the use of reactive starting materials—such as acid chlorides and anhydrides—and special reaction media of activators. Thus low-temperature polycondensation of dicarboxylic acid chlorides with dihydric phenols at room temperature or with slight heating to about 50°C has been achieved by carrying out the reaction in the presence of a tertiary amine[15,17-49]:

$$x\,\mathrm{ClOCRCOCl} + x\,\mathrm{HOArOH} \xrightarrow{2x\,\mathrm{NR}'_3} [\mathrm{-OCRCOOArO-}]_x + 2x\,\mathrm{NR}'_3\cdot\mathrm{HCl}.$$

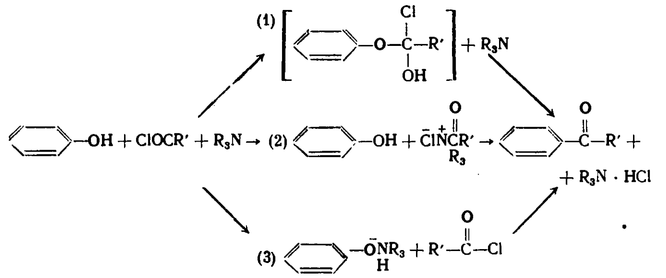
The conversion of dicarboxylic acid chlorides into polyamides by reaction with diamines can be successfully carried out in an amide solvent, for example dimethylacetamide[20-22]. In two-stage syntheses of heat resistant and thermostable polymers such as polyimides, the first stage, involving the formation of a high-molecular-weight polyamidoacid, has been successfully achieved in solvents such as dimethylacetamide, dimethylformamide, and dimethylsulphoxide[23,24]:



In a two-stage synthesis of polyoxadiazoles good results are obtained when the first reaction stage, involving the formation of a polyhydrazide, is carried out under conditions of low-temperature polycondensation in hexamethylphosphoramide (HMPA)[25]:

$$\mathrm{ClOCRCOCl} + \mathrm{H_2NHNOCR'CONHNH_2} \xrightarrow{\mathrm{HMPA}} \cdots\mathrm{-OC\dot{R}CONHNHCOR'CONHNH-}\cdots$$

We shall consider briefly certain features of the formation of polymers by low-temperature polycondensation in solution. Despite the fact that the acylation of phenols by carboxylic acid chlorides in the presence of tertiary amines is widely used in practical organic chemistry, the problem of the role of the base in this process has still not been solved. In principle, several hypotheses concerning the role of the base in the acylation of phenols are possible[15]: (1) the first reaction step is the formation of a complex of the acid chloride and phenol which breaks down under the action of the base to form an ester bond; (2) the base forms a reactive complex with the carboxylic acid chloride the reaction of which with phenol yields an ester bond; (3) a reactive complex of the base and phenol is formed and then readily reacts with the carboxylic acid chloride:



At present it is still impossible to state a preference for a particular mechanism. However, studies aimed at solving this problem are being carried out, in particular at the Institute of Organic Derivatives of the Elements of the USSR Academy of Sciences. At the present stage of the investigation we believe that the first reaction stage most probably takes place via mechanism (2), but this is still a very arbitrary assumption and the elucidation of the problem requires further study.

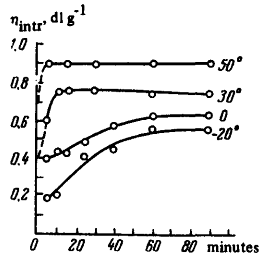


Figure 1. Variation of the intrinsic viscosity of polyarylate F-2 solution in tetrachloroethane with time for different polycondensation temperatures

Very few data have been published on the rate of low-temperature polyesterification in solution. However, there is no doubt that it is fairly high, since in most cases the reaction reaches completion in a very short time.

Fig. 1 presents data on the variation of the molecular weight of polyarylate F-2 in the polycondensation of terephthalic acid chloride with phenolphthalein in dichloroethane solution in the presence of triethylamine at various temperatures (concentration of acid chloride 0.2 M, molar ratio acid chloride : phenolphthalein : triethylamine = 1 : 1 : 2).[17] They indicate a high rate of this reaction. Indeed at 50°C the increase in the molecular weight and the formation of the polymer cease roughly five minutes from the start of the reaction. Even when the polyesterification is carried out at −20°C, the formation of the polymer is virtually complete after 1 h.

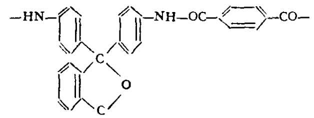
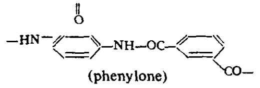
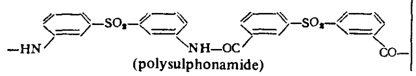
The low-temperature polycondensation of terephthalic acid chloride with phenolphthalein takes place in a very interesting way in the presence of a tertiary amine in acetone, which does not dissolve the resulting polymer[18]. Here after the first minute of polycondensation the yield of the polyarylate (the polymer is precipitated as it is formed) is already 95%. At the same time the molecular weight of the polymer increases considerably when the reaction is continued. It goes on increasing to almost the same extent when the precipitated polymer is separated after the first minute of the process, washed free of the starting materials with acetone, and treated with a fresh portion of pure acetone.

This is undoubtedly evidence that in the synthesis of the polyarylate in acetone the molecular weight of the polymer may increase as a result of reactions of the terminal groups of the polymer chains even after the precipitation of the polymer. Probably this is favoured by the high polarity of the acetone and its consequent high solvating power, which facilitates the interaction between the terminal groups of the polymer chains.

Successful low-temperature polyesterification is also dependent on the purity of the starting materials and the tertiary amine, the relative amounts of the starting materials, their concentration in solution, and other factors[26]. Polymers with highest molecular weights are obtained when carefully purified starting materials are introduced into the reaction in equimolar proportions.

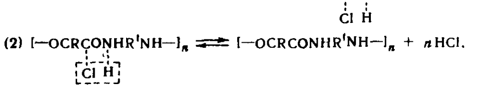
Low-temperature polyamide formation, used successfully in particular for the synthesis of heat resistant aromatic polyamides such as, for example, polyphenyleneisophthalamide[21,22], polyamides based on anilinephthalein, anilinofluorene, etc. has also been developed in recent years[27]. Table 7 lists certain examples of these polyamides obtained at the Institute of Organic Derivatives of the Elements of the USSR Academy of Sciences by Sokolov and coworkers[28].

Table 7. Aromatic polyamides

Polymer	Softening temp.*,°C	Temp. of onset of weight loss in air, °C
	390	450
 (phenylone)	280	—
 (polysulphonamide)	278	—

* Determined from thermomechanical curves

The polycondensation of dicarboxylic acid chlorides with diamines in solution may involve several competing reactions[15,20]:



$$(1)\ n\mathrm{ClOCRCOCl} + n\mathrm{H_2NR'NH_2} \longrightarrow [\mathrm{-OCR-}\underset{\mathrm{Cl}}{\mathrm{C}}\mathrm{O}\underset{\mathrm{H}}{\mathrm{N}}\mathrm{HR'NH-}]_n,$$

$$(2)\ [\mathrm{-OCR}\underset{\boxed{\mathrm{Cl}}}{\mathrm{C}}\mathrm{O}\underset{\boxed{\mathrm{H}}}{\mathrm{N}}\mathrm{HR'NH-}]_n \rightleftharpoons [\mathrm{-OCRCONHR'NH-}]_n + n\mathrm{HCl}.$$

(3) acceptor + HCl ⇌ acceptor salt,

$$(4)\ \mathrm{H_2NR'NH_2} + \mathrm{HCl} \rightleftharpoons \mathrm{HCl\cdot H_2NR'NH_2},$$

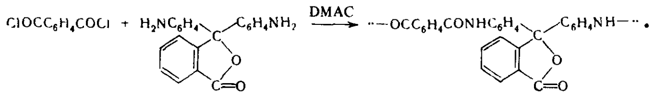
$$(5)\ \mathrm{HCl\cdot H_2NR'NH_2} + \mathrm{HCl} \rightleftharpoons \mathrm{HCl\cdot H_2NR'NH_2\cdot HCl},$$

(6) ClOCRCOCl + acceptor ⇌ saltlike product.

The first three reactions favour the formation of the polymer, while the last three lead to the breakdown of the equimolar proportions of the starting materials and stimulate the termination of the growing polymer chain, i.e. reduce the molecular weight of the polyamide. The ease of their occurrence is determined both by the chemical nature of the starting materials employed and the process conditions.

The role of the substance binding the hydrogen chloride evolved in low-temperature polyamide formation may be fulfilled by tertiary and secondary amines, the initial diamines themselves, and weakly basic organic solvents.

Low-temperature polyamide formation in solution is rapid. This can be inferred if only from the fact that the polycondensation of isophthalic acid chloride with anilinephthalein[20] at −30°C is terminated after several minutes:



The rate of low-temperature polycondensation is of course determined largely by the chemical nature of the starting materials. For example, according to the data of Sokolov and coworkers[28], the time required for the formation of a polyamide from isophthalic acid and di(aminophenyl)sulphone by low-temperature polycondensation is about 30 min, while in the case of poly-*m*-phenyleneisophthalamide it is about 1 h.

Table 8. Low-temperature polyamide formations

Starting materials		Solvent	η_{intr}, dl g^{-1}	Remarks
acid chloride	diamine			
Isophthalic	Anilinephthalein	DMAC*	1.14	solid acid chloride used in reaction
"	"	DMF**	polymer is not formed	ditto
"	"	DMAC	0.22	acid chloride introduced into reaction as soln. in DMAC
Terephthalic	"	"	1.45	solid acid chloride used in reaction
Isophthalic	*m*-phenylenediamine	"	1.52	ditto
"	*p*-phenylenediamine	"	1.60	"
"	*m*-phenylenediamine	"	0.40	acid chloride introduced into reaction as soln. in DMAC
"	"	DMF	0.08	solid acid chloride used in reaction

* DMAC = dimethylacetamide.
** DMF = dimethylformamide.

The products of low-temperature polyamide formation are greatly influenced by the order and method of the introduction of the starting materials into the reaction. When the process is carried out in dimethylacetamide, best results are obtained by adding the solid acid chloride (Table 8) to a solution of the diamine in dimethylacetamide, since it is then probably possible to avoid or weaken many undesirable side processes, which are stimulated by the amide solvent[20,22,24].

NN-Diethylacetamide, hexamethylphosphoramide, and *N*-methylpyrrolidinone can also be used as solvents for low-temperature polyamide formation. On the other hand, when the process is carried out in diethylformamide, high-molecular-weight polyamides are not as a rule obtained. Sokolov and coworkers explained this by the fact that in dimethylformamide side reactions predominate over the main process[29].

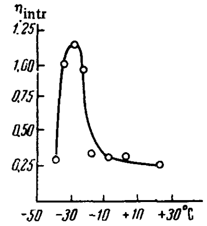
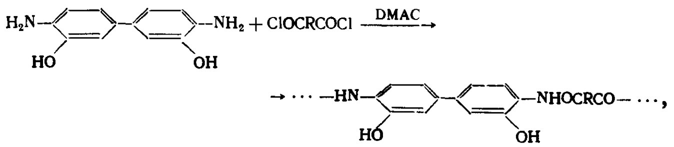


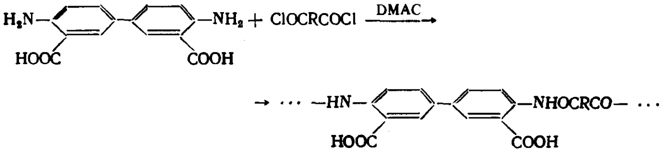
Figure 2. Variation of the viscosity of the polyamide obtained from isophthalic acid chloride and anilinephthalein with polycondensation temperature

The molecular weight of the polyamide synthesised by low-temperature polycondensation is significantly influenced by the reaction temperature. Fig. 2 shows that in the polycondensation of isophthalic acid chloride with anilinephthalein in dimethylacetamide a polymer with the highest molecular weight is formed at -30°C.[20] According to the data of Savinov and Sokolov[22], poly-*m*-phenyleneisophthalamide with the highest molecular weight is produced when the reaction is performed in dimethylacetamide at 0°C. According to Morgan's data[15], highest molecular weights are achieved in the polycondensation of terephthalic acid chloride and *trans*-2,5-dimethylpiperazine in chloroform at or below room temperature.

Other low-temperature polycondensations in solution are not unaffected by temperature either. Thus the optimum temperature for the polycondensation of the acid chloride of di-(4-carboxyphenyl) ether with the dihydrazide of the same acid in hexamethylphosphoramide is 0–5°C.[25] Polyhydroxyamides have been synthesised at somewhat higher temperatures, approximately between 17° and 40°C, from 3,3′-dihydroxybenzidine and the chlorides of various dicarboxylic acids in dimethylacetamide[30,31]:



and also by the condensation of 4,4′-diaminobiphenyl-3,3′-dicarboxylic acid and an acid chloride:



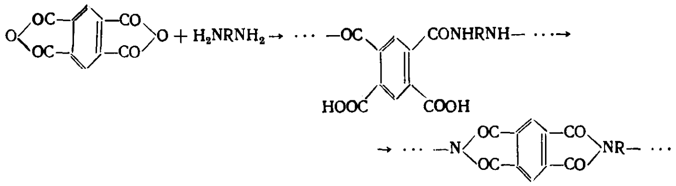
Probably an increase of reaction temperature, leading to an increase of the rate of the main reaction, is desirable in the case of less reactive diamines such as dihydroxy- and dicarboxy-diamines. On the other hand, in the polycondensation of still less reactive di-(4-bromoacetylphenyl) ether with 4,4′-dimercaptobiphenyl in hexamethylphosphoramide, it is desirable to increase the reaction temperature at a certain stage from 20°C to as much as 100°C in order to obtain a polymer with a higher molecular weight[32].

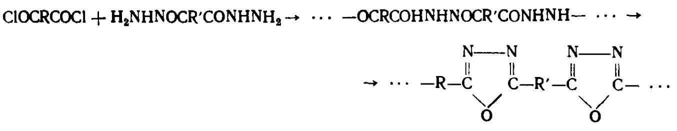
$$x\,\mathrm{BrCH_2COC_6H_4OC_6H_4COCH_2Br} + x\,\mathrm{HSC_6H_4C_6H_4SH} \xrightarrow{\mathrm{HMPA}}$$

$$\rightarrow \cdots -\mathrm{CH_2COC_6H_4OC_6H_4COCH_2SC_6H_4C_6H_4S}- \cdots + 2x\,\mathrm{HBr}$$

The rule of the equivalence of functional groups, which consists in the fact that polymers of high molecular weight are obtained when the starting materials are reacted in stoichiometric proportions, operates in most cases of low-temperature polycondensation.

Among heat resistant and thermostable polymers, cyclochain polymers have attracted much attention recently. Because of their infusibility and insolubility, the only reasonable and useful method of synthesis of many of them was until recently two-stage polycyclisation with formation in the first reaction stage of a high-molecular-weight intermediate which is soluble and therefore can be processed, for example a polyamidoacid in the case of polyimides and polyhydrazides in the case of polyoctadiazoles, which after the formation of the appropriate article are cyclodehydrated to give polymers with a cyclochain structure:



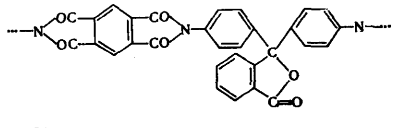


$$\mathrm{ClOCRCOCl} + \mathrm{H_2NHNOCR'CONHNH_2} \rightarrow \cdots -\mathrm{OCRCOHNHNOCR'CONHNH}- \cdots \rightarrow$$

$$\rightarrow \cdots -\mathrm{R}-\overset{\displaystyle \mathrm{N}\!-\!-\!\mathrm{N}}{\underset{\displaystyle \mathrm{O}}{\mathrm{C}\quad\mathrm{C}}}-\mathrm{R'}-\overset{\displaystyle \mathrm{N}\!-\!-\!\mathrm{N}}{\underset{\displaystyle \mathrm{O}}{\mathrm{C}\quad\mathrm{C}}}- \cdots$$

Apart from the evident advantages of this method—for example, articles can be manufactured from infusible and insoluble polyimides—in many cases the final stage of polymerisation has certain disadvantages also, namely (1) the difficulty of obtaining high-molecular-weight polymers in a block or in a thick sheet because of the vigorous hydrolysis of the polyamidoacid by the water evolved in its cyclisation, (2) the degradation of polyimides by the solvents remaining in the polymer even after heat treatment at elevated temperatures, and (3) the necessity to employ high temperatures (frequently of the order of 300°C) and a high vacuum to obtain polyimide articles with satisfactory physical properties.

Recently methods have been found at the Institute of Organic Derivatives of the Elements of the USSR Academy of Sciences for the preparation of heat resistant soluble polyimides, their synthesis involving the use of starting materials containing a central carbon atom in a bulky cyclic group[32-35]. The solubility of such polyimides, in particular anilinephthalein polyimides,



and their stability at high temperatures in many solvents led to a different method for their synthesis—single-stage high-temperature polycondensation in solution[31,34].

Table 9. Synthesis of polyimides by single-stage polycondensation in solution

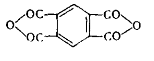
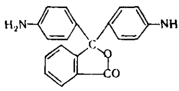
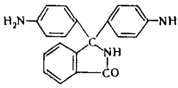
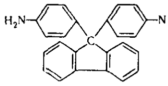
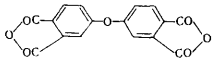
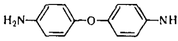
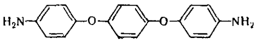
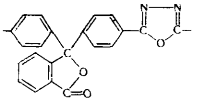
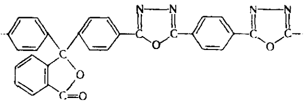
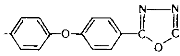
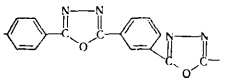
Reaction conditions						η_{intr} of 0.5% soln. at 25°, dl g^{-1}
starting materials						
dianhydride	diamine	solvent	concn. of soln. M	reaction temp., °C	duration of reaction, h	
		nitrobenzene	0.40	210	7	1.65
ditto -"- -"-	то же -"- -"-	benzonitrile	0.40	195	8	1.14
-"-		1-chloro-naphthalene	0.40	200	8	0.63
		sulpholane	0.40	200	4	0.68
-"-		nitrobenzene	0.30	210	7	1.18
		"	0.12	200	7	0.65
		"	0.40	210	10	0.98
ditto		"	0.40	210	17	0.58

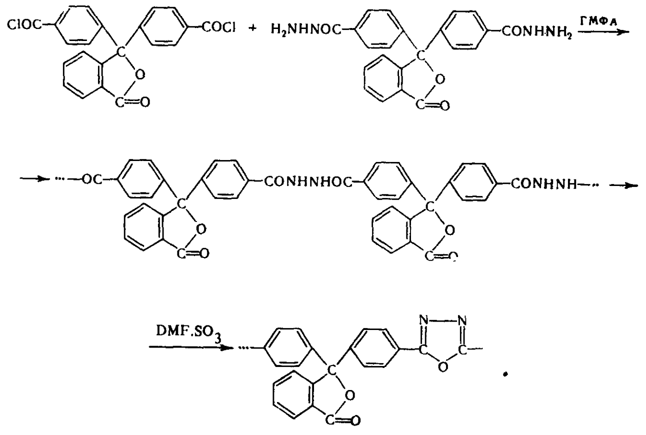
Table 10. Poly-1,3,4-oxadiazoles

Structure of elementary unit	Softening temp., °C	Temp. of onset of decomp. in air, °C
	390	400 (3 deg min^{-1})
	390	450 (3 deg min^{-1})
	370	420 (10 deg min^{-1})
	does not soften before decomp.	450 (10 deg min^{-1})

In the synthesis of such a polyimide by high-temperature polycyclisation in nitrobenzene the initial product is an amidoacid, which, being insoluble in the reaction medium, is precipitated. The subsequent polymerisation (polycyclisation) reaction takes place at 160–210°C and is accompanied by quantitative conversion of the insoluble amidoacid into soluble polyimide. In this method of synthesis of polyimides the difficulties associated with the degradation of the polyamidoacids and polyimides are eliminated and it is no longer necessary to subject the polyimide articles to high-temperature vacuum treatment.

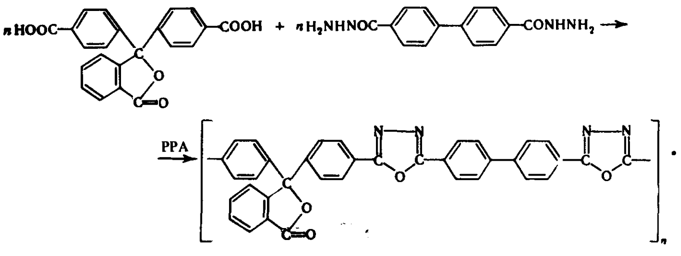
The single-stage method for the separation of soluble polyimides based on anilinephthalein was also extended successfully to the synthesis of high-molecular-weight polyimides based on various tetracarboxylic acid and diamines (Table 9).

We shall consider briefly yet another class of heat resistant and thermostable polymers with a cyclochain structure—polyoxadiazoles. Table 10 lists as an illustration the softening temperatures and the temperatures corresponding to the onset of decomposition of certain polyoxadiazoles[36,37]. They can be synthesised by two-stage methods and also in one stage. Using the two-stage method of synthesising polyoxadiazole, particularly from di-(4-carboxyphenyl) ether, Korshak et al.[25] obtained good results when the first stage, involving the polycondensation of the acid chloride of di-(4-carboxyphenyl) ether with its dihydrazide, was carried out in hexamethylphosphoramide. In the second stage, involving the conversion of the polyhydrazide into polyoxadiazoles, the polymer is usually heated in a vacuum under very severe conditions (about 300°C, 25–30 h). However, it has recently been shown, for polyoxadiazoles obtained from diphenylphthalide-4,4′-dicarboxylic acid as an example, that polyhydrazides can be cyclodehydrated successfully at atmospheric pressure under milder conditions, namely by heat treatment at 100°C for 5 h, when the complex of an amide solvent, for example dimethylformamide (DMF) or dimethylacetamide with sulphur dioxide, is to be used as the cyclodehydrating agent[36,38]:



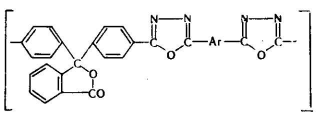
It was noted that polyoxadiazoles may be synthesised also in one stage. Here the process is carried out in polyphosphoric acid (PPA). In a study of the synthesis of soluble polyoxadiazoles based on diphenylphthalide-4,4′-dicarboxylic acid very good results were obtained using this method.

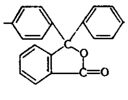
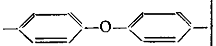
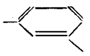
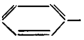
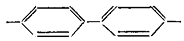
In this case the acid and the hydrazide are allowed to react in equimolar proportions. For example, :



The reaction is carried out gradually by heating the reaction mixture to 140°C and maintaining it at this temperature for several hours.

Table 11. Intrinsic viscosities of polyoxadiazoles obtained by various methods



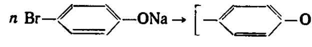
Ar	η_{intr} of 0.5% soln. in 3:1 trichloroethane: phenol mixture, dl g^{-1}		
	thermal cyclodehydration of polyhydrazides	chemical cyclodehydration of polyhydrazides in the presence of DMF.O_3	polycondensation in PPA*
	0.67	0.55	3.00
	1.10	0.90	3.50
	0.70	0.60	1.00
	0.58	0.70	1.90
	0.89	0.80	4.75

* PPA = polyphosphoric acid (Ed. of Translation).

Table 11 presents the results obtained in the synthesis of polyoxadiazoles from diphenylphthalide-4,4'-dicarboxylic acid by various methods. They show that polycondensation in polyphosphoric acid yields high-molecular-weight polymers[36].

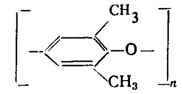
In recent years considerable progress has been achieved also in the synthesis of aromatic polyethers and polysulphones. Despite the fact that these materials are less heat resistant than aromatic polyamides, polyesters, and particularly polymers with a cyclochain structure, they nevertheless have valuable properties; they are heterochain polymers with reasonably good heat resistant properties. Therefore we shall consider briefly their synthesis.

For a long time considerable difficulties were encountered in the synthesis of aromatic polyethers. It was impossible to obtain polymers with a high molecular weight. Recently, various methods have been employed in their synthesis. Thus, a method has been described for the preparation of a polyether with a 1,4-phenyl structure from sodium *p*-bromophenoxide by a modified Ullman condensation:

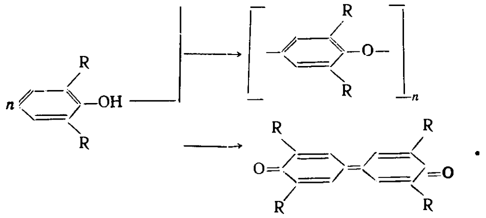


Copper(I) chloride combined with various organic bases (pyridine, *NN*-dimethylformamide, *NN*-dimethylacetamide) is employed as a catalyst. The reaction is carried out at 200°C in dimethoxybenzene, nitrobenzene, or benzophenone with careful exclusion of oxygen and moisture. Since the polymer obtained has the capacity to form fibres, its molecular weight is fairly high. It is also fairly heat resistant: it can be moulded at 300–350°C.[39]

A new variety of non-equilibrium condensation, namely oxidative dehydropolycondensation, proved to be a very interesting procedure for the preparation of aromatic polyethers. The General Electric Company manufactures by this method on an industrial scale a polyether with the following structure:



Its glass point is 205°C and the crystals melt at 267°C. According to thermogravimetric data, the degradation of the polymer in an inert atmosphere begins at about 400°C. Its synthesis became possible when it was established that certain 2,6-disubstituted phenols react by the following mechanism in the presence of oxygen with an amide complex of copper as catalyst:



With 2,6-dimethylphenol, the process takes place readily giving a polymer with a high molecular weight, while the yield of side products is very low. In general the formation of polymers of this type by oxidative dehydropolycondensation is successful when the dimensions of the constituents in the *ortho*-position are small.

On the other hand, if one of the substituents is, for example, a t-butyl group or both substituents are isopropyl groups, the corresponding diphenoquinone is formed preferentially and not the polymer. Substituents which increase the oxidative potential of the phenol retard the polycondensation. Thus, whereas 2,6-dimethylphenol readily undergoes polycondensation at room temperature, the polycondensation of 2-chloro-6-methylphenol requires a temperature of 60°C and for comparable rates of the process with 2,6-dichlorophenol a still higher temperature is needed[39].

Copper chloride in pyridine is usually employed as a catalyst for the oxidative dehydropolycondensation of 2,6-disubstituted phenols; other primary, secondary, or tertiary amines may be used instead of pyridine.

An interesting case of non-equilibrium polycondensation developed in recent years is the polycondensation of the phenoxides of dihydric phenols with aromatic dihalogeno-derivatives in which the halogens are labile because of the presence of electronegative substituents in the molecule[40–42].

An example of this type of reaction is that of the phenoxide derived from dian‡ with di-(4-chlorophenyl) sulphone in dimethyl sulphoxide, which leads to the formation of the so called "polysulphone" (this product was developed and is manufactured by the Union Carbide Company):

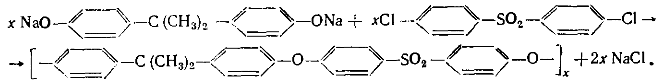


Table 12. Synthesis of polysulphone from di-(4-chlorophenyl) sulphone

Dian salt	Solvent	Duration of reaction, h	Reaction temp., °C	η_{intr} of soln. with 0.2 g/100 ml $CHCl_3$	Yield, %
Na	dimethyl sulphoxide	1	160—165	1.0	>99
K	dimethyl sulphoxide	4	195—200	0.65	>99
Na	sulpholane	3	200—210	0.75	>99
Na	diphenyl sulphone	11	230—250	0.40	—
Na	di-n-propyl sulphoxide	3.5	200—210	0.08	98
Na	benzophenone	8.5	220—230	—	53

The glass point of this polymer, which is fairly thermostable, is 195°C. On heating in an inert atmosphere for 30 min at 400°C, it remains unchanged. The heat resistance of polymers of this type can be varied by altering their chemical structure. For example, the glass point of the corresponding polymer obtained from di-(4-hydroxyphenyl) sulphone is 245°C. In general polycondensation of this type is carried out at elevated temperatures in anhydrous dipolar aprotic solvents, among which dimethyl sulphoxide and sulpholane (1,1-dihydroxytetrahydrothiophen) proved to be the most effective. Probably highly polar solvents of this type not only dissolve the polymer formed but also promote a higher rate of reaction, as it were catalysing the process. On the other hand, Table 12 shows that less polar organic solvents do not facilitate the reaction[40]. Johnson et al.[40], who made a detailed study of the interaction of the phenoxides derived from dihydric phenols with dihalogeno-compounds, noted that the reaction is sensitive to admixtures of water and other nucleophilic substances, because these interfere with the synthesis of a polymer having a high molecular weight. Polymers with the highest molecular weight are obtained when the starting materials enter into the reaction in equimolar proportions. The rate of this reaction depends on the basicity of the phenoxide obtained from the dihydric phenol and the electronegativity of the substituent in the dihalogeno-derivative. The reactivity of dihydric phenols evidently varies in inverse proportion to their acidity.

Thus alkali metal phenoxides derived from di(hydroxyphenyl) sulphone, which is a comparatively acid dihydric phenol, reacts much more slowly with di-(4-chlorophenyl) sulphone than the corresponding phenoxides obtained from dian. The reactivity of aromatic dihalogeno-derivatives (Table 13) is determined both by the nature of the activating group and the halogen: difluoro-compounds are more reactive than dichloro-compounds[40]. Sodium and potassium phenoxides may be employed in the reaction. The phenoxides of other metals (lithium, calcium, or magnesium) derived from dian are not suitable because of their insolubility in dimethyl sulphoxide[40].

It is clear from the foregoing that many types of heat resistant and thermostable polymers are successfully obtained by the polycondensation method. Non-equilibrium polycondensation processes are the most important. Most of these are reactions discovered and investigated in recent years. There is no doubt that a more profound study of such reactions and the discovery of their mechanisms constitute the tasks of the immediate future.

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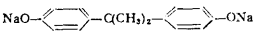
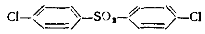
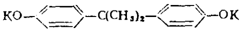
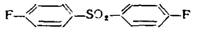
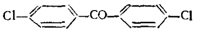
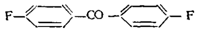
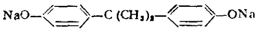
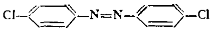
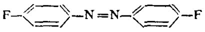
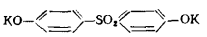
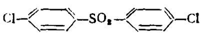
‡ Di-(*p*-hydroxyphenyl)dimethylmethane (Ed. of Translation).

Table 13. Reactivities of the starting materials in the synthesis of polysulphones in dimethyl sulphoxide

Phenoxide from dihydric phenol	Dihalogeno-derivative	Reaction conditions: conc., %	duration of reaction, h	reaction temp., °C	η_{intr}, dl g^{-1}
		20	4	135	0.71
ditto	ditto	40	1	160	1.35
		20	0.5	25—145	0.94
ditto		10	18	135	0.16
»		20	0.5	135	1.0
		40	6	160	0.26
ditto		40	<1	25—160	1.5
		20	29	150	0.2

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the Elements, USSR Academy of
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Outer-sphere Complexes of Tervalent Cobalt

V.E.Mironov

Certain theoretical postulates concerning the formation of outer-sphere complexes have been described. Various approaches to the investigation of these compounds have been considered. Data are presented showing the necessity to take into account the packing term in unitary cratic thermodynamic functions of outer-sphere complexes. Methods for and the results of investigations of various classes of cobalt(III) outer-sphere complexes have been discussed. It is suggested that the formation of transition metal outer-sphere complexes takes place in steps as a result of directional forces. Like inner-sphere interactions, this process takes place in accordance with limiting and characteristic co-ordination numbers. The types of bonds involved in the formation of outer-sphere complexes have been examined.
The bibliography includes 232 references.

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1. INTRODUCTION

Interest in the study of outer-sphere complexes (OSC) increased sharply in the last ten years because outer-sphere coordination processes determine the mechanisms and the rates of many reactions, provide a more profound understanding of catalysis [1], yield a partial model of the transition state, and lead to the discovery of new methods for the isolation, purification, and detection of many metals [2,3], and also have a marked effect on inner-sphere interaction. Many types of complex compounds exist in aqueous solutions solely because of outer-sphere association [4,5]. Recently a number of theoretical postulates have been formulated [6] concerning the formation of such complexes. The data on the thermodynamics and structure of cobalt(III) outer-sphere complexes have played an important role in the formulation of these postulates but the complexes have not so far been reviewed.

This paper constitutes an attempt to review and examine critically the published data and also the results obtained by the author of the review and his coworkers for cobalt(III) outer-sphere complexes.

Complexes of di- and ter-valent cobalt are most frequently encountered [3]. A characteristic feature of most of the cobalt(III) complexes is a low rate of inner-sphere electrolytic dissociation and a constant coordination number of six [7,8]. The compounds have an octahedral configuration. Almost all cobalt(II) complexes are labile and their coordination number is four or six [9].

At present cobalt(III) outer-sphere complexes have been investigated in greatest detail compared with analogous compounds of other metals. This situation arose partly because of the inertness of the inner sphere of cobalt(III) and the lability of the outer-sphere complexes. The low rate of dissociation of the inner-sphere complex made it possible to investigate the cobalt(III) outer-sphere complexes by many methods used for the study of labile inner-sphere coordination [10] and it also permitted the application of the most effective modern methods, such as, for example, circular dichroism spectroscopy [11]. The outer sphere complexes of other metals such as chromium, platinum, rhodium, iridium, etc. frequently have advantages, which are indicated in the description of the properties of the cobalt(III) complexes, but for various reasons [5] these complexes have not been investigated systematically.

The study of cobalt(II) outer sphere complexes is difficult because of the high lability of the inner sphere of this ion, but infrared [12,13], Raman [14], and electronic spectroscopy [15-18] permits the study of outer-sphere complexes in these and other systems with similar properties. The most promising approach for the investigation of cobalt(II) outer-sphere complexes is a combination of thermodynamic and electronic spectroscopic methods [15-17]. The methods proposed for the study of outer-sphere complexes in the present author's earlier investigations [4,5,19-27] are also suitable for the study of the analogous cobalt(II) complexes.

2. SOME GENERAL DATA ON OUTER SPHERE COORDINATION

According to Werner's theory, all saturated complex compounds are capable of outer-sphere interaction. However, the theoretical postulates formulated at present concerning the formation of outer sphere complexes[6] are valid only for transition metal, lanthanide, and probably actinide compounds. Ions of other metals are capable of outer-sphere association but the occurrence of outer-sphere coordination has not been demonstrated for them. In fact the study of the outer-sphere interaction of ions with filled *d* orbitals indicates the absence of stepwise outer-sphere coordination[28].

Numerous literature data show[5,6,29-47] that the capacity of transition metals for interaction is determined by the main and subsidiary valences and also by additional specific forces, the effect of which is directed to fixed positions in space. The nature of these forces is determined by the nature of the Werner complexes functioning as the central groups of the outer sphere complexes. The directional effect of the additional forces determines the stereochemistry of the second coordination sphere.

Like inner-sphere interaction, outer-sphere complex formation processes take place in stages and involve a decrease in the strength of the bond between the outer-sphere ligands and the inner sphere on going from the *n*th to the $(n+1)$th outer-sphere ligand. Sometimes deviations from this rule are observed[4,5]. This happens when inner-sphere coordination is superimposed on the outer-sphere interaction or when the activity coefficients of the interacting and product ions are altered. Similar deviations may be attributed also to the geometrical characteristics of the outer coordination sphere.

Outer-sphere interaction, like inner-sphere complex formation, is characterised by limiting and characteristic coordination numbers[6]. Inner-sphere complexes with octahedral configuration have limiting outer-sphere coordination numbers of 8 and 12 and characteristic numbers of 2 and 4. An especially large number of octahedral inner-sphere cobalt(III) complexes coordinate four outer sphere ligands[30,38-42,45,46]. There are few data on outer-sphere complexes the central ions of which are Werner complexes with tetrahedral and square configurations. According to theoretical considerations[6], one may assume that tetrahedral complexes have limiting outer-sphere coordination numbers of 4 and 6 and a characteristic number of 4. The outer-sphere coordination numbers of complexes with a square configuration are probably 2 and 4.

The charge, dimensions, geometrical configuration, and type of inner-sphere ligand, the electronic state of the Werner complex, and also the nature of the medium, temperature, and pressure determine the stability, structure, and number of ligands combined in the outer-sphere complex. However, the charge and dimensions of inner-sphere complexes do not influence the coordination numbers of the outer-sphere complexes. These characteristics have a major effect on the thermodynamic functions of outer-sphere coordination[4]. A decrease of the dielectric constant of the medium and an increase of the electron-accepting properties of the inner-sphere complex usually increase the stability of the outer-sphere complex.

The sites of contact between the outer-sphere ligands and the inner-sphere complex are points with the most effective charges of the interacting species. The centres of the edges or faces of the octahedral and tetrahedral complexes and the reactive atoms of the inner-sphere ligands[31,43,44,47] not involved in inner-sphere interaction frequently form the closest bond in the outer sphere complex.

Comparison of data on the stability of typical ion pairs and triplets with the stability typical of outer-sphere coordination complexes shows[5] appreciable differences between these two groups of association complexes. The difference consists in the characteristic coordination number. The latter is unity for typical ion pairs and triplets. Saturated complex cations (in the sense of Werner's theory) show a much higher capacity for outer-sphere coordination than complex anions[5]. The latter rarely form stable-outer sphere complexes in which they behave as the central group. Both complex and simple anions have a pronounced capacity for addition to central groups as ligands. The explanation is that all anions tend to exhibit electron-donating properties and do not have appreciable electron-accepting properties.

The interaction between ions and molecules of water or another highly polar solvent leads to the formation around the ions of three concentric shells[48-50] and therefore the overall concentration (C_M) of a conventionally free ion M can be expressed[51] by the equation

$$C_M = \sum_{n=0}^{N} \sum_{n_1=0}^{N_1} \sum_{n_2=0}^{N_2} ([MS_n]S_{n_1}S_{n_2}), \tag{1}$$

where N, N_1, and N_2 are the maximum numbers of solvent molecules S in the first, second, and third solvation shells of the ion M. The square brackets in this equation define the first solvation shell and the symbols of the substances in round brackets denote their equilibrium concentrations. The ionic charges have been omitted for simplicity.

The first solvation shell of the association complexes is identical in many ions with the Werner coordination sphere[52-58]. The second solvation shell of the association complex is characterised by a lower degree of order in the solvent structure than in the pure solvent. The bond between the solvent molecules in the second shell and the ion M is usually formed via the molecules of the first shell but $N_1 > N$.[59] The state of the solvent molecules in the third solvation shell does not differ fundamentally from that in the pure solvent and $N_2 \gg N_1$.

Inner-sphere complex formation in solutions is a process in which the solvent molecules in the Werner coordination sphere of the central ion are displaced by any ligand other than the solvent molecule[60]. Such a process is always accompanied by the formation of a direct bond between the central atom and the ligand.

It is suggested that outer-sphere complex formation be regarded[61,62] as a process in which solvent molecules in the second shell of the association complex, with the composition defined by formula (1), are substituted. Such a process is accompanied by the formation of bonds between the central ion M and the outer sphere ligand A via an inner sphere ligand L and by secondary interaction between M and A as a result of charge transfer from A to the antibonding orbitals of ML_n.[35]

The formation of a successive series of outer-sphere complexes of the central group $[ML_nS_{N-n}]$ may be represented by the equilibrium

$$[ML_nS_{N-n}]S_{N_1} + q[AS_P] \rightleftarrows [ML_nS_{N-n}]A_qS_x + (qP + N_1 - x)S, \tag{2}$$

where $q = 1, 2, 3, \ldots$ The above formulation of reaction (2) is valid if the addition of each outer-sphere ligand is accompanied by the elimination from $[ML_nS_{N-n}]S_{N_1}$ of an arbitrary number of solvent molecules.

When outer-sphere complex formation occurs in solution with a high concentration of inert salts, then one or several ions of the inert salt are detached from the central group together with solvent molecules in the course of reaction (2). This postulate has been found to hold in practice[30].

The equilibrium constant for reaction (2) ($^P\omega_{nq}$) is related to the stability constant ω_{nq} of the outer-sphere complex $[ML_nS_{N-n}]A_qS_x$ formed by the equation

$$\omega_{nq} = {}^P\omega_{nq} \cdot (S)^{x-N_1-qP} \tag{3}$$

when the activity coefficients of all three components of equilibrium (2) are constant and arbitrarily set equal to unity.

The equilibrium constants for reaction (2) and similar processes, expressed on the molal and molar scales consist of a unitary component, characterising the nature of the interacting species, and a packing or cratic component, defined by the number of interacting species[63]. The packing term in equilibrium (2) is $(S)^{x-N_1-qP}$.

Some time ago Bjerrum pointed out[64] the necessity to correct the equilibrium constants for the packing term. This has also been noted in other investigations[65,66].

Gurney[63] examined the problem of the standard state in the study of solutions starting with the concept of the separation of the overall entropy of the process into unitary and cratic components. The difference between the standard states of the solvent (pure solvent) and the solute (hypothetical or real solutions) makes it necessary to take into account two components of the equilibrium constant—the free energy and entropy terms. Only the use of the mole fraction scale eliminates the asymmetry in the choice of the standard state for the solvent and solution, but this method of expressing concentrations is inconvenient in practice[67].

It is interesting to note that the correction of the formation constants of outer-sphere complexes for the cratic terms eliminates many contradictions in data on the stability of these compounds[30]. Unfortunately there are very few literature data necessary for such correction of the thermodynamic functions of both inner-sphere and even more so outer-sphere complexes.

The enthalpy of complex formation in solutions is a unitary constant when it is determined from thermochemical measurements. The cratic term varies with temperature and therefore the process enthalpies calculated from the temperature variation of the equilibrium constants can differ fundamentally from the values obtained from thermochemical measurements.

3. FIRST STUDIES ON OUTER-SPHERE COMPLEXES OF TERVALENT COBALT

The first studies on cobalt(III) outer sphere complexes in solution were made by Brintzinger as early as 1935.[38,39,68] The author notes[38] the necessity to distinguish two types of complex: comparatively simple complexes such as hexamminecobalt(III) chloride, aquopentamminecobalt(III) bromide, etc. and more complicated compounds where saturated complexes (in the sense of Werner's theory) play the role of the central ion or ligand. According to Brintzinger[33], the central ion in the latter type of complex may be any complex cation and anion and therefore there are many more of the complicated complexes than of the simple complexes. The above postulates put forward by Brintzinger are valid also in the light of modern investigations. It is necessary to make only one modification namely that complex anions show little tendency to behave as coordination centres in outer-sphere complexes compared with complex cations.

Brintzinger demonstrated[38,39,68] the formation of a large number of outer-sphere complexes by dialysis and also by transport measurements.

The molecular weight data for outer-sphere complexes found by dialysis have been criticised[7,29] on account of the error involved. Indeed this method is unsuitable for the accurate determination of the number of molecules of water or another solvent in various solvation shells of an association complex the composition of which is represented by formula (1),[29] but it frequently makes it possible to determine the molecular weight of complex ions[69] and outer-sphere association complexes[39] with adequate reliability[70]. Moreover, the validity of Brintzinger's data showing that hexamminecobalt(III) ions move towards the anode in the presence of an excess of outer-sphere anionic ligand species is unequivocal[70] and the critics of Brintzingers investigations unfortunately did not take this into account.

The first studies of cobalt(III) outer-sphere complexes showed that in 2 M solutions of sodium nitrate hexaammine, trisethylenediamine-, and various acidopentammine-, and acidotetrammine-complexes of cobalt(III) do not interact appreciably with nitrate ions[69]. However, in 2 M ammonium sulphate solutions, in 1.5 M potassium oxalate solutions[38], in 0.5 M potassium hexacyanoferrate(II) solutions[68], and in 1.5 M potassium pyrophosphate solutions[39] all the above and a number of other simple and mixed cobalt(III) complexes form outer-sphere complexes with a coordination number of 4 when the outer sphere ligands behave as monodentate species. Immediately after their preparation, cobalt in these solutions migrates to the anode under the influence of an electric field. Thus the first studies on cobalt(III) outer-sphere complexes already demonstrated unambiguously the addition of several anionic ligands in the outer sphere.

The addition to CoL_N^{3+} complexes of even one hexacyanoferrate(II) ion leads to the formation of a negatively charged association complex. Consequently further addition of outer-sphere ligands cannot occur because of electrostatic forces. Similar situations are encountered also in other systems. However, many investigators still believe that the interaction between complex and outer-sphere ions in aqueous solutions is virtually non-existent[29] or can be accounted for[7,8,67,71] within the framework of the theory of electrostatic interaction. The results of Brintzinger's work and other early investigations of cobalt(III) complexes have been discussed in detail in a number of monographs[7,72,73].

4. TWO APPROACHES TO THE STUDY OF COBALT(III) OUTER SPHERE COMPLEXES

The present author's work showed[4,5,74-77] that the association of any ions in any solvent can be characterised quantitatively on the basis of the law of mass action (LMA). A knowledge of the true composition of the interacting and product species is necessary for such description of the process. Hence it follows that the association of saturated complexes (in Werner's sense) with outer sphere ions is also a process obeying the law of mass action. The validity of this postulate is confirmed by numerous investigations[5].

Many workers believe[78-82] that the dissociation of complexes in aqueous solutions into complex and outer-sphere ions should be characterised by formal activity coefficients. There exists a view that large complex ions show less tendency towards association than simple ions. A number of objections have also been made[83-86] to the use of the law of mass action to characterise quantitatively association interactions with participation of complex ions. However, recent measurements of osmotic coefficients and activity coefficients of hexammine- and acidopentamminecobalt(III) complexes disprove [87-91] the view that outer-sphere interaction can be usefully characterised with the aid of the activity coefficients of complex salts. These data confirm the view expressed by the author of this review more than ten years ago [92] and constitutes the second approach to the study of outer-sphere complexes with calculation of the law of mass action constants on the basis of measured activity coefficients. The first approach to the study of such complexes consists in a direct determination of the changes in thermodynamic functions in the course of outer-sphere interaction.

A pronounced dependence of the outer-sphere complex formation constants on the concentration of complex salts was observed [81] in early measurements of activity coefficients. New studies have shown [87-90] that, with a correct approach to the calculation of the outer-sphere association constants from the activity coefficients, the association constants remain invariant over a wide range of the concentrations of various salts. Moreover, it has been observed that the activity coefficients of numerous acidopentamminecobalt(III) salts are much lower than those of simple electrolytes of a similar type and do not pass through a minimum even in solutions at concentrations of about 2.5 M.

Very convenient methods have now been developed [87-91] for the calculation of the thermodynamic functions of outer-sphere complexes with one ligand from osmotic and activity coefficients. These methods have been used to investigate cobalt(III) outer-sphere complexes.

5. ALLOWANCE FOR THE PACKING TERM OF THE UNITARY CRATIC FUNCTIONS OF COBALT(III) OUTER-SPHERE COMPLEXES

The principal standard state used in the study of stepwise outer-sphere coordination is a solution with a high and constant ionic strength maintained by means of inert salts. Studies on solutions with variable ionic strengths cannot yield accurate thermodynamic characteristics of outer-sphere complexes, since there is no way of finding the activity coefficients of individual ions (particularly complex ions) in solutions with high concentrations of ligand ions, where the majority of outer-sphere complexes are formed.

The thermodynamic functions of outer-sphere complexes referred to solutions with various constant ionic strengths as standards can be adjusted to zero ionic strength [93-97] but various complications frequently arise in such recalculations [98,99]. For example [30], in aqueous solutions with perchlorate ion concentrations of about 0.1 M, hexamminecobalt(III) ions form association complexes with perchlorate ions in which the latter are probably separated from the complex ion by water molecules. The location of perchlorate ions in the third coordination shell of the association complex, the composition of which is represented by formula (1), is confirmed by the absence of an appreciable effect of perchlorate ions on the electronic spectra of hexamminecobalt(III) and the circular dichroism spectra of (+)-trisethylenediaminecobalt(III). [32] The formation of cobalt(III) outer-sphere complexes in aqueous lithium or sodium perchlorate solutions is accompanied by the partial dissociation from the conventionally free central group of one or several perchlorate ions [30,100], which requires the introduction into the unitary-cratic values of the thermodynamic functions of outer sphere complexes of a correction for the packing effect. Recently the present author developed [30] an approximate method for applying such a correction. It is interesting to note that an increase of temperature from 25° to 45°C reduced sharply the cratic terms of the thermodynamic functions for formation of hexamminecobalt(III) halide complexes.

The need to apply a correction for the packing effect follows from numerous data [41,101-104]. For example, it has been shown [102] that the chloropentamminecobalt(III) ion forms with perchlorate ions, usually regarded as inert, more stable association complexes than with nitrate, chloride, azide, and acetate ions. Electrophoretic studies have shown [103,104] that cobalt complexes with three molecules of ethylenediamine, 2,2′-dipyridyl, and 1,10-phenanthroline also interact with perchlorate ions more strongly than with many other singly-charged ions.

A particularly striking example of the necessity to take into account the packing term follows from the work of Larsson [41], who investigated the association of *trans*-dithiocyanatobisethylenediaminecobalt(III) with thiocyanate ions in 3 M aqueous solutions of a mixture of sodium perchlorate and thiocyanate at 20°C by an ion-exchange method. The calculations without a correction for the packing term led to the detection of only the complex with a single ligand having a stability constant of 0.30. This constant could not account for various properties of the system investigated. The use of an extraction method enabled Larsson to investigate the perchlorate association complexes of *trans*-dithiocyanatobisethylenediaminecobalt(III) and to introduce a correction for the packing term. After applying the correction, it was found that three thiocyanate complexes are formed in the system, with overall stability constants of 1.42, 0.88, and 0.30.

6. METHODS FOR THE INVESTIGATION AND CERTAIN GENERAL FEATURES OF COBALT(III) OUTER-SPHERE COMPLEXES

It can now be regarded as proved that all coordination-saturated complex cobalt(III) cations are capable of stepwise coordination in the outer sphere of various anions [30,32] and also molecules [93,105-108] with electron-donating properties. The outer-sphere coordination of ligands by inner-sphere cobalt(III) complexes involves an increase of the intensity of the charge-transfer bands in electronic spectra [109,110] and is equally reflected in the results of thermodynamic studies of outer-sphere complexes [30].

The study of the addition of a seventh ammonia molecule [107,108], of outer-sphere ethylenediamine molecules [93,105], and a number of other ligands [30,44,47] made a considerable contribution to the proof of the occurrence of outer-sphere coordination by cobalt(III) complexes. These investigations showed that the stepwise outer-sphere interaction constants are independent of the methods of determination and the ratios of their logarithms yield reasonable values for the statistical and ligand effects [29] when the correct limiting coordination numbers for the second shell are employed [6].

Interesting data on the stepwise formation of cobalt(III) outer-sphere complexes were obtained in studies on circular dichroism spectra [30-32,35,36,45,46,111-113], since this method is free from the many disadvantages characteristic of customary electronic spectroscopy and measurements of optical rotatory dispersion [11]. The high sensitivity of circular dichroism spectra and different signs of the dichroic molar absorption coefficients in successive stages of outer-sphere coordination made it possible to investigate accurately the stepwise outer-sphere interaction.

The circular dichroism spectra of the selenite complexes of (+)-trisethylenediaminecobalt(III) were investigated with particular care. The results obtained by Larsson[31] agreed well with the present author's data[45] but the stability constants calculated in these investigations[31,45] were inexplicably high[30,114]. This finding can be accounted for by the presence of several conformations of (+)-trisethylenediaminecobalt(III).[114] Moreover, it is now clear[30] that data on dichroic absorption cannot always be used for the simultaneous determination of the stability constants and molar dichroic absorption coefficients, because the latter may be zero, which greatly distorts the stability constants. Despite these limitations, the study of circular dichroism spectra in combination with data from thermodynamic methods gives a clear idea about the stereochemistry and bonds in the outer-sphere complexes of cobalt(III) and a number of other metals[111,115].

The stability of a large series of cobalt(III) outer-sphere acido-complexes in dilute aqueous and non-aqueous solutions with variable ionic strengths was investigated conductimetrically[10,116-119]. The stability constants calculated from the data obtained by this method are usually referred to solutions at zero ionic strengths as standards. Conductimetric measurements were used to determine the thermodynamic functions of outer-sphere complexes with one ligand only.

Electronic spectroscopy has been most frequently used to investigate cobalt(III) outer-sphere complexes[120-131], the data thus obtained permitting the calculation of the stability constants (the first and more rarely the second stability constants) and to solve approximately the problem of the nature of the outer-sphere coordination bonds.

A number of studies on the thermodynamics of cobalt(III) outer-sphere complexes were made by the solubility method[30,97-100,132-136]. Measurements were made of the solubility of sparingly soluble iodates[133-135], perchlorates[97-100], hexacyanoferrates(III),[136] and other hexa- or pent-amminecobalt(III) salts in solutions with different concentrations of outer-sphere ligands. In a number of other studies[133] the solubility of sparingly soluble salts containing outer-sphere ligands was investigated as a function of the concentration of inner-sphere cobalt(III) complexes.

Studies on the kinetics of complex formation[61,62,102,137-142] and various versions of the potentiometric method[30,135,143,144] made a considerable contribution to the thermodynamics of cobalt(III). Outer-sphere complexes with the anions of weak acids were investigated[120,135,144] by pH titration. The study of the redox potentials of the cobalt(III)–cobalt(II) system proved very useful and promising in the investigation of cobalt(III) outer-sphere complexes[30,143]. The use of electrodes reversible with respect to the outer-sphere anionic ligands is less suitable because the stability of the majority of outer-sphere complexes is comparatively low and therefore the equilibrium and overall concentrations of the ligands are almost equal.

In studies on the outer-sphere complexes of various metals the e.m.f.'s of cells with ion transport were usually measured. The conventional diffusion potentials of such cells were determined experimentally in accurate investigations[28,30,145] but normally they were calculated from the Henderson equation. The latter method of finding the diffusion potentials is unreliable[28,30] in studies on unstable complexes. Cells without transport have not so far been used to investigate outer-sphere complexes although this approach may prove to be very useful[146].

Isolated studies have been made on cobalt(III) outer-sphere complexes by extraction[34,41], ion-exchange[40,41], and electrophoretic[103,104] methods.

Interesting data on chromium(III)[147,148] and iron(III)[149] outer-sphere complexes were obtained by nuclear magnetic resonance. Recently this method was applied also in the study of cobalt(II) outer-sphere complexes[44,150].

Several systems with stepwise cobalt(III) outer-sphere complex formation were investigated polarimetrically[33,35,42,136]. Trisdiaminecobalt(III) compounds were studied. The investigations led to the determination of the composition and the calculation of the stepwise outer-sphere coordination constants and also the demonstration that there is no difference in the tendency towards the formation of outer-sphere complexes by the racemate and the dextro- and leavo-rotatory isomers[30]. However, the stability constants found from the polarimetric measurements are frequently inaccurate[114] and optically active outer-sphere ligands interact in different ways with dextro- and leavo-rotatory isomers[151].

Infrared spectroscopic studies led to a number of conclusions concerning the nature of the chemical bond in cobalt(III) outer-sphere complexes and to the solution of the problem of the stability of these complexes[152-154]. However, it should be noted that the applicability of the infrared spectroscopic method in the study of outer-sphere complexes is limited and the method is altogether inapplicable to dilute solutions. This is also true of Raman spectra.

The polarographic[155-163] and amperometric[164] methods proved to be useful in the study of cobalt(III) outer-sphere complexes. The shift of the half-wave potential or the changes in diffusion current[159] following the addition of the outer-sphere ligands to cobalt(III) complexes were measured by these methods.

The possibility of using the chronopotentiometric transition to study cobalt(III) outer-sphere complexes has been justified theoretically[165] and confirmed experimentally.

This isopiestic[87-91] and thermochemical[30,93,105,166,167] methods have been shown to be promising.

So far there are no literature data on the thermodynamic functions of cobalt(III) outer-sphere complexes with an outer-sphere coordination number greater than unity referred to solutions at zero ionic strength as standards. Possibly modern methods for the conversion of the thermodynamic functions from one standard state to another will help fill this gap[168-170].

7. HEXAMMINE COBALT(III) COMPLEXES

Numerous data have been published[10,41,71,95-100,103,104,106,116,123,171-177] on the stability of single-ligand outer-sphere complexes where the central group is the hexamminecobalt(III) ion, but the enthalpies and entropies of formation of these compounds have not been determined with adequate reliability; on the other hand the formation of polyligand complexes has been studied only in isolated cases[34,41,100,104].

An advance in the study of hexamminecobalt(III) complexes has been the demonstration of the formation of an outer-sphere chelate ring. This has been shown[175] by investigating the ultraviolet and circular dichroism spectra of a solution of hexamminecobalt(III) perchlorate in the presence of an excess of diethyl-(+)-tartrate ions. The appearance of a new absorption band in the spectrum of this system at about 3000 Å was attributed to charge transfer from the outer-sphere ligand to the complex ion and to a *d–d* electronic transition.

The contradictory nature of the literature data on the stability of single ligand (particularly chloride and bromide) complexes of hexamminecobalt(III) has been the subject of several controversies[4,5,40,100,126]. The reason for these controversies were examined in earlier publications[4,40,98].

Certain thermodynamic functions for a number of hexamminecobalt(III) complexes with various anions have been determined with sufficient reliability to allow their comparison. These data show that the stability of single-ligand association complexes of this cation increases in the following series of anions: lactate[134] < thiocyanate[134] < hydroxide[137] < iodide[97] < azide[97] < bromide[97] < chloride[97] < < tartrate[134] < malonate[134] < sulphate[95] < sulphite[124] < < thiosulphate[174] < fluoride[30] < oxalate[10] < triphosphate[119] < tetraphosphate[119]. The logarithm of the stability constant increases in this series from 0.68 to 4.44 at 25°C and zero ionic strength of the aqueous solution. This series suggests that an increase of the charge and a decrease of the dimensions of the outer-sphere ligands almost always entail an increase of the stability of the outer-sphere complex. There are only a few deviations from this rule—for example, the position in the series of the hydroxide ion. The charge and dimensions of this ion suggest a higher stability of the hydroxo-complex than is indicated by the literature data[137]. The reason for this discrepancy may be the specific features of the hydration or the association of the OH^- ion or it may be due to experimental error. The results of quantitative studies on the stability of sulphate, sulphite, and thiosulphate complexes of hexamminecobalt(III) are extremely contradictory[10].

Deviations from the expected position in the stability series of single-ligand hexamminecobalt(III) association complexes may be caused by hydrogen bonds between the outer-sphere ligands and the inner-sphere ammonia molecules, the effect of which is superimposed on that of the charge and ligand radius. However, the study of infrared spectra and in particular the vibration frequencies of the N–H bond indicates[177] the absence of an appreciable contribution of hydrogen bonding even in the formation of the fluoride complexes of hexamminecobalt(III). This finding may be related to the non-linearity of the Co–N–H group. A strong hydrogen bond formed in the presence of a linear N–M–A structure, where A is an outer-sphere ligand leads[178,179] to the maximum distance between A and cobalt and is clearly reflected in the N–H frequency, but the latter may not in fact change when a non-linear N–H–A group is formed. Consequently the conclusion[177] that there is no hydrogen bond in hexamminecobalt(III) complexes requires further confirmation, particularly since in outer-sphere trisethylenediamine-, diamminebisethylenediamine-, and dichlorobisethylenediaminecobalt(III) complexes a hydrogen bond has been detected[44] by proton magnetic resonance.

A steady decrease of the enthalpy and entropy is observed in the interaction of the following series of outer-sphere ligands with the hexamminecobalt(III) cation: chloride > bromide > iodide > azide.

The formation of chloride[97] and probably fluoride[30] complexes of hexamminecobalt(III) complexes involve an increase of entropy. The enthalpy change prevents the formation of monohalide complexes of this cation in solutions at low ionic strengths. The magnitude of the hindering enthalpy effect diminishes with increase in the size of the halide ion, but the entropy contribution diminishes still further. This results in a decrease of the stability of the outer-sphere complexes in the ligand series fluoride > chloride > bromide > iodide and the logarithms of the stability constants vary in inverse proportion to the crystallographic radii of the halide ions[180]. In contrast to the monohalide complexes, the monoazide complex of hexamminecobalt(III) is formed by virtue of the decrease of the enthalpy with an insignificant effect of the entropy factor[97]. The sulphate and thiosulphate complexes are formed because of the increase of entropy in the presence of only a slightly unfavourable enthalpy effect[95,174].

Far-reaching conclusions concerning the enthalpies and entropies of formation of hexamminecobalt(III) complexes are impossible at present, since these quantities are not accurate, having been determined from the association constants found at only two or three temperatures. Direct thermochemical studies[30,100] confirm this.

The errors in the determination of the stability constants of the outer-sphere complexes of hexamminecobalt(III) and related ions may be estimated on the basis of nine investigations[95,119,125,134,157,159,165,181,182] carried out during the period between 1930 and 1967. The constant for the association of $Co(NH_3)_6^{3+}$ with sulphate ions in aqueous solutions at zero ionic strengths and 25°C was calculated in these investigations. The average value of the logarithm of the constant is 3.30 and the error in its determination amounts to approximately 6%. However, a decrease in the association constant usually entails an increase in the error of its determination.

The formation of polyligand complexes of hexamminecobalt(III) has been demonstrated by Brintzinger[38,39,68] and has been confirmed in recent years for sulphate[40], halide[40,100], thiocyanate[110], thiosulphate[40], carbonate[110], salicylate[40], ammine[108], and aquo-compounds[173]. The majority of the data on the polyligand complexes have been obtained by ion-exchange[40], extraction[34], solubility[100,108], and spectrophotometric[110] methods and by studying the adiabatic compressibility of solutions with the aid of an ultrasonic interferometer[173]. Almost all these data are qualitative or semi-quantitative. Rigorously quantitative studies have not so far been made on the polyligand complexes. However, one may note that hexamminecobalt(III) forms complex anions with an outer-sphere coordination number of 3.[38,39] Judging from anion-exchange data, the stability of these complexes decreases[40] in the following series of outer-sphere ligands: iodide > bromide > > chloride > fluoride thiosulphate > sulphate. This series is the reverse of the series corresponding to the variation of the stability of the single-ligand association complexes[10]. The reversal of the stability series of the cobalt(III) association complexes for high degrees of coordination is a consequence of the large contribution of the entropy term to the addition of the first outer-sphere ligand[95]. It is reasonable to suppose that the enthalpy term varies little with the number of the successive outer-sphere ligands, while the entropy term may decrease. Hence the reversal of the stability series for higher cobalt(III) outer-sphere complexes may be understood.

The inverse stability series of the outer-sphere complexes is also the opposite of that expected from a purely electrostatic interaction. The extent of the formation of higher outer-sphere complexes increases with the polarisibility of the ligands, which has been attributed[35] to charge transfer from the complex ion to the outer-sphere ligand. This is in good agreement with electronic spectroscopic data[110].

Experimental determination of the limiting coordination number of outer-sphere complexes is difficult because of their low stability, although extraction with non-aqueous solvents helps solve this problem. Thus in the study of extraction by cyclohexanone it was shown[41] that hexamminecobalt(III) probably coordinates eight salicylate ions. This finding is consistent with theoretical postulates concerning outer-sphere coordination[6].

It has been established[183] that the fourth chloride ion adds to hexamminecobalt(III) in 7 M aqueous hydrogen chloride solutions because under these conditions the solubility curve for hexamminecobalt(III) chloride passes through a minimum. Hence the constant for the addition of the fourth chloride ion is about 0.1.

It is interesting to note that the hexamminecobalt(III) ion combines in aqueous solutions with as many water molecules as CoL_3^{3+} ions, where L is ethylenediamine, propylenediamine, trimethylenediamine, and diethylenetriamine. Consequently all the above complexes have an outer sphere of the same composition.

The determination of the change in the volume of the solution on association of hexamminecobalt(III) with the first sulphate ion[184] showed that the volume change is almost the same as in the conversion of aquopentamminecobalt(III) into sulphatopentamminecobalt(III). Hence it follows that it is not always possible to distinguish inner- and outer-sphere complexes by dilatometric measurements.

Several studies have been devoted to the effect of pressure on the formation of chloride and sulphate complexes of hexamminecobalt(III).[117,118] The investigations were carried out conductimetrically. It has been found for the chloride complexes that the formation constant of the complex with one ligand passes through a minimum at a pressure of about 400 kg cm^{-2} and 25°C. Calculations by the van't Hoff equation showed that at pressures of 300 and 500 kg cm^{-2} the volume changes are 17 and 13 cm^3 $mole^{-1}$. These values consist of the volume change of the ions themselves and of the solvating solvent. The first type of change predominates at low pressures and the second at high pressures, where the dielectric constant of water increases with pressure.

The association of hexamminecobalt(III) has been investigated[118] in sulphate solutions at 25–40°C and pressures in the range 1–600 atm. It was found that the association is accompanied by a small positive enthalpy change at pressures below 200 atm and an enthalpy effect of the opposite sign at pressures in excess of 400 atm. The interaction is accompanied by an increase in the volume and entropy of the system, an increase of pressure and temperature reducing appreciably the contribution of the entropy component to the free energy. This has been attributed[118] to the decrease in the dielectric constant of water.

The study of the infrared spectra of freshly prepared aqueous solutions of hexamminecobalt(III) salts in the presence of an excess of sodium sulphate showed[12] the occurrence of slight outer-sphere interaction: the sulphate ion is probably coordinated as a monodentate ligand.

Interesting data on outer-sphere interactions were obtained[172] by comparing the results of conductimetric and ultraviolet spectroscopic measurements. It was found that the formation constants of single-ligand hexamminecobalt(III) complexes with chloride, bromide, iodide, and sulphate ions calculated from conductimetric data are much higher than the values obtained by ultraviolet spectroscopy. The constants were calculated on the assumption that association complexes with one ligand species only are formed. The neglect of the formation of complexes with two ligands or association complexes involving the third solvation shell of the species represented by formula (1) accounts for the observed difference. The involvement of the third shell is indicated by the virtual equality of the constants for the addition of hexammine cobalt(III) of perchlorate, chloride, and iodide ions[172], although perchlorate ions do not affect the ultraviolet spectra.

Solubility measurements led to the conclusion[108] that the hexamminecobalt(III) ion forms complexes with acetone in aqueous solutions. These compounds are probably similar to the ketone complexes of actinides[185]. It is not known whether such complexes can be regarded as products of outer-sphere coordination, because it is difficult to distinguish typical outer-sphere complex formation and solvation leading to the formation of the second solvation shell. Additional studies on the interaction between cobalt(III) complexes and various molecules are necessary.

8. TRISETHYLENEDIAMINECOBALT(III) COMPLEXES

The results of studies on the outer-sphere interaction of the trisethylenediaminecobalt(III) ion with various anions by potentiometric[30], calorimetric[30], and spectroscopic[31-36,40-46] methods constitute the main bulk of the experimental data on trisdiaminecobalt(III) outer-sphere complexes.

The circular dichroism spectra of (+)-trisethylenediaminecobalt(III) hardly change in the presence of perchlorate, chlorate, nitrite, nitrate, borate, and tetraborate ions[32,43,113]. This fact indicates the absence of measureable amounts of outer-sphere complexes. The ions enumerated above interact with trisethylenediaminecobalt(III), occupying the third coordination sphere.

Halide, pseudohalide, sulphate, sulphite, thiosulphate, selenite, tellurite, phosphate, phosphite, hypophosphite, arsenate, arsenite, hexafluoroarsenate, hexacyanoferrate(II), carbonate, oxalate, malonate, succinate, maleate, fumarate, tartrate, lactate, formate, acetate, propionate, diethyldithiocarbamate, and benzenehexacarboxylate ions have a significant influence on the circular dichroism spectrum of an aqueous solution of (+)-trisethylenediaminecobalt(III) perchlorate. Their effect is reflected[32,45] in a change in the rotatory powers *R* determined from the area of the corresponding circular dichroism bands—E_a at 4900 Å and A_2 at 4300 Å. All the ions which influence the circular dichroism spectrum form typical outer-sphere complexes.

The rotatory power of the low-frequency component E_a decreases and that of the high-frequency component A_2 increases at low concentrations of the anion. At high concentrations the opposite changes are observed, which suggests[31,32,35-37,45,46] that outer-sphere complexes of different compositions with different circular dichroisms spectra are formed when the concentration of the outer-sphere ligands is varied. The validity of this hypothesis is confirmed by careful potentiometric and thermochemical studies[30]. The e.m.f. of cobalt(III)–cobalt(II) electrodes was measured in the potentiometric experiments. The diffusion potentials of the cells were determined experimentally[28,30]. Some experiments were performed by the familiar method[4,5,186-188] for the determination of the changes in activity coefficients due to the replacement of the inert ClO_4^- ions by anionic ligands in solutions with high and constant ionic strengths maintained with lithium or sodium perchlorate. The corrections for the observed changes in activity coefficients were applied to the experimental data. The heats of formation were calculated from the thermochemical measurements and the stability constants found potentiometrically and from the solubility of trisethylenediaminecobalt(III) perchlorate. Part of the results of these investigations are compiled in Table 1, which shows that sulphate, carbonate, thiosulphate, sulphite, selenite, and tellurite ions form a series of outer-sphere complexes in which the trisethylenediaminecobalt(III) cation behaves as the central ion. The formation constants for the outer sphere complexes found by solubility, potentiometric, and calorimetric methods agree with one another for all degrees of outer-sphere coordination. The errors in the determination of the constants listed in Table 1 increase with increasing *n*, as for inner-sphere complexes.

Table 1. Stepwise thermodynamic functions of formation of outer-sphere complexes of the type $[Coen_3]A_n^{3-2n}$ in 3 *N* solutions of $Na(ClO_4, A)$ at 25°C.

Ionic ligand	*n*	κ_n	ΔH_n, kcal g-ion^{-1}	ΔS_n, e.u.
Sulphate	1	3.6	1.7	8.5
	2	1.4	0.80	3.5
	3	0.40	0.40	−0.5
Carbonate	1	2.9	1.2	6.0
	2	1.4	0.30	2.0
	3	0.40	0	−2.0
Thiosulphate	1	5.3	0.80	6.0
	2	1.7	0.40	2.5
	3	1.0	0.20	1.0
	4	0.50	0	−1.5
Sulphite	1	4.1	1.9	9.0
	2	1.5	1.0	4.0
	3	0.85	0.50	2.0
	4	0.40	0	−2.0
Selenite	1	3.6	1.4	7.0
	2	1.4	0.40	2.0
	3	0.70	−0.20	0
	4	0.30	0	−2.0
Tellurite	1	2.0	1.1	5.0
	2	1.1	0.50	1.0
	3	0.50	0	−2.0

The systems which were investigated up to high concentrations of the anionic ligands may be characterised, to within the experimental error, by four outer-sphere complexes. This agrees well with the data examined earlier in this review and also indicates a characteristic coordination number of four. The stepwise stability constants, and the enthalpy and entropy changes at all stages of outer-sphere coordination for all the complexes investigated decrease steadily with increasing coordination number or, more precisely, with increasing number of the successive ligands added to the complex (Table 1).

The substitution of outer-sphere ligands in the series sulphate, sulphite, and thiosulphate and tellurite, selenite, and sulphite increases the stability of the outer-sphere complexes at all coordination stages (Table 1). The enthalpies and entropies of formation in the first of the above two series change less regularly than the stability constants but in the second series the components of the free energy vary almost as regularly as the stability constants. The existence of these series indicates an important role of electrostatic interactions in the formation of outer-sphere complexes.

Sulphate ions exhibit a lower capacity for outer-sphere association than sulphite ions. This fact is associated with the presence of lone-pair electrons in sulphite ions[32]. Similar relative stabilities have been observed for selenate and selenite complexes of trisethylenediaminecobalt(III).[32]

The majority of outer-sphere complexes are formed by virtue of the increase of entropy, while the enthalpy change hinders their formation (Table 1). An increase of the number of the successive ligand combined reduces the entropy component. The addition of a third doubly charged ligand to trisethylenediaminecobalt(III) involves a negative or a small positive entropy change. The fourth ligand always adds a negative entropy change. This finding can be explained by the absence from the third coordination sphere of the association complex, the composition of which is represented by formula (1), of perchlorate anions when the outer sphere contains two anionic ligands of the type listed in Table 1.

For the outer-sphere complex series with the (+)-trisethylenediaminecobalt(III) central ion as an example, it has been established[30,35,45] that the circular dichroism spectra are characterised by changes in rotatory powers of alternating sign at even and odd stages of outer sphere coordination. Relative to the rotatory powers of the free complex ion, $R[A_2]$ increased and $R[E_a]$ decreased on formation of outer-sphere complexes with odd *n*. On the other hand, these changes were of the opposite sign at even stages of outer-sphere coordination. Thus for $n = 2$, $R[A_2]$ and $R[E_a]$ did not differ from the analogous characteristic for the free (+)-trisethylenediaminecobalt(III) ion. The facts considered show that symmetry elements are lost at odd stages of outer-sphere coordination and are fully (for $n = 2$) or partially (for $n = 4$) recovered in outer-sphere complexes with an even value of *n*. This finding constitutes unambiguous evidence that outer-sphere complexes are formed as a result of forces directed to fixed positions in space.

Electronic transitions of the *d*–*d* type in octahedral cobalt(III) complexes are forbidden by the selection rule. Deviations from this rule are shown[31] by (+)-trisdiaminecobalt(III) complexes as a result of the loss of a centre of symmetry. The deviations increase on formation of an asymmetric outer coordination sphere.

Electrostatic forces favour a centrosymmetric linear environment of the inner-sphere complexes on formation of outer-sphere complexes with two ligands. A tetrahedral configuration of outer-sphere complexes with four ligands is more favourable from the electrostatic standpoint than a planar square outer-sphere ligand environment of the inner sphere. An increase of the polaribility of the ions may also influence the structure of the outer sphere. Further studies are necessary to solve the problem of the geometrical configuration of the outer sphere.

The much smaller frequency shifts in the circular dichroism spectra of trisdiaminecobalt(III) as a result of the formation of outer-sphere complexes than the shifts caused by inner-sphere interaction suggest that outer-sphere coordination has only a slight direct effect on the *d* orbitals of cobalt(III). This effect is not shown at all in the visible part of the usual spectra[189].

The appearance of bands in the circular dichroism spectra as a result of an interionic electronic transition from an outer sphere ligand to the complex ion confirmed that the ions forming the outer-sphere complex exhibit mutual orientation. The closest and most probable approach of the outer sphere ligands to their coordination centre is determined by many factors, including steric factors[32,43]. The problem of the configuration of the monophosphate complex of trisethylenediaminecobalt(III) was examined from these standpoints. Interesting conclusions were arrived at also from a study of the interaction between this central ion in outer-sphere complexes with polyanions[112]. The latter have a very strong effect on the circular dichroism spectra of trisethylenediaminecobalt(III).

Numerous data have been published[96,116,120,161,190,191] on the stability of single-ligand complexes of trisethylenediamine- and, more rarely, trispropylenediamine-cobalt(III). The majority of them refer to highly dilute aqueous solutions. Under such conditions, an increase in the size of the trisdiaminecobalt(III) and outer sphere ions and a decrease of the charge of the latter reduces the stability of the outer-sphere complexes. The variation of the stability is largely consistent with the series quoted in Section 7 of this review for hexamminecobalt(III) association complexes[30,192].

It has been shown[191] that the addition of dioxan to water sharply increases the stability of trisdiaminecobalt complexes with OH^- ions, while the addition of heavy water does not have a significant effect.

Proton magnetic resonance data[44] unambiguously indicate the formation of a second coordination sphere around trisethylenediaminecobalt(III) in various solvents. Outer-sphere coordination sharply increases the activation energy for conformational transformations in the inner sphere.

The problem of the stability of CoL_3^{3+} complexes, where L = 2,2′-dipyridyl and 1,10-phenanthroline, with various ligands can be solved only qualitatively on the basis of data at present available. The study of these outer-sphere complexes by electrophoretic[103,104] and potentiometric[193] methods suggests that the replacement of 2,2′-dipyridyl by 1,10-phenanthroline reduces the stability of the cobalt(III) outer-sphere complexes.

Thermochemical study of trisethylenediaminecobalt(III) association complexes with halide ions shows that for the series of the outer-sphere ligands fluoride, chloride, bromide, and iodide the formation of outer-sphere complexes entails a sharp decrease of the entropy contribution and a decrease of the enthalpy term hindering complex formation. Since the enthalpy changes less and the formation of the outer-sphere complexes involves an increase of entropy, the stability of the association complexes with one ligand species diminishes in the above series[30].

9. ACIDO- AND AQUO-PENTAMMINECOBALT(III) COMPLEXES

The interaction of acido- and aquo-pentamminecobalt(III) complexes with various anions has been investigated by solubility[102,194], spectrophotometric[95,123,127,195], pH titration[135,195], kinetic[102], and isopiestic methods[87-91]. The formation of chloropentamminecobalt(III) complexes has been investigated most thoroughly. The association constants were determined from the solubility of the iodate of this complex, by pH titration, and by kinetic methods[102,135], the result agreeing to within 5–30%. The stability of the single-ligand complexes of chloropentamminecobalt(III) increases for the following series of outer-sphere anions: acetate < chloride < nitrate < azide < perchlorate < < glycolate < succinate < malate < tartrate < malonate < < sulphate < maleate < phthalate. This series is not consistent with the electrostatic characteristics of the outer-sphere ligands, but the available data show[102,135] that the stability of outer-sphere complexes with doubly-charged anions is higher than that of the complexes with singly-charged anions. The constants for the addition of sulphate and succinate ions to chloropentamminecobalt(III) agree with the analogous characteristics of the divalent nickel, zinc, cobalt, manganese, cadmium, and copper complexes[196]. All the above metals probably form with these ligand complexes which are largely of the outer-sphere type. This has been confirmed by other investigations[17,18].

The data in Table 2 shows that the stability of the monosulphate complexes of the acidopentamminecobalt(III) ion falls with decrease of the charge, but the stability of the outer-sphere complex remains high when L = F^-, the fluoride ion being small. The nature of ligands with the same charge also has an appreciable influence on the stability of the outer-sphere complexes. This problem should be the subject of a detailed investigation.

Table 2. Logarithms of the stability constants of outer-sphere complexes of the type $[Co(NH_3)_5L]SO_4^{Z-2}$ at 25°C in 0.1 M $NaClO_4$ solutions according to polarographic data[157].

L	lg ω_1	L	lg ω_1	L	lg ω_1	L	lg ω_1
NH_3	2.1	NO_2^-	1.7	N_3^-	1.2	F^-	1.85
H_2O	1.9	CH_3COO^-	1.65	SO_4^{2-}	1.0	—	—

Measurements have shown[87-91] that the activity coefficients of acidopentamminecobalt(III) nitrates, halides, and perchlorates are almost equal in solutions at concentrations less than 0.1 M but at higher concentrations decrease for the following series of outer-sphere ligands: chloride > bromide > iodide > nitrate and change little when the inner-sphere anions are substituted. It has been suggested[88] that, judging from the activity coefficients, the stability of the outer-sphere complexes cannot be accounted for by Coloumbic interaction.

The stability constants of single-ligand complexes of acidopentamminecobalt(III) complexes were calculated from the activity coefficients of their various salts[88,90]. The constants remained invariant when the salt concentrations were altered by a factor of 10–20. The stabilities of the outer-sphere complexes were compared on the basis of the constants referred to solutions at an ionic strength of 0.1 as standards. This comparison showed that the stability of the nitrate, iodide, and bromide complexes of acidopentamminecobalt III) increases with the size of the complex ion, while the stability of the chloride complexes varies in the opposite sense. The replacement of the *trans*-isomer of bisethylenediaminenitroamminecobalt(III) by the *cis*-isomer resulted in an increase of the stability of the halide outer-sphere complexes. This is because the *cis*-isomer has a higher dipole moment than the symmetrical *trans*-isomer. Nitrate ions, which show little tendency towards polarisation, interact to an equal degree with the *cis*- and *trans*-isomers.

The substitution in acidopentamminecobalt(III) of four ammonia molecules by two ethylenediamine molecules reduced appreciably the stability of the outer-sphere complexes. This is probably due to the contribution of dispersion forces to outer-sphere interaction[92].

A spectrophotometric method has been used to investigate the aquation of pentamminecobalt(III) containing the sulphate ion in the inner sphere and the formation of the monosulphate complex of aquopentamminecobalt(III).[95, 122,123] It was established that the aquation equilibrium involving the formation of an outer-sphere complex is displaced towards the latter. This is favoured by the enthalpy change with a small antagonistic entropy effect. Similar equilibrium with phosphate ions is strongly displaced towards the inner-sphere complex[197].

Equations have been derived for the effect of ionic strength on the stability of monosulphate complexes of aquopentammine- and hexammine-cobalt(III) complexes[95]. The form of these equations shows that the cratic contribution to the stability constants is probably represented by the coefficient of the square root of the ionic strength of the test solution in the denominator.

The chromate complex of aquopentamminecobalt(III) was studied spectrophotometrically and by pH titration[198]. Both enthalpy and entropy changes favour the formation of this outer-sphere complex, which results in a high formation constant (3.07×10^5).

10. DIACIDOTETRAMMINECOBALT(III) COMPLEXES

Diacidotetramminecobalt(III) complexes have been the subject of a large number of studies[41,93,105,128,129,131,150, 198–211]. The halide, thiocyanate, and sulphate association complexes of dichloro-, bromochloro-, and dithiocyanatobisethylenediaminecobalt were mainly investigated. A considerable proportion of these studies on outer-sphere complexes were performed in non-aqueous solvents. Stepwise outer-sphere coordination by diacidotetramminecobalt(III) ions has been demonstrated in only a few studies[41,140], but recently its occurrence has been unambiguously proved[47].

Combination of anion-exchange and extraction data led to the suggestion that three thiocyanate complexes are formed by the dithiocyanatobisethylenediaminecobalt(III) cation in 3.0 M aqueous solutions of a mixture of sodium perchlorate and thiocyanate. The results of a study of the kinetics of the substitution of the inner-sphere ions in diacidobisethylenediaminecobalt(III) complexes, could be explained only by stepwise outer-sphere coordination[47].

A spectrophotometric study[198,199] of the interaction of *cis*- and *trans*-dichlorobisethylenediaminecobalt(III) complexes with chloride and acetate ions in methanol solutions led the authors to the conclusion[71] that only the *cis*-isomer forms outer-sphere association complexes. Recent work[203] demonstrated that this is erroneous. It proved possible to show that the *trans*-isomer also forms outer-sphere complexes, but less stable than the *cis*-compound which has a high dipole moment. The low association constant for the *trans*-isomer calculated from the experimental data is also due to the neglect of the association of the chloride ion and the cation with which the ligand was introduced into the solution[207].

Thermochemical[93,105] and spectrophotometric[128,137,202] methods have been used to investigate the association of *cis*- and *trans*-dichloro-, bromochloro-, and chlorodimethylformamidecobalt(III) complexes with halide ions in *NN*-dimethylformamide (DMF), dimethyl sulphoxide (DMSO) and *NN*-dimethylacetamide (DMA). Earlier, such association was investigated by a semiquantitative kinetic method[138,140]. It was found that an increase of the size of the halide ions usually reduces the formation constant of the outer-sphere complex, but the constant is not a linear function of the crystallographic radius of the halide ion. Thus the constants for the addition of bromide and iodide ions to *cis*-dichlorobisethylenediaminecobalt(III) are almost equal. This indicates a considerable contribution to the formation of the outer-sphere complex by charge transfer from the ligand to the central group[199].

The enthalpy change in outer-sphere association is due to the formation of the outer-sphere complex and the desolvation of the interacting species. The small enthalpy of formation of chlorodimethylformamidebisethylenediaminecobalt(III) chloride shows[202] that the desolvation energy is a little higher than the association energy.

Bromide ions are solvated by dimethylformamide to a greater extent than chloride ions[212] and therefore the formation of outer-sphere complexes with bromide ions entails a greater increase of entropy than the formation of the chloride complexes[202].

The addition of the second chloride ion to *cis*-dichlorobisethylene diaminecobalt(III) takes place owing to the decrease of enthalpy and is accompanied by a decrease of entropy[202], in contrast to the addition of the first chloride ion.

An increase of the charge, a decrease of the dimensions, and conversion of the *trans*- into the *cis*-isomers of the complexes under consideration almost always increases the stability of the outer-sphere complex. A change of solvent reduces the stability of the majority of the outer-sphere complexes in the following series: DMF > DMA > DMSO. This lowering is correlated with the dielectric constants of the solvents[213,214].

The distances of average approach of the ions in outer-sphere complexes were calculated[93,199] from the stability constants in DMA, DMF, and DMSO, and were found to be smaller than the dimensions of the free complex ion. This has been explained[93,105] by postulating that the outer-sphere complexes are not formed solely by electrostatic forces. The absence of a contribution by the Coloumbic interaction to the formation of outer-sphere complexes of diacidotetramminecobalt(III) with two ligands is confirmed also by the stepwise thermodynamic functions[202] of formation of the complexes[215]. The presence of hydrogen bonds between the Werner complex and the outer-sphere ions or molecules has been confirmed by studies on proton magnetic resonance in systems containing dichlorobisethylenediaminecobalt(III) ions[44,150].

Outer-sphere complexes with a cation of the diacidotetrammine type have been assigned (on the basis of kinetic studies) a tetragonal-pyramidal structure[204], but this hypothesis requires confirmation.

11. OUTER-SPHERE INTERACTION OF COBALT(III) ACIDO-COMPLEXES

Cobalt(III) acido-complexes usually behave as ligands like any simple or complex anions. The species produced by the outer-sphere association of acido-complexes of cobalt(III) with cations showing a tendency towards the formation of covalent bonds are frequently converted into heteromononuclear complexes[164,216] or are intermediate between the latter and ion pairs. Only the interactions of the hexacyanocobalt(III) ion with alkali metals[217], lanthanides[219], cadmium[218], and hexammine- and trisethylenediaminecobalt(III)[218] cations have so far been investigated in detail in aqueous[217], mixed[219], and non-aqueous solvents.

A detailed examination of outer-sphere association complexes of cobalt(III) acido-complexes does not come within the scope of the present review, since the formation of such compounds does not characterise the capacity of cobalt(III) to form an outer coordination sphere.

12. SOME HYPOTHESES CONCERNING THE BOND IN COBALT(III) OUTER-SPHERE COMPLEXES

The numerous literature data examined in this review show that the formation of cobalt(III) outer-sphere complexes, like that of the outer-sphere complexes of other transition metals, cannot be accounted for solely by electrostatic forces. The contribution of hydrogen bonds[44] is hardly ever sufficient to prevent the mutual repulsion of the complex and outer-sphere ions bearing similar and high charges.

The type of bond in cobalt(III) outer-sphere complexes frequently depends on the structure of the inner sphere[32,220]. The presence of charge-transfer bands in the ultraviolet spectra of cobalt(III) outer-sphere complexes indicates[109-110] the occurrence of donor–acceptor electronic interaction as in the molecular complexes of benzene with iodine and other similar compounds[221,222]. It has been shown[223] that the electron is transferred from the readily oxidisable outer-sphere ligand to the central cobalt(III) ion in the complex converting it into an almost typical divalent state. This is evidence of possible formation of a dative bond in which the electron from the outer-sphere ligand is transferred to a lower free orbital of the inner-sphere complex. This mechanism of addition of outer sphere ions is denoted by the symbol *a* and is represented by the formula $M + A = M^{\delta-}A^{\delta+}$, where the symbol M denotes an inner-sphere complex with any charge, A denotes an outer-sphere ligand and the charge symbols $\delta-$ and $\delta+$ of the reaction products characterise the redistribution of electrons in the course of the formation of the outer-sphere complex. A typical example of mechanism *a* is the formation of hexamminecobalt monoiodide[109].

The stability of the bond linking the fourth (and succeeding) outer-sphere halide ions to the hexamminecobalt(III) cation increases with the dimensions of the outer-sphere ligand[5]. This phenomenon is attributed to the "hardness" (in Pearson's terminology[224]) of the central group of the outer-sphere complex and is interpreted[225] as evidence for $d\pi$–$d\pi$ interaction. It may be supposed that in this type of bond the electrons are displaced from the filled orbitals of hexamminecobalt(III) to the large halide ions or other outer-sphere ligands. This type of bond in outer-sphere complexes is denoted by the symbol *b* and is represented by the formula $M + A = M^{\delta+}A^{\delta-}$.

Mechanism *a* increases the number of electrons in the antibonding orbitals of the inner-sphere complexes and makes the inner-sphere bonds more labile[226], which is reflected in an enhanced reactivity of cobalt(III) complexes.

The outer-sphere bond types represented by mechanisms *a* and *b* are extreme. There is no doubt about the existence of intermediate bond types. This is confirmed by data on the solubility of non-electrolytic cobalt(III) complexes in aqueous salt solutions[227]. These data were explained within the framework of the formation of outer-sphere complexes[30]. In addition, the stability of the solvation shells of the reactant and product ions and molecules may play a decisive role in the formation of outer-sphere complexes.

Aquo-complexes of cobalt(III) and chromium(III) are known[4,228] to show a smaller tendency towards outer-sphere interaction with small singly-charged anions than the analogous compounds with ammonia and ethylenediamine. This difference has been explained[71] by the high positive charge on the periphery of the inner-sphere complexes the ligands of which have a large number of protons. However, one should remember[88] that hydrated cations may enter into the structure formed by water molecules. Such incorporation hinders a close contact with the anions. Ammine complexes of cobalt(III) combine with water in the second coordination sphere more slowly and less strongly, which facilitates their outer-sphere interaction with other ligands. Moreover, large complex ions enter into the structure of the solvent, forming cavities[229], the dimensions of which are sufficient to accomodate small outer-sphere ligands. Large and highly charged ligands form more stable associated species with aquo-complexes than with ammine compounds because the bonds between the water protons and the oxygen atoms of the oxy-anions are stronger than the analogous bonds with the ammine protons[230].

Dispersion forces may play a definite role in the formation of outer-sphere complexes. Forces of this type in fact lead[88] to enhanced stability of hexamminecobalt(III) complexes when ethylenediamine is gradually replaced by ammonia.

Hydrogen bonds are also important for the formation of outer-sphere complexes[44]. As a result of these forces, inner-sphere ligands combine with hydrogen and many metal ions[231] and sometimes also anions and solvent molecules.

Further expansion of work on cobalt(III) outer-sphere complexes constitutes an important task. The concept of additional specific forces must be developed or rejected. The necessity for a thorough investigation of outer-sphere complexes was pointed out also in one of the latest papers by Bjerrum[232].

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Lensovet Leningrad
Technological Institute

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Nuclear Quadrupole Resonance in Studies on Molecular Compounds

Yu.K.Maksyutin, E.N.Gur'yanova, and G.K.Semin

The review describes and gives a systematic account of data on the application of the nuclear quadrupole resonance method in studies on donor-acceptor complexes. Particular attention is paid to factors responsible for the changes in the principal parameters of nuclear quadrupole resonance spectra.
The bibliography includes 87 references.

CONTENTS

I. INTRODUCTION

The formation of a donor–acceptor bond between two valence-saturated molecules can be regarded as the result of charge transfer from the donor to the acceptor molecule[1]. The transfer of an electron from a higher, as regards energy, occupied molecular orbital (MO) of the donor to a lower vacant molecular orbital of the acceptor is accompanied by a change in electron distribution and a corresponding change in the electric field gradient at a particular atomic nucleus of the complex. Therefore the nuclear quadrupole resonance (NQR) method is very effective in studies on molecular compounds. Its application is interesting also because the field gradient is significantly influenced by various steric factors, in addition to the charge distribution in the molecule. Starting in 1953, when the first two NQR spectra of donor–acceptor complexes were published[2], the number of publications on charge-transfer complexes has steadily increased every year. However, very frequently quadrupole resonance data are non-systematic and their interpretation very contradictory.

Since in the vast majority of studies the effect of complex formation on the quadrupole spectrum of the acceptor was investigated, the type of the acceptor served as a basis for the subdivision of the available data into different sections. The type of the acceptor is determined by the type of the orbital to which the electron is transferred: for π-acceptors it is the π-electron system of aromatic and unsaturated compounds, for σ-acceptors (I_2, ICl, RX, etc.) it is a σ-molecular orbital (usually antibonding), and for v-acceptors (metal halides, organometallic compounds) it is a vacant orbital of the central atom. In the discussion of the experimental data much attention has been devoted to the analysis of those spectra which had not been fully analysed from the standpoint of chemical structure in the original papers.

The review is not concerned with problems of self-association and intramolecular coordination since the same molecule then behaves simultaneously as the donor and the acceptor. Nor are data included on the quadrupole splittings of the NMR spectra of deuterium in hydrogen bonds. A review on this topic has been recently published[3].

2. THE NUCLEAR QUADRUPOLE RESONANCE METHOD

Nuclei with spin $I \geqslant 1$ typically have a non-spherical distribution of the positive nuclear charge. A measure of the deviation from the spherical distribution is the nuclear quadrupole moment Q. The quadrupole moment is positive when the charge ellipsoid is extended in the direction of the spin and negative when the ellipsoid is compressed in this direction. In the interaction between the quadrupolar nucleus and an inhomogeneous electric field due to the electrons surrounding it, there arise energy levels associated with definite orientations of the nucleus relative to the principal axes of the tensor of the electric field gradient. Thus the difference between the levels and hence the frequency of the transition depend on the quadrupole moment of the nucleus and the electric field gradient q. The frequencies of the transitions between the levels corresponding to different orientations of the nuclear spin lie in the radiofrequency range.

These transition frequencies are a source of information about the electronic structure of the molecules. With a suitable choice of the system of coordinates, the field gradient tensor q is defined by three components:

$$q_{xx}=\frac{\partial^2 V}{\partial x^2},\quad q_{yy}=\frac{\partial^2 V}{\partial y^2},\quad q_{zz}=\frac{\partial^2 V}{\partial z^2}.$$

It is assumed that q_{zz} is the largest component and q_{xx} the smallest. All three components are related by the Laplace equation

$$q_{xx}+q_{yy}+q_{zz}=0. \qquad (1)$$

For an axially symetrical field ($q_{xx} = q_{yy}$), the energy levels are given by the simple expression

$$E_m=\frac{eQq_{zz}}{4I(2I-1)}[3m^2-I(I+1)], \qquad (2)$$

where $m = I, I-1, \ldots, -I+1, -I$ is the magnetic quantum number of the nucleus and characterises the orientation of the spin in the external field. Since the square of m appears in the equation, the energy levels (with the exception of $m = 0$ for integral spins) are doubly degenerate. The selection rule for transitions between levels is of the type $\Delta m = \pm 1$ and the transition frequency is given by

$$\nu_{m+1,m} = \frac{3eQq_{zz}}{4I(2I-1)} \frac{2|m|+1}{h}. \tag{3}$$

The quantity eQq_{zz}/h (or eQq_{zz} in frequency units, usually MHz) is called the quadrupole interaction constant.

On the other hand, when there is no axial symetry, i.e. $q_{xx} \neq q_{yy}$, the expressions for the energies become more complex and include an asymmetry parameter $\eta = |q_{zz} - q_{yy}|/q_{zz}$. For example, for nuclei with $I = 3/2$,

$$E_{\pm 1/2} = \frac{eQq_{zz}}{4}\left(1 + \frac{\eta^2}{3}\right)^{1/2}, \tag{4}$$

$$E_{\pm 3/2} = -\frac{eQq_{zz}}{4}\left(1 + \frac{\eta^2}{3}\right)^{1/2}. \tag{5}$$

The frequency of the corresponding transition,

$$\nu = \frac{eQq_{zz}}{2}\left(1 + \frac{\eta^2}{3}\right)^{1/2} \tag{6}$$

depends simultaneously on two parameters: eQq_{zz} and η. When η has not been determined by the Zeeman effect, a certain indeterminacy appears in the interpretation of data on the quadrupole resonance of the nuclei. For halogen atoms $\eta < 0.2$, which gives rise to only slight changes in frequency. For this reason, it is assumed that η for halogens is either zero or has a definite value, adopted on the basis of structural data. For the majority of other quadrupole nuclei, at least two frequencies are observed in the spectra, from which it is possible to calculate both eQq_{zz} and η. Evidently there must be a fully defined relation between these two parameters and the electronic structure of the molecule.

The charge e at a distance r from the nucleus gives rise to a field gradient at the latter:

$$q_{zz} = e\frac{3\cos^2\theta - 1}{r^3}, \tag{7}$$

where θ is the angle between the direction of the radius vector $\bar{r}$ and the z axis. For an electron in an atom, the field gradient depends on the symmetry of its orbital ψ:

$$q_{zz} = e\int \psi^2 \frac{3\cos^2\theta - 1}{r^3} dv, \tag{8}$$

where dv is a volume element.

Since the s orbital is spherically symetrical, its electrons do not contribute to the field gradient at the nucleus. For the same reason, the field gradient due to filled electron shells is zero. The contributions to the gradient by d and f electrons are insignificant for transition elements, and are in most cases neglected. The principal contribution to the field gradients comes from the p electrons of the valence shells. If the gradient due to one p_z electron is denoted by q_0 (or q_{at}), then, according to Eqn. (1), we have for an axially symetrical field

$$q_{xx} = q_{yy} = -\frac{1}{2}q_{at}, \tag{9}$$

i.e. the contribution to the field gradient by p_x and p_y electrons is smaller by a factor of 2 than the contribution by p_z electrons.

In an examination of the changes in the field gradient of an atom in a chemical bond, it is extremely convenient to estimate the gradient in terms of the population N of the p states (here the z axis coincides with the direction of the σ bond):

$$q_{zz} = \left(\frac{N_x + N_y}{2} - N_z\right) q_{at} = U_p q_{at} \tag{10}$$

The quantity U_p denotes "the number of non-balanced p electrons". The quantity q_{at} is usually determined from atomic spectra or by the atomic beam method. When the gradients are replaced by quadrupole interaction constants, Eqn. (10) can be written in the form

$$eQq_{zz} = U_p (eQq)_{at}. \tag{11}$$

Examination of the free chlorine atom as an example shows that two unshared pairs of its p electrons yield $N_x = N_y = 2$ and the valence electron gives $N_z = 1$. Then, according to Eqns. (10) and (11), $eQq_{zz} = eQq_{at}$. The chlorine atom in chemical compounds, usually the more electronegative species, attracts an additional charge. Then $N_z = 1 + i$ (i is the degree of ionic character of the bond) and $eQq_{zz} = (1 - i)eQq_{at}$. In sp-hybridisation the contribution to the field gradient by the electron in the p_z orbital diminishes $(1 + i)s$ owing to its partial s character. However, $3s^2$ electrons acquire a certain porportion of p_z character and make a contribution $2s$ to the field gradient. As a result, the gradient diminishes and

$$eQq_{zz} = (1 - i)(1 - s)\, eQq_{at}. \tag{12}$$

In aromatic and unsaturated compounds the participation of one of the unshared pairs of p electrons in the conjugation system entails a decrease of the p_x or p_y electron density at the chlorine atom and a corresponding decrease of the quadrupole interaction constant:

$$eQq_{zz} = [(1 - i)(1 - s) - \pi]\, eQq_{at}. \tag{13}$$

Eqn. (13) shows that the field gradient in the molecule depends on three parameters: i, s, and π. This gives rise to some indeterminacy in the interpretation of the NQR spectra. In many cases a knowledge of the asymmetry parameter may help significantly. By definition, $\eta = |q_{xx} - q_{yy}|/q_{zz}$ is a direct measure of the difference between the populations of the p_x and p_y orbitals. Therefore the asymmetry parameter may provide information about the double bond character. Quite often it is possible to estimate some of these three parameters from structural considerations or results obtained by other methods. Usually however, as with many other techniques, the relevant information is obtained by comparing the data within the limits of a single series or several series of compounds.

Measurements of quadrupole spectra are possible only for substances in the solid state, since in the gas or liquid molecular rotation averages out the field gradient and there is no splitting of quadrupole levels. Therefore the interpretation of the data may be somewhat complicated by the influence of the crystal lattice. However, similar difficulties are usually encountered also in studies by other methods (the solvent effect, etc.). It has been shown[4] that the effect of the crystal lattice does not as a rule exceed 2% of the measured frequency, while for a series of compounds with similar structures the standard deviation is about 0.3%.

In a description of the method as a whole one must emphasise particularly its high sensitivity to changes in the structural parameters of the molecules. A more detailed description of the essential features of the method and its applications can be found in a number of monographs and reviews[5-9].

3. FREQUENCY SHIFTS AND THE SPLITTING OF THE NUCLEAR QUADRUPOLE RESONANCE SPECTRA OF CHARGE-TRANSFER COMPLEXES

As mentioned above, the formation of a donor–acceptor type of complex is due to a partial charge transfer from the donor to the acceptor molecule. The charge transferred, the distribution corresponding to it, and the accompanying changes in the electronic structure of the interacting molecules, give rise to fairly significant changes in the field gradient at each atom of the complex.

Furthermore, new steric interactions may arise and those existing previously may change on complex formation, which naturally entails additional changes in the field gradient. The indeterminacy introduced by the crystal field is of course still present. The combination of all these factors can give rise to a very complicated pattern of NQR spectroscopic effects associated with complex formation. Therefore it is useful to carry out a preliminary analysis of the effects of the individual factors and to determine under what conditions each of them operates and what role it plays.

We shall examine the role of charge transfer or the electronic factor. The wave function of the ground state of the complex D.A can be represented as follows[1,10]:

$$\psi_N = a\psi_0(D\cdot A) + b_1\psi_1(D^+A^-)\,. \qquad (14)$$

Using this approximation, relations have been obtained[11] between the changes in the field gradient Δq_{ZZ}, on the one hand, and the degree of charge transfer b^2 and its density c^2 at the given atom, on the other:

$$\Delta q_A = \frac{b^2}{1+S^2}\sum_t c_{At}^2 q_t \text{ for the acceptor} \qquad (15)$$

$$\Delta q_D = -\left(1 - a^2 + \frac{b^2S^2}{1+S^2}\right)\sum_r c_{Dr}^2 q_r \text{ for the donor} \qquad (16)$$

where S is the overlap integral of the interacting molecular orbitals and t the atomic orbital of the atom investigated, participating in the formation of the donor–acceptor bond. We may recall that $q_s = 0$, $q_{p_z} = q_{at}$, $q_{p_x} = q_{p_y} = -q_{at}/2$ and the quantities q_d and q_f may be neglected. We shall now consider the application of Eqn. (15) to acceptors of various types (σ, π, v). For simplicity, we shall for the moment confine ourselves to halogen-containing molecules. In the first place, Eqn. (15) shows that the change in the gradient as a result of charge transfer is directly proportional to the degree of charge transfer b^2. The direction of the shift may be predicted beforehand even without calculating the electron distribution. For σ acceptors (I_2, ICl, CCl_4, $CHCl_3$, etc.), an increase of the σ-electron density of the molecule is accompanied by an increase of the population of the p_z orbital of the halogen and consequently a decrease of the field gradient. In the simplest case of a diatomic σ acceptor (I_2, ICl, IBr, etc.) Eqn. (15) yields a simple expression for the relative change in the field gradient or, putting $\eta = 0$ in Eqn. (6), the relative frequency shift:

$$\frac{\Delta q_{zz}}{q_{zz}} = \frac{\Delta\nu}{\nu} = -\frac{b^2}{2(1+S^2)}\,. \qquad (17)$$

For π acceptors (chloranil, picryl chloride, etc.) charge transfer to the π orbital increases the population of the p_x orbital of the halogen atom, which increases its field gradient. Since $q_{p_x} = -q_{at}/2$, we find, after substituting Eqn. (15) in Eqn. (13), that the field gradient at the halogen atom of the acceptor molecule increases as a result of charge transfer by an amount

$$\Delta q_{zz} = \frac{b^2}{2}c_A^2 q_{at}\,. \qquad (18)$$

The subscript t may be omitted, since the p_x orbital is non-hybridised.

As already stated, the p-electron density is closely linked to the asymmetry parameter η. Then the degree of charge transfer can be related, to an adequate degree of approximation, to the change in the asymmetry parameter $\Delta\eta$ by the expression[12]:

$$\Delta\eta = -b^2c_A^2\,. \qquad (19)$$

Eqns. (18) and (19) yield a direct relation between the changes in the characteristics of the NQR spectra and the degree of charge transfer for π acceptors. The corresponding relations for σ and π donors have been given by one of the present authors[12].

The analysis of the shifts is more complex for v acceptors. The formation of complexes by v acceptors involves in the vast majority of cases a complete rearrangement of the entire electron system of the molecule and the appearance of one or several additional vacant orbitals. The rearrangement of molecular geometry naturally involves changes in the M–X bond parameters (amount of ionic character, double bond character, etc.). Therefore, exception in certain cases, a detailed analysis of the change in the field gradient is possible only on the basis of a detailed calculation for each specific complex. The entire process may be represented approximately as consisting of two stages: direct rearrangement of the acceptor molecule MX_n and charge transfer to the vacant orbital produced, in accordance with the distribution of the charge. One can assume with reasonable certainty that, within the limits of a restricted range of complexes of the same acceptor with different donors, the change in electron distribution solely due to the rearrangement of the electron system will be approximately the same for all the complexes. Then the variation from complex to complex within the limits of this series can be fully attributed to the differences in the degree of charge transfer. An increase in the degree of charge transfer will favour an increase in electron density in the σ system of the acceptor and hence a decrease of the field gradient at the atoms X. This is the qualitative aspect of the problem. On the other hand, as already stated, the quantitative relation between the quadrupole shift and charge transfer can be revealed only by detailed calculations. However, one may suppose that this relation is fairly complicated. Sometimes, the valence bond method may be used to analyse the NQR spectra of complexes having similar compositions and structures, particularly when there is a possibility of observing the NQR spectra not only due to X atoms but also due to the central atom.

In the molecule of an n donor the coordination due to the unshared electron pair causes a shift of electron density towards the atom involved in the formation of the dative bond. When the group R contains a halogen atom X, this shift is accompanied by decrease of the ionic character of the C–X bond, which in turn leads to a high-frequency shift of the NQR spectrum of the halogen.

Thus in the general case the direction of the NQR frequency shift due to the electronic factor for both donors and acceptors is determined by the orbital involved in complex formation. On the other hand, the magnitude of the shift depends on the degree of charge transfer and the nature of charge distribution.

We shall consider how steric factors affect NQR spectra. On formation of a complex, the coordinating centres of the interacting molecules can approach one another to within distances ranging from the sum of the van der Waals radii (weak complexes) to the sum of the covalent radii (stable complexes). Both the structure of the interacting molecules themselves and their relative positions in the complex play a major role in the spectroscopic effects of complex formation[12,13]. The effect of steric factors can be ultimately divided into three types. Firstly, steric factors can prevent the mutual approach of the donor and acceptor molecules, restricting the possibility of charge transfer. Then, even when the donor has pronounced dative properties, the degree of charge transfer may be slight. This means that in this case steric factors affect electronic factors, whose relation to the field gradient has already been examined. Secondly, steric interactions can distort the geometrical structure of the molecules: they may cause changes in bond length, distort the valence angles, etc. There will be corresponding changes also in the field gradient of the atoms. Thirdly, steric effects can lead to the deformation of the electron shells of the atoms investigated due to polarisation. The last two factors are not related to the degree of charge transfer and are of independent importance. The combination of all three factors can alter significantly from complex to complex even within the limits of the same series. For this reason, their effect on the field gradient is specific for each concrete case.

Thus the change in field gradient as a result of complex formation is determined by two principal factors: electronic effects and steric interactions. On the other hand, both factors affect one another and, on the other, they compete with one another. It may be supposed that, depending on the intensity of the donor–acceptor interaction, the electronic factor will predominate in the NQR spectra of the stable complexes and the geometrical factor will predominate in those of weak complexes. The influence of the combination of the two factors leads to a very complex pattern of spectroscopic shifts which must be duly taken into account in the analysis of the NQR data.

Apart from the frequency shift, an important characteristic of the NQR spectra is their multiplicity. When the molecule contains several identical atoms with quadrupole nuclei, their frequencies may be expected to be different. Such splitting of the spectrum can be caused by differences in the electronic state of the atoms (chemical non-equivalence), steric effects, and the effect of the crystal field. The splitting due to crystal field effects is as a rule within the limits of the usual 2% range, while the splitting due to the chemical non-equivalence can be very considerable, depending on the type of electron distribution in the molecule.

This makes it possible, on the one hand, to predict the nature of the splitting in the spectrum of a complex from its electron distribution and, on the other hand, to draw conclusions from the type of splitting concerning the geometrical and electronic structure of the complex. An approximate analysis of this type has been made[12,14] for the octahedral *cis*- and *trans*-complexes $MX_4.2D$ (where X = halogen) (Fig. 1). Using molecular orbitals of symmetry O_h, the authors showed that in the *trans*-complexes all four halogen atoms have the same σ-electron density and are chemically equivalent. Therefore the splitting in the NQR spectra of the octahedral *trans*-complexes is possible only owing to the crystal field effects. Fig. 1*a* shows the hypothetical form of the spectrum of such a complex. Analogous calculation for the *cis*-complex shows that the σ-electron density for the two positions of the halogen atom (equatorial and axial) is different. Therefore considerable splitting, due to the chemical non-equivalence of these positions, should be observed in the NQR spectra of such complexes (Fig. 1*b*). Yet another interesting consequence of this calculation is noteworthy, namely that, for the same degree of charge transfer, the average shift of the NQR spectrum of the halogen in the *cis*- and *trans*-complexes is different. This must be taken into account in a comparison of the properties of donors (treated as bases) in complexes of different structures. In the simplest case the type of splitting in the spectra due to chemical non-equivalence can be determined with the aid of the symmetry properties of the complex. In symmetry operations the molecular orbitals of the complex are transformed in accordance with the irreducible representations of its point group. Therefore in symmetry operations chemically equivalent atoms will be interchanged. Hence it is not difficult to determine the number of non-equivalent positions of the halogen atom.

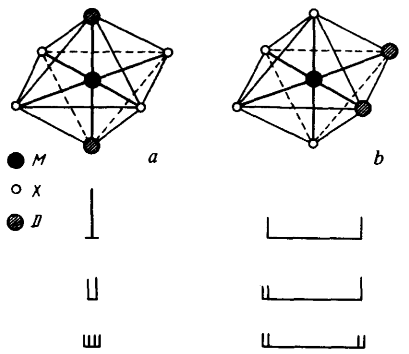

Figure 1. Schematic representation of the splitting in the NQR spectra of the octahedral complexes $MX_4.2D$: *a*) *trans*-structure; *b*) *cis*-structure.

In an analysis of the splitting in the spectra particular attention must be paid to the effect of steric factors. The role of the deformation of the angles and bonds in spectral splitting can be so marked that its importance in some cases can approach or even exceed that of chemical non-equivalence. However, as for the frequency shifts, the effect of steric factors on the splitting is highly specific for each concrete case.

4. π-ACCEPTOR COMPLEXES

Among π acceptors, the NQR method was used to study the complexes of polyhalogenobenzenes[13,15], chloranil[15,16], and picryl chloride[12,17,18]. The studies were based only on chlorine-35 frequencies.

Charge transfer in complexes of this type increases the electron density in the π system of the acceptor and consequently the spectroscopic shift should occur at high frequencies. The degree of charge transfer in the π complexes is slight and usually lies in the range 1–6%.[19] For this reason, even under conditions of complete localisation of the transferred charge at the halogen atom the quadrupole frequency shift will not exceed 5%. Hence it is easily seen that in the complexes of these acceptors steric interactions will have a dominant effect on the NQR spectra.

The effect of the geometrical structure of the molecules (or the geometrical factor) on the shift of the quadrupole spectra on complex formation was first demonstrated for the complexes of halogenobenzenes[13]. Calculation by Hückel's method[20] showed that halogenobenzenes have almost identical and very weak acceptor properties. According to X-ray diffraction analysis[21], the distance between the components of the complex is not reduced as compared with the sum of the van der Waals radii of the components. Both these findings indicate that in this case the usual intermolecular interactions predominate. This view is confirmed also by a series of physicochemical experiments[22,23].

Table 1. ^{35}Cl NQR spectra of the complexes $C_6F_5Cl.D$.

Donor	$\nu_{^{35}Cl}$, MHz
——	39.410
Benzene	38.717
Mesitylene	38.68
Chlorobenzene	39.36
Aniline	38.64
Triethylamine	39.284
Toluene	39.16

Table 1 shows that in five chloropentafluorobenzene complexes with various bases[13] the chlorine-35 frequency shifts are independent of the dative properties of the donors, a measure of which is provided by the ionisation potentials, and are determined mainly by the geometrical structure of the molecules. Thus the ionisation potentials of mesitylene and benzene (8.39 eV[24] and 9.25 eV[25]) are significantly different, but the symmetry types of both molecules are similar and the chlorine-35 frequency shift is virtually identical in both cases. In all the remaining complexes the molecular structure of the donors is extremely varied and the frequency shifts show significant differences. This suggests, in the first place, that in the complexes of chloropentafluorobenzene the degree of charge transfer is small and, in the second place, that molecular geometry plays a dominant role in the spectroscopic effects.

The nature of a slight low-frequency shift is still obscure. One can only note that the extremely short spin–lattice relaxation times for these complexes indicate that their benzene rings rotate (although at frequencies lower than those observed by NQR). Such rotation may lead to the averaging of the field gradient and hence to a lowering of the frequency.

The complexes of chloranil with mesitylene and hexamethylbenzene are more stable. The distance between the components of the complex is somewhat smaller than the sum of the van der Waals radii[26] and the degree of charge transfer is approximately 3%.[19] The observed shifts of the quadrupole spectra of these complexes occur at high frequencies, as was to be expected, but are very small (0.075 MHz[15] and 0.107 MHz[16] respectively). However, the available experimental data are too few to arrive at any definite conclusions.

A more systematic investigation of the effect of the electronic and geometrical factors on the quadrupole frequency shift has been made[12,18] for complexes of picryl chloride with aromatic donors (Table 2).

Picryl chloride can be very conveniently investigated by the NQR method. The two nitro-groups in the *ortho*-positions relative to the chlorine atom are displaced from the plane of the ring and make an angle of 80–90° with it[27]. The chlorine atom is to some extent protected from the direct steric effect of the donor molecule. When account was taken of the corresponding donor symmetry, this made possible a number of interesting conclusions concerning the effect of various factors on the NQR frequency shift.

Table 2. ^{35}Cl NQR spectra of picryl chloride complexes with aromatic donors.

No.	Donor	ν, MHz	$\Delta\nu$, MHz	Remarks
1	——	39.385	+0.193	
2	Benzene	39.578	+0.193	
3	Fluorobenzene	39.683	0.298	
4	Chlorobenzene	39.956	0.571	
5	Bromobenzene	39.988	0.613	
6	Toluene	40.075	0.690	*Anti*-isomer
		39.662	0.277	*Syn*-isomer
7	Iodobenzene	40.250	0.865	
8	Phenol	40.544	1.159	
9	Nitrobenzene	39.466	0.081	
10	*p*-Xylene	39.425	0.040	
11	*p*-Iodotoluene	39.431	0.046	
12	*p*-Cresol	39.501	0.166	
13	*p*-Bromotoluene	39.606	0.221	
14	*p*-Chlorotoluene	40.152	0.767	*Anti*-isomer
		39.907	0.522	*Syn*-isomer
15	*p*-Fluorotoluene	40.040	0.655	
16	Mesitylene	40.383	1.002	
17	Durene	39.970	0.585	
18	Pentamethylbenzene	40.264	0.879	
19	Naphthalene	39.935	0.550	
20	Anthracene	39.802	0.417	
21	Phenanthrene	39.914	0.529	

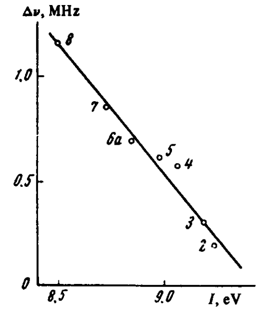

Figure 2. Variation of the ^{35}Cl NQR frequency shift for picryl chloride in complexes with monosubstituted benzene derivatives as a function of the ionisation potential of the donor (the points are numbered in accordance with Table 2).

In complexes with monosubstituted benzenes the symmetry of the donor molecules is identical and therefore one may assume that the steric interactions are also approximately the same. It has been shown for such complexes that the shift of the chlorine-35 quadrupole frequency of the acceptor varies linearly with the ionisation potential of the donor (Fig. 2). Since the degree of charge transfer in a series of complexes of the same acceptor is linearly related to the ionisation potential of the donor[28], the nature of this correlation confirms the linearly of Eqn. (15), i.e. the linearity of the relation between the quadrupole frequency shift and the degree of charge transfer.

In complexes with *para*-substituted toluenes the symmetry of the donors can also be regarded as identical. However, the presence of the *para*-substituent intensifies the effect of the steric interaction. There are two most probable positions of the *donor* molecule in the complex depending on the orientation of the CH_3 group in relation to the bulky picryl chloride group (*syn*- or *anti*-).

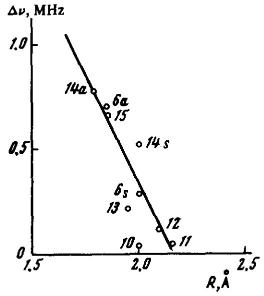

Figure 3. Variation of the ^{35}Cl NQR frequency shift for picryl chloride as a function of the van der Waals radius of the *para*-substituent in complexes with *para*-derivatives of toluene [the points are numbered according to Table 2; *a*—anti-conformation; *s*—syn-conformation].

Table 2 shows that in the majority of complexes there is only one conformation, believed[18] to be the *anti*-conformation. The doublet structure of the spectrum in many cases indicates the existence of both conformations.

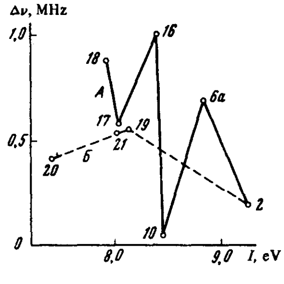

Figure 4. Variation of the ^{35}Cl NQR frequency shift for picryl chloride as a function of the ionisation potential of the donor in complexes with polymethylbenzenes (A) and condensed aromatic systems (B) (the points are numbered according to Table 2).

Furthermore, with increase of the bulk of the *para*-substituent, the distance between the components of the complex also increases, which reduces the degree of charge transfer. Therefore an increase of the bulk of the *para*-substituent in the donor molecule should cause a fall of the quadrupole frequency shift. Fig. 3 shows the variation of the quadrupole frequency shift with the van der Waals radius of the *para*-substituent. Evidently the relation is fairly well approximated by a straight line.

The effect of the molecular structure of the donor on the shift is well illustrated by the spectra of the complexes of picryl chloride with polymethylbenzenes and condensed aromatic systems (Fig. 4). With increase in the number of methyl groups in the donor molecule, the ionisation potentials of the donor decreases, but the effect of its molecular symmetry is so great that the shift does not show a definite variation from complex to complex, although its general direction is maintained. The same tendency is observed also in the spectra of the complexes of picryl chloride with polycyclic aromatic systems.

Thus the investigations show that (1) after exclusion of the effect of the geometrical factor the linearity of the relation between the quadrupole frequency shift and the degree of charge transfer is confirmed and that (2) in the presence of the combined effect of the electronic and geometrical factors the role of the latter may be very significant.

5. σ-ACCEPTOR COMPLEXES

As already stated, charge transfer to an antibonding σ orbital of the acceptor leads to a low-frequency shift in the quadrupole spectrum of the halogen. The magnitude of this shift is determined by the distribution of the transferred charge. Since in the majority of complexes of this type the degree of charge transfer is small, the frequency shift should depend significantly on the geometrical factor.

Table 3. ^{81}Br NQR spectra of the complexes $Br_2.D$.

Donor	$\nu_{^{81}Br}$, MHz	Δν, MHz
—	319.509	—
Benzene	319.616	+0.107
Fluorobenzene	319.469	−0.040
Chlorobenzene	319.483	−0.026
Bromobenzene	317.803	−1.704
	215.92*	−8.69
Dioxan	314.77	−4.74
Acetone	318.336	−1.173
Ethyl ether	320.499	+0.990

*Bromine-81 in bound C_6H_5Br.

Among complexes of σ acceptors, those of Br_2 with various *n* and π donors have been most thoroughly investigated[29-32]. Table 3 shows that, with the exception of the bromine complexes with benzene and ethyl ether, the observed low-frequency shifts are usually small and lie in the range 0.01–4%. In the spectra of the complexes $Br_2.C_6H_6$ and $Br_2.O(C_2H_5)_2$ small high-frequency shifts were observed. Comparison of the data shows that the shifts are not determined by the dative properties of the donors. As for the complexes of π acceptors, steric interactions play a dominant role in the spectroscopic effects. An attempt was made[32] to compare the dative properties of the donors with the quadrupole interaction constants of bromine atoms calculated by Eqn. (6) from the experimental frequencies for various arbitrarily specified asymmetry parameters. However, the attempt was unsuccessful because of the specificity of the steric factors.

For the complex $Br_2.C_6H_5Br$, observations were also made of the ^{81}Br NQR frequencies for the bromine atom in the aromatic system. The low-frequency direction of the shift agrees with expectation and the magnitude of the shift is 4%. In this case complex formation involves the unshared pair of electrons of the bromine atom and not the π-electron system of the ring[33]. The magnitude of the shift determines directly the decrease of electron density at the p_x orbital of the bromine atom as a result of the charge transfer. The charge transfer was estimated[32] as 8% from the relative change of the field gradient $\Delta q_{zz}/q_{zz(obs)}$. However, according to Eqn. (18), in such an estimate it is more valid to employ q_{at} instead of $q_{zz(obs)}$, since the population of the $3p_x$ orbital is influenced neither by the degree of s-hybridisation nor the amount of ionic character of the C–Br bond, on which q_{zz} depends. Generally speaking, this inaccuracy is of secondary importance in a rough estimate but may be significant in more accurate calculations. The use of q_{at} yields an estimate of about 5% for the degree of charge transfer. On the other hand, the degree of charge transfer determined from the shift of the spectrum of the Br_2 acceptor is 2%. The discrepancy between the fractions of charge transferred found for the donor and the acceptor may be accounted for by the involvement in complex formation of the vacant d orbitals of the bromine atoms in the Br_2 molecule. A similar hypothesis was also made for the complex of carbon tetrabromide with p-xylene[34,35]. The involvement of d orbitals favours a decrease of the p_z-electron density and consequently a high-frequency shift of the quadrupole spectrum of the bromine atom.

A remarkable feature of the spectra, characteristic of all bromine complexes, has also been noted[32]: the frequencies of both bromine atoms in the acceptor molecules fully coincide, without any signs of a broadening of the band. This type of phenomenon implies that their chemical and crystallographic environments are fully equivalent. X-Ray diffraction studies showed[36–39] that the complexes of bromine with benzene, acetone, and dioxan have a chain structure. It may be supposed that a chain structure obtains also in all other cases, since otherwise signs of crystallographic splitting should be observed.

The complexes of I_2, ICl, and IBr with various donors are widely known and have been fairly thoroughly investigated by other methods. X-Ray diffraction analysis has shown[40] that the length of the I–X bond in the complexes is much greater than in the initial compound, while the I... D distances are smaller than the sum of the van der Waals radii of the coordinating atoms. For a large series of complexes with amines, the degree of charge transfer has been estimated by various methods[41,42] as 20–50%. According to these data, a decrease of the frequencies in the NQR spectra by about 10–25% was to be expected. However, contrary to expectation, experiments showed[43,44] that eQq_{zz} for ^{127}I in complexes of this kind increases.

The suggested low degree of charge transfer[43,44] is inconsistent with the above results from other methods. It is also difficult to accept that, with the observed increase of eQq_{zz} (from 2156 MHz for I_2 to 3000–3100 MHz for $I_2.D$, where D = pyridine), a charge transfer of 20–50% plays an insignificant role. It is more realistic to suppose that in these complexes charge transfer is accompanied by sp^3d-hybridisation of the iodine atom[42]. We shall consider the effect of sp^3d-hybridisation and charge transfer on eQq_{zz} in greater detail. For simplicity, we shall confine ourselves to the complex $I_2.D$, where the ionic character of the I–X bond may be neglected. Five sp^3d-hybrid wave functions of the iodine atom are of the following form[45]:

$$\begin{aligned}
\sigma_1 &= \frac{1}{\sqrt{6}}(s - d_{z^2} + 2p_x),\\
\sigma_2 &= \frac{1}{\sqrt{6}}(s - d_{z^2} - p_x + \sqrt{3}\,p_y),\\
\sigma_3 &= \frac{1}{\sqrt{6}}(s - d_{z^2} - p_x - \sqrt{3}\,p_y), \qquad (20)\\
\sigma_4 &= \frac{1}{2}(s + d_{z^2} + \sqrt{2}\,p_z),\\
\sigma_5 &= \frac{1}{2}(s + d_{z^2} - \sqrt{2}\,p_z).
\end{aligned}$$

The σ_1, σ_2, and σ_3 orbitals are occupied by unshared electron pairs, the σ_4 orbital is involved in the formation of a covalent bond, and σ_5 is an acceptor orbital. After the summation of the electron densities of the p_x, p_y, and p_z orbitals, it is readily seen [Eqn. (10)] that the field gradient due to the sp^3d-hybrid valence shells of iodine is $\frac{3}{2}q_{at}$ and charge transfer leads to its decrease. Hence the degree of charge transfer in the complexes investigated is about 40–50%, which agrees fairly well with the previous results based on the dipole moments and infrared spectra.

In the complexes of carbon tetrachloride and carbon tetrabromide with various donors electrons are transferred to an antibonding σ orbital of the acceptor molecule. As already stated, this should be accompanied by a low-frequency shift of the halogen spectra. The available data for the complexes $CCl_4.D$[15,29,46,47] are non-systematic and contradictory and therefore will not be discussed. The spectra of CBr_4 complexes with a number of π donors[29,48] consist of 2–3 lines located in most cases in the same frequency range as the spectra of the initial compounds. Using X-ray diffraction data, the low-frequency lines in the spectra of the complexes were assigned[49] to the bromine atoms in the immediate vicinity of the aromatic system. The attempts to compare their frequencies with the ionisation potentials of the donors were unsuccessful. It is believed that this may be caused by intermolecular reorientation of the donor in the complex and by the difference between the Ar... Br distances.

In the complexes $AsI_3.3S_8$, $SbI_3.3S_8$, $SnI_4.2S_8$, and $SnI_4.4S_8$[50–53] coordination also involves the iodine atoms and not the central metal atom[54–56]. They too can be classified as complexes with acceptors of the σ type.

The large changes in the quadrupole interaction constants of iodine-127, antimony-121, and antimony-123 and in the arsenic-75 frequencies in the complexes $AsI_3.3S_8$ and $SbI_3.3S_8$ originate not from charge transfer but from a rearrangement of the crystal lattice when the individual compound is converted into the complex. Thus the crystals of pure AsI_3 have a layer structure with six adjacent I atoms surrounding one ^{75}As atom. On the other hand, in the complex the AsI_3 molecule has a pyramidal structure. The changes in the gradient following such rearrangement are of course appreciable. The changes in the iodine-127 quadrupole interaction constants in the remaining complexes are very slight and their interpretation is difficult.

Thus the investigation of the NQR spectroscopic effects of complex formation by σ acceptors suggests that (1), since the degree of charge transfer in these complexes is low, the geometrical factor plays the principal role in the spectroscopic effect and (2) there is a general tendency towards a low-frequency shift as a result of charge transfer.

6. THE HYDROGEN BOND

The hydrogen bond is also of the donor–acceptor type [1]. Protic acids usually behave as proton donors in the hydrogen bond. Thus they can be regarded as electron acceptors of the σ type. Using the generally adopted hypotheses concerning the nature of the hydrogen bond, this makes it possible to maintain a common approach to the analysis of the quadrupole shifts. Among systems with hydrogen bonds, complexes of certain halogen-containing acids (CCl_3COOH, $CHCl_3$, HCl, HBr) with various donors have been investigated by the NQR method [15,17,46,47,58].

The transmission of the effect of complex formation to the halogen atoms of the acceptors, which are usually remote from the coordinating centre, is achieved by an inductive mechanism and leads to an increase of the ionic character of the R–X bond. For this reason, the quadrupole spectra of the halogen-containing acids should exhibit a low-frequency shift.

The hydrogen bonds in dilute solutions are frequently investigated using acids capable of self-association. In the solid state such acids form polymeric structures when the same molecule behaves simultaneously as a donor and an acceptor. On addition of a base to such an acid (in studies by the NQR method the pure components are usually mixed), a dynamic equilibrium is established in the liquid between the self-associated species and the complex. On crystallisation both forms of associated species are maintained and the NQR spectrum shows simultaneously the frequencies of the self-associated species as well as the complex, altered by the steric and crystal field effects. It is very difficult to analyse in detail and assign the frequencies in such spectra. For this reason, it is more convenient to employ an average frequency shift in the analysis of the results. The average frequency shift will be greater, the more basic is the donor. Although this approach is very approximate, the results may be of definite interest.

A large number of molecular compounds of trichloroacetic acid with oxygen-containing substances have been investigated [59]. The multiplicity of the NQR spectra of trichloroacetic acid in these compounds is higher than in the spectrum of the initial acid and the limits of the frequency range are greatly extended. These changes were fully attributed [59] to crystal effects ignoring the possibility of charge transfer. However, trichloroacetic acid is a fairly powerful acceptor and therefore the role of hydrogen bonds may be significant. As a rule, the second component added to trichloroacetic acid was either another acid or a base. Since in the mixtures there is a possibility of the formation of associated species with a wide variety of compositions, it is interesting to examine in the light of the above considerations the distribution of the mean frequencies along the frequency scale for mixtures of both types. Fig. 5 shows such a distribution as a function of $N(\nu_{av})$. As was to be expected, the average frequencies of the complexes with bases are displaced to the low-frequency region, while those with acids remain the same as the mean frequency of the initial trichloroacetic acid (40.010 MHz).

A similar behaviour is possible also for weak acids incapable of self-association (for example, chloroform). In this case, the wek acidity favours a greater degree of dissociation of the complexes and therefore the spectrum may show together with the frequencies of the complex those of the initial acid. However, with increasing basicity of the donor, the low-frequency shift of the average frequency should increase. This tendency is observed in the spectra of the complexes of chloroform with various donors [15,46,47,58]. The chlorine-35 shifts of bound chloroform in all the complexes investigated are of the low-frequency type and are usually in the range 1 to 2.5%. A more detailed analysis is difficult, since the donors investigated have various frequencies and it is difficult to estimate the role of the geometrical factor. One can only note that on going from aromatic to oxygen-containing donors and from the latter to amines, the average low-frequency shift increases.

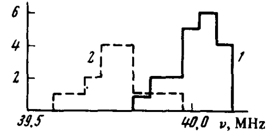

Figure 5. Frequency distribution for [^{35}Cl]trichloroacetic acid in molecular compounds with acids (1) and bases (2).

Interesting results were obtained from the NQR spectra of complexes of HCl with chlorine-containing amines [60–64]. Hydrogen chloride is close to the ionic state in such complexes and therefore the frequencies of its chlorine atoms should be close to zero, the possibility of their observation being limited in consequence. The frequencies of the chlorine present in the donors were observed in the spectra. In complexes of HCl with aliphatic amines there are high-frequency shifts in accordance with the decrease of the ionic character of the C–X bond, their magnitude reaching about 10%.

Table 4. NQR spectra of the hydrochlorides of *p*-halogenoanilines $(p\text{-}XC_6H_5NH_3)^+Cl^-$.

Compound	ν_X, MHz	$\Delta\nu/\nu$, %
$p\text{-}IC_6H_4NH_2$	261.14 521.15	
$(p\text{-}IC_6H_4NH_3)^+Cl^-$	288.28 572.15	+10.1
$p\text{-}BrC_6H_4NH_2$	221.862	
$(p\text{-}BrC_6H_4NH_3)^+Cl^-$	232.043	+4.6
$p\text{-}ClC_6H_4NH_2$	34.146	
$(p\text{-}ClC_6H_4NH_3{}^+Cl^-$	35.448	+3.8
$(p\text{-}ClC_6H_4NH_3)^+Br^-$	34.572	+1.8

In HCl complexes with *p*-halogenoanilines the effect of complex formation is transmitted to the halogen atoms in two ways. The ionic character of the C–X bond decreases via an inductive mechanism and a high-frequency shift should be observed. However, in complex formation the conjugation between the *p*-electrons of the ring and the unshared pair of the nitrogen atom is broken and the unshared pair now participates in complex formation. As a result, the conjugation between the halogen and the ring increases. The enhanced double bond character is indicated by the increase of the asymmetry parameter of the iodine atom to 7% in p-iodoanilinium chloride compared with pure p-iodoaniline ($\eta = 3\%$).[64] The increase of the conjugation between the halogen and the ring reduces the p_X electron density at the halogen, which should favour a low-frequency shift in the spectrum.

It has been shown[62-64] (Table 4) that the inductive effect prevails and the relative high-frequency shifts increase in the sequence $Cl < Br < I$. Comparison of the chlorine frequencies of p-chloroaniline in complexes with HCl and HBr shows that their H–Cl and H–Br bonds retain a certain amount of covalent character.

Thus the data quoted demonstrate that all the factors which operate in σ-acceptor complexes apply to hydrogen bonds. On the one hand, the self-association and dissociation phenomena hinder the interpretation of the NQR data and on the other serve as an additional source of information concerning the role of hydrogen bonds in solids.

7. v-ACCEPTOR COMPLEXES

The complexes of metal halides have been most completely investigated by the NQR method. In the vast majority of cases the frequencies of the halogen atoms bound to the central atom were studied. As a rule they show low-frequency shifts which are interpreted as due to an increase of the ionic character of the M–X bond. When the central atom has a quadrupolar nucleus, there is a possibility of a more complete study of the changes in the electronic structure of the acceptor molecule as a result of complex formation. Since the third section of this review dealt with a preliminary examination of the nature of the shifts and splittings in the spectra of v-acceptor complexes, we can proceed directly to a discussion of the experimental results. These can be conveniently arranged in order of the increasing Periodic Group number of the central atom.

Among Group II metal halides, 1 : 1 complexes of mercury chloride and bromide with various n-donors have been investigated by the NQR method[65,66] (Table 5). The relative low-frequency shifts of $HgCl_2$ chlorine-35 in the complexes are quite considerable, amounting to 7–15%. The complexes $HgCl_2.D$ in the solid state consist of polymeric structures comprising trigonal bipyramids linked via the edges, with the Hg atom in the centre and the donor molecule in the equatorial phase[67]. The same chlorine atom is equatorial relative to one bipyramid and axial relative to another. Therefore the splitting in the NQR spectra of complexes of this kind may be due only to crystal field effects. If one assumes that the change in the parameters of the Hg–X bonds following the change in the hybridisation of the mercury atom is the same for all complexes, the quadrupole frequency shift should be proportional to the degree of charge transfer. Indeed Table 5 shows that a decrease of the ionisation potential of the donor entails an increase of the average shift of the $HgCl_2$ chlorine-35 quadrupole frequency. It is difficult to expect a rigorously linear relation, since the geometrical factor plays a very significant role, but the general tendency is maintained.

For the complexes $HgBr_2.D$, both low-frequency and high-frequency shifts are observed. It is difficult to expect that only the geometrical factor is responsible for the 8% high-frequency shift in the spectra of the $HgBr_2$. dimethoxyethane complex. The change in the double bond character of the Hg–Br bond may also play a very significant role.

Table 5. ^{35}Cl and ^{81}Br NQR spectra of the complexes $HgX_2.D$.

No.	Complex	ν_X, MHz
1	$HgCl_2$	22.522 22.874
2	Dimethylformamide.$HgCl_2$	20.208 20.456
3	Dimethoxyethane.$HgCl_2$	21.326
4	Dimethylsulphoxide.$HgCl_2$	19.878 19.494
5	Dioxan.$HgCl_2$	21.196
6	Tetrahydrofuran.$HgCl_2$	20.584 19.272
7	$HgBr_2$	122.90 130.93
8	Dimethyl sulphoxide.$HgBr_2$ (2 : 1)	128.08 134.78 141.45 141.84
9	Dimethoxyethane.$HgBr_2$	141.23 140.40
10	Dimethylformamide.$HgBr_2$	122.87 134.60 136.00

Among compounds in Group III elements, the NQR spectra of complexes of aluminium chloride and bromide and also gallium chloride with n-donors have been investigated[2,12,68,70,71]. The only available spectrum, of the complex of $AlCl_3$ with ethyl ether[2], does not yield any definite conclusions concerning the structure, since so far the ^{35}Cl NQR spectrum of pure aluminium chloride has not been obtained. In all the aluminium bromide spectra investigated[68] appreciable low-frequency shifts of the quadrupole frequencies of the bromine atoms were observed (Table 6). Comparison of the spectra shows that in the spectrum of the complex $AlBr_3$.pyridine, which is more stable than the complexes $AlBr_3.OR'R''$ and therefore gives rise to a higher degree of charge transfer[60], there is a more pronounced low-frequency shift. Complexes of aluminium bromide with ether are of interest also from another point of view. The splitting in the NQR spectra of $AlBr_3$ in complexes with ethers of various structures indicates the occurrence of significant steric interactions between the hydrocarbon groups of the ether and the bromine atoms of the $AlBr_3$ molecule. The type of this interaction is such that, an increase in the bulk of the group increases the quadrupole frequency of the adjacent bromine atom compared with that of the bromine atom adjacent to a smaller group.

Among the halide complexes of Group III elements, those of gallium chloride with a number of n-donors have been investigated in greatest detail[70,71]. Both chlorine-35 and gallium-69 (central atom) frequencies were found in the NQR spectraof these complexes. The variation of the NQR frequencies within the limits of a series of complexes investigated are very considerable: 16–18.5 MHz for chlorine-35 and 0–25 MHz for gallium-69. Unfortunately, the main paper on the subject[70] does not give the numerical results of the measurements and all data are presented as plots of ν_{Cl} against ν_{Ga}, ν_{Cl} against $-\Delta H$, and ν_{Ga} against $-\Delta H$, where $-\Delta H$ is the heat of complex formation in the gas phase. Nor are the relations obtained discussed from the standpoint of the chemical structure. Although lack of concrete data restricts the interpretation of the NQR spectra obtained, the observed correlations permit a number of interesting conclusions.

Table 6. ^{81}Br NQR spectra of the complexes $AlBr_3.D$.

Donor	ν_{av}, MHz
	92.00
Ethyl ether	83.49
Phenetole	85.73
Phenyl ether	86.33
Dimethyl sulphide	81.62
Pyridine	82.22

The relations between ν_{Cl} and $-\Delta H$ and between ν_{Ga} and $-\Delta H$ obtained by the author (Fig. 6) show that an increase in the strength of the donor–acceptor bond, i.e. an increase in the degree of charge transfer, entails a low-frequency shift of the frequencies of both the halogen and the central atom. Furthermore, the presence of such relations confirms directly the earlier conclusion that the effect of charge transfer on the NQR spectroscopic shift predominates over the effect of steric factors in complexes of v acceptors.

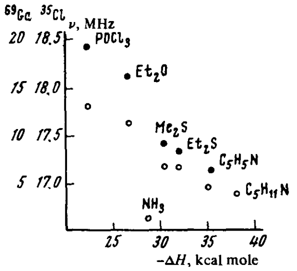

Figure 6. Variation of the average ^{35}Cl (o) and ^{69}Ga (o) NQR frequencies with the energy of the donor–acceptor bond in the complexes $GaCl_3.D$ (Figure taken from Tong[70]).

The correlation between the chlorine-35 and gallium-69 frequencies, presented by the author in a graphical form and in the form of the equation

$$\nu_{Cl} = 16.326 + 0.826\,\nu_{Ga},$$

is of considerable interest. The equation permits the estimation of the type of distribution of the transferred charge in the $GaCl_3$ acceptor molecule. Assuming that the sp^3-hybridisation of the gallium atom remains unchanged, the equation can be reformulated as follows:

$$\Delta e_{3Cl} = 2.5\,\Delta e_{Ga},$$

where Δe_{3Cl} is the overall change in electron density at all three chlorine atoms as a result of charge transfer and Δe_{Ga} is the analogous change at the gallium atom. This equation characterises the distribution of the transferred charge in the $GaCl_3$ acceptor molecule, i.e. 2/7 of the charge is localised at the central Ga atom and 5/7 is distributed among the three chlorine atoms. These results are notable because they refer to one of the first experimental estimates of the distribution of the transferred charge.

Above it was shown (Section 2) that the multiplicity of the spectra of the complexes may be used to investigate their geometrical structures. In addition to a theoretical examination of this problem, Babushkina et al.[4] made an experimental study of a number of hexaco-ordinated tin tetrachloride complexes. By comparing the experimental splitting of the chlorine-35 spectra with the theoretical scheme for the complexes $MX_4.2D$ with various geometrical structures, the structures of a number of octahedral $SnCl_4.2D$ complexes were established. Some of these complexes were investigated also by other workers[2, 46, 65, 72].

Table 7. ^{35}Cl NQR spectra of the complexes $SnCl_4.2D$.

Complex	ν, MHz	Structure
$SnCl_4\cdot 2\,(C_2H_5)_2O$	19.438 19.473	*trans-*
$SnCl_4\cdot CH_3O\,(CH_2)_2OCH_3$	19.620	*trans-*
$SnCl_4\cdot CH_3O\,(CH_2)_4OCH_3$	19.428 20.160	*trans-*
$SnCl_4\cdot 2POCl_3$	19.035 19.807 21.146	*cis-*
$SnCl_4\cdot 2C_2H_5OH$	17.498 17.750 20.120 20.568	*cis-*
$SnCl_4\cdot C_6H_5NO_2$	20.832 20.952 23.152 23.208 23.336	*cis-*

The complexes $SnCl_4.2C_2H_5OH$, $SnCl_4.2POCl_3$, and $SnCl_4.C_6H_5NO_2$ have been assigned the *cis*-structure (Table 7). On the basis of the average low-frequency shift, the dative properties of the donors can be arranged in the series $C_2H_5OH > POCl_3 > C_6H_5NO_2$. The complexes $SnCl_4.2(C_2H_5)_2O$, $SnCl_4.CH_3OCH_2CH_2OCH_3$, and $SnCl_4.CH_3O(CH_2)_4OCH_3$ have the *trans*-configuration and the last two complexes have a chain structure in the solid state (Fig. 7). Since the complexes $SnCl_4.RO(CH_2)_2OR$ have the *cis*-structure in solution, it was concluded that the *cis*-form isomerises to the *trans*-form when the complexes are crystallised from solutions.

The literature data[73-75] on the structures of certain complexes confirm these results. High-frequency shifts of the $POCl_3$ chlorine-35 transition have been found for the complex $SnCl_4.2POCl_3$. On average they amount to 4%. The shifts indicate that, on formation of the complex with $SnCl_4$, the ionic character of the P–Cl bond diminishes by 2.1%.

The structure of the octahedral complexes of antimony pentachloride of type $SbCl_5.D$ is very close to that of the octahedral complexes of tin tetrachloride. Their symmetry belongs to the point group C_{4v}. Consequently 4 of the 5 chlorine atoms should be equivalent (equatorial atoms). The non-equivalent (axial) atom is in the *trans*-position in relation to the donor molecule. Accordingly,

when steric factors and the crystal field effects are disregarded, the ^{35}Cl NQR spectra of the complexes $SbCl_5.D$ should consist of 2 lines with an intensity ratio of 4 : 1.

The spectra of two antimony pentachloride complexes ($SbCl_5.CH_3CN$ and $SbCl_5.POCl_3$) have been obtained[72,76]. As was to be expected, the ^{35}Cl NQR spectrum of the $SbCl_5$ molecule in the complex with acetonitrile consists of two lines with an intensity ratio of 4 : 1 and a splitting of 1.5 MHz. The frequency assignment gives rise to no doubt in this case. The steric effect of the donor molecules in the complex $SbCl_5.POCl_3$ on the quadrupole frequencies of the equatorial chlorine atoms in $SbCl_5$ is so great that the resulting splitting exceeds the frequency difference caused by the chemical non-equivalence. For this reason, in order to assign the frequencies, it was necessary to investigate[76] their temperature variation.

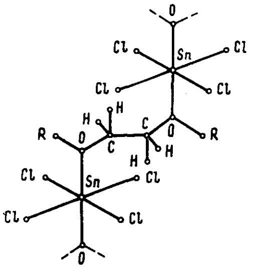

Figure 7. Structure of the complex $SnCl_4.RO(CH_2)_2OR$.

The chlorine-35 frequency shifts together with the quadrupole interaction constants of antimony-121 and antimony-123 (spins of 5/2 and 7/2 respectively) make it possible to estimate the degree of charge transfer and the type of its distribution in the acceptor molecule. For simplicity we shall assume that, when the sp^3d-hybridisation of the antimony atom changes to sp^3d^2-hybridisation, the amount of ionic character of the Sb–Cl bond is unaltered. Then the increase of electron density at the chlorine atoms can be fully attributed to charge transfer. The overall charge transfer is about 35%. Using the hybrid orbitals, it is possible to calculate that the increase of the charge at the antimony atom as a result of complex formation is approximately 5 and 10% respectively for $SbCl_5.CH_3CN$ and $SbCl_5.POCl_3$. Thus the overall degree of charge transfer is about 40–45% for both complexes. It is interesting to note that the charge transferred is preferentially localised at the chlorine atoms, probably due to their high electronegativity.

As for the complexes of antimony pentachloride, the presence of two isotopes (antimony-121 and antimony-123) permits the determination of eQq_{zz} and η for antimony trichloride and tribromide in complexes with various aromatic bases[47,65,76–85]. Extensive experimental data have revealed the following trends in the changes of quadrupole spectra on formation of the complexes $SbX_3.D$ and $2SbX_3.D$: (1) the shift of eQq_{zz} for antimony is in most cases towards higher frequencies; (2) for 2 : 1 complexes, eQq_{zz} is usually higher than for 1 : 1 complexes; (3) for 1 : 1 complexes, some parallelism in the increase of eQq_{zz} with increase of the ionisation potential of the donor is observed; (4) the average $SbCl_3$ chlorine-35 frequencies in the complexes are slightly displaced to the low-frequency region relative to the frequency of the initial $SbCl_3$; in antimony tribromide complexes such shifts are hardly ever observed; (5) in most of the $2SbX_3.D$ complexes the two acceptor molecules are non-equivalent.

The interpretation of the changes in eQq_{zz} in these complexes is very complicated, since on complex formation the partially sp^3-hybridised atomic orbitals of antimony become in addition partially d-hybridised. Neglecting the d-hybridisation, the authors[79–84] interpret the decrease of eQq_{zz} by electron transfer to the p_x or p_y atomic orbitals of antimony and the increase by transfer to the p_z orbital. However, this interpretation is not unique. In the first place, direct transfer of electrons to the p_x, p_y, or p_z orbitals is impossible, since three of the sp^3-hybrid orbitals participate in the formation of Sb=Cl bonds and the fourth is occupied by an unshared electron pair. Moreover, sp^3d-hybridisation leads to a change in the distribution of electron density between the s, p, and d orbitals. For a sufficiently high degree of d-hybridisation, the contribution to eQq_{zz} due to such redistribution may be very considerable. Therefore neglect of d-hybridisation can lead to an incorrect interpretation of the experimental data.

The overall change in eQq_{zz} on complex formation can probably be regarded as a result of the operation of two principal effects (excluding the steric and crystallographic effects): sp^3d-hybridisation with a corresponding change in the populations of the p orbitals and charge transfer to the vacant orbital.

It has been shown by infrared spectroscopy[86] that the complex $2SbCl_3.C_6H_6$ has C_{2v} symmetry. From this point of view, and also taking into account the maximum repulsion between the "ligands" and the unshared pair of the antimony atom, sp^3d_{xy}-hybridisation is most appropriate[45]. Then an increase of the degree of d-hybridisation hardly alters the p_z character of the unshared electron pair and reduces significantly the populations of the p_x and p_y orbitals. Consequently a change in hybridisation leads to an increase of eQq_{zz} [see Eqn. (10), remembering that the sign of q_{at} for antimony is the opposite of that for the halogen]. Charge transfer to the vacant hybrid orbital corresponds to an increase of p_x- and p_y-electron density and leads to a decrease of eQq_{zz}. This view appears to be more appropriate for the explanation of the available experimental data. One may assume that in complexes of the same acceptor, for example $SbCl_3$, the degree of d-hybridisation is approximately the same and leads to the same increase of eQq_{zz}. Then, following an increase in the degree of charge transfer, eQq_{zz} in this series of complexes will diminish. Such a tendency is observed very distinctly in the complexes $SbCl_3.D$; when the ionisation potential of the donor falls, the degree of charge transfer increases and eQq_{zz} diminishes. In a complex $2SbX_3.D$ the degree of charge transfer to one of the acceptor molecules will of course be smaller than in a complex $SbX_3.D$ and therefore eQq_{zz} for D will, of course, be greater. The increase of the antimony field gradient in most of the complexes and the slight low-frequency shifts in the quadrupole spectra of the halogens suggests a low degree of charge transfer in these complexes. Steric factors would then, of course, play a very significant role. Despite the large number of experimental data, a more detailed analysis of the effects of the electronic and steric factors in these complexes is still difficult.

An attempt has been made[86] to establish the steric structure of the complex $2SbCl_3.C_6H_6$ by the Zeeman analysis of the quadrupole spectra. It was shown that the geometry of both $SbCl_3$ molecules is distorted only slightly. The relative positions of all three molecules in the complex can probably be elucidated in detail by X-ray diffraction analysis.

As for the antimony trichloride complexes, only slight chlorine-35 frequency shifts were observed in the complexes $AsCl_3.Ar$.[65,85] By analogy with the splitting of the chlorine-35 frequencies and the splitting of the spectra of antimony trichloride complexes, the authors established that the structure of the $2AsCl_3.D$ complexes investigated is analogous to that of the corresponding complexes $2SbCl_3.D$.

While in the above investigations the spectroscopic shifts of the acceptors for various dative properties of the donors were mainly compared, Rogers and Ryan[72] attempted to use the frequency shifts of the donors to compare the acceptor properties of certain metal halides. According to the $POCl_3$ chlorine-35 shift in the complexes $MX_n.POCl_3$, the acceptor properties of the metal chlorides vary in the sequence $SbCl_5 > FeCl_3 > SnCl_4 > TiCl_4$. After appropriate development, it will probably be possible to use this method for the determination of the electron affinities of acceptors.

Thus the effect of complex formation by *v* acceptors on NQR spectra is as follows.

1. The change in the field gradient at the central atom is determined mainly by two factors—the change in the hybridisation of the valence shell and in the degree of charge transfer. In most cases the effect of electronic factors is considerable, while steric factors play a secondary role.
2. The frequencies of the quadrupole spectra of the halogens are displaced towards lower values as a result of an increase of the ionic character of the M–X bond. This shift is higher, the greater is the degree of charge transfer. An appreciable effect of steric factors is characteristic of weak complexes.
3. The type of splitting in the spectra is largely determined by the symmetry of the complex formed. This splitting is caused by the chemical non-equivalence of the halogen atoms in the complex. The magnitude and nature of the splitting can serve as an additional source of information about the electronic and steric effects in the complexes investigated.

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The results of the investigations demonstrate in the first place that the shift of the NQR frequencies for the complexes is closely related to the degree of charge transfer. Although there is as yet no direct experimental proof of this relation, theoretical studies and many indirect experimental data suggest that this relation should be of the type of direct proportionality. The type of splitting in the spectrum is determined by the distribution of electron density in the molecule and the symmetry of the complex. Steric effects can, on the one hand, obscure the effects of electronic factors and, on the other hand, they can serve as an additional source of information about the steric structure of the complexes in the crystal.

Summarising the results of the investigations, we should note that, despite the small number of studies, NQR has proved useful as a very effective method for the investigation of molecular compounds. It is effective because NQR is directly related to the distribution of electron density among the bonds in the molecule. Even slight changes, as regards energy, in electron distribution are reflected in NQR spectroscopic parameters. From this point of view, the NQR method is very promising for chemical structure analysis.

The temperature variation of the frequencies and the asymmetry parameters is of great interest for the investigation of charge-transfer complexes. Recent studies have shown that these relations can yield information about the intra- and inter-molecular motions in crystals.

The review does not deal at all with the problem of the effects of complex formation on the spin–lattice (T_1) and spin–spin (T_2) relaxation times. The number of studies in this field is so far small. This branch of NQR spectroscopy has been scarcely applied in the study of molecular compounds.

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Institute of Organic Derivatives of the
Elements, USSR Academy of Sciences,
Moscow

Karpov Physicochemical
Institute, Moscow

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Investigation of the Association of Alcohols and Phenols by the NMR Method

A.I.Brodskii (deceased), V.D.Pokhodenko, and V.S.Kuts

The review discusses and analyses the literature on the study of the association of alcohols and phenols by the NMR method. The methods for the determination of the equilibrium constants and heats and entropies of formation of the association complexes of the above substances in both inert and basic solvents are described for equilibria of different types.

The polar and steric effects of the substituents in alcohols and phenols on the thermodynamic functions for the formation of self-association complexes and also of association complexes with polar molecules has been analysed.

The bibliography comprises 151 references.

CONTENTS

I. INTRODUCTION

In recent years the nuclear magnetic resonance (NMR) method has been widely used in structural investigations and also in the study of problems such as isomerism, tautomeric equilibria, reaction rates, and others[1-3]. An important application of the method is also the study of intermolecular interaction and in particular association processes in hydrogen-bonded systems. The wide use of NMR for this purpose is due to its many advantages compared with the traditional procedures for the investigation of hydrogen bonds, for examples infrared spectroscopy. The advantages include primarily the relative simplicity of the NMR spectra and a fairly high sensitivity of the method, which allows the observation of shifts due to the formation of hydrogen bonds even in the case of relatively weak interactions. The availability of a frequency scale for NMR measurements permits the determination of the lifetime of the association complex formed by hydrogen bonding or the limits of existence of the complex. When strong intramolecular hydrogen bonds are formed, the band due to the OH group in infrared spectra is frequently so diffuse that it is very difficult to observe. In contrast, the detection of such bonds by NMR spectroscopy does not present difficulties, since the NMR signals in liquid specimens and in solutions are as a rule fairly narrow. The NMR method permits the investigation of aqueous solutions, the study of which by infrared spectroscopy is difficult due to the opacity of water as a solvent in the relevant regions of the infrared spectrum.

Numerous studies on association processes using NMR undertaken after the initial investigations[4,5] showed that a general property of systems with intermolecular hydrogen bonds is a parallel shift of the proton signal of the OH group with temperature and with dilution. Studies on the concentration and temperature dependence of the NMR signal yielded extensive data on the characteristics of hydrogen bonds, led to the determination of the degree of association in various systems, and made it possible to establish the effects of polar and steric factors in molecules on the thermodynamic characteristics of the formation of association complexes.

The problems associated with the application of the NMR method in the study of hydrogen-bonded systems are discussed in a number of monographs and reviews[1-3,6-12]. However, most of them do not deal with the many studies carried out in recent years.

This review presents a discussion of the results obtained in studies by NMR of the association of alcohols and phenols. In this connection the methods for the determination of the equilibrium constants and other thermodynamic properties of the formation of association complexes are briefly described. The self-association processes of alcohols and phenols in inert solvents and their association with bases are discussed.

The review is not concerned with problems of the hydrogen bond theory, which are discussed at a contemporary level in a number of publications[13-16] or with the nature of and methods for the calculation of chemical shifts accompanying hydrogen bond formation[13,17-24].

II. SELF-ASSOCIATION

1. Self-association Equilibrium Constants

In pure liquids and also in solutions of many substances in an inert solvent, there is a possibility of the formation of association complexes of molecules of one kind. In contrast to other spectroscopic methods[1], in the NMR spectrum the proton involved in the hydrogen bond gives rise to one averaged signal, the chemical shift of which corresponds to a mean screening for all the existing states when account is taken of their statistical weight. This is because the frequency with which hydrogen bonds are formed and dissociated exceeds by several powers of ten the frequency at which resonance absorption by protons is usually observed[25,26]. This property is responsible for certain unusual features in the method used to find the association parameters—equilibrium constants and thermodynamic functions—from NMR data.

Consider the monomer—n-mer equilibrium[2,27,28]:

$$nA \rightleftarrows (A)n \,. \qquad (I.1)$$

We shall denote by A_0, C and S the initial concentration of substance A, the equilibrium concentration of the association complex, and the initial concentration of the inert solvent (with $A_0 + S = 1$), and by n the number of monomeric molecules entering into the composition of the self-association complexes. Then the equilibrium constant expressed in mole fractions is

$$K = \frac{c\,[1-(n-1)\,c]^{n-1}}{(A_0 - n\,c)^n}\,. \qquad (I.2)$$

The chemical shift of the average signal τ in cyclic association is defined by the expression

$$\tau = \frac{n\,c}{A_0}\,\tau_n + \frac{(A_0 - n\,c)}{A_0}\,\tau_m = n\,\alpha\,\Delta\tau + \tau_m, \qquad (I.3)$$

and in linear association by the expression

$$\tau = \frac{(n-1)\,c}{A_0}\,\tau_n + \frac{A_0 - (n-1)\,c}{A_0}\,\tau_m = \alpha\,(n-1)\cdot\Delta\tau + \tau_m, \qquad (I.3^a)$$

where τ_m and τ_n are the chemical shifts of the proton in the free and hydrogen-bonded states, τ is the observed chemical shift of the proton, $\alpha = C/A_0$ the degree of self-association, and $\Delta\tau = \tau_n - \tau_m$.

It is clear from Eqns. (I.2), I.3), and (I.3^a) that, when τ_m, τ_n, and the initial concentration A_0 are known, it is possible to find the degree of association α and the equilibrium constant K for the formation of the association complexes. However, the determination of exact values of τ_m and τ_n is a complex problem. The difficulties in the determination of the first chemical shift are associated with the inadequate sensitivity of modern NMR apparatus, which precludes measurements at very low concentrations where the existence of the solute in the monomeric state is most likely. Moreover, even at the lowest concentration there is no certainty that the given substance is entirely present as the monomer (this applies, for example, to carboxylic acids). The chemical shift τ_n cannot be determined accurately because of the presence in concentrated solutions of association complexes of species with a degree of polymerisation different than that of n-meric molecules and also because of the possible presence of unassociated molecules. Therefore various approximations are usually employed in the determination of association parameters from NMR data.

Let us consider the variation of the chemical shift at low concentrations of the solute ($A_0 \to 0$). At the point $A_0 = 0$ the slope of the extrapolated chemical shift–concentration curve is defined by the following expressions: for a cyclic association complex,

$$\left(\frac{d\tau}{dA_0}\right)_{A_0\to 0} = n\,\Delta\tau\left(\frac{d\alpha}{dA_0}\right)_{A_0\to 0}, \qquad (I.4)$$

and for a linear association complex,

$$\left(\frac{d\tau}{dA_0}\right)_{A_0\to 0} = (n-1)\,\Delta\tau\left(\frac{d\alpha}{dA_0}\right)_{A_0\to 0} \qquad (I.4^a)$$

The quantity $(d\alpha/dA_0)_{A_0\to 0}$ is found by differentiating Eqn. (I.2) with respect to A_0. It has been shown[27-29] that only for monomer–dimer equilibrium ($n = 2$) is $(d\alpha/dA_0)_{A_0\to 0}$ and hence the slope of the chemical shift–concentration curve non-zero. Then

$$\left(\frac{d\alpha}{dA_0}\right)_{A_0\to 0} = K_2\,.$$

Examination of the variation of the chemical shift at very low concentrations ($A_0 \to 0$) does not eliminate the difficulty in the determination of the equilibrium constant because of the complexity of the accurate measurement of $\Delta\tau$,[29] although it does make it possible to establish the type of association. However, it should be noted that a non-zero slope of the concentration variation of the chemical shift at low concentrations is observed also for the monomer + (n −1)-mer ⇌ n-mer association[28].

At moderate and high concentrations of the solute, in contrast to the region of low concentrations, the concentration variation of the chemical shift deviates from linearity even in the monomer–dimer equilibrium, as follows from the simultaneous solution of Eqns. (I.2) and (I.3) or (I.2) and (I.3^a). Moreover, the deviation of the relation from linearity also occurs due to the presence in solution of association complexes of higher orders than at low concentrations.

For simplicity, it is usually assumed that even at high concentrations only one type of association occurs in solution. In this approximation simultaneous solution of Eqns. (I.2) and (I.3) with $|\tau_m| > |\tau_n|$ leads to the expression[12]

$$\frac{\tau_m - \tau}{\tau_m - \tau_n} = n\,K\,A_0^{n-1}\left(\frac{\tau - \tau_n}{\tau_m - \tau_n}\right)^n. \qquad (I.5)$$

Since

$$\frac{\tau_m-\tau}{\tau_m-\tau_n}+\frac{\tau-\tau_n}{\tau_m-\tau_n}=1,$$

Eqn. (I.5) can be reduced to the form

$$\sqrt[n]{\frac{\tau_m-\tau}{A_0^{n-1}}}=\sqrt[n]{n\ \ K\ \ (\tau_m-\tau_n)}-\sqrt[n]{n\ \ K\ \ (\tau_m-\tau_n)^{1-n}}\ \ (\tau_m-\tau) \tag{I.6}$$

or

$$(\tau-\tau_n)^n A_0^{n-1}=(\tau_m-\tau_n)^n/n\ \ K-(\tau_m-\tau_n)^{n-1}\ \ (\tau-\tau_n)/n\ \ K\,. \tag{I.6a}$$

Eqns. (I.6) and (I.6^a) permit the graphical determination of the association order n, $\Delta\tau$, and the equilibrium constant. The accuracy of the determination of the last two quantities by this method depends entirely on the accuracy of the determination of the chemical shift of the monomer τ_m or the chemical shift of the n-mer τ_n.

The dependence of the chemical shift on the logarithm of the solute concentration usually has a point of inflection[12,30–32], the position of which is determined by the degree of association. Indeed, knowing the approximate values of τ_m and τ_n and taking the second derivative of the logarithmic form of Eqn. (I.5) with respect to the logarithm of the concentration, we find that at the point of inflection

$$n=\left(\frac{\tau_p-\tau_n}{\tau_m-\tau_p}\right)^2$$

where n is the integral value of the association order and τ_p the chemical shift at the point of inflection. Combination of Eqn. (I.5) with its logarithmic form and the derivative of the latter with respect to the logarithm of the concentrations yields

$$\tau_m=\tau_p+\frac{1}{\sqrt{n}-1}\left(\frac{d\tau}{d\ln A_0}\right)_p,$$

$$\tau_n=\tau_p-\frac{\sqrt{n}}{\sqrt{n}-1}\left(\frac{d\tau}{d\ln A_0}\right)_p, \tag{I.7}$$

$$\ln K=(n-1)(-\ln A_0)_p-\frac{n+2}{2}\ln n.$$

The method described permits the determination of the association order from approximate values of τ_m and τ_n and also the calculation of the equilibrium constant and more accurate values of τ_m and τ_n.

If the point of inflection in the relation between the chemical shift and the logarithm of the concentration is outside the limits of measured values of τ, the association parameters are usually determined by comparing the experimental variation of the chemical shift τ with that calculated from the modified Eqn. (I.5) for different n.[30,32] It is noteworthy that this method is far from accurate and frequently yields markedly different results for the same systems[33].

The above methods for the determination of association parameters make it possible to find fairly reliably only the association order n, while the accuracy of the calculated equilibrium constant is lower. The reliability of the calculated equilibrium constants may be significantly enhanced using, for example, the linearity of the dependence of the chemical shift on the degree of association α. By determining α from Eqn. (I.2) and substituting it in Eqn. (I.3), we find that

$$\tau=n\,\alpha(K,A_0)\,\Delta\tau+\tau_m\,. \tag{I.8}$$

By varying K successively in the function $\alpha(K, A_0)$, we find its value which gives the maximum correlation coefficient of the linear equation (I.8). This method has the advantage that it is not necessary to know τ_m and $\Delta\tau$ in order to find K. It was used in our determination[34] of the monomer–dimer equilibrium constants in the study of the association of dihydric and trihydric phenols.

In a number of investigations it has been shown[35–37] that the quantities τ_m and $\Delta\tau$ are almost independent of temperature. This made it possible to determine the heat of formation of the dimeric association complexes (ΔH) from the variation of the slope of the chemical shift–concentration curve with temperature using Eqn. (I.4):

$$\ln\left(\frac{d\tau}{dA_0}\right)_{A_0\to 0}=-\frac{\Delta H}{RT}+\text{const.} \tag{I.9}$$

In the monomer–n-mer equilibrium the heat of formation of the association complexes is determined either from the temperature variation of the point of inflection in the relation between the chemical shift and the logarithm of the concentration [Eqn. (I.7)] or from the temperature variation of the chemical shift at a given concentration[33]. In this case combination of Eqns. (I.2) and (I.3) with the equation $RT\ln K = -\Delta H + \Delta S T$ leads to the expression

$$\ln\left(\frac{\tau_m-\tau}{(\tau-\tau_n)^n}\right)=-\frac{\Delta H}{RT}+\text{const.} \tag{I.10}$$

In the approximation discussed ΔH is determined by varying n in such a way that the maximum correlation coefficient of the linear equation (I.10) is obtained for the given τ_m and τ_n.

A significant disadvantate of the method described is the need for accurate values of τ_m and τ_n, which are almost impossible to determine from the temperature variation alone. There is more justification for the use of these quantities found from the concentration variation in combination with data on the temperature variation of the chemical shift at a given concentration in order to determine the effect of temperature on the equilibrium constant.

2. Alcohols

In the study of the self-association of aliphatic alcohols (methyl, ethyl, isopropyl, and t-butyl), it was found that the difference between the chemical shifts of the monomeric species and species associated to the maximum extent (the self-association shift $\Delta\tau$) is approximately constant and of the order of 5 p.p.m.[35,38] This shift is so large that, on maximum dilution, the signal of the OH proton is displaced towards stronger fields than those in which the signal of the CH_3 is located. However, despite the approximately equal values of $\Delta\tau$ for these alcohols, the degree of their self-association decreases appreciably on going from methyl to t-butyl alcohol[39,40].

The composition of the multimers formed in the self-association of aliphatic alcohols has been investigated in a number of studies. Thus, by comparing the results of the measurements of the concentration dependence of τ^{OH} for methyl and t-butyl alcohol with calculated data for the monomer–dimer, monomer–trimer, and monomer–tetramer equilibria, it was found[30,41] that methanol is present in solution mainly as tetrameric association complexes and t-butyl alcohol mainly as trimeric complexes. In contrast, the study of the concentration variation of τ^{OH} for ethanol in carbon tetrachloride at very high dilutions showed[42] that the association complexes of this alcohol are predominantly dimeric. This finding agrees with the results of an infrared spectroscopic study by the same investigators[43]. Assuming that aliphatic alcohols are present in solution as dimers, the heats of formation of the association complex ΔH were determined[35] and were found to be very close to the values obtained by the infrared spectroscopic method[43]. The dimeric association of aliphatic alcohols is also indicated by other results[44].

A detailed study of the composition of the association complexes of the alcohols and their thermodynamic characteristics was made by Feeney and Walker[33]. Since the values of ΔH for the bond O–H...O are usually in the range between 3 and 6 kcal mole^{-1},[1] they calculated from the temperature variation of τ^{OH} for methyl, ethyl, and t-butyl alcohols the heats of formation of the linear and cyclic dimers, trimers, and tetramers. From the ΔH values thus obtained, only those in the range 3–6 kcal mole^{-1} were selected. The results led to the conclusion that methyl alcohol forms in solution both linear and cyclic tetramers. In ethanol both linear and cyclic trimers and tetramers are possible, while for t-butyl alcohol ΔH indicates the presence in the solution predominantly of cyclic trimers. In their investigation a number of critical remarks were made concerning the results obtained in earlier studies. Thus Feeney and Walker[33] believe that the method involving the comparison of experimental and calculated concentration variation for *n*-mers[30] cannot be used for an accurate determination of either the type or the parameters of association. This method can indicate the order of association predominating only at a particular concentration, which makes it difficult to compare the results obtained in different investigations. On the other hand, the conclusion arrived at by Becker et al.[42] that monomer–dimer equilibrium occurs in alcoholic solutions is doubtful, since their investigation was made at a very high dilution. At higher concentrations the existence of other types of *n*-mers is quite possible.

The formation of cyclic t-butyl alcohol trimers is explained[33–45] by steric hindrance of the t-butyl groups which prevents the linear association of the molecule. Moreover, the specific stability of the six-membered ring formed makes some contribution to this form of association. It is noteowrthy that Huyskens et al.[46] suggest also the existence of non-cyclic chains of associated molecules, in addition to the cyclic species, in t-butyl alcohol solutions.

The data examined show that the problem of the composition of the association complexes of aliphatic alcohols in solution is far from being finally resolved. One may suppose that the formation of hydrogen bonds in solution produces varying extents of intermolecular association. This is indicated by a number of data. Thus Vanthiel et al.[47] observed in the infrared spectrum of pure methyl alcohol at low temperatures a number of distinct bands, which they believe can be accounted for by the presence of different types of association complexes: dimeric, trimeric, tetrameric, and polymeric. Studies on dilute solutions of methyl alcohol at room temperature led to the same conclusion[48]. X-ray diffraction analysis of alcoholic solutions[49] showed that at low concentrations monomer–dimer equilibrium occurs, higher association complexes being formed on increasing the concentration.

The effect of the introduction of a halogen atom into the alkyl group of the alcohol on its self-association has been investigated in a number of studies. It has been shown that the degree of self-association diminishes in the series ethanol > monochloroethanol > dichloroethanol > trichloroethanol[50–52]. These data are confirmed by the results of the investigation of chlorinated ethanols by the infrared spectroscopic method[53]. A comparative study of ethanol and trifluoroethanol led to a similar conclusion[54]. The chemical shift of the OH proton in monomeric trifluoroethanol obtained by extrapolation to infinite dilution occurs in the region of lower fields than for ethanol itself, which is due to the greater electronegativity of the CF_3 group compared with CH_3. The lower slope of the concentration variation of τ^{OH} at infinite dilution of trifluoroethanol compared with ethanol indicates that the latter has the higher degree of association in solution.

Comparison of propyl, allyl, and propargyl alcohols showed that the presence of the double bond and even more so a triple bond increases the degree of self-association of the alcohol[39]. It is believed that the effect is due to the increased acidity of the OH proton and the decrease of steric hindrance in the series of alcohols propyl > allyl > propargyl.

There are some NMR data, mostly qualitative, on the degree of association and the nature of the multimers formed in different alcohols[55,56]. Since the slope of the concentration variation of τ^{OH} for 2-methoxyethanol is not zero, it was concluded that the monomer–linear dimer equilibrium occurs in the solution of this alcohol[33]. Similar association is proposed also for 3-ethylpentan-3-ol,[57] a number of but-3-en-1-ol derivatives, and phenylethyl alcohol[58].

As the concentration of diacetone alcohol in carbon tetrachloride or cyclohexane decreases, the OH proton is displaced towards stronger fields, i.e. the self-association complexes break down, but intramolecular hydrogen bonds between the hydroxyl proton and the carbonyl oxygen are maintained[54]. The presence of both inter- and intramolecular hydrogen bonds has also been noted for a number of diols[59–61] and substituted ethylene glycols[62], the formation of hydrogen bonds in the latter being strongly influenced by the steric properties of the adjacent groups.

The chemical shift of the OH proton in a number of substituted 2-hydroxybenzophenones is relatively insensitive to changes in concentration but is altered approximately by 10 Hz when the temperature is raised from −25° to +80°C.[63] This is evidence of the presence in the compounds investigated of strong intramolecular hydrogen bonds the formation of which has been suggested also for diastereoisomeric α- and β-aminoalcohols[64]. An unusual intramolecular hydrogen bond between the hydroxyl proton and the oxygen of the methoxy-group has been observed in the study of solutions of substituted benzyl alcohols[65].

An interesting effect of hydrogen bonds was observed by Oki and Iwamura[66], who showed that an intramolecular hydrogen bond exists between the hydroxyl proton and the ring π electrons in aryldimethylmethanol, this being confirmed also by infrared spectroscopic data[67]. The signal due to the OH proton in aryldimethylmethanol shifts towards stronger fields on dilution[66], which is evidence of self-association of this compound in solution, the monomer-dimer equilibrium constant of the ring-substituted aryldimethylmethanols varying linearly with Hammett's σ constants for the substituents. A similar intramolecular interaction between the OH proton and π electrons has also been observed[68] in allyldimethyl- and benzyldimethylmethanol; in addition, intermolecular association complexes exist in solutions of the above alcohols.

Comparison of the chemical shifts of the OH and SH protons in methanol and methanethiol in gaseous, liquid, and solid phases indicates a much higher stability of the association complexes of methanol compared with its thioanalogue.[69]. In view of the linear variation of τ^{SH} for ethanethiol[70], n-propanethiol, and phenylmethanethiol[71] with concentration in carbon tetrachloride, it was concluded that monomer–dimer equilibrium occurs in their solutions. The degree of self-association of aliphatic mercaptans decreases from methanethiol to t-butanethiol[72,73], in accordance with the known polar and steric properties of the alkyl group. The slope of the linear relation between τ^{SH} and temperature decreases in the same sequence[74].

Magnetic screening of the OH proton in aliphatic hydroperoxides (from n-propyl to n-octyl peroxide) is lower than for the OH proton in alcohols; its magnitude is similar to the screening of the proton in the carboxy-group of aliphatic acids[75,76]. When hydroperoxides are dissolved in carbon tetrachloride, the signal of the OOH proton shifts towards stronger fields, which indicates the breakdown of the self-association complexes.

3. Phenols

In the early studies on phenols by the NMR method[13,29,77,78] considerable changes in τ^{OH} on dilution with an inert solvent were already observed. However, the degree of self-association of phenols in solution is lower than for alcohols, as can be seen, for example, from a comparison of the concentration variation of the chemical shifts τ^{OH} of phenol and benzylalcohol in carbon tetrachloride[39,40], but is higher than for aniline and particularly for thiophenol[79].

Much work has been done on the effect of various substituents in phenol on its self-association. There is reason to believe that the introduction of electronegative substituents in the *para*- and *meta*-positions of phenols lowers the degree of self-association[39,41], while electropositive substituents increase it[80].

The problem of the effect of *ortho*-substituents on the self-association of phenols was investigated in greater detail. This effect is determined both by the change in the steric accessibility of the phenolic hydroxyl and the formation of intramolecular hydrogen bonds. The introduction of alkyl substituents in the *ortho*-position of phenol lowers its degree of the self-association, as already shown in the early studies on *o*-cresol[39] and 2,6-dimethylphenol[80]. The effect of *ortho*-alkyl substituents on the degree of self-association can be readily illustrated by a comparison[81] of the concentration dependence of the chemical shifts of the hydroxyl protons of 2,6- and 3,5-dimethylphenols in an inert solvent. The slope of the concentration variation of τ^{OH} for the phenol with methyl groups in the *ortho*-positions is much lower than for the phenol with the same substituents in the *meta*-positions. A detailed study of the effect of *ortho*-alkyl substituents on the self-association of phenols has been made[28,82–84]. The overall data obtained in these investigations indicate that an increase in the bulk of the *ortho*-substituents entails a sharp decrease of the degree of self-association of phenols. In 2,6-di-t-butylphenol the bulk of the *ortho*-substituents is so great that it precludes the mutual approach of the hydroxy-groups of two molecules to a distance sufficient for the formation of a hydrogen bond. In inert solvents this phenol is present in the monomeric state and its τ^{OH} is independent of concentration. At low concentrations (less than 0.1 p.p.m.) intermolecular hydrogen bonds are not formed also in solutions of 2,6-dimethyl- and 2,6-di-isopropyl-phenols[84,85]. The chemical shift due to intermolecular hydrogen bonds of *ortho*-substituted phenols is well correlated with the shift of the OH stretching vibration frequency in the infrared spectrum[84]. The importance of the effect of steric screening of the OH groups on the self-association of phenols has also been emphasised by Brodskii et al.[34], who investigated the concentration variation of τ^{OH} for many substituted *ortho*- and *para*-dihydric phenols. *Para*-dihydric phenols with t-butyl groups in their *ortho*-positions do not undergo self-association, while *ortho*-dihydric and trihydric phenols with bridging $-CH_2^-$ groups form dimeric intermolecular association complexes, the equilibrium constants and thermodynamic characteristics of which have been determined.

The introduction of a halogen atom in the *ortho*-position of phenol reduces its degree of self-association[40]. This is consistent with the decrease in the accessibility of the OH group and with the possibility of the formation of an intramolecular hydrogen bond. The heat of formation of the O–H... halogen bond is low, in agreement with Raman spectroscopic data[86]: it varies from 2.4 to 1.7 kcal mole^{-1} on going from *ortho*-chloro- to *ortho*-iodophenol[87]. ΔH for the formation of intermolecular association complexes diminishes in the same sequence[88]. A linear relation between τ^{OH} and the frequency shift of the OH stretching vibrations in infrared spectra has been found for many *ortho*-substituted phenols[89].

In contrast to *ortho*-halogenophenols, which tend to form both intra- and inter-molecular hydrogen bonds, certain *ortho*-substituted phenols form intramolecular hydrogen bonds which are so stable that the intermolecular association is not observed in their solutions. These include, in the first place, *ortho*-nitrobenzene, salicylaldehyde, methyl salicylate, and others[40,90–93]. A comparative study of the concentration dependence of τ^{OH} for *para*-, *meta*-, and *ortho*-nitrophenols showed[94] that the first two phenols, which have no intramolecular hydrogen bonds, form self-association complexes in solution, while the *ortho*-isomer is monomeric.

Data on the composition of the multimers of phenols in the monomer–multimer equilibria are contradictory. Thus a monomer–dimer equilibrium has been suggested[29,82,95,96] for various phenols. However, analysis of the concentration variation of τ^{OH} for many phenols led to the conclusion[30,92] that they are predominantly trimeric, while di-*ortho*-alkyl phenols are largely tetrameric[11]. Thiophenols exist in inert solvents exclusively as monomers and dimers[97].

III. ASSOCIATION

1. Equilibrium Constant for the Formation of Binary Association Complexes

When a substance A dissolves in a solvent B forming hydrogen bonds with A, association complexes with A and B are formed. On the assumption that the self-association of A may be neglected, the following equilibrium is established in the solute–solvent system in the case of binary association:

$$A + B \rightleftarrows AB. \tag{II.1}$$

Its equilibrium constant is given by the expression:

$$K = \frac{\beta(1 - \beta A_0)}{(1 - \beta)(B_0 - \beta A_0)}, \tag{II.2}$$

where A_0 and B_0 are the initial mole fractions of the solute and the solvent ($A_0 + B_0 = 1$), $\beta = x/A_0$ is the degree of association of A with the solvent B, and x is the equilibrium concentration of the association complex AB.

The chemical shift of the proton of A which formed an association complex AB with the solvent B is given by the expression

$$\tau = \beta\,\Delta\tau + \tau_A \qquad (II.3)$$

where $\Delta\tau = \tau_{AB} - \tau_A$ and τ_A and τ_{AB} are the chemical shifts of the free substance A and A hydrogen-bonded to B.

The chemical shifts τ_A and τ_{AB} are usually determined[12,99–100] by extrapolating the concentration variation of the overall chemical shift to $B_0 \rightarrow 0$ and $A_0 \rightarrow 0$ respectively.

In the extreme case with $A_0 \rightarrow 0$, Eqns. (II.2) and (II.3) yield[27,101]

$$(\tau)_{A_0\rightarrow 0} = \frac{K}{1+K}\Delta\tau + \tau^A, \qquad \left(\frac{d\tau}{dA_0}\right)_{A_0\rightarrow 0} = -\frac{K}{(1+K)^2}\Delta\tau\,. \qquad (II.4)$$

Simultaneous solution of Eqns. (II.4) permits the determination of τ_A, τ_{AB}, and K. An interesting method for determining these quantities has been proposed by Mathur and coworkers[102,103]. Substitution of Eqn. (II.2) in Eqn. (II.3) when $B_0 \gg A_0$ yields the linear equation (II.5); all the association parameters can be determined from the slopes and intercepts of the corresponding plots:

$$\frac{1}{\tau - \tau_A} = \frac{1}{K\,\Delta\tau B_0} + \frac{1}{\Delta\tau}\,. \qquad (II.5)$$

Somewhat modified expressions of this type were obtained in special cases in other investigations[82,104]. It is noteworthy that in the methods described the accuracy of the determination of the equilibrium constant and $\Delta\tau$ is fully determined by the reliability with which τ_A is found.

More accurate association parameters can be obtained by analysing the variation of the chemical shifts over a wide range of concentrations[105,106]. Indeed simultaneous solution of Eqns. (II.2) and (II.3) gives the expression

$$\tau = \frac{(1+K) - \sqrt{(1+K)^2 - 4A_0B_0K(1+K)}}{2A_0(1+K)}\Delta\tau + \tau_A. \qquad (II.6)$$

Hence it is clear that, by choosing different values of K, a value can be found such that the sum of the squares of the differences between the calculated and experimental shifts is a minimum. The use of approximate formulae[107] for the estimation of the initial value of K close to the optimum value permits a rapid and reliable determination of the association parameters. An algorithm for the solution of this problem on electronic computers has been developed on the basis of Eqns. (II.2) and (II.6).[108] Nevertheless, it is noteowrthy that the value of this method is somewhat reduced by the need to know accurately τ_A and $\Delta\tau$. This difficulty may be overcome if the condition for a minimum sum of squares of the deviations is replaced by the condition of a maximum correlation coefficient for the linear equation (II.6),[109] which amounts to the same thing for a linear system.

The presence of the inert solvent S in the system causes some displacement of equilibrium, which affects the equilibrium constant. In this case the variation of the chemical shift with concentration is given by the expression[27]:

$$\tau = \frac{(1+KP) - \sqrt{(1+KP)^2 - 4A_0B_0K(1+K)}}{2A_0(1+K)}\Delta\tau + \tau_A, \qquad (II.7)$$

where $P = 1 - S$ and S is the mole fraction of the inert solvent ($A_0 + B_0 + S = 1$). When $P = 1$, Eqn. (II.7) becomes identical with Eqn. (II.6).

If self-association of one of the components takes place in the solution as well as the association of A and B, the two types of equilibria compete, namely self-association described by Eqn. (I.1) and association described by Eqn. (II.1).[27,110] When self-association complexes A_2 and association complexes AB are formed simultaneously in the system under the condition $A_0 + B_0 = 1$, the equilibrium constants are given by the following relations:

$$K_{A_2} = \frac{\alpha[1 - A_0(\alpha+\beta)]}{A_0[1-(2\alpha+\beta)]^2}, \qquad K_{AB} = \frac{\beta[1 - A_0(\alpha+\beta)]}{[1-(2\alpha+\beta)][B_0 - A_0\beta]}, \qquad (II.8)$$

where $\alpha = c/A_0$ and $\beta = x/A_0$ are the degrees of self-association and mutual association respectively, c and x being the equilibrium mole fractions of the complexes A_2 and AB. In this case the observed chemical shift is given by the expression:

$$\tau = 2\alpha\,\tau_{A_2} + \beta\,\tau_{AB}, \qquad (II.9)$$

where τ_{A_2} and τ_{AB} are the chemical shifts of substance A hydrogen-bonded to another species A or B respectively. To facilitate further analysis, the starting point for the reckoning of the chemical shift τ in Eqn. (II.9) was assumed to be the value for substance A in the monomeric state ($\tau_A = 0$). When the degree of self-association is infinitely low ($\alpha \rightarrow 0$ for $A_0 \rightarrow 0$), we obtain from Eqns. (II.8) and (II.9)

$$(\tau)_{A_0\rightarrow 0} = \frac{K_{AB}}{1+K_{AB}}\tau_{AB}, \qquad (II.10)$$

and the slope of the concentration variation of the chemical shift for the cyclic dimer is

$$\left(\frac{d\tau}{dA}\right)_{A_0\rightarrow 0} = \frac{1}{(1+K_{AB})^2}\left[2K_{A_2}\tau_{A_2} - K_{AB}\tau_{AB}\left(1 + \frac{2K_{A_2}}{1+K_{AB}}\right)\right]. \qquad (II.11)$$

For a linear dimer, the first term in square brackets in Eqn. (II.11) is replaced by $K_{A_2}\tau_{A_2}$.

When monomer-n-mer self-association of one of the components takes place in the solution in addition to association, the asymptotic value of the chemical shift at $A_0 \rightarrow 0$ [Eqn. (II.10)] does not change and the limiting slope of the concentration variation of the chemical shift is given by the expression

$$\left(\frac{d\tau}{dA_0}\right)_{A_0\rightarrow 0} = -\frac{K_{AB}}{(1+K_{AB})^2}\tau_{AB}. \qquad (II.12)$$

The presence of an inert solvent in the system alters the conditions defined by Eqn. (II.8). It is then necessary to consider two possibilities.

1. In the general case the concentrations A_0 and B_0 cannot be neglected in comparison with S. Then, bearing in mind that $A_0 + B_0 + S = 1$, we obtain

$$(\tau)_{A_0\rightarrow 0} = \frac{K_{AB}P}{1+K_{AB}P}\tau_{AB}, \qquad (II.13)$$

and the limiting slopes for a cyclic dimer is

$$\left(\frac{d\tau}{dA_0}\right)_{A_0\rightarrow 0} = \frac{1}{(1+K_{AB}P)^2}\left[2K_{A_2}\tau_{A_2} + \frac{K_{AB}^2P^2(1+K_{AB})}{1+K_{AB}P}\tau_{AB} - K_{AB}(1+K_{AB}P)\left(1 + \frac{2K_{A_2}}{1+K_{AB}P}\right)\tau_{AB}\right]. \qquad (II.14)$$

For a linear dimer, the first term in square brackets in Eqn. (II.14) is replaced by $K_{A_2}\tau_{A_2}$. When self-association complexes of an order higher than two (dimers) are present in solution, then

$$\left(\frac{d\tau}{dA_0}\right)_{A_0\to 0}=\frac{K_{AB}P}{(1+K_{AB}P)}\left(K_{AB}P\frac{1+K_{AB}}{(1+K_{AB}P)^2}-1\right)\tau_{AB}\ . \qquad (II.15)$$

Naturally, when $P = 1$, Eqns. (II.13), (II.14), and (II.15) become identical with Eqns. (II.10), (II.11), and (II.12) respectively.

2. The concentrations A_0 and B_0 tend to zero simultaneously ($P \to 0$) so that one can put $S = 1$. Then for dimeric cyclic self-association, we have

$$\begin{aligned}(\tau)_{A_0\to 0}&=0\,,\\ \left(\frac{d\tau}{dA_0}\right)_{A_0\to 0}&=2K_{A_2}\tau_{A_2}+K_{AB}\tau_{AB}.\end{aligned} \qquad (II.16)$$

In the case of linear dimers the first term in the second Eqn. (II.16) is $KA_2\tau_{A_2}$, while in the formation of self-association complexes of an order higher than two (dimers) it is zero.

When several types of equilibria (for example $A + A \rightleftharpoons A_2$, $A + B \rightleftharpoons AB$, and $B + B \rightleftharpoons B_2$ occur simultaneously in solution, simple expressions cannot be obtained for the asymptotic quantities $(\tau)_{A_0} \to 0$, $(d\tau/dA_0)_{A_0} \to 0$, $(\tau)_{B_0} \to 0$, and $(d\tau/dB_0)_{B_0} \to 0$. Several examples of the analysis of such complex systems have been described[111-115].

The chemical shift of the proton in a hydrogen bond can be represented in a general form as a function of the concentrations of the components in solution (x_i), the equilibrium constants for the formation of the association complexes (K_{ij}), and the chemical shifts of the protons in various states (τ_i and τ_{ij}):[12,116]

$$\tau_{obs}=f(x_i,\ K_{ij},\ \tau_i,\ \tau_{ij}). \qquad (II.17)$$

Eqn. (II.17) can be represented by a power series in terms of x_i, the coefficients of different powers of x_i being mixed non-linear functions of τ_i, τ_{ij}, and K_{ij}. The solution of this system by least squares yields a series of inhomogeneous non-linear equations and therefore the parameters τ_i, τ_{ij}, and K_{ij} are not determined unambigously. More accurate values of these parameters can be found, for example, by the "direct search" method[117].

The procedures described for the determination of the equilibrium constants for different types of association do not take into account the non-ideality of the solution and consequently the values of K are obtained in this way with an accuracy determined by a factor which depends on the activity coefficients of the substances undergoing association[118-120].

The determination of the thermodynamic characteristics of the association process in the presence of simultaneous self-association of the components in solution is a complex problem which becomes considerably simplified when it is known with certainty that one of the components does not undergo self-association and only forms association complexes with the second component.

Then the thermodynamic characteristics of the formation of association complexes may be found from the temperature variation of the chemical shift of the proton in the substance which does not undergo self-association. In the presence of a large excess of the solvent ($B_0 \gg A_0$) the product βA_0 in Eqn. (II.2) may be neglected and the following form of the van't Hoff equation is obtained[84,109,121-123]:

$$R\ln\left(\frac{\tau_A-\tau}{\tau-\tau_{AB}}\cdot\frac{A_0+B_0}{B}\right)=-\frac{\Delta H}{T}+\Delta S\,. \qquad (II.18)$$

The chemical shift τ_{AB} and the heat (ΔH) and entropy (ΔS) of formation of the association complex are determined from the conditions of the maximum correlation coefficient for the linear equation (II.18) when τ_{AB} is varied.

2. Alcohols

The study of the concentration variation of the chemical shift of the hydroxyl proton in aliphatic alcohols showed[39,40,50] that the degree of their self-association strongly depends on the solvent, being higher in cyclohexane than in carbon tetrachloride and chloroform. This was explained by the formation of intermolecular hydrogen bonds between the alcohol and the solvent, which leads to a decrease of the degree of the alcohol–alcohol self-association. In general, dilution of an alcohol solution by a solvent having basic properties is accompanied by two processes: dissociation of the multimers and association of the monomers with the solvent[39,101,142]. The changes of the chemical shift in the NMR spectra under the influence of these effects are of the opposite sign: the dissociation of the multimers shifts the OH proton signal towards stronger fields, while association with the base causes the opposite shift towards weaker fields. In weakly basic solvents dissociation of multimers predominates and the τ^{OH} signal is displaced towards stronger fields, while in stronger bases association predominates and the τ^{OH} signal is displaced towards weaker fields. Hence it is clear that the shift due to the formation of hydrogen bonds on association will be greater the more acid the solute and the more basic the solvent. This has served as a basis for assessing the relative acidities of many alcohols by comparing their chemical shifts due to the formation of association complexes with the same base[39]. It was shown that the introduction of chlorine atoms into the methyl group of ethanol increases the shift due to the formation of an association complex with the base, i.e. the acidity of the OH proton increases in the sequence ethanol < monochloroethanol < dichloroethanol < trichloroethanol. This sequence is consistent with the increasing inductive effect of chlorine atoms, which is confirmed by the infrared and ultraviolet spectroscopic studies of solutions of these substances[53,125] and also by the pK values[126].

On the other hand, when the alcohol behaves as a base, for example, in a mixture with chloroform, the chemical shift due to association decreases from ethanol to chlorinated ethanol, in agreement with the decreasing basicity of the hydroxyl oxygen in this sequence[51].

Similarly, it has been shown that the capacity of association with a base, and hence the acidity of the OH proton, increases appreciably in the series propanol < prop-1-enol < prop-1-ynol[39], while the opposite sequence holds in chloroform[51].

A comparative study of the formation of association complexes of t-butyl alcohol in acetone and dioxan showed that dioxan is a stronger base[120].

The association of alcohols with various classes of organic compounds has been investigated in a number of studies[30,40,101]. The formation of 1 : 1 association complexes has been observed in the systems benzyl alcohol–acetone[127] and methanol–pyridine[128]. It has been shown[101,129] that alcohols undergo association with nitriles, the strength of the bond in the methanol–acetonitrile association complex being greater than in the methanol–methyl isocyanide complex, in agreement with the results of an investigation of the vibration spectra of these systems[129]. The bond strength in the association complexes of 2-propanol with *N*-methylacetamide and *NN*-dimethylacetamide[104] is close to that found in the system alcohol–dimethylformamide by infrared spectroscopy[130].

The replacement of the hydroxyl oxygen by sulphur in the alcohol leads to a decrease of bond strength in the association complex with the base[73,131], although the acidity of the proton donor increases. This effect is probably due to the characteristics of the electronic structure of sulphur, which are responsible for the proton-donating and proton-accepting functions of the mercapto-group.

3. Phenols

Phenols, which are stronger acids than alcohols, form more stable association complexes with bases. The formation of such complexes by phenols with various solvents have been investigated in detail by a number of workers.

In the first place one should note the effect of the differences in the acid properties of the phenol and the base on the stability of the complex. Thus the shifts due to the formation of association complexes of 22 phenols with dimethyl sulphoxide are linearly correlated with Hammett's σ constants for substituents, increasing with the acid properties of the phenol[132]. A similar relation was obtained for systems comprising *meta*- and *para*-substituted phenols on the one hand and pyridine on the other[133], which agrees with data for substituted phenol–amine systems obtained by ultraviolet spectroscopy[134,135]. On the other hand, the shift due to association involving phenols is proportional to the basicity of the electron donor[136,137].

A detailed study of systems comprising mixtures of phenols with amines, ethers, sulphoxides, and phosphorus- and carbonyl-containing compounds[138] revealed a linear relation between the shifts due to association and the heats of formation ΔH of the association complexes. Similar results were obtained also by comparing the shifts $\Delta\tau$ due to association and the heats of formation ΔH of the association complexes in phenol–substituted pyridine systems[139]. Earlier similar linear relations were found by comparing the heats of formation of the association complexes with the frequency shifts in the infrared spectra[140,141] and it was emphasised in the second study that a relation of this kind should be observed only for similar compounds with comparable steric effects of the substituents.

With increase of the distance between the atoms forming the hydrogen bond, the strength of the latter diminishes. In agreement with this finding, a linear relation between the chemical shift due to association and the hydrogen bond length was obtained[13] in a study of the association of phenols with bases.

A linear relation between the shift $\Delta\tau$ in NMR spectra and the frequency shift $\Delta\nu$ in infrared spectra on formation of an association complex has been noted in many investigations[13,142–144]. This shows that the variation of these parameters with the electronic structure of the molecules is similar in both cases.

The linear relations examined above, apart from their purely theoretical importance, may also prove useful in determining a number of characteristics of substances which had not been investigated hitherto.

Earlier the effects of intramolecular hydrogen bonds in phenol on its self-association was noted. These bonds have a similar effect also on the capacity of phenols for association. The very weak intramolecular hydrogen bond in *o*-chlorophenol does not prevent either its association even with relatively weak bases such as ether and dioxan[39] or the exchange of the OH proton with methyl alcohol[142]. In contrast, the strong intramolecular hydrogen bonds in *o*-nitrophenyl, salicylaldehyde, and methyl salicylate appreciably hinder their association with basic solvents[39].

Phenols with bulky *ortho*-substituents, which, as already noted, do not undergo self-association in inert solvents, form association complexes with bases, as shown by the shift towards weaker fields of the signal due to the hydroxyl proton in the phenols[28,82–94,150]. The stability of phenol–base association complexes and the chemical shift τ^{OH} on formation of the hydrogen bond diminish with increasing bulk of the *ortho*-substituents in the phenol molecule[28], the association complexes with a stronger base, for example acetone, proving more stable than those with ether.

The study of the association of 2,6-dialkylphenols with dioxan[82] showed that bimolecular complexes are formed in the system. In view of the similarity of the curves relating the chemical shift of the OH proton to the concentration of phenol in dioxan and ethanol, it was suggested[82] that the hydrogen bond in the 2,6-di-t-butylphenol–ethanol complex is formed between the proton of the phenolic hydroxyl and the oxygen of the alcohol. Pokhodenko and Kuts[145], who investigated the effect of the nature of the *para*-substituent in 2,6-di-t-butylphenol on the formation of association complexes with t-butyl alcohol, arrived at a similar conclusion. It was shown that there is a linear relation between the chemical shift of the proton of the phenolic hydroxyl in the association complex and Hammett's σ^- constants for the substituents, with a slope having the same value as in the relation obtained from a similar comparison for monomeric phenols[145–148]. The chemical shift of the hydroxyl proton in t-butyl alcohol on formation of association complexes with phenols also varies linearly with the constants of the substituents in the phenol, but its proportionality coefficient has the opposite sign. This shows that the degree of self-association of the alcohol diminishes with increasing degree of the phenol–alcohol association. These findings are related to the dependence of the stability of the phenol–alcohol association complexes on the electron density at the oxygen and hydrogen atoms in the phenolic hydroxyl. This is consistent with the observed[145] linear relation between the chemical shifts of the proton in the phenol–alcohol association complexes and the association order and also with the autopolarisability of the O...O bond in the complex. Later studies[122] of the temperature variation of the chemical shift of the proton signal from the OH group in a number of *para*-substituted 2,6-di-t-butylphenols on association with ethanol showed that the equilibrium constants and the heats of formation of the association complexes increase linearly with enhancement of the electron-accepting properties of the *para*-substituent in the phenol, i.e. with increase of its acidity. In the same study it was also found that an increase in the stability of the phenol–alcohol association complex entails a lowering of the potential barrier to proton exchange between the phenolic and alcoholic hydroxyls. This finding constitutes experimental confirmation of the opposite variation of the strength of the hydrogen bond (represented by ΔH) and the activation energy E for proton exchange, demonstrated by Sokolov[14,15].

With increased bulk of the *ortho*-substituents in the phenol, the equilibrium constant for the formation of the association complex with methanol diminishes, although the stability of the complex remains virtually unchanged[85]. This is due to the change in the steric effect, as shown by the linear increase of the entropy of formation of the association complex with increasing overall bulk of the *ortho*-substituent. A similar effect of steric factors was observed also in an investigation of the association of 2,6-di-t-butyl-4-methylphenol with aliphatic alcohols[121,123]. It was shown that the heat of formation of the complex changes only slightly on going from methyl to t-butyl alcohol and the change in the degree of association is due to the change in the entropy of formation of the hydrogen bond, which increases linearly with the bulk of the alkyl residue of the alcohol.

The association of phenols with strong bases, such as substituted pyridines, amines, and others is accompanied by the formation of ionic species in which the proton of the phenolic hydroxyl is transferred to the nitrogen atom of the base[39,139,149]. This type of ionisation is more appreciable the more pronounced is the acidic character of the proton donor. The degree of ionisation of course increases on going from alcohols to phenols and from oxygen-containing to nitrogen-containing bases, which are more powerful electron-donating agents.

Complexes of thiophenols with bases have been much less investigated. It is known that their stability is low and as a rule does not exceed 2–3 kcal mole^{-1},[102-103] the degree of association of substituted thiophenols with acetone increasing with the electron-accepting capacity of the substituent due to the increasing strength of the hydrogen bond in the association complexes[151].

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Pisarzhevskii Institute of
Physical Chemistry,
Academy of Sciences of
the Ukrainian SSR

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Reactivity of Trivalent Phosphorus Derivatives

B.E.Ivanov and V.F.Zheltukhin

The review deals with the most important features of phosphorus(III) derivatives, which determine their chemical properties. These are the biphilicity of the phosphorus atoms due to the presence of a free electron pair and unfilled *d* orbitals and the ambidentate properties of phosphorus(III) derivatives determined by the specific contribution of both nucleophilic elements (O, N, S) and elements with vacant *d* orbitals (Si, Sn) directly linked to the phosphorus atom. Certain limits and characteristics of this contribution have been elucidated and the mechanism of the relevant reactions has been discussed.
The last section deals with the specificity of the behaviour of phosphorus(III) compounds with a phosphorus-halogen bond. The significant role of the *d* orbitals of the phosphorus atom in its chemical reactivity is discussed.
The bibliography comprises 196 references.

CONTENTS

I. INTRODUCTION

Considerable advances in the practical applications of organophosphorus derivatives and the important role of phosphorus compounds in vital processes are responsible for the considerable interest in the chemistry of these compounds. During the last 15–20 years the preparative chemistry of organophosphorus compounds has been considerably developed and an enormous amount of experimental data have accumulated, systematic and general accounts of which have been published in numerous reviews and monographs. Theoretical studies have also been pursued, but the theoretical approach to problems of the reaction mechanism and reactivity of organophosphorus compounds proved to be more difficult, particularly for phosphorus(III) derivatives, and the results obtained have been less significant compared with advances in classical organic chemistry.

This review was undertaken to examine the chemical properties of phosphorus(III) derivatives. It does not give an exhaustive compilation of studies on definite types of reaction but an attempt is made to establish certain relations which determine the chemical behaviour of phosphorus(III) derivatives in reactions. Hudson, Kirby, and others partially dealt with some of these problems in their monographs or reviews. Other problems have been formulated in a definitive form only very recently.

II. THE CONCEPT OF "BIPHILICITY" FOR PHOSPHORUS(III) DERIVATIVES

Phosphorus(III) compounds are very reactive and can enter into a wide variety of reactions. The phosphorus atom can behave either as a nucleophilic or an electrophilic centre. There are also a number of reactions in which the nucleophilic and the electrophilic properties of phosphorus are shown simultaneously.

Thus the nucleophilic properties of phosphines are well known[1,2]:

$$R_3P + R'I \rightarrow R_3\overset{+}{P}R'\overset{-}{I},$$

but in the presence of powerful nucleophilic agents phosphines are also capable of substitution reactions[3]:

$$R_2P{-}R + Na \rightarrow R_2PNa + NaR.$$

A dual reactivity is characteristic also of many other phosphorus(III) compounds, for example[4,5]:

$$(RO)_3P + R'I \rightarrow [(RO)_3\overset{+}{P}R']\overset{-}{I} \rightarrow (RO)_2P(O)R' + RI,$$
$$(RO)_3P + nR'MgI \rightarrow (RO)_{3-n}PR'_n + nROMgI.$$

The capacity of phosphorus(III) compounds to behave both as electron donors and electron-acceptors has been reflected also in the formation of complexes. Kirby[6] concluded that tertiary phosphines can behave as electron-donating species (as a result of the free electron pair of the phosphorus atom) in complex-formation reactions with metal cations, forming complexes similar to those which metals form with amines. The stability of the phosphine complexes is lower than that of the corresponding amine complexes.

However, the formation of complexes with cations such as Ag^+, Pt^{2+}, and certain others takes place via the interaction of their *d* electrons with the vacant *d* orbitals of the phosphorus atom. This is confirmed by the finding[7] that the introduction of strong electron-accepting groups into the phosphine molecule, for example CF_3, entails an increase in the stability of the complex with Pt^{2+} and by the fact that phosphorus trichloride can be displaced from the complex $Ni(PCl_3)_4$ by phosphorus tribromide or trifluoride but not by triphenylphosphine[8].

The dependence of the electron-donating or electron-accepting capacity of phosphorus(III) compounds on the substituents at the phosphorus atom has been clearly revealed by the stability of the complexes formed. Thus the stability of phosphorus(III) complexes with boranes (substances with markedly electron-accepting properties) increases in the series[9]

$$R_3P > (>N)_3P > (RO)_3P >> PCl_3 .$$

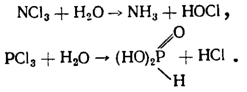
The introduction of electron-accepting substituents, for example, halogens, sharply reduces the electron density at the phosphorus atom, with a corresponding increase of the capacity of such compounds to behave as electron acceptors. Phosphorus(III) halides form complexes with electron donors such as amines[10,11], phosphines[12], and arsines[13]. Phosphorus-containing ligands can be arranged in the following sequence in terms of the stability of the complexes which they form[14]:

$$PCl_3 > PBr_3 >> RPCl_2 >>> R_2PCl \ .$$

Evidently the stability of the two types of phosphorus(III) complexes described above varies with the type of substituent in the opposite sense.

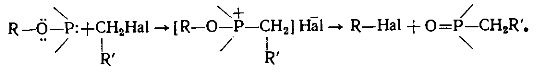
There are many examples of reactions in which phosphorus(III) compounds can behave as nucleophilic or electrophilic agents depending on the type of substituent or the second reactant. Such dual reactivity is one of the specific features of phosphorus(III) atoms. It can be explained by a combination of two factors: the presence at the phosphorus atom of both a free electron pair and vacant *d* orbitals. A characteristic feature of the phosphorus atom is that the participation of its *d* orbitals in the formation of new bonds requires a considerable positive charge, under the influence of which the levels of the *d* orbitals are lowered and their participation in the formation of new bonds becomes energetically favourable[15]. The origin of the positive charge at the phosphorus atom is apparently insignificant. It can be induced by electron-accepting substituents in the initial phosphorus(III) compounds or it can arise as a result of attack of an electrophilic agent on the phosphorus atom.

The presence of vacant *d* orbitals determines the capacity of phosphorus(III) compounds to behave as electron acceptors. The specificity of such involvement of *d* orbitals of the phosphorus atom is clearly illustrated by an example such as the hydrolysis of halogeno-derivatives of nitrogen and phosphorus[16]:

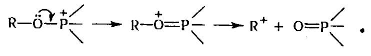


$$NCl_3 + H_2O \to NH_3 + HOCl\,,$$
$$PCl_3 + H_2O \to (HO)_2P(=O)H + HCl\ .$$

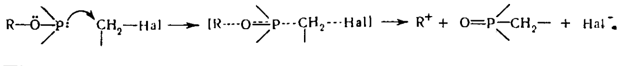
In 1962 Syrkin[17] formulated the following postulate: "All outer electrons and all outer orbitals participate in the simultaneous general lowering of the energy of the molecule formed". The application of this principle in the discussion of the reactivity of phosphorus(III) compounds can explain many important features of their behaviour in numerous reactions. Indeed all reactions of phosphorus(III) derivatives involving an increase in valence are based on the participation of both the free electron pair and the vacant *d* orbitals. One of the best investigated examples of this reaction is the Arbuzov rearrangement:



Within the framework of the electronic theory, this reaction may be described as follows. The process begins with the nucleophilic attack of the free electron pair of the phosphorus atom on the electrophilic carbon atom by an S_N2 bimolecular substitution mechanism. The positive charge at the phosphorus atom in the quasiphosphonium cation thus produced makes its *d* orbitals available for reaction. This increases the degree of interaction of the *p* electrons of the oxygen atom with the *d* orbitals of the phosphorus atom and leads to the formation of a new π bond. Probably this process may involve an intermediate stage with formation of an oxonium cation and subsequent elimination of a carbonium cation:



Analysis of extensive experimental data shows that the decomposition of the intermediate quasiphosphonium salt probably takes place by a unimolecular mechanism[18-21]. Moreover, depending on the environment of the phosphorus atom, processes involving a nucleophilic transfer of the electron pair of the phosphorus atom and the interaction of the oxygen *p* electrons with the *d* orbitals in the course of the Arbuzov rearrangement can occur either at different times or synchronously:

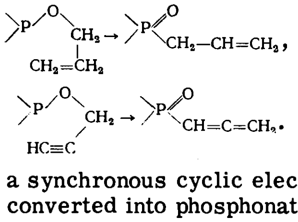


Theoretical examination of the possibility of the participation of the phosphorus *d* orbitals in the formation of additional bonds showed that the formation of fairly strong bonds via the *d* orbitals is possible only when the electron density at the phosphorus atom is reduced[15]. This in fact is the reason for the occurrence of two types of reactions, leading to an increase of the valence of trivalent phosphorus.

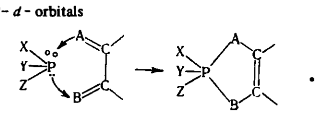
For compounds where the substituents can increase the electron density at the phosphorus atom, the rate-limiting process is the nucleophilic attack by the free electron pair on the electrophilic centre of the second reactant. When the free electron pair is transferred, the electron density at the phosphorus atom is reduced synchronously and conditions are created for the formation of additional σ and π bonds via the *d* orbitals, as shown above for Arbuzov rearrangement. This is satisfactorily consistent with data on the oxidation of phosphorus(III) derivatives by oxygen, peroxides, and peracids[22] and also on their interaction with sulphur[23]. For derivatives where the trivalent phosphorus atom has a reduced electron density, the rate-limiting process is the interaction of the reaction centre having an enhanced electron density with the vacant *d* orbitals of phosphorus. An example of such interaction is that of phosphorus trichloride with amine *N*-oxides[2] and sulphoxides[25]. In this case the process begins with nucleophilic attack by oxygen on the vacant *d* orbitals of the phosphorus atom:

$$R_3N \to O + PCl_3 \to R_3\overset{+}{N}-O-\overset{-}{P}Cl_3 \to R_3N + O{=}PCl_3\,.$$

In this connection the intramolecular rearrangement of the allyl and propargyl esters of acids derived from trivalent phosphorus, investigated in detail by Pudovik et al[26], is also of interest. The authors suggest that the process begins by attack by the free electron pair of the phosphorus atom on the unsaturated centre. However, in this case there is a possibility of a primary interaction between the π electrons of the olefin and the vacant *d* orbitals of the phosphorus atom:

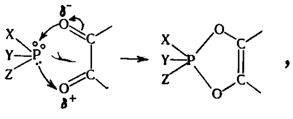


As a result of a synchronous cyclic electron transfer, phosphite is also converted into phosphonate in this case. The concept of the simultaneous utilisation of the free electron pair and the vacant *d* orbitals accounts also for the possibility of the participation of various acids derived from trivalent phosphorus in reactions with diketones, $\alpha\beta$-unsaturated carbonyl compounds, and diene hydrocarbons:



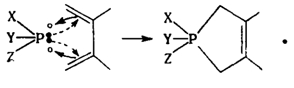
Depending on the electron density of the phosphorus atom, the rate-limiting step in this reaction can be either the transfer of the free electron pair of the phosphorus atom to the electrophilic centre or, conversely, the nucleophilic interaction of the conjugated system with the *d* orbitals of the phosphorus atom[27].

In reactions of $\alpha\beta$-dicarbonyl compounds with esters, ester-amides, and amides of acids derived from phosphorus(III), the nucleophilic properties of which have been revealed in a number of interactions, the rate-limiting process is most likely nucleophilic attack by the free electron pair of the phosphorus atom on the electrophilic centre of the conjugated system and conversely:



where X, Y, Z = OR or NR_2. The electrophilic behaviour of phosphorus in various acid chlorides derived from phosphorus(III) suggests that in this case the rate-limiting process is the interaction of the vacant *d* orbitals of phosphorus with the π-electrons of the conjugated system.

Arbuzov and coworkers and also Petrov and Razumova showed that the reactivity of dienes in interactions with trivalent phosphorus compounds increases in the sequence dimethylbutadiene < isoprene < butadiene < piperylene[28-33]. The ease of the interaction of phosphorus(III) acid derivatives of the type RPX_2 and R_2PX with diene systems increases in the sequence where R has the following significance: NCS < Cl < SR < F < OR < NR_2.[34,35] All these findings convincingly demonstrate that in these cases the rate-limiting step is the interaction of the π-electrons of the diene system with the vacant *d* orbitals of the phosphorus atom followed by the involvement of the free electron pair in the formation of a pentacovalent adduct:



Therefore all the factors favouring an increase in the electron-donating capacity of the conjugated diene and reducing the electron density of the phosphorus atom tend to increase the rate of such processes.

Heteroconjugated systems, which are readily polarised or already have both nucleophilic and electrophilic centres, are capable of interacting at a fairly high rate with any derivatives of phosphorus(III) acids. Depending on the type of the substituents at the phosphorus atom, the rate-limiting step may be the interaction of the free electron pair with an electrophilic centre, or of the π electrons of the heteroconjugated systems with the vacant *d* orbitals[36,37]. It is quite logical to postulate that the interaction in the system (X, Y, Z,)P: $+\underset{|}{A} = \underset{|}{C}-C = B$ involves synchronous formation of the P−A and P−B bonds (at least for the *cis*-form of the conjugated system), since any transition, having once begun, induces the next. By the term "synchronous" we imply that the structures $\gt\bar{P}-A-\underset{|}{C}-\underset{|}{C}-\bar{B}$ and $\bar{A}-\underset{|}{C} = \underset{|}{C}-B-\overset{+}{P}\lt$ are not formed as kinetically independent species or there is no minimum corresponding to them in the energy diagram for the reaction. Such treatment is not of course correct in all cases. Thus it is known[38] that in the interaction of phosphorous triamide with benzil the dipolar form is fairly stable and one cannot of course exclude the possibility that in certain cases it can exist also as a kinetically independent structure, particularly since the contribution of the *trans*-forms of the conjugated systems to the formation of pentacovalent adducts has not so far been accurately established. However, one must always distinguish whether the P−A or the P−B bond is formed faster, i.e. whether the process begins with nucleophilic attack by the free electron pair of phosphorus or with the interaction of the vacant *d* orbitals with the π electrons of the conjugated system—one of these processes will be rate-limiting for the reaction as a whole.

Kirby and Warren (Ref. 6, p. 22) suggested the term biphilicity for the capacity of the trivalent phosphorous atom to donate both an electron pair and *d* orbitals in a single process involving the formation of a new compound and defined it as follows: "A biphilic compound can donate electrons to the substrate to form a σ bond and also to accept electrons at the same centre, which results in the formation of a second σ or π bond".

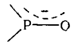
The definition of "biphilicity" as the capacity of the same reaction centre (in this case the phosphorous atom) to function consecutively or synchronously as an electron donor or acceptor in an interaction with another reactant, involving the formation of two new bonds, differs fundamentally from concepts such as ambidentate properties, dual reactivity, and amphoteric properties; as a concept defining the properties of the reaction centre, it merits recognition.

III. AMBIDENTATE PROPERTIES OF PHOSPHORUS(III) DERIVATIVES (DUAL REACTIVITY)

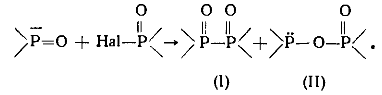
In an estimation of the nucleophilic properties of phosphorus(III) derivatives account must also be taken of the fact that many of these have two nucleophilic centres. Phosphorus(III) compounds with substituents of the type $R\ddot{S}$, $R\ddot{O}$, and $R_2\ddot{N}$ may be included among systems of this kind. Although the ambidentate nature of many phosphorus(III) compounds has been known for a long time and was demonstrated for the first time by A.E. and B.A. Arbuzov[39,40] in 1932 in the interaction of dialkyl phosphite salts with phosphorus-containing acid chlorides and by Kabachnik[41] and Michaelis[42] in the interaction of thiophosphites [phosphorothi-ites] with alkyl halides, these data have not been reviewed systematically and have been inadequately taken into account in the assessment of the occurrence of particular processes with participation of esters, thioesters, and amides of acids derived from phosphorus(III).

Two mesomeric forms, $\gt\bar{P}=O \leftrightarrow \gt\ddot{P}-\bar{O}$, are possible for an anion of the type $\gt\bar{P}=O$. Depending on the type of substituents at the phosphorus atom, the reaction conditions, and the second reactant, the nucleophilic centre can be either the oxygen or the phosphorus atom.

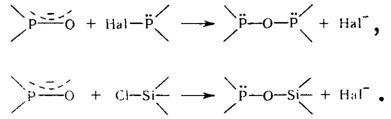
In the interaction with alkyl halides and carboxylic acid halides[40] and in reactions involving addition to an activated C=C double bond, a carbonyl group, and a C=N bond,[44] the phosphorus atom behaves as the nucleophilic centre in the anion



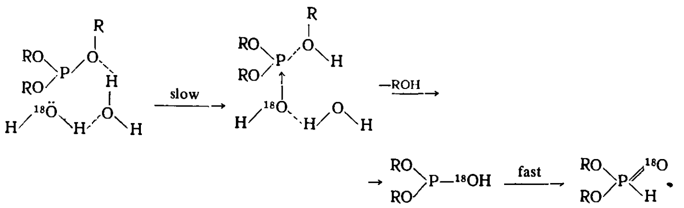
In the reaction of dialkyl phosphite salts with phosphorus(V) chlorides[45] both possible reaction products are formed, the yield of product (I) reaching 90%:



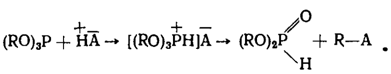
However, in reactions with phosphorus(III) acid chlorides[46] or with chlorosilanes[47-49] the oxygen atom behaves as the nucleophilic centre and trivalent phosphorus compounds are formed preferentially:



Until recently it was believed that esters of phosphinous and phosphorous acids interact in all reactions with electrophilic reagents with participation of the free electron pair of the phosphorus atom. Aksnes and Aksnes[50], who investigated the kinetics of the neutral hydrolysis of phosphites by water with labelled oxygen and analysed the hydrolysis products by infrared spectroscopy, showed that the alkoxy-radical is exchanged for the hydroxy-group with labelled oxygen. On this basis, they concluded that the oxygen of the ester group is protonated in an intermediate stage and the hydrolysis is described by the equation

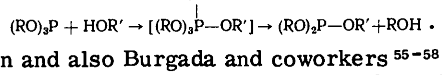


It is now generally accepted that the hydrolysis of phosphites in an acid medium[51] involves the protonation of the phosphorus atom in the phosphite with subsequent decomposition of the intermediate complex to dialkylphosphorous acid:



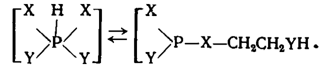
$$(RO)_3P + \overset{+}{H}\overset{-}{A} \rightarrow [(RO)_3\overset{+}{P}H]\overset{-}{A} \rightarrow (RO)_2P\begin{smallmatrix}\nearrow O\\ \searrow H\end{smallmatrix} + R{-}A\,.$$

Transesterification of phosphorus(III) acids is analogous to neutral hydrolysis in many of its details. By analogy with the acid hydrolysis of phosphites, some workers believe[52-54] that in this case the phosphorus atom is also protonated and the breakdown of the intermediate complex is accompanied by the exchange of the alkoxy-groups:



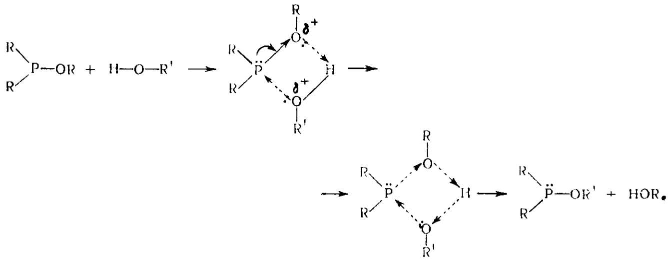
$$(RO)_3P + HOR' \rightarrow [(RO)_3\overset{H}{\overset{|}{P}}{-}OR'] \rightarrow (RO)_2P{-}OR' + ROH\,.$$

Grechkin and also Burgada and coworkers[55-58] showed that the transesterification of the esters and amides of trivalent phosphorus acids with ethanolamine or glycol involves the formation of a pentacovalent product with a spiro-structure and, what is most interesting, there is a possibility of an interconversion of the pentacovalent and trivalent forms:



The isolation of the pentacovalent spiro-product with a phosphorus–hydrogen bond and the demonstration of the interconversions of the trivalent and pentacovalent forms constitutes unquestionable proof of the possible occurrence of transesterification with participation of the free electron pair of the phosphorus atom.

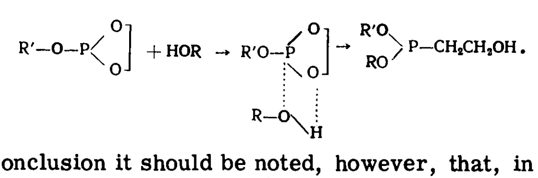
In a study of the kinetics of the transesterification of phosphinic and phosphinous acids with alcohols of different structures, Pudovik and Evstaf'ev showed that the rate of transesterification varies with the *pK* of the alcohol in the opposite sense for trivalent and pentavalent phosphorus acid esters[59-62]. The rate of transesterification of pentavalent phosphorus acid esters, which is a nucleophilic substitution reaction at the tetrahedral phosphorus atom, falls with increase of the acid properties and with decrease of the basic properties of the alcohol. For trivalent phosphorus acid esters, the opposite relation holds. This enabled the authors to suggest that, like neutral hydrolysis, the transesterification involves the initial protonation of the oxygen atom of the alkoxy-group of the phosphinite:



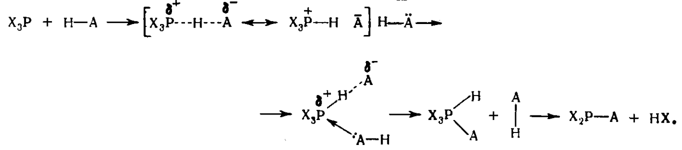
The formation of an 'onium' oxygen atom gives rise to a change in both the bonding pair and in the type of *d–p* interaction of the oxygen–phosphorus bond. This leads to a reduced electron density at the phosphorus atom and gives rise to the possibility of a nucleophilic interaction between the free electrons of the oxygen atom of the alcohol and the vacant *d* orbitals of the phosphorus atom. Such cyclic synchronous electron transfer results in the formation of a "new" phosphinite and a "new" alcohol molecule.

Although these data are apparently in conflict with the results of Grechkin and Burgada, the two sets are in fact complementary rather than mutually exclusive. It may be supposed that, while the initial reversible transition involving the protonation of the phosphorus atom is most likely to be determined by steric factors, in transesterification with alcohols the conditions for thermodynamic equilibrium constitute the decisive factor.

The possibility of the protonation of oxygen is confirmed by data[63] on the transesterification of a cyclic phosphite with alcohols:

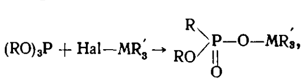


In conclusion it should be noted, however, that, in reactions between phosphorus(III) compounds and substances containing a mobile hydrogen atom, the species responsible for the reaction may not be the trivalent phosphorus compound itself but its complex with a proton donor HA, in which the phosphorus atom behaves as the reactive electrophilic centre:



The ambidentate properties of trivalent phosphorus acid esters have been reflected also in the formation of complexes with a number of elements. The formation of a copper(I) complex was suggested by A. E. Arbuzov[64] as a typical reaction of phosphorus(III) acid esters. Later investigations[65,66] permitted a more detailed study of the metal–phosphorus bond formed.

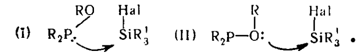
A number of investigators showed that interaction of phosphorus(III) acid esters with halogeno-compounds of silicon and tin takes place according to the equation[67–71]:



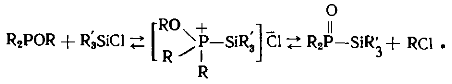
where M = Si or Sn.

Malatesta[68] suggested that the reaction with alkyl halides initially involves the isomerisation of trialkyl phosphite to alkyl phosphonate, which gives rise to the final product by reacting with the halogeno-derivatives of silicon and tin.

However, Pudovik and Muratova[72] showed that esters of dialkylphosphinous acid can react with halogeno-derivatives of silicon and tin to form stable intermediate complexes. They believe that the complexes are formed as a result of a donor–acceptor interaction between the free electron pair of the phosphorus or oxygen atom and the vacant *d* orbitals of the silicon or tin atom:

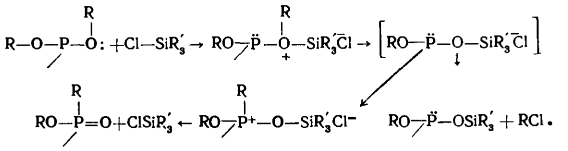


If the complex formation involves the participation of the free electron pair of the phosphorus atom and the vacant *d* orbitals of silicon or tin, then the available date on the behaviour of compounds of this kind would lead to the expectation that the breakdown of this complex would result either in the initial materials or compounds with a phosphorus–silicon bond:



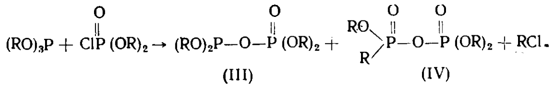
Alkylation of the phosphorus atom is quite unlikely, since this would involve the interaction of the carbonium ion formed with the positively charged phosphorus atom.

On the other hand, if the complex is formed as a result of a donor–acceptor interaction between the free electron pair of the oxygen atom in the alkoxy-radical of the phosphinite and the vacant *d* orbitals of the silicon or tin atom, then the remaining free electron pair of phosphorus in the intermediate complex would interact with the resulting carbonium ion with formation of a phosphorus–carbon bond:

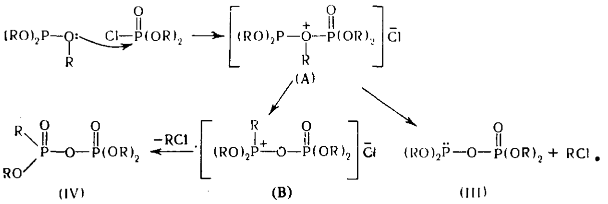


In such donor–acceptor interaction the carbonium ion formed can interact also with the halide anion, as a result of which a phosphorus(III) compound of the type $>\ddot{\mathrm{P}}-\mathrm{O}-\mathrm{SiR}_3$ is formed.

The formation of such a compound has been reported[48], confirming the validity of the mechanism discussed above. It may be supposed that a similar mechanism obtains also in the reaction of triethyl phosphite with a phosphorochloridate ester[45,73,74]:



The authors do not discuss the possible pathways in the formation of subphosphoric acid esters (III), while the formation of compound (IV) is accounted for by the isomerisation of (III) under the influence of the alkyl halide formed. However, the specificity of the structure of the product formed suggests that in this case also the participation of the oxygen atom of the alkoxy-group of the phosphite as a nucleophilic species in the primary step of the interaction is most likely:

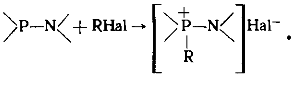


The carbonium ion R^+ is eliminated from the intermediate complex A and interacts with the free electron pair of the trivalent phosphorus atom, which leads to the formation of a quasiphosphonium salt B, or with the chloride ion to form an alkyl halide and compound (III). The decomposition of the salt B yields the product (IV).

It is noteworthy that the examination of the ambidentate properties of trivalent phosphorus acid esters is made very difficult by the fact that few data characterising their behaviour with different reagents are available; the data on the structure of the products formed are not in most cases sufficient to arrive at a conclusion concerning the participation of the phosphorus or oxygen atom in the initial reaction steps, since the structure of the final products may not depend on the mode of attack.

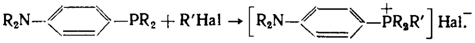
The opposite behaviour is observed for compounds with the bond $>\ddot{\mathrm{P}}-\ddot{\mathrm{N}}<$ or $>\ddot{\mathrm{P}}-\ddot{\mathrm{S}}-$for the vast majority of reactions, the structure of the final product permits a fairly reliable conclusion concerning the participation of the free electron pair of a particular atom in the initial reaction steps. This has been shown in greatest detail for the amides and amido-esters of trivalent phosphorus acids.

There exists also the view that in trivalent phosphorus acid amides the nucleophilic properties of the nitrogen atoms are reduced and those of the phosphorus atom are enhanced. This is attributed to the occurrence of intense *d–p* interaction[75]. However, only a few reactions of the amido-esters and amides of phosphorus(III) acids take place with participation of the free electron pair of the phosphorus atom, for example reactions with alkyl halides[76,77]:

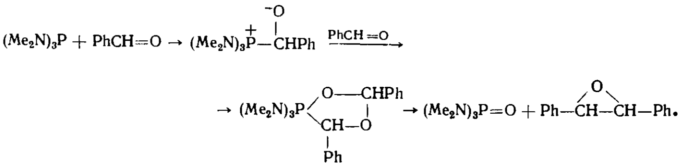


It is interesting to note that the formation of phosphonium salts is observed for both β-aminoethylphosphine[78] and for *p*-aminophenylphosphines[79]:

$$R_2\ddot{N}-CH_2CH_2\ddot{P}R_2 + R'Hal \rightarrow [R_2N-CH_2CH_2-\overset{+}{P}P_2P'] Hal^-,$$



To account for the formation of an epoxide in the interaction of phosphorous triamides with aldehydes, Mark suggested the following reaction mechanism[80]:



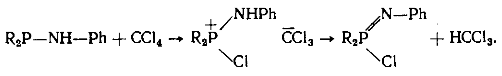
The phosphorus atom behaves as a nucleophilic centre in this reaction. The mechanism is confirmed by measurements of phosphorus-31 chemical shifts and the changes in the PMR spectra of the reaction mixtures.

Hudson and coworkers[81-83] also believe that the phosphorus atom behaves as a nucleophilic centre in the interaction of phosphorous triamides with carbon tetrachloride, which they believe to involve a mechanism with participation of a "positively charged" halogen:

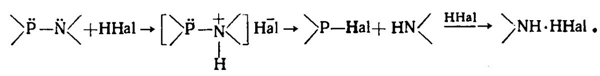
$$(Me_2N)_3P + Cl_4C \rightarrow [(Me_2N)_3\overset{+}{P}Cl\overset{-}{C}Cl_3 \rightarrow (Me_2N)_3\overset{+}{P}CCl_3\overset{-}{Cl}];$$

$$(Me_2N)_3\overset{+}{P}-CCl_3 + (Me_2N)_3P \rightarrow (Me_2N)_3\overset{+}{P}-Cl + (Me_2N)_3P{=}CCl_2.$$

According to their data, in the interaction of *N*-phenyl diphenylphosphinous amide with carbon tetrachloride proton exchange in the ion pair formed leads to the formation of a phosphinimine and chloroform:



The interaction of phosphorus(III) compounds having a P–N bond with hydrogen halides[84-86] differs fundamentally in the reaction products from the analogous reactions of phosphites:



The formation of acid halides with retention of the valence of phosphorus shows that the nitrogen atom behaves as a nucleophilic centre. The interaction of aminophosphines with secondary phosphines takes place similarly[87]:

$$(CH_3)_2P-N(CH_3)_2 + HP(CH_3)_2 \rightarrow (CH_3)_2P-P(CH_3)_2 + HN(CH_3)_2.$$

The appreciably greater basicity of the nitrogen atom compared with phosphorus is indicated by the interaction of dialkyl-(α-aminomethyl)phosphine with secondary phosphines[88]:

$$R'_2P-CH_2NR_2 + HPPh_2 \rightarrow R'_2P-CH_2-PPh_2 + HNR_2.$$

These data and also the fact that the valence of phosphorus remains unchanged suggest that the phenolysis, alcoholysis, and amidolysis reactions of phosphorus(III) acid amides take place with participation of the free electron pair of the nitrogen atom[89-93].

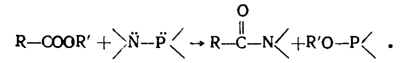
The study of the reactions of alcohols with phosphorous tri(dialkyl amides) showed that the dialkylamine hydrochloride present as an impurity in the triamide has a considerable influence on the rate of the process[94]. The influence of impurities on the rate and also on the mode of reaction has been demonstrated for the interaction of phosphorous triamides with phenolic Mannich bases[95-97].

It is noteworthy that virtually all the reactions investigated with amido-esters and amides of trivalent phosphorus acids were carried out in the presence of appreciable amounts of amine hydrochlorides as impurities. Such acid impurities may lead to the formation either of an activated complex or a phosphonium salt, which probably accelerates the transesterification. This hinders the interpretation of the interaction between trivalent phosphorus acid amides and compounds with a mobile hydrogen atom as a reaction involving the initial protonation of the nitrogen atom.

The complexity of this problem is not restricted to the effects of impurities. In the reactions of trivalent phosphorus acetamides with compounds having a mobile hydrogen atom an activated complex may be formed initially and then react with a second reactant molecule having a mobile hydrogen atom. It is quite likely that the interaction of the amides with hydrogen halides and acetic acid takes place in this way[43,48,49]:

$$>\ddot{P}-NEt_2 + 2HOCOCH_3 \rightarrow >\ddot{P}-OCOCH_3 + Et_2\overset{+}{N}H_2\overset{-}{O}COCH_3.$$

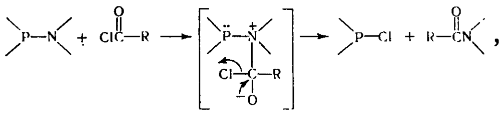
An interesting example of catalysis by compounds with a "hydrogen atom" is the interaction of trivalent phosphorous acid amides with carboxylic acid esters[89]:

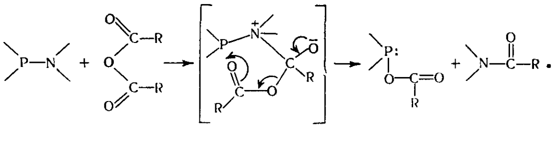


$$R-COOR' + >\ddot{N}-\ddot{P}< \rightarrow R-\overset{\overset{O}{\|}}{C}-N< + R'O-P< .$$

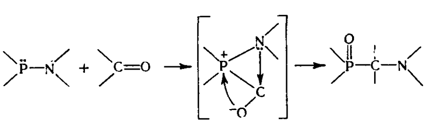
These reactions hardly occur with benzoate and acetate esters. However, phenylacetamide and malonamide are formed in high yields.

The examples of reactions of trivalent phosphorus acetamides with compounds containing a carbonyl group quoted below show that here too the nitrogen atom is the nucleophilic centre: these are reactions with carboxylic acid halides[100-102] and anhydrides[103-106]:

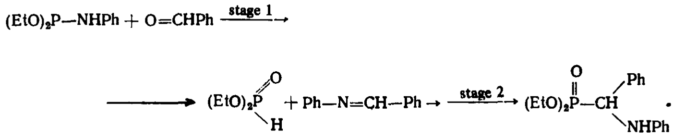




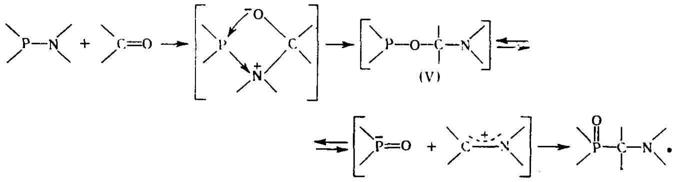
The main products of the reactions of trivalent phosphorus acid amides with aldehydes and ketones are derivatives with the group $>P(O)-\overset{|}{\underset{|}{C}}-N$, [107-110] the formation of which has been explained as follows:



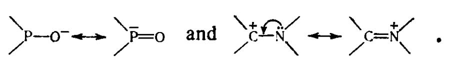
However, Hudson showed[111] that in the reaction between diethyl *N*-phenylphosphoramidite and benzaldehyde, diethylphosphorous acid and the corresponding Schiff base may be isolated as the main products in the initial period:



This was confirmed by following the reaction by infrared spectroscopy and kinetic measurements. As a result, Hudson proposed the following mechanism for the interaction of trivalent phosphorus acid amides with aldehydes:

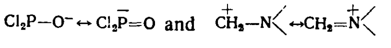


Hudson explains the possibility of the rearrangement of the intermediate compound (V) by the high stability of the ion formed on its decomposition:



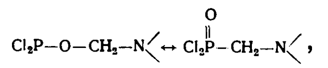
This hypothesis does not contradict the literature data on the dependence of the stability of phosphites on their structure. Thus attempts to obtain phosphites by the interaction of trivalent phosphorus acid chlorides with hydroxymethyl derivatives of various kinds[112–115] always resulted in the formation of the corresponding phosphonates and not esters of phosphorus(III) acids.

Even earlier than Hudson, the idea of resonance-stabilised ions,



$$Cl_2P-O^- \leftrightarrow Cl_2\bar{P}=O \text{ and } \overset{+}{C}H_2-N\langle \leftrightarrow CH_2=\overset{+}{N}\langle$$

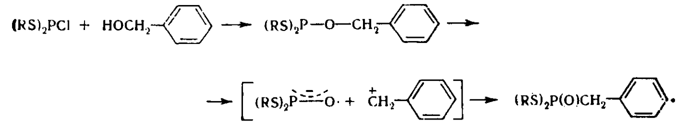
was employed by Rumpf[116] to explain the rearrangement



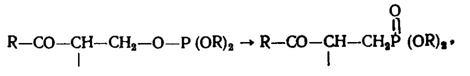
$$Cl_2P-O-CH_2-N\langle \leftrightarrow Cl_2\overset{O}{\overset{\|}{P}}-CH_2-N\langle ,$$

which takes place readily in the interaction between trivalent phosphorus and hydroxymethylamides.

Similar reactions were observed by A. E. Arbuzov and Nikonorov[117] between dialkyl phosphorochloridodithi-ite and benzyl alcohol:



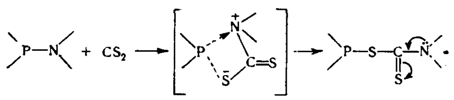
The capacity of phosphites for thermal rearrangement to phosphonates was demonstrated by Rizpolozhenskii and Mukhametov in the reaction with a γ-oxoalkoxy-radical[118]:



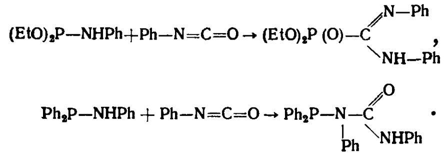
$$R-CO-\underset{|}{C}H-CH_2-O-P(OR)_2 \rightarrow R-CO-\underset{|}{C}H-CH_2\overset{O}{\overset{\|}{P}}(OR)_2 .$$

B. A. Arbuzov and coworkers[119] believe that the rearrangement of the phosphite $R-CONHCH_2OP(OR)_2$ to the phosphonate $R-CONHCH_2-P(O)(OR)_2$ can occur also in the interaction of hydroxymethylamides with triethyl phosphite.

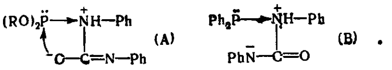
The study of the reactions of phosphoramidites and aminophosphines with carbon disulphide, carbon dioxide, and isocyanates confirms the validity of Hudson's reaction mechanism. Thus in the reaction of carbon disulphide[120] or carbon dioxide[121] with trivalent phosphorus acid amides the process stops at the stage involving the formation of a new phosphorus(III) derivative, the stability of which can probably be explained by the conjugation in the thioamide group:



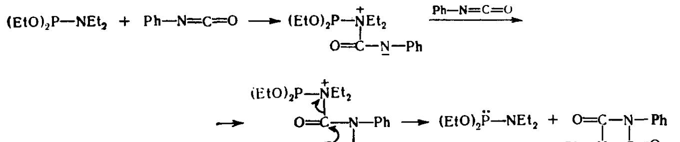
Interesting features of the rearrangement in the intermediate complex were observed in the study of the reaction of diethyl N-phenyl phosphoramidite and diphenylphosphinous anilide with isocyanates[122,123]:



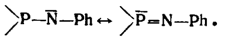
The authors explained the difference by the fact that in the intermediate complex A the alkoxy-groups make the phosphorus atom selective with respect to oxygen as a nucleophilic centre, while phenyl groups favour the interaction with the less powerful nucleophilic centre—the nitrogen atom (intermediate complex B):



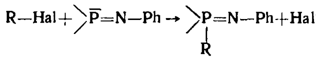
Finally, in contrast to dialkyl N-phenylphosphoramidite, dialkyl NN-diethylphosphoramidite causes only the dimerisation of the isocyanate:



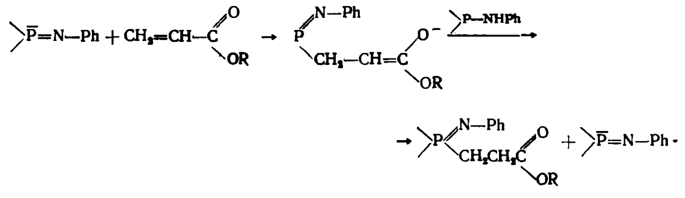
Kabachnik and Gilyarov suggested that, like dialkylphosphorous acids, N-phenylphosphoramidites can exist in two tautomeric forms[124] and found that the anion formed after the elimination of a proton from the aniline-nitrogen constitutes an ambidentate system like the anion of dialkylphosphorous acid:



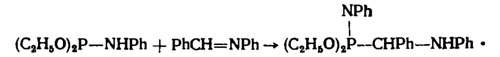
In reactions with alkyl halides the phosphorus atom is the nucleophilic centre in this anion:



In the reaction of N-phenylphosphoramidites with $\alpha\beta$-conjugated systems in the presence of basic catalysts[125], the electrophilic centre is also attacked by the phosphorus atom:

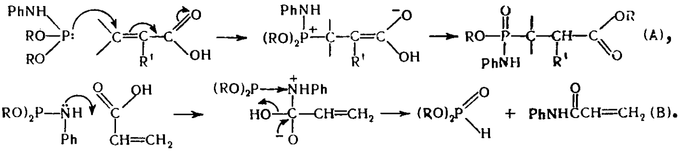


N-phenylphosphoramidites react with Schiff bases similarly[126,127]:



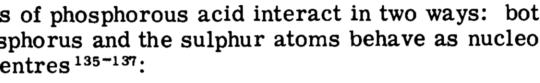
$$(C_2H_5O)_2P{-}NHPh + PhCH{=}NPh \rightarrow (C_2H_5O)_2\overset{NPh}{\overset{|}{P}}{-}CHPh{-}NHPh\,\cdot$$

N-Phenylphosphoramidite reacts somewhat differently[128] with $\alpha\beta$-unsaturated carboxylic acids. In this case the ambidentate properties of both reactants are revealed: either the free electron pair of the phosphorus atom reacts with the electrophilic terminal carbon atom of the conjugated C=C double bond (pathway A) or the free electron pair of the nitrogen atom attacks the carbonyl carbon atom of the unsaturated acid (pathway B):



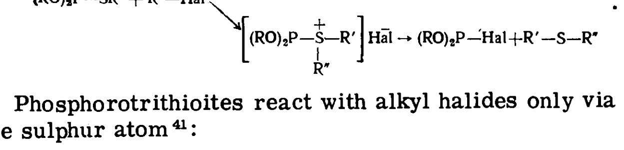
The second pathway begins to predominate when the steric hindrance at the terminal C=C bond increases. Thus the interaction of *N*-phenylphosphoramidite with cinnamic acid leads to the formation of diethyl phosphite and cinnamic acid anilide only.

Compounds with the bond $\gt\ddot{P}{-}SR$ have been investigated in less detail than other types of phosphorus(III) compounds and their chemical behaviour is not known as completely as that of compounds with the $\gt\ddot{P}{-}\ddot{N}\lt$ bond. It has been established that the thioesters of trivalent phosphorus acids are oxidised by hydrogen peroxide and peracids with formation of compounds having the $\gt P{=}O$ group and combine with sulphur to form compounds containing the $\gt P{=}S$ group[129,130]. Interaction of the thioesters with alkyl halides leads to products other than those obtained in the reactions of alkyl halides with esters, ester-amides, and amides of acids with phosphorus(III). The esters of dialkyl-, alkyl-, and diaryl-phosphinothious acids react with alkyl halides only via the free electron pair at the phosphorus atom[131,132]:



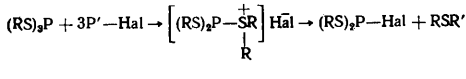
$$\begin{matrix}R'\\R''\end{matrix}\!\!>\!P{-}SR + R'''{-}Hal \rightarrow \left[\begin{matrix}R'\\R''\end{matrix}\!\!>\!\overset{+}{P}\!<\!\begin{matrix}R'''\\SR\end{matrix}\right]\bar{Hal} \rightarrow \begin{matrix}R'\\R''\end{matrix}\!\!>\!\overset{S}{\overset{\|}{P}}{-}R''' + R{-}Hal.$$

The interaction of esters of alkyl- and phenyl-phosphonodithious acids with alkyl halides also leads to the alkylation of the phosphorus atom[133,134]. The instability and the capacity for intermolecular rearrangement to phosphonothioates characteristic of the esters of phenylphosphonodithious acid should be noted[131]. Mixed *O*, *S*-esters of phosphorous acid interact in two ways: both the phosphorus and the sulphur atoms behave as nucleophilic centres[135-137]:



$$(RO)_2P{-}SR' + R''{-}Hal \begin{cases}\nearrow \left[(RO)_2\overset{+}{P}\!<\!\begin{matrix}R''\\SR'\end{matrix}\right]\bar{Hal} \rightarrow RO{-}\overset{O}{\overset{\|}{P}}\!<\!\begin{matrix}R''\\SR'\end{matrix} + R{-}Hal\\ \searrow \left[(RO)_2P{-}\underset{R''}{\underset{|}{\overset{+}{S}}}{-}R'\right]\bar{Hal} \rightarrow (RO)_2P{-}Hal + R'{-}S{-}R''\end{cases}$$

Phosphorotrithioites react with alkyl halides only via the sulphur atom[41]:

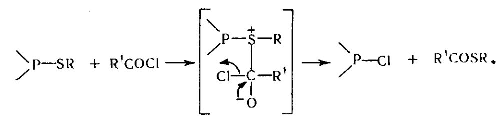


$$(RS)_3P + 3P'{-}Hal \rightarrow \left[(RS)_2P{-}\underset{R}{\underset{|}{\overset{+}{S}}}R\right]\bar{Hal} \rightarrow (RS)_2P{-}Hal + RSR'.$$

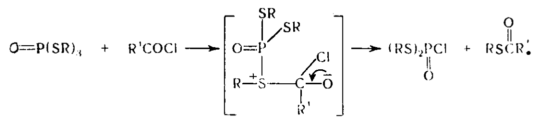
Triphenyl phosphorotrithioites reacts similarly with alkyl halides[138]. However, it is striking that, in contrast to triphenyl phosphite, its intermediate product cannot be isolated:

$$(PhS)_3P + 3CH_3I \rightarrow 3\,PhSCH_3 + PI_3.$$

The nucleophilic interaction of phosphorus(III) thioesters with an unsaturated electrophilic carbon centre has been investigated only in reactions with acid halides. It was shown[137,139,140] that in phosphorotrithioites and in alkyl(aryl)-phosphonothioites and -phosphonodithioites the nucleophilic centre is the sulphur atom:



It is remarkable that even in the molecule of phosphorotrithiolic acid the sulphur atoms can participate in reactions with carboxylic acid halides:

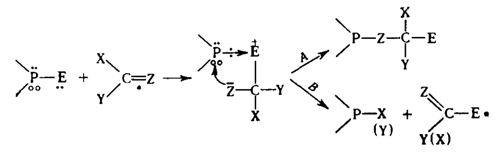


One of the most interesting problems which follow from the examination of the above experimental data is the discovery of the factors which control the selectivity in ambidentate phosphorus–element systems. Although the available experimental data do not provide an exhaustive solution of the problem in many of its aspects, certain relations are revealed quite clearly.

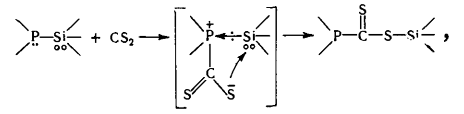
In the first place a fairly sharp difference in selectivity when the P–E system reacts with an electrophilic centre at a saturated and an unsaturated carbon atom is striking. While in the first case the phosphorus atom behaves as the nucleophilic centre of the system, in the second case attack by the free electron pair of the second element (particularly nitrogen and sulphur) is most typical.

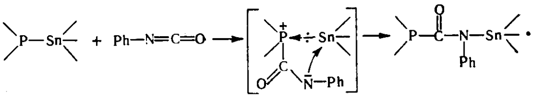
If the phosphorus atom is the nucleophilic centre, a quasiphosphonium complex is formed and the final product is always a derivative of tetracoordinate phosphorus, which depends on the nature of the substituent. On the other hand, when the nucleophilic centre is not the phosphorus atom but another element (O, S, N) directly linked to it, the structure of the final product as a rule indicates a number of rearrangements of the reaction complex formed initially. The specificity of the properties of the phosphorus atom—the presence of both a free electron pair and vacant *d* orbitals—is responsible for the possibility of rearrangements of this kind.

Indeed, when E behaves as the nucleophilic centre in the reaction of the system P–E (E = O, N, or S) with an unsaturated electrophilic carbon atom, an intermediate reaction complex is formed. The reduction of electron density at the atom (the formation of a positive charge) is compensated both by a shift of the binding electron pair of the $P \div E$ bond and a change in the type of $d{-}p$ interaction (it disappears). An increase in electron density at the Z atom may be compensated by interaction with the vacant *d* orbitals of the phosphorus atom, which becomes possible only after the reduction of electron density of the latter due to the shift of the binding electron pair of the P–E bond in the initial nucleophilic attack by E:

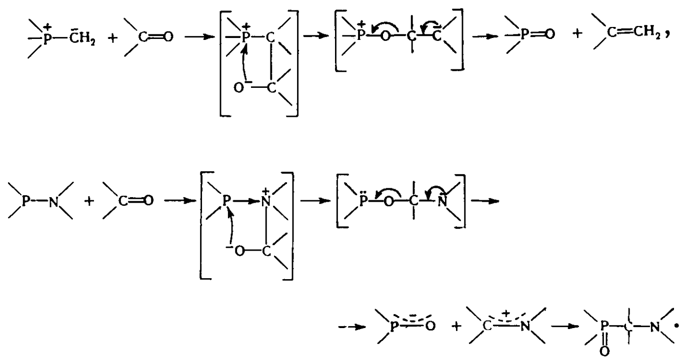


Further reaction of the intermediate reaction complex is determined mainly by the nature of the substituents X and Y. If they are electron-donating, then pathway A will predominate via the stabilisation of the intermediate complex. Electron-accepting substituents X and Y (X = Cl or Br) most often lead to the stabilisation of the intermediate complex via pathway B. This explanation is confirmed both by the experimental data described above and the results obtained in the study of the interaction of compounds of the type $R_3Si-PPh_2$ and $R_3Sn-PPh_2$ with carbon disulphide, isocyanates, and many other electrophilic agents[141-144]. Tin and silicon have only vacant *d* orbitals. Therefore in their compounds with trivalent phosphorus the latter is the only nucleophilic centre and their interaction with an unsaturated electrophilic centre leads to a situation opposite to that described above:





It is striking that the mechanism discussed is essentially analogous to the mechanism proposed to account for the Wittig reaction[145]:



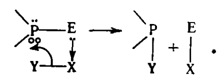
Examination of a wide range of examples of the ambidentate behaviour of derivatives of acids with phosphorus(III) shows that the nucleophilic properties of E in the system P–E diminish in the sequence S > N > O. There is no doubt that this problem is directly linked to the nature of the *d–p* interaction in the P–E system. The changes in nucleophilic properties in the series O, N, and S should be reflected appreciably also in the type of interaction between phosphorus(III) derivatives and heteroconjugated systems. The first studies on these lines, by Pudovik and coworkers[146], led to the discovery of the characteristic features of the behaviour of these systems.

Apparently the concept of the ambidentate properties of phosphorus(III) compounds can significantly facilitate the theoretical analysis of the possible reaction mechanisms in the reaction system and can give a fairly correct indication of the structure of the final reaction products. Therefore it is both urgent and necessary that attention be drawn to the assessment of the ambidentate property as a real property of phosphorus(III) derivatives.

IV. SUBSTITUTION REACTIONS AND CHARACTERISTICS OF SYSTEMS WITH A PHOSPHORUS–HALOGEN BOND IN A SERIES OF PHOSPHORUS(III) DERIVATIVES

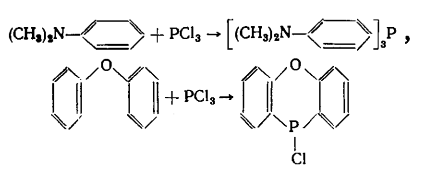
Substitution reactions are most common for phosphorus(III) compounds. They are characteristic of both primary and secondary phosphines as well as the amides, esters, and halides of acids containing phosphorus(III). They frequently take place at very high rates.

Substitution reactions in phosphorus(III) compounds in which the electron density at the phosphorus atom is enhanced and it behaves as a typical nucleophilic centre were analysed in detail in the previous section. A reduced electron density at the phosphorus atom, as a necessary condition for the interaction between a nucleophilic agent and a *d* orbital of phosphorus, arises via the primary attack by the free electron pair of E on the electrophilic centre of the second reactant:

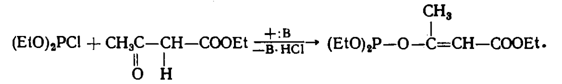


A second type of substitution reaction involves the usual nucleophilic substitution at the phosphorus atom as an electrophilic centre. The introduction of a chlorine (bromine or iodine) atom into any derivative of phosphorus(III) is known to reduce sharply its nucleophilic properties. For example, even powerful nucleophilic agents such as Alk_3P and $(\rangle N)_3P$ can react with only the most reactive compounds after the replacement of the alkyl or amino-group by chlorine[147-150], while $RPCl_2$ and $\rangle NPCl_2$ are incapable of alkylation by alkyl halides. The nucleophilic properties of PCl_3 are not revealed in any reaction and the study of PCl_3 complexes have shown that the phosphorus atom exhibits distinct electron-accepting properties[11-14].

Substitution reactions are most typical for trivalent phosphorus acid chlorides. These reactions take place extremely readily with the majority of the usual nucleophilic agents: alcohols[151], mercaptans[152], phenols[153], and amines[154]. It is noteworthy that the ease of reaction of phosphorus(III) acid chlorides and compounds of the type P–E (where E = N, O, or S) varies in the opposite sense as a function of the nucleophilic properties of the nucleophilic agent. Similar reactions take place with activated benzene derivatives[155,156] (with formation of a P–C bond).

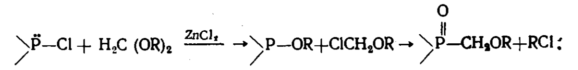


or compounds having a mobile H – C bond, such as acetoacetic ester, the product containing an enol ester bond[157]:

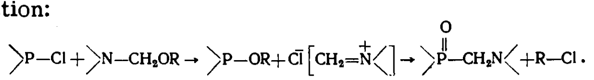


$$(EtO)_2PCl + CH_3C(O)\text{—}CH(H)\text{—}COOEt \xrightarrow[-B\cdot HCl]{+:B} (EtO)_2P\text{—}O\text{—}C(CH_3){=}CH\text{—}COOEt.$$

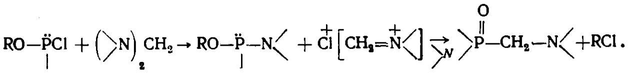
Many substitution reactions, which are of the exchange type in a wider sense than the usual nucleophilic substitution, are known at present. Frequently these reactions constitute the first step in multistage processes leading to the formation of phosphorus(V) derivatives. In many cases these stages can be separated. Thus, while formals do not react with phosphorus(III) derivatives without a catalyst, in its presence the reaction takes place readily[158]:



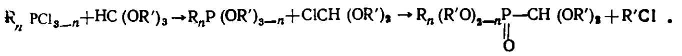
The replacement in the formal of even one alkoxy-group by an amino-group leads to a sharp increase of the rate of reaction:



The reactions with di(dialkylamino)methane take place even more readily[159]:

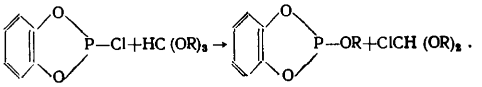


In the orthoesters of carboxylic acid the replacement of an alkoxy-group does not require any catalyst, unlike formals[160–163]:



$$R_n\,PCl_{3-n} + HC(OR')_3 \rightarrow R_nP(OR')_{3-n} + ClCH(OR')_2 \rightarrow R_n(R'O)_{2-n}P(O)\text{—}CH(OR')_2 + R'Cl\ .$$

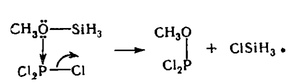
These reactions can be carried out in stages until the substitution of the last halogen at the phosphorus atom. However, in the case of pyrocatecholphosphorous acid chloride [phenylene phosphorochloridite] the reaction ceases after the exchange of one alkoxy-group[162,163]:



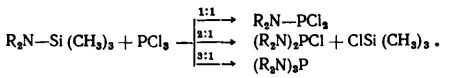
It is remarkable that $Si(OR)_4$ does not undergo a similar interaction with PCl_3 under mild conditions. However, the reaction with PBr_3 and PI_3 takes place vigorously with formation of an alkyl halide and resinous products of unknown structure[164]. The reaction between alkoxytrimethylsilane and PCl_3 takes place in stages[165]. While in the system $(H_3Si)_2O + PCl_3$ no interaction is observed, when there is even only one methoxy-group at the silicon atom the reaction takes place according to the mechanism[166]

$$H_3SiOCH_3 + PCl_3 \rightarrow H_3SiCl + CH_3OPCl_2.$$

The author suggests that the initial stage includes the formation of a four-centre transition complex and the decisive factor is the electron-donating capacity of the oxygen in the Si – O bond:



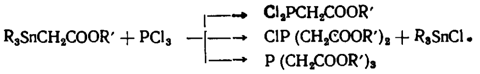
In agreement with this, the exchange reactions of compounds containing an amino-group (which has more pronounced electron-donating properties) and an Si – N bond take place more readily and proceed to higher degrees of substitution[167,168]:



$$R_2N\text{—}Si(CH_3)_3 + PCl_3 \rightarrow \begin{cases} \xrightarrow{1:1} R_2N\text{—}PCl_2 \\ \xrightarrow{2:1} (R_2N)_2PCl + ClSi(CH_3)_3\,. \\ \xrightarrow{3:1} (R_2N)_3P \end{cases}$$

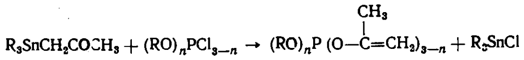
$PhPCl_2$, Ph_2PCl_2, and $O-PCl_3$ react in exactly the same way. This reaction is typical not only for phosphorus(III) halides but also for halogeno-derivatives of sulphur: S_2Cl_2, $SOCl_2$, RSO_2Cl.[169] Probably many other reactions also involve the same mechanism[170,171]:

$$PCl_3 + PhS\text{—}Sn(CH_3)_3 \rightarrow ClSn(CH_3)_3 + (PhS)_3P,$$



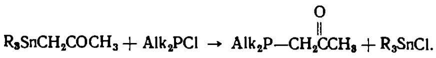
$$R_3SnCH_2COOR' + PCl_3 \rightarrow \begin{cases} Cl_2PCH_2COOR' \\ ClP(CH_2COOR')_2 + R_3SnCl\,. \\ P(CH_2COOR')_3 \end{cases}$$

However, with analogous α-ketone or aldehyde derivatives the mode of reaction depends on the substituent at the phosphorus atom[172]:



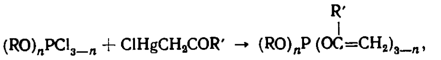
$$R_3SnCH_2COCH_3 + (RO)_nPCl_{3-n} \rightarrow (RO)_nP(O\text{—}C(CH_3){=}CH_2)_{3-n} + R_3SnCl$$

and at the same time



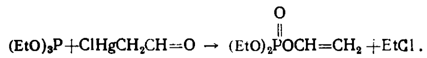
$$R_3SnCH_2COCH_3 + Alk_2PCl \rightarrow Alk_2P\text{—}CH_2C(O)CH_3 + R_3SnCl.$$

A difference between phosphorochlorodites[173–175] and phosphites[176] is observed also in reactions with α-(halogenomercuri)carbonyl compounds:



$$(RO)_nPCl_{3-n} + ClHgCH_2COR' \rightarrow (RO)_nP(OC(R'){=}CH_2)_{3-n},$$

where $n = 1 - 2$ and $R' = H$ or CH_3, and

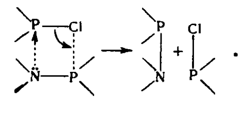


$$(EtO)_3P + ClHgCH_2CH{=}O \rightarrow (EtO)_2P(O)CH{=}CH_2 + EtCl\,.$$

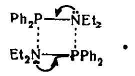
There is also a wide variety of reactions of halogeno-derivatives of phosphorus(III) with other derivatives of trivalent and quinquevalent phosphorus. These are primarily disproportionation reactions in the series of phosphorus(III) derivatives, a typical feature of which is the formation of equilibrium systems[177–180]:

$$PhPCl_2 \rightarrow Ph_2PCl + RCl_3,$$
$$PCl_3 + P(OEt)_3 \rightleftarrows ClP(OEt)_2 + Cl_2POEt,$$
$$PCl_3 + P(OPh)_3 \rightleftarrows ClP(OPh)_2 + Cl_2POPh,$$
$$PCl_3 + P(NR_2)_3 \rightleftarrows ClP(NR_2)_2 + Cl_2PNR_2,$$

and many others[181–183]. The rate of reaction increases in the sequence Ph < PhO < AlkO > R_2N. All these findings suggest that the exchange reactions involve a cyclic mechanism:

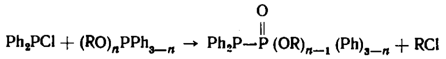


Moreover, the capacity of phosphorus(III) derivatives for such cyclic interactions may be the cause of the formation of relatively stable association complexes. Recently Evdakov and coworkers[184] showed that the rate of oxidation of dialkylaminodiphenylphosphine without solvent or in polar solvents is relatively low, but increases sharply in non-polar solvents. They explain the relatively low capacity of this compound for oxidation in a free state by the formation of association complexes:



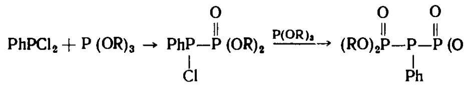
In a non-polar solvent this substance is present in the form of "free" molecules more available for chemical interaction with other reactants.

While the exchange reactions in the series of acid halides derived from phosphorous acid do not lead to a change in the valence of phosphorus, the reactions of halogenophosphines have a mechanism involving the Arbuzov rearrangement[185]:



$$Ph_2PCl + (RO)_nPPh_{3-n} \rightarrow Ph_2P-\overset{\overset{\displaystyle O}{\|}}{P}(OR)_{n-1}(Ph)_{3-n} + RCl$$

or



$$PhPCl_2 + P(OR)_3 \rightarrow PhP(Cl)-\overset{\overset{\displaystyle O}{\|}}{P}(OR)_2 \xrightarrow{P(OR)_3} (RO)_2\overset{\overset{\displaystyle O}{\|}}{P}-P(Ph)-\overset{\overset{\displaystyle O}{\|}}{P}(OR)_2 .$$

While the reaction between a secondary phosphine and a halogeno-derivative of trivalent phosphorus takes place according to the equation[186]

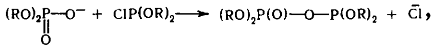
$$\rangle P-H + Hal-P\langle \rightarrow \rangle P-P\langle + HHal,$$

in the case of tertiary phosphines the reaction takes place in quite a different way[187]:

$$(C_4H_9)_3P + PhPCl_2 \rightarrow (C_4H_9)_3PCl_2 + (PhP)_4 ,$$
$$(C_4H_9)_3P + Ph_2PCl \rightarrow (C_4H_9)_3PCl_2 + Ph_2P-PPh_2 .$$

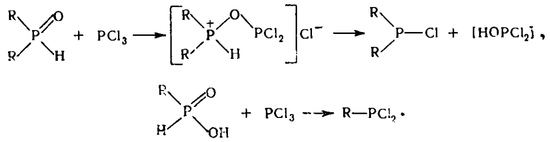
Substitution reactions can take place with phosphorus(V) derivatives as nucleophilic agents and the nature of the nucleophilic centre may be various[188–192]:

$$(RO)_2\dot{P}\overset{-}{=}\dot{O} + ClP(OR)_2 \longrightarrow (RO)_2P-O-P(OR)_2 + \bar{Cl} ,$$



$$(RO)_2P(=O)-O^- + ClP(OR)_2 \longrightarrow (RO)_2P(O)-O-P(OR)_2 + \bar{Cl} ,$$

$$[Ph_3P{=}CHR \longleftrightarrow Ph_3\overset{+}{P}-\bar{C}HR] + ClPPh_2 \longrightarrow [Ph_3\overset{+}{P}-CHR-\ddot{P}Ph_2]\bar{Cl} ,$$

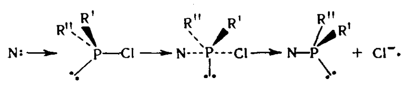


The fact that in the last two reactions[191,192] the decisive factor is the nucleophilic properties of the oxygen atom in the P = O group and not a tautomeric equilibrium between the quinquevalent and trivalent forms of phosphorus is confirmed by the finding that[193]

$$SiHal_4 + nO{=}PPh_3 \rightarrow Hal_{4-n}Si\{[-O-\overset{+}{P}Ph_3]\bar{Cl}\}_n \quad (n = 2,\ 4) .$$

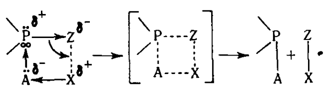
This structure of the adducts was based on infrared spectroscopic and conductimetric data.

The examples of substitution or exchange reactions with participation of a phosphorus – halogen bond quoted above fall far short of exhausting the available literature data. Nevertheless they are extremely typical and are adequate for the discussion of certain problems of the mechanism of those reactions. With the usual nucleophilic agents, substitution reactions at an electrophilic phosphorus atom can take place via a classical S_N2 bimolecular nucleophilic substitution mechanism:



However, so far there are no quantitative data in the literature concerning the true mechanism of the substitution reaction or the elucidation of the role and contribution of the phosphorus *d* orbitals in this mechanism. Nevertheless, the numerous examples quoted, mainly of exchange reactions, can be very readily explained qualitatively if one takes into account the significant contribution of the *d* orbitals of the trivalent phosphorus atom as an electrophilic centre in the substitution reactions. The involvement of the *d* orbitals should alter significantly the type of reaction as a whole.

In the nucleophilic attack by the second reactant on the phosphorus atom a free electron pair of the nucleophilic agent is transferred to the *d* orbitals of the phosphorus atom. According to quantum-chemical concepts, such interaction can be favourable only in the presence of a reduced electron density at the phosphorus atom[15]. Therefore, with increasing electronegativity of the substituent or the number of substituents at the phosphorus atom, its positive charge increases also, which facilitates, owing to the energy factor, the participation of the phosphorus *d* orbitals in the nucleophilic substitution reaction. The involvement of the *d* orbitals of the phosphorus atom makes possible electron transfer via a four-centre cyclic mechanism:



In those cases where the group Z can be readily eliminated in the form of an anion and the process is facilitated by its additional interaction with the electrophilic centre of the second reactant (X = H, $-Si\langle$, etc.), a process of this kind takes place without a change in the valence of the phosphorus atom, i.e. a substitution reaction occurs. Therefore the group Z need not necessarily be eliminated in the form of an anion, since the possibility of a synchronous cyclic electron transfer eliminates the necessity for charge separation both in the transition complex and in the final product, in contrast to classical nucleophilic substitution of type S_N1 or S_N2.

Thus the primary interaction between the electrons of the nucleophilic agent and *d* orbitals of the phosphorus atom leads in the first instants essentially to an increase of coordination and of the valence of the phosphorus atom, but cyclic electron transfer can reduce them both in the final reaction product. Such stabilisation is not the only one possible. One of the other pathways may be a further increase of the valence with retention or increase of the degree of coordination of the phosphorus atom in the final reaction products—these are examples of the reactions mentioned above in which the phosphorus atom exhibits biphilic properties.

The examples of substitution reactions quoted above for the series of phosphorus(III) derivatives reveal a considerable role of the phosphorus *d* orbitals in chemical reactions. Even a purely qualitative hypothesis of this kind can serve as a firm basis for the understanding of the behaviour of phosphorus as a biphilic reagent in an even greater range of chemical reactions.

To estimate the role and contribution of the *d* orbitals of phosphorus in any of its reactions, it is necessary to know at least its relative electron density. On the other hand, a knowledge of this quantity is necessary for the estimation of the nucleophilic properties of the free electron pair of the phosphorus atom. Depending on the nature of the substituent, the charge at the phosphorus atom may change due to the inductive effect of the added group and its capacity for conjugation with the phosphorus *d* orbitals. It is interesting that the π-electron systems of substituents are incapable of $p-\pi$ conjugation with the unshared electron pair of phosphorus, which is explained by the enhanced s-character of the pair[194]. The determination of the contribution of conjugation with the d orbitals to the overall electron density at the phosphorus atom as well as the determination of the latter are undoubtedly some of the most difficult and urgent problems in the chemistry of phosphorus(III) derivatives.

The attempts by Van Wazer and coworkers[195,196] to determine the conjugation effect for phosphorus(III) derivatives by comparing the calculated ^{31}P chemical shifts with the experimental values cannot be regarded as satisfactory because their conclusions concerning the electron density at the phosphorus atom are difficult to reconcile with the chemical properties of the corresponding derivatives. Moreover, the theoretical principles of the calculation of the ^{31}P chemical shifts have been seriously criticised[197]. Thus it might have been expected that dialkylchlorophosphine should be more nucleophilic than trialkyl phosphites. However, the former is much less reactive in classical substitution reactions with alkyl halides[147-149]. On the other hand, the phosphine is incomparably more reactive than phosphites in substitution reactions where the phosphorus atom exhibits its biphilic properties.

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Explanations without internal contradictions are at present possible for only a few reactions of trivalent phosphorus. We have attempted to assess on the basis of the chemical properties of phosphorus(III) derivatives the role of the free electron pair and the d orbitals of the phosphorus atom and the effect of substituents and their nature in various reactions. In view of the complexity and the controversial nature of the problems discussed, the specific views expressed cannot be regarded as definitive. The principal aim of the present review was to reveal the many-sided nature of the reaction mechanisms of trivalent phosphorus and to draw attention to the most important problems.

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Arbuzov Institute of Organic
and Physical Chemistry,
USSR Academy of Sciences,
Kazan

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The Present State of the Theory of the Oxidation of Cyclo-olefins

A.A.Syrov and V.K.Tsyskovskii

The review deals with various methods for the oxidation of cyclo-olefins by molecular oxygen, nitric acid, aqueous solutions of palladium and gold chlorides, and also ozonolysis. The effect of the structure of the olefin, the solvent, and reaction conditions on the mechanism of action of the oxidant have been analysed. The aim of the review is to formulate, by examining the reaction mechanisms, the principal trends in the applied studies on the synthesis of aliphatic oxygen-containing compounds (acids, aldehydes, and alcohols) from cyclo-olefins. It has been shown that the use of ozone fulfills most closely the desired aim.

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Introduction

The view that processes involving oxidation by molecular oxygen of straight-chain alkanes, alkylbenzenes, and cycloalkanes constitute the most rapid and cheapest methods for the synthesis of acids, alcohols, and compounds with mixed functional groups has now become firmly established. Indeed, considerable advances have been made in studies on the oxidation of these compounds and many processes have been applied in industry. At the same time, the use of cyclo-olefins for this purpose is of no less interest but studies in this field have not yet gone beyond the initial research stage.

Cyclo-olefins are cyclic compounds with a double bond in the ring. According to modern quantum-mechanical views[1] on the nature of the double bond, one of the bonds between the carbon atoms is formed by hydrid sp^2 orbitals. A vacant $2p$ orbital remains at each carbon atom and these two form a π bond by partial overlapping of the electron clouds. The plane of the $2p$ orbitals is perpendicular to that of the sp^2 orbitals. The mutual overlapping of the electronic orbitals is greater in σ bonds than in π bonds and the former are more stable.

There exists also another description of the double bond, proposed by Pauling[2,3]: two tetrahedrally disposed orbitals at each carbon atom overlap one another forming "banana" bonds.

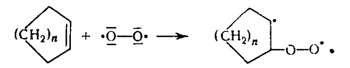
Since the π bond is highly polarisable, multiple C–C bonds readily react with electrophilic agents, i.e. have nucleophilic properties, and are also capable of combining with radicals if the latter are sufficiently reactive.

To facilitate the addition of radicals, it is evidently necessary either to weaken the π bond or to activate the radical. Powerful electrophilic agents such as chlorine, bromine, nitric acid, lead tetra-acetate, potassium permanganate, ozone, and others react as oxidants. In the oxidation the two electrons forming the covalent bond may be transferred either in two stages, one electron at a time (giving a radical process) or by an ionic mechanism, both electrons being involved at once. Substituents at the double bond with a negative inductive effect (–*I* effect) (carbonyl, nitryl, and nitro-groups and others) diminish its nucleophilic properties. The electron density of the π bond and hence also the rate of electrophilic addition are then reduced[4].

I. OXIDATION OF CYCLO-OLEFINS BY MOLECULAR OXYGEN

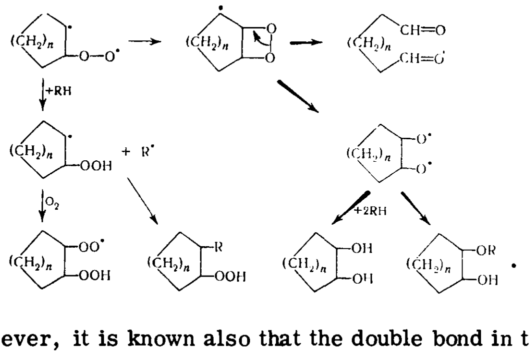
1. The Addition of Oxygen to the Double Bond

The discovery of processes underlying the mechanism of the oxidation is inconceivable without the knowledge of the structure of the oxygen molecule. Mulliken[5] was the first to devote much attention to this problem. According to physical data, the oxygen molecule should have the properties of biradicals (the presence of two unpaired electrons, triplet state, paramagnetism). Therefore oxygen should add directly to the double bond in cyclo-olefin oxidation reactions:



(I.1)

The most probable pathway of further reaction is the formation of a cyclic peroxide, the subsequent rearrangement or radical decomposition of which may lead to the formation of both aliphatic dialdehydes and cycloalkanediols:



(I.2)

However, it is known also that the double bond in the oxygen molecule is fairly stable, the O–O distance (1.2074 Å) being close to the length of the C=O double bond[6] (1.21 Å).

All these data suggest that the electronic structure of the oxygen molecule is more complex than would appear on the basis of the biradical hypothesis. The outer electronic shell of the oxygen atom is known to contain six electrons (two electrons in the 2*s* orbitals and four electrons in the 2*p* orbitals). It is suggested that a three-electron bond is formed when the atoms are combined to form a molecule[7]. Then each oxygen atom uses one of its four valence orbitals for an unshared pair, one for the formation of a single bond, and two for the formation of three-electron bonds:

$$:\!O \div\!\div\!\div O\!: \qquad (I.3)$$

The saturated O=O structure is also possible but it is less favourable energetically and is encountered in one of the excited states (singlet). The reactions with participation of singlet oxygen (for example the oxidation of cyclo-olefins) constitute a new developing branch of chemistry and are outside the scope of the present review†.

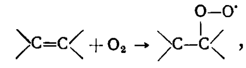
The problem of the electronic state of the oxygen molecule has been discussed on the basis of the molecular orbital method in books by Slater, Spice, and Coulson[25-27]. The molecular orbital method explained for the first time why the oxygen molecule is paramagnetic.

In order to convert O_2 into a biradical, it is necessary to raise the energy by 60–70 kcal mole^{-1}:[28]

$$:\!O \div\!\div\!\div O\!: \rightarrow \cdot\overline{\underline{O}}{-}\overline{\underline{O}}\cdot \ . \qquad (I.4)$$

Such rearrangement of the electron clouds can be induced either thermally or photochemically and at temperatures ≤ 200°C it probably takes place to an insignificant extent (about 10^{-5}%). Consequently, under ordinary conditions the oxidation of hydrocarbons could take place if the activation energy for the removal of hydrogen by the oxygen molecule (or for the addition of the latter to the double bond) were sufficiently low. However, experimental activation energies for the initial steps in the oxidation[29] of various hydrocarbons,

$$RH + O_2 \rightarrow R^\cdot + HO_2^\cdot, \qquad (I.5)$$



$$>\!C{=}C\!< + O_2 \rightarrow >\!\underset{}{C}(O{-}O^\cdot){-}\dot{C}\!<, \qquad (I.6)$$

amount to 15–30 kcal mole^{-1}.

The rearrangement of electron clouds in the oxygen molecule takes place very readily only on interaction with a radical already present in the system, which gives rise to the possibility of the development of a radical reaction chain. The theory of slow radical branched-chain reactions, based largely on the work of Semenov[30] and his school, has been developed in studies on the liquid-phase oxidation of hydrocarbons, in particular cyclo-olefins, which have been activated in some way.

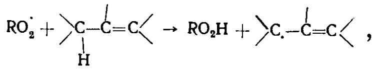
We shall consider in greater detail the existing hypotheses on the oxidation of unsubstituted and substituted cyclo-olefins by molecular oxygen and by other oxidants.

2. Oxidation of Unsubstituted Cyclo-Olefins

The oxidation of cyclohexene and cyclopentene (60° and 80°C) is known to involve the formation[31-42] of a fairly stable hydroperoxide with an HOO group in the *α*-position relative to the double bond. The process kinetics and the mechanism of the formation of the *α*-hydroperoxide from cyclohexene were investigated by Hendry and Russell[43], Erofeev and coworkers[44-49], Mayo and coworkers[50], and others[51].

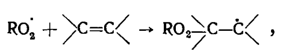
Numerous studies have been made on the composition and structure of the oligomeric peroxide products formed in the oxidation of cyclohexene[52-57].

In 1956 Reppe and coworkers[58,59] reported the synthesis of epoxycyclo-octane by the oxidation of cyclo-octene by molecular oxygen at 60°C in the presence of a cobalt catalyst. This advance led to new investigations of the effect of ring size on the oxidation mechanism. According to the cummunication by Mayo and coworkers[50], in the oxidation of a series of cyclo-olefins ranging from C_5 to C_8 at 50–80°C there is a gradual change in reaction mechanism. Thus in the oxidation of cyclopentene 86% of the initial olefin reacts by a mechanism involving the abstraction of the allyl hydrogen atom with ultimate formation of cyclopentenyl hydroperoxide:



(I.7)

while in the reaction of cyclo-octene the addition mechanism predominates (70%):

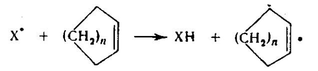


(I.8)

with formation of the epoxide, suberic aldehyde, and polymers[58].

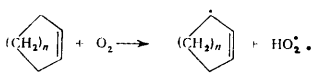
These data are consistent with the observation of de Rosh and Balaceanu[28], who suggested the following reaction mechanism:

$$\text{initiator} \longrightarrow 2X^\cdot, \qquad (I.9)$$



(I.10)

In order to assess the possibility that oxygen adds to the double bond of the cyclo-olefin, we shall consider elementary chain initiation steps in the absence of initiating additives:



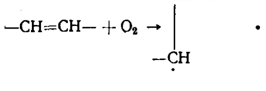
(I.11)

Reaction (I.11) is endothermic, since its heat is

$$q_{(I.11)} = q_{\text{allyl C-H}} - 47 \text{ kcal mole}^{-1} \text{ (the O-H bond dissociation energy in the HO}_2^\cdot\text{radical)},$$

$$84 \text{ kcal mole}^{-1} \geqslant q_{\text{allyl C-H}} \text{ (Ref.60)} \geqslant 77 \text{ kcal mole}^{-1}.$$

The experimental activation energies[29] $E_{(I.11)}$ for reaction (I.11) amount to 15–30 kcal mole^{-1} for different compounds:

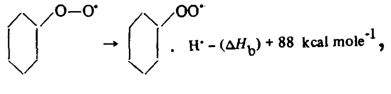


$$-CH{=}CH- + O_2 \rightarrow \begin{array}{l} -CH{-}O{-}O^\cdot \\ \ \ | \\ -\dot{C}H \end{array} . \qquad (I.12)$$

The activation energy for reaction (I.12) is probably fairly high. In the case of styrene[61] it is 30 ± 2 kcal mole^{-1}. To calculate the heat of reaction (I.12) for cyclohexene, we have

$$C_6H_{12} \rightarrow C_6H_{11}^\cdot + {}^\cdot H - 88^{62} \text{ (Ref.62) kcal mole}^{-1}, \qquad (a)$$

$$C_6H_{11}^\cdot + O_2 \rightarrow C_6H_{11}OO^\cdot + 20 \text{ (Refs 28 and 61) kcal mole}^{-1}, \qquad (b)$$



(c)

since the effect of the peroxy-group O–O$^\cdot$ on the elimination of a hydrogen atom from the *α*-position is probably

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†For the chemistry of singlet oxygen, see Refs. 8–24.

insignificant. Next we used the tabulated heats of formation of the substances from the elements[63]:

$$\text{cyclohexene } \Delta H_{\text{form}} = -6.4 \text{ kcal mole}^{-1},$$

$$\text{cyclohexene } \Delta H_{\text{form}} = -29.5 \text{ kcal mole}^{-1},$$

$$2H \rightarrow H_2 + 104 \text{ kcal mole}^{-1}.$$

Hence, according to Hess's law the heat of reaction is

$$\Delta H_b = 88 - \Delta H_H + [-20 + 83 + \Delta H_{C_6H_{12}} - \Delta H_H],$$

$$q_{(I.12)} = \Delta H_b - \Delta H_{C_6H_{10}} = 28.9 \text{ kcal mole}^{-1}.$$

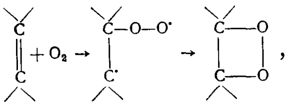
Since we do not know the heat of formation of cyclo-octene, it will be calculated from the known heats of hydrogenation of *cis*-cyclo-octene (−23.53 kcal mole^{-1}) and the heat of formation of cyclo-octane (−29.81 kcal mole^{-1}):[63,64]

$$\Delta H_{\text{form}} = -6.28 \text{ kcal mole}^{-1}.$$

Then, assuming that the energy of the dissociation of a hydrogen atom from the methylene group of cyclo-octane[65] is 94 kcal mole^{-1}, we determine the heat of addition of oxygen to the double bond of cyclo-octene, as in the procedure described above: 40.47 kcal mole^{-1}.

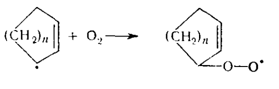
For endothermic reactions, $E > q$ and therefore, by comparing the heats and activation energies for reactions (I.11) and (I.12), it is not difficult to show that reaction (I.11) is more likely in the cyclo-olefin series.

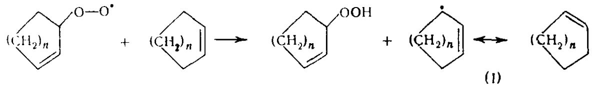
The hypothesis of the possible formation of a cyclic peroxide[33,57,66]:


(I.13)

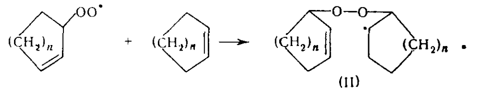
have not so far found experimental confirmation but it still has some supporters[67,68].

Usually the removal of a hydrogen atom from the allyl system by a peroxy-radical [stage (I.15)] requires a smaller activation energy than its radical addition to a double bond [stage (I.16)]:[69]


(I.14)

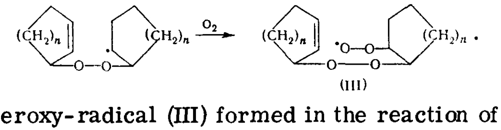


(I.15)



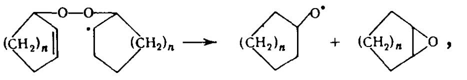
(I.16)

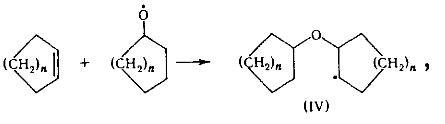
The formation of the allyl radical (I) was established in early studies described in the review of Criegee[70] and Rosenwald[71]. According to Waters[69], the competing radical addition reaction becomes appreciable as the reaction temperature increases. However, Mayo[50] did not find a difference in the reaction mechanism when cycloheptene was oxidised at 60° and 80°C. Probably, the 20 deg difference is insufficient:



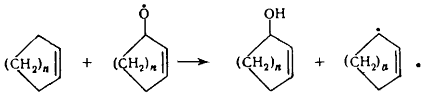
(I.17)

The peroxy-radical (III) formed in the reaction of (II) with oxygen by mechanism (I.17) may undergo further reactions similar to (I.15) or (I.16). The decomposition of the radical (II) [reaction (I.18)] competes with reaction (I.17). It probably predominates in the oxidation of cyclo-octene:


(I.18)



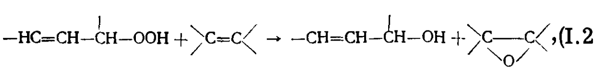
(I.19)


(I.20)

According to Mayo[72], owing to the competition between the elementary stages (I.17) and (I.18), the pathway taken by the oxidation reaction should depend on the partial pressure of oxygen‡.

The yield of epoxides cannot exceed 50% if they are formed only as a result of reaction (I.18). The Prilezhaev reaction occurring simultaneously makes a definite contribution to the accumulation of peroxides in amounts exceeding 50%.[28,50,74-78]

The possibility that epoxides are formed by the mechanism proposed by Hock[37] cannot be excluded[79]:


(I.21)

but special experiments[80] confirmed that the ability of α-peroxides derived from cyclo-olefins to give rise to epoxides in the presence of catalysts at the concentrations usually employed in oxidation reactions is insignificant.

Some investigators[81] believe that the principal epoxide-forming agents in the oxidation of acyclic (C_3) and cyclic (C_6) olefins are acylperoxy radicals, since alkenylperoxy-(alkylperoxy-)radicals are insufficiently reactive in reactions of this kind. Alcohol was not found in the early stages of oxidation in these experiments[79]. It is believed[81] that this supports the above hypothesis.

An epoxyalkane was not found in the simultaneous oxidation of isopropylbenzene and propene at 80–90°C in the presence of azobis(isobutyronitrile) as an initiator[81], although a high concentration of $RO_2^{\cdot}$ radicals was detected by the ESR method[82]. Possibly, under the conditions chosen by these investigators[81], the reaction $RO_2^{\cdot} + {>}C{=}C{<}$ does not occur because of steric hindrance or insufficient reactivity of the peroxy-radical.

The behaviour of radicals in reactions involving addition to a double bond or the abstraction of an allylic hydrogen atom has for a long time attracted the attention of chemists, since it provides information about the energy of a particular radical[83,84]. Kinetic[85-87] and thermochemical[60] data are now available which confirm the hypothesis[88,89] of the interaction of $RO_2^{\cdot}$ with the olefin double bond.

The absence of an alcohol in the initial reaction period can be readily explained if it is assumed that reaction (I.19)

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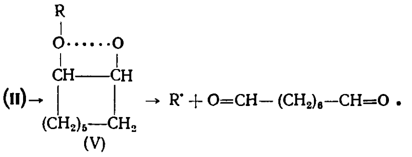
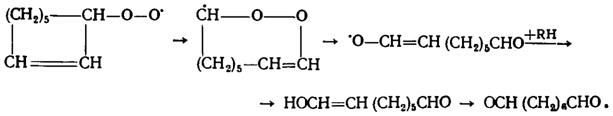
‡For a more detailed description of this problem, see Mayo[73].

predominates over reaction (I.20). The aliphatic aldehydes are probably formed as a result of the decomposition of radical (V):



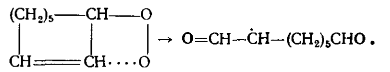
(I.22)

However, together with the mechanism quoted above, one cannot exclude other pathways involving the isomerisation and breakdown of the peroxy-radical [reactions (I.23) and (I.24)]:



(I.23)

The incorporation of the peroxy-group O−O in the cyclo-octene chain reduces the strain in the ring[4]:

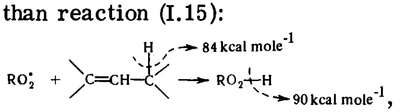


(I.24)

In the oxidation of n-butane and propene[81,90–93] it was shown that such reactions may occur in the liquid phase. Under oxidation conditions, aldehydes are converted into peracids and the latter undergo the Prilezhaev reaction and participate in the formation of epoxycycloalkanes. However, aldehydes and the corresponding acids were found in insignificant amounts in the oxidation of cyclo-octene.

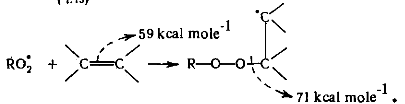
Probably the different compositions of the final products found in the oxidation of cyclohexene and cyclo-octene must be explained on the basis of the differences between the structures of the two cyclo-olefins. It is therefore necessary to assume that in the oxidation of cyclo-octenes the activation energy $E_{(I.15)} > E_{(I.16)}$, while in the oxidation of cyclohexene the opposite relation holds: $E_{(I.15)} < E_{(I.16)}$.

If account is taken of Benson's data[60] on bond dissociation energies, it becomes clear that reaction (I.16) is more exothermic than reaction (I.15):



(I.15)

$$q_{(I.15)} = 84 - 90 = -6 \text{ kcal mole}^{-1}$$



(I.16)

$$q_{(I.16)} = 59 - 71 = -12 \text{ kcal mole}^{-1}$$

In accordance with the concepts developed by Vitvitskii[94], we suggest that the activation energy $E_{(I.16)}$ for reaction (I.16) does not vary in the series of cyclo-olefins, while $E_{(I.15)}$ must depend greatly on the structural characteristics of the given cyclo-olefin. In fact, the number of hydrogen atoms which may participate in the radical substitution reaction (I.15) decreases from 4 in cyclopentene to 2 in cyclo-octene[50].

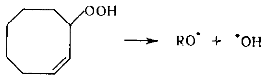
Since among $\geqslant C_5$ cyclo-olefins the cyclopentene ring is the most planar[95], the removal of an α-hydrogen atom from cyclopentene by a peroxy-radical according to mechanism (I.15) leads to the formation of an allyl radical, which may be regarded as a hybrid of two resonance forms and which does not require the expenditure of additional energy on the rearrangement of the ring. An analogous conclusion, which explains the formation of cyclohexenyl α-hydroperoxide, can be readily reached by examining the stereochemistry of cyclohexene.

Cyclohexene is known to have the "half chair" conformation in which four carbon atoms are located in one plane. Two of the remaining atoms are below and above this plane[96]. The "half boat" form is then less stable than the "half chair" form by only 2.7 kcal mole^{-1}.[97]

For the principle of maximum overlap of the orbitals to operate in the allyl radical derived from cyclohexene[50], it is necessary that one of the two non-coplanar carbon atoms should move to the plane of the four carbon atoms. According to the data of Anet and Haq[98], this can be achieved by overcoming a potential barrier of only 5.2 kcal mole^{-1}. For comparison, we may note that a similar inversion of the cyclohexane ring can occur only by overcoming a potential barrier of 14 kcal mole^{-1}.[99] Even under ordinary conditions the fraction of molecules having the "half boat" conformation may be appreciable and in substituted cyclohexenes can actually predominate[100,101].

The low yield of cyclo-octenyl α-hydroperoxide in the oxidation of *cis*-cyclo-octene is probably due to hindrance by energy factors, since in reaction (I.15) it would be necessary to overcome a fairly high energy barrier, which consists of the normal heat of reaction, the energy which must be expended to rearrange the ring in the formation of the allyl radical, and the energy necessary for the rearrangement of the valence shell of the carbon atom attacked.

The homolytic decomposition of cyclo-octenyl α-hydroperoxide with subsequent isomerisation is probably not the only pathway, since epoxides are already detected in the early stages of the oxidation reaction:

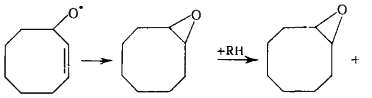


(I.25)

$$\text{ROOH} + M^{2+} \rightarrow \text{RO}^{\cdot} + M^{3+} + {}^{-}\text{OH}, \quad \text{(I.26)}$$

or

$$\text{RO}_2^{\cdot} + \text{RO}_2^{\cdot} \rightarrow 2\text{RO}^{\cdot} + \text{O}_2, \quad \text{(I.27)}$$



(I.28)

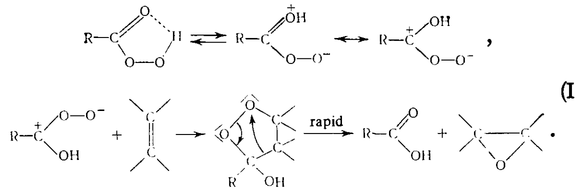
The probability of reaction (I.28) should be greater for cyclo-octene than for cyclohexene, bearing in mind the internal steric saturation of the first compound.

The presence of trigonal carbon atoms reduces the ring strain and it would appear that the C_8 ring, in which the angle between the C−C bonds is 135°, should enter into reactions involving addition to the double bond with considerable difficulty, much less readily at any rate than cyclohexene. The cyclohexane molecule is known to be very stable when all the carbon atoms are in the tetragonal form[4]. Nevertheless attempts at a direct conversion of cyclohexene into an epoxy-derivative by oxygen have so far been unsuccessful. This contradiction is difficult to explain at present.

Thus, according to the concepts developed, cyclic α-hydroperoxides, allyl alcohols, and ketones are obtained by a radical substitution mechanism [reaction (I.15)] and the epoxides and products formed on ring opening at the site of the double bond (i.e. aliphatic aldehydes and acids) are formed by a radical addition mechanism.

(a) The coupled oxidation reactions of olefins with aldehydes, which are used to synthesize epoxides[102–106] in yields greater than 50% or ethers[107,108], have been known for a long time. The study of the oxidation of cyclohexene in cumene[109], ethylbenzene, and other compounds which readily give rise to hydroperoxides, and also (its oxidation) in the presence of various aldehydes showed that coupled processes of this kind involve a radical–chain mechanism.

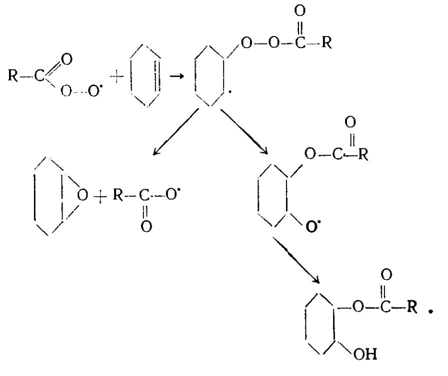
At the same time, systematic studies on the kinetics and mechanism of the interaction of peracids with various olefins (the Prilezhaev reaction) were begun in order to discover the component most active in the formation of chains in joint oxidation reactions. For a long time it was believed that the first stage of this reaction is the heterolytic breakdown of the peracid. However, Kwart and Hoffman[110] suggest a 1,3-dipolar addition mechanism to account for the experimental results:



(I.29)

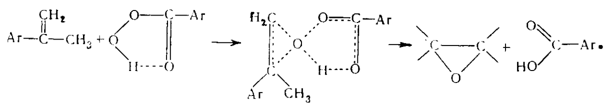
It is now believed, on the basis of kinetic investigations, that the conversion of olefins into epoxy-derivatives by reaction with peracids involves the intermediate formation of an olefin–peracid π complex[111,112,113].

In his study of coupled oxidation, Wittig[114] noted that olefins retard the oxidation of aldehydes. Walling[115] and Ikawa[80] found an explanation for this phenomenon: when aldehydes are oxidised in the presence of olefins, the concentration of acylperoxy-radicals falls, since the latter participate in the following reaction:



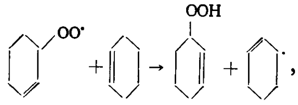
(I.30)

This mechanism has been generally accepted[28,80,116–118], but, as shown, for example, by studies on the oxidation of methylstyrene in the presence of benzaldehyde[119], in some reactions the fraction of epoxides formed by a radical mechanism may be appreciable (> 10%):



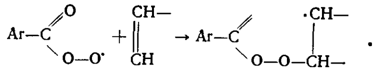
(I.31)

Using the data on the oxidation of cyclohexene in the presence of a small amount of benzaldehyde, Ikawa[80] concluded that, together with benzoylperoxy-radicals, cyclohexenylperoxy-radicals also participate in the epoxide-formation reaction. Indeed, the formation of the α-hydroperoxide predominates in the oxidation of cyclohexene on its own:



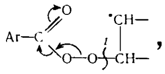
(I.32)

while in the joint oxidation of benzaldehyde and cyclohexene under comparable conditions, the reaction involving the addition of the benzoylperoxy-radical takes place:



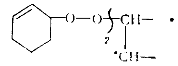
(I.33)

As a result of the inductive effect (shown by arrows)



(I.34)

the dissociation energy of bond 1 should be less than that of bond 2:



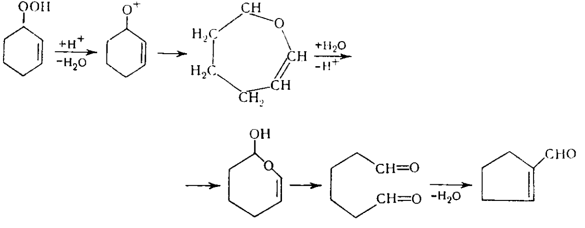
(I.35)

Therefore the addition of the cyclohexenylperoxy-radical to the cyclohexene double bond may be easier, since the following relation has been observed in many radical addition reactions: the greater is the heat of reaction of the radical with the molecule the lower is the activation energy[30].

Thus, according to the current views on the oxidation mechanism, in order to obtain aliphatic oxygen-containing compounds (aldehydes and acids) from cyclo-olefins, either the addition of the peroxy-radical at the site of the double bond or its isomerisation is necessary.

The question arises what conditions would favour the isomerisation of peroxy-radicals or their addition at the site of the double bond. Apparently this requires the choice of appropriate solvents, catalysts, and material for the walls of the reactor in which the oxidation is carried out[120,121] (i.e. the study of the mechanism of homogeneous-heterogeneous catalysis) or deliberate preparation of the required site for attack by oxygen (activation of the double bond, the use of more reactive peroxy-radicals, etc.).

(b) Effect of the solvent. Shine and Snyder[122] investigated the oxidation of cyclohexene by oxygen at 60–80°C in the presence of acetic anhydride and showed that under these conditions cyclohexenyl α-hydroperoxide decomposes heterolytically:



(I.36)

It is known that strongly associated solvents frequently alter the mode of the chain oxidation process[123]. However, so far there is very little information about the effect of such solvents on the mechanism of cyclo-olefin oxidation[124,125].

It has now been established that the formation of intermolecular hydrogen bonds in the oxidation of hydrocarbons has a significant effect on the kinetics, for example in the radical decomposition of hydroperoxides[29]. Together with alcohols and ketones, the latter participate in the reaction with the peroxy-radical and the new radicals thereby formed lead to chain branching. The rate of the elementary steps and hence the rate of the overall oxidation process depends significantly on the properties of the solvent[126,127]. This is because the elementary chain propagation ($RO_2^{\cdot} + RH \xrightarrow{k_2} ROOH + R^{\cdot}$) and chain termination ($RO_2^{\cdot} + RO_2^{\cdot} \xrightarrow{k_6}$ molecular product) reactions, which determine the overall rate of the process, involve the interaction of two dipoles, the magnitude of which depends on the dielectric constant of the medium. The effect of the solvent is particularly pronounced in the oxidation of polar organic compounds (ethyl methyl ketone, ethanol, etc.). The composition of the reaction product is determined by the competition between two pathways in the chain propagation reaction[128]: the interaction of $RO_2^{\cdot}$ with the initial molecule:

$$RO_2^{\cdot} + RH \xrightarrow{k_2} ROOH + R^{\cdot} \qquad (I.37)$$

and the breakdown of $RO_2^{\cdot}$ into products with lower molecular weights:

$$RO_2^{\cdot} \xrightarrow{k_1} R'O^{\cdot} + R''CHO\,. \qquad (I.38)$$

Dilution of ethyl methyl ketone or ethanol with a non-polar solvent (benzene) increases the amount of $RO_2^{\cdot}$ radical decomposition products, since benzene reduces the dielectric constant of the medium. As a result, the rate of reaction W_2 falls. At the same time, the rate of the mutual recombination reaction

$$[2RO_2^{\cdot} \xrightarrow{k_6} \text{molecular products}] \qquad (I.39)$$

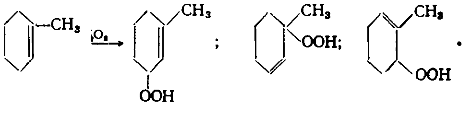
decreases even faster than the rate of reaction (I.37).[129]

However, the amount of theoretical and experimental information about the effect of the solvent on the elementary stages in radical reactions (for example, in the oxidation of non-polar substances) is still inadequate. This makes deliberate control of liquid-phase oxidation reactions significantly more difficult.

3. Oxidation of Substituted Cyclo-olefins

The role of substituents in the oxidation of cyclo-olefins can be followed on the basis of studies already carried out. It is known that the site chosen for attack by oxygen depends in many ways on the nature of the substituent and also on the relative positions of the double bond and the substituent.

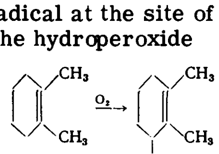
(a) Oxidation by molecular oxygen of compounds in which the substituents have a positive inductive effect. Only methylolefins have been investigated on these lines[51,130,131]. Bolland[131], who oxidised methylcyclohex-1-ene, isolated only three of the theoretically expected six α-hydroperoxide isomers:



(I.40)

The determination of the position of the hydroperoxy-group is fairly difficult and therefore the experimental results are contradictory.

In the oxidation of a cyclo-olefin with methyl substituents at the double bond, which should increase its nucleophilic properties and should apparently facilitate the addition of the peroxy-radical at the site of the double bond, Criegee[70] obtained the hydroperoxide



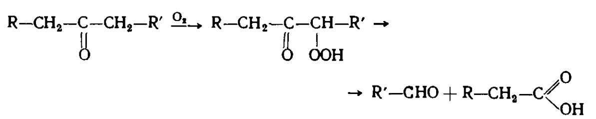
(I.41)

In contrast, Dupont[132] showed that the oxidation of 1,2-dimethylcyclohex-1-ene yields 1,2-dimethylcyclohexane-1,2-diol and 1,2-dimethylcyclohex-1-ene-3-one and a very small amount of αω-diacetylbutane.

It should be noted that, apart from the inductive effect exerted via 2–3 carbon atoms, the number of methylene groups in the chain is of considerable importance.

The South African investigators Arndt et al.[133] reported that in the oxidation of 5-methylnonane the substitution of the hydrogen atom at the tertiary carbon atom is 19 times faster than at a secondary carbon atom. However, under these conditions oxygen does not attack solely the tertiary carbon atom.

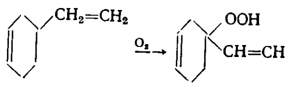
A departure from the α-mechanism



$$R{-}CH_2{-}\underset{\underset{O}{\|}}{C}{-}CH_2{-}R' \xrightarrow{O_2} R{-}CH_2{-}\underset{\underset{O}{\|}}{C}{-}\underset{\underset{OOH}{|}}{CH}{-}R' \rightarrow R'{-}CHO + R{-}CH_2{-}C\overset{\nearrow O}{\searrow OH} \qquad (I.42)$$

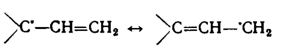
suggested by Langenbeck and Pritzkow[134] (cyclohexanone, tetralone) was observed by Obukhova et al.[135] in the oxidation of 6-undecanone.

(b) Effect of substituents with a negative inductive effect. According to the data of Brill[136] and Tepenitsyna[137], the main reaction product in the oxidation of 4-vinylcyclohexene is a tertiary hydroperoxide:



(I.43)

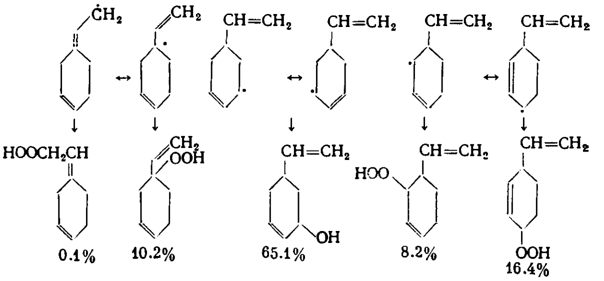
Electronegative substituents as a rule facilitate the removal of a hydrogen atom from a tertiary carbon atom. Since the polar effect of the vinyl group is not very pronounced, the resonance stabilisation of the radical



(I.44)

should favour α-substitution.

Nevertheless, Farrissey[138] observed the formation of a complex mixture of hydroperoxides in the oxidation of 1-vinylcyclohex-4-ene:



(I.45)

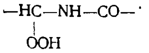
A similar deviation from the normal relative activity is shown by those cyclic olefins in which either the tertiary allyl carbon atom or the double bond in which it is involved are outside the ring[138]. According to the transition state theory, the formation of an allyl radical requires the maximum overlapping of the *p* and π orbitals, for which it is necessary that the C–H bond dissociated should be axial relative to the plane of the double bond. If the double bond or its allyl carbon atom are outside the ring, this requirement involves a loss of a degree of freedom of rotation[139]. Moreover, the H–H interaction between the allyl and the vinyl hydrogen in such a conformation is a maximum[140].

Consequently when an H atom is dissociated from a tertiary carbon atom, both of the above factors can markedly increase the energy of the transition state.

The polar effect of the carboxy-group should hinder the dissociation of a hydrogen atom from $H-\overset{\diagdown}{\underset{\diagup}{C}}-COOH$ more than from $H-\overset{\diagdown}{\underset{\diagup}{C}}-CH_2-COOH$ because the electric field due to the dipole of the HOOC group decreases in proportion to the cube of the distance[69].

The oxidation of compounds with an unprotected carboxy-group is frequently accompanied by decarboxylation. This side reaction may become the main one under certain conditions. For example, in the oxidation of cyclohexanecarboxylic acid in acetic acid the main product is cyclohexanone[141] and in the oxidation of methyl cyclohexanecarboxylate[142] the main products are the monomethyl esters of butanetricarboxylic and α-oxopimelic acids. Evidently in this case it is important to know the location in space of both the $\overset{\diagup}{\underset{\diagdown}{C}}=O$ group and the hydrogen atom at the tertiary carbon atom.

Azanovskaya and Ablova[143,144] investigated the effect of substituents on the oxidisability of cyclo-olefins without determining the position of the hydroperoxy-group formed in this process. They investigated ethers and esters (acetate and benzoate) and halogeno- and amino-derivatives of cyclohex-1-en-3-ol. It was found that ethers are oxidised most readily. Cyclohexenol is oxidised with greater difficulty than with cyclohexene[145]. Esters react only in the presence of initiators. The amino-derivatives were not oxidised at all (even in the presence of an initiator). However, the inhibiting effect of the amino-group is not always shown. For example, in the oxidation of ε-caprolactam a hydroperoxide is formed:



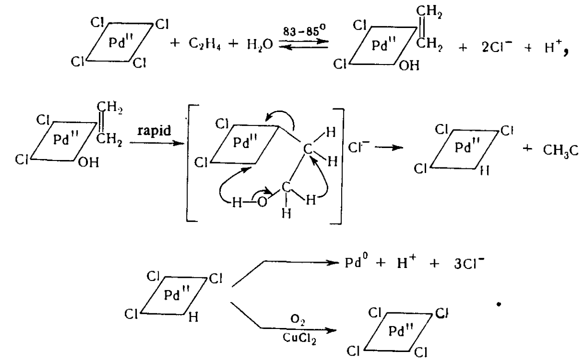
$$-\underset{\substack{|\\OOH}}{HC}-NH-CO- \qquad (I.46)$$

together with its decomposition products[147]. Here the basicity of the imino-group is low due to the conjugation of the carbonyl π bond and the unshared electron pair of the nitrogen atom.

Thus the data discussed in the present review lead to the conclusion that the total experimental and theoretical facts available at present on the oxidation of cyclo-olefins by molecular oxygen are insufficient to allow a reliable prediction of the conditions for the selective ring opening at the site of the double bond and the formation of aliphatic dicarboxylic acids.

II. OXIDATION OF CYCLO-OLEFINS TO CARBONYL COMPOUNDS. CATALYSIS BY PALLADIUM, GOLD, MERCURY, AND THALLIUM SALTS

The oxidation of cyclo-olefins in the presence of aqueous solutions of palladium and gold salts has not been adequately investigated, since the main effort of investigators has been concentrated on the elucidation of the mechanism of the oxidation of aliphatic olefins[148]. It is now known that saturated cyclic ketones can be obtained in this way from cyclic olefins[149,150], while aliphatic olefins yield acyclic aldehydes and ketones[151]. For example, when ethylene is introduced into an aqueous solution of palladium chloride, reaction probably takes place by the following mechanism[152]:



(II.1)

The studies on the oxidation of olefins in the presence of mercury and palladium salts have been reviewed by Halpern[152].

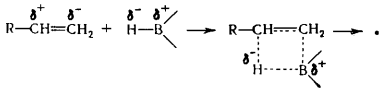
III. OXIDATION OF CYCLO-OLEFINS BY ELECTROPHILIC AGENTS

In order to obtain aliphatic oxygen-containing compounds from cyclo-olefins, it is probably more convenient (compared with molecular oxygen) to employ typical electrophilic agents such as lead and thallium acetates, nitric acid, ozone, etc.[153]

The mechanism of the oxidising action of lead tetra-acetate has been elucidated to a considerable degree by the fundamental work of Criegee[153]. However, because of their high cost, lead tetra-acetate and especially thallium tri-acetate[154,155] cannot compete with molecular oxygen or nitric acid.

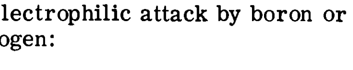
1. Hydroboration–Oxidation

The addition of boranes to unsaturated compounds involves a four-centre transition state[156]:



$$R-\overset{\delta^+}{C}H=\overset{\delta^-}{C}H_2 + \overset{\delta^-}{H}-\overset{\delta^+}{B}\diagdown \longrightarrow \underset{\overset{\delta^-}{H}\cdots\cdots\overset{\delta^+}{B}}{R-CH\overset{\cdots}{=}CH_2} \longrightarrow . \qquad (III.1)$$

However it is still not clear which factor is more important in this step: electrophilic attack by boron or nucleophilic attack by hydrogen:

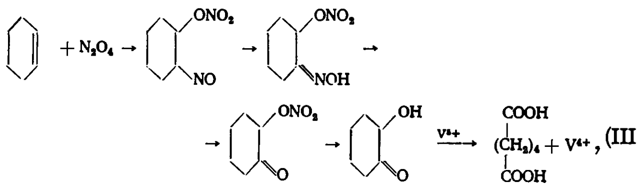


$$\rightarrow R-CH_2-\underset{\substack{|\\ \diagup B \diagdown}}{CH_2} \xrightarrow{[H_2O_2]} R-CH_2-CH_2OH .$$

Hydroboration may be a convenient method for the preparation of alcohols when a cheap source of diborane is available[157,158]. These problems are dealt with in greater detail in Brown's monograph[156].

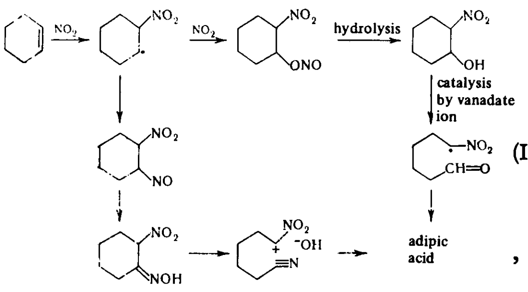
2. Oxidation of Cyclo-olefins by Nitric Acid

The interest in the use of nitric acid for the selective cleavage of the ring at the double bond increased greatly after the discovery of the catalytic effect of ammonium metavanadate mixed with copper powder[159]. However, this process has many disadvantages, most of which are associated with the high corrosivity of nitric acid. The mechanism of the oxidation of cyclo-olefins by nitric acid in the presence of a catalyst is still obscure in many ways[160,161]. Franz[162] suggests that in this reaction nitrogen tetroxide is the most active reagent. The tetroxide is formed on decomposition of intermediate compounds produced as a result of the oxidative dissociation of nitric acid:

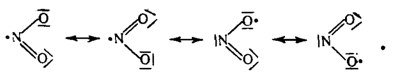

(III.2)

$V^{4+} + HNO_3 \rightarrow V^{5+}$.

Gut and Lindenmann[163] put forward a mechanism according to which the oxidation begins with a free radical addition of NO_2 to the cyclo-olefin double bond:

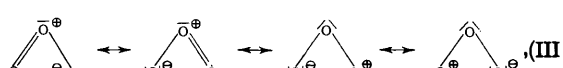


(III.3)


(III.4)

3. Ozonolysis

It has been firmly established that ozone[6],


(III.5)

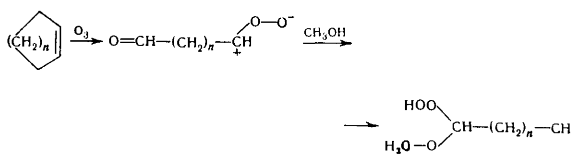
adds quantitatively at the site of the double bond. An extensive literature shows a pronounced interest in the problem of the utilisation of ozone as an oxidant[164,165]. There is no doubt that, after improvement in the design of ozonisers, ozone will find very wide application.

Data are already available on the technical application of ozone for the conversion of aliphatic olefins into alcohols and aldehydes and also for the conversion of oleic acid into azelaic and pelargonic acids in high yields[167,168]. There has been a recent report on the construction of a factory for the ozonolysis of soya bean oil with a projected output of 4500 tons per year[169].

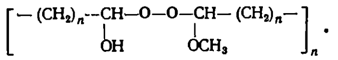
The addition of ozone to the double bond of an olefin is very rapid and therefore the rate of reaction is limited mainly by the rate of migration of ozone to the olefin.

The application of modern physical experimental methods made it possible to begin an investigation of the kinetics of the interaction between ozone and olefins. According to the data of Williamson and Cvetanovic[170,171], the rate constant for the second-order reaction between ozone and cyclopentene in carbon tetrachloride at 25°C is 2×10^5 litre $mole^{-1}\ s^{-1}$.

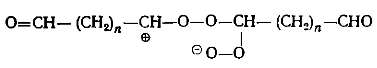
Without considering the problem of the mechanism of the primary attack on the double bond by ozone, we may note that the composition and origin of the ozonolysis products of cyclo-olefins in proton-donating solvents (for example in methanol at ±50°C) can be accounted for by Criegee's mechanism:


(III.6)

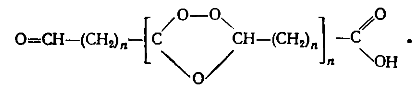
The formation of methoxyhydroperoxides constitutes the main reaction pathway. One cannot exclude the possibility that aldehyde and hydroperoxy-groups react with one another during ozonolysis[172,173] with formation of an oligomer:


$$\left[-(CH_2)_n-\underset{OH}{CH}-O-O-\underset{OCH_3}{CH}-(CH_2)_n-\right]_n .\qquad (III.7)$$

Moreover there is a possibility of the dimerisation of dipolar ions by the following mechanism:


$$O{=}CH-(CH_2)_n-\underset{\oplus}{CH}-O-O-\underset{\ominus O-O}{CH}-(CH_2)_n-CHO\qquad (III.8)$$

or their polymerisation:


(III.9)

Pathways (III.8) and (III.9) are not unique and their contribution to the overall reaction mechanism is small.

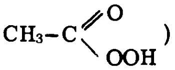
Methoxyhydroperoxides (together with polyperoxides) can be subsequently oxidised by a suitable oxidant[174,175] to acids or reduced catalytically to aldehydes or alcohols[176,177].

The attempts to combine in one stage processes involving the ozonolysis of cyclo-olefins and the oxidation *in statu nascendi* of the peroxy-products are extremely interesting. For this purpose, cyclo-olefins have been subjected to ozonolysis in acetic acid[178] (at 40–80°C) and also in aqueous emulsion or an alkaline solution of hydrogen peroxide[179] (at 20–25°C). The yield of dicarboxylic acids was ≥ 80%.

Oxidation by lower peracids (C_1–C_3) of alkoxyhydroperoxides obtained by the ozonolysis of substituted cyclo-olefins in alcohols permits the synthesis of various derivatives of aliphatic polycarboxylic acids (for example, butane-1,2,4-tricarboxylic acids from 4-vinylcyclohex-1-ene or cyclohex-1-ene-4-carboxylic acid[180,181]).

The ozonolysis proper takes place fairly readily without the need for special apparatus and the solvents employed are as a rule available commercially. A certain risk of detonation of peroxides and ozonides can be eliminated by selecting appropriate process conditions.

It is noteworthy that many aspects of the detailed mechanism of the ozonolysis of cyclo-olefins have not yet been elucidated[182] and the composition of the products depends to a considerable extent on the solvent and the ozonolysis conditions.

Nevertheless, regardless of the composition of the peroxy-products, their subsequent processing by oxidation or reduction gives a fairly high final yield of acids, aldehydes, or alcohols (≥ 80%). Therefore, bearing in mind the likely availability of oxidants (O_2, H_2O_2, and  $CH_3-C(=O)OOH$) and reductants [H_2, $(iso-C_3H_7O)_3Al$, $LiAlH_4$, CH_3-S-CH_3, etc.), we are inclined to believe that ozonolysis may be the most suitable method for the conversion of cyclo-olefins into aliphatic oxygen- containing compounds.

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All-Union Petrochemical
Processes Research Institute,
Leningrad

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Nuclear Magnetic Resonance and Its Applications in Chemical Research

E.I.Fedin

The fundamentals of nuclear magnetic resonance spectroscopy are briefly described. The applications of the method in chemistry are demonstrated and the possible developments of the application of nuclear magnetic resonance in studies on molecular and crystal structures are indicated.
The bibliography includes 75 references.

CONTENTS

I. INTRODUCTION

Nuclear magnetic resonance (NMR) is one of the outstanding discoveries of the twentieth century, which has now taken an honourable place among the principal methods for research in structural chemistry. The method needs no special recommendation. The literature devoted to NMR is enormous. The bibliography in Leche's monograph published in 1963 includes about three thousand references and in the last two years more than two hundred papers, dealing either with the method itself or demonstrating its possibilities in various branches of solid state physics, molecular physics, in structural studies, and in the solution of the principal problems of theoretical chemistry, have been published. This journal has already included a review on the chemical applications of NMR. The aim of the present review is to give a simple systematic account of the principles of NMR and its main applications, and this has largely determined its form. However, the embodiment of this aim in print may fall short of these words—of the kind that might have been used in a lecture or in a leisurely conversation. Therefore it must be emphasised that the description of the principal problems of NMR spectroscopy within the framework of a journal article is exceptionally difficult and the present review is merely a compromise between the intention and the feasibility of its realisation.

The treatment of the subject should include a detailed description of problems such as magnetic anisotropy of bonds, multiplicity of the spectra, and the role of the strength of the permanent magnetic field and of interactions with nuclei having a spin $I > 1/2$; certain facts are included for the first time in a review of this type. Its bibliography in no way claims to give an exhaustive coverage of the literature. The interested reader should consult the required references in monographs[1-10].

II. MAGNETIC PROPERTIES OF ATOMIC NUCLEI

Many stable nuclei have spins $I > 0$ (Table 1). The presence of the spin leads to a magnetic moment: if the spin I is compared with the circulation of the nuclear charge, then its rotation is equivalent, in accordance with the usual classical concepts of magnetic phenomena, to a circular current which gives rise to a magnetic moment $\mu = e\hbar/2m_{\mathrm{p}}c$. For a proton,

$$\mu_p \simeq \frac{4.8\times10^{-10}\times1\times10^{-27}}{23\times10^{10}\times1836\times9\times10^{-28}} \simeq \frac{1}{2}\times10^{-23}.$$

As a rule, heavier nuclei have magnetic moments smaller than μ_{p}. The existence of the nuclear magnetisation of matter was confirmed experimentally in 1937 by Lazarev and Shubnikov[11], who measured the static magnetic susceptibility of solid hydrogen in the temperature range between 1.76° and 4.22°K. The magnetic properties of atomic nuclei have played a notable role in many branches or optical spectroscopy, in electron spin resonance (ESR) spectroscopy, in nuclear quadrupole resonance (NQR), etc. The vast majority of NMR studies have been made on nuclei having a spin $I = 1/2$. Their sequence in terms of decreasing numbers of relevant papers is as follows: ^{1}H, ^{19}F, ^{31}P, ^{13}C, ^{29}Si, etc.

III. RESONANCE CONDITIONS

A nucleus with a spin $I = 1/2$ has two allowed orientations in an external magnetic field: roughly speaking, the magnetic moment of such a nucleus may be oriented either parallel or antiparallel to the vector H_0. Evidently the parallel orientation is energetically favourable and the antiparallel orientation is not. When a specimen containing such nuclei is placed in a magnetic field H_0, its energy structure becomes enriched by two magnetic energy levels, the distance between which is

$$\Delta E = g\mu_0 H_0 \quad (1)$$

where $g = \mu/I\mu_0$ is the splitting factor (i.e. gI is the number of nuclear magnetons μ_0 in the experimental value of the nuclear magnetic moment). Therefore transitions between the levels involve the following energy quanta:

$$h\nu_0 = g\mu_0 H_0 \quad (2)$$

or, in other words, at a frequency

$$\nu_0 = \frac{g\mu_0}{h} \cdot H_0 = \gamma_0 H_0 \quad (3)$$

there is an effective interaction between the electromagnetic radiation incident on the specimen and the series of energy levels of the magnetic moments of the nuclei.

Table 1. Properties of the nuclei.

Isotope	γ_0, Hz g^{-1}	Natural content, %	Spin I	Isotope	γ_0, Hz g^{-1}	Natural content, %	Spin I
1	2	3	4	1	2	3	4
^{1}H	4257.7	99.984	$^{1}/_{2}$	^{95}Mo	277.4	15.78	$^{5}/_{2}$
^{2}H	653.6	$1.56 \cdot 10^{-2}$	$^{1}/_{2}$	^{97}Mo	283.3	29.60	$^{5}/_{2}$
^{6}Li	626.5	7.43	1	^{103}Rh	134.0	100	$^{1}/_{2}$
^{7}Li	1654.7	92.57	$^{3}/_{2}$	^{105}Pd	174	2.23	$^{5}/_{2}$
^{9}Be	598.3	100	$^{3}/_{2}$	^{107}Ag	172.2	51.35	$^{1}/_{2}$
^{10}B	457.5	18.83	3	^{109}Ag	198.1	48.65	$^{1}/_{2}$
^{11}B	1366.0	81.17	$^{3}/_{2}$	^{111}Cd	902.8	12.86	$^{1}/_{2}$
^{13}C	1070.5	1.108	$^{1}/_{2}$	^{113}Cd	944.4	12.34	$^{1}/_{2}$
^{14}N	307.6	99.635	1	^{113}In	931.0	4.16	$^{9}/_{2}$
^{15}N	431.5	0.365	$^{1}/_{2}$	^{115}Sn	1322.0	0.35	$^{1}/_{2}$
^{17}O	577.2	$3.7 \cdot 10^{-2}$	$^{5}/_{2}$	^{117}Sn	1577.0	7.67	$^{1}/_{2}$
^{19}F	4005.5	100	$^{1}/_{2}$	^{119}Sn	1587.0	8.68	$^{1}/_{2}$
^{23}Na	1126.2	100	$^{3}/_{2}$	^{121}Sb	1019.0	57.25	$^{5}/_{2}$
^{25}Mg	260.6	10.05	$^{5}/_{2}$	^{123}Sb	551.8	42.75	$^{7}/_{2}$
^{27}Al	1109.4	100	$^{5}/_{2}$	^{123}Te	1159	0.89	$^{1}/_{2}$
^{29}Si	846.0	4.7	$^{1}/_{2}$	^{125}Te	1345	7.03	$^{1}/_{2}$
^{31}P	1723.5	100	$^{1}/_{2}$	^{127}I	851.9	100	$^{5}/_{2}$
^{33}S	326.6	0.74	$^{3}/_{2}$	^{129}Xe	1178	26.24	$^{1}/_{2}$
^{35}Cl	417.2	75.4	$^{3}/_{2}$	^{131}Xe	349.0	21.24	$^{3}/_{2}$
^{37}Cl	347.2	24.6	$^{3}/_{2}$	^{133}Cs	558.5	100	$^{7}/_{2}$
^{39}K	198.7	93.08	$^{3}/_{2}$	^{135}Ba	425	6.59	$^{3}/_{2}$
^{41}K	109.2	6.91	$^{3}/_{2}$	^{137}Ba	476	11.32	$^{3}/_{2}$
^{43}Ca	286.5	0.13	$^{7}/_{2}$	^{139}La	601.4	99.91	$^{7}/_{2}$
^{45}Sc	1034.3	100	$^{7}/_{2}$	^{141}Pr	1130	100	$^{5}/_{2}$
^{47}Ti	240.0	7.75	$^{5}/_{2}$	^{143}Nd	220	12.2	$^{7}/_{2}$
^{49}Ti	240.1	5.51	$^{7}/_{2}$	^{145}Nd	140	8.3	$^{7}/_{2}$
^{50}V	424.5	0.24	6	^{147}Sm	147	15.07	$^{7}/_{2}$
^{51}V	1119.3	99.7	$^{7}/_{2}$	^{149}Sm	119	13.84	$^{7}/_{2}$
^{53}Cr	240.6	9.54	$^{3}/_{2}$	^{151}Eu	1000	47.8	$^{5}/_{2}$
^{55}Mn	1055.3	100	$^{5}/_{2}$	^{153}Eu	460	52.2	$^{5}/_{2}$
^{59}Co	1010.3	100	$^{7}/_{2}$	^{171}Yb	690	14.3	$^{1}/_{2}$
^{63}Cu	1128.5	69.09	$^{3}/_{2}$	^{173}Yb	198	16.1	$^{5}/_{2}$
^{65}Cu	1209.0	30.91	$^{3}/_{2}$	^{175}Lu	570	97.4	$^{7}/_{2}$
^{67}Zn	263.5	4.12	$^{5}/_{2}$	^{181}Ta	460	100	$^{7}/_{2}$
^{69}Ga	1021.8	60.2	$^{3}/_{2}$	^{185}Re	958.6	37.1	$^{5}/_{2}$
^{71}Ga	1298.4	39.8	$^{3}/_{2}$	^{187}Re	968.4	62.9	$^{5}/_{2}$
^{73}Ge	148.5	7.61	$^{9}/_{2}$	^{189}Os	330.7	16.1	$^{3}/_{2}$
^{75}As	729.2	100	$^{3}/_{2}$	^{191}Ir	81	38.5	$^{3}/_{2}$
^{77}Se	813.1	7.5	$^{1}/_{2}$	^{193}Ir	86	61.5	$^{3}/_{2}$
^{79}Br	1066.7	50.57	$^{3}/_{2}$	^{195}Pt	915.3	33.7	$^{1}/_{2}$
^{81}Br	1149.8	49.43	$^{3}/_{2}$	^{197}Au	69.1	100	$^{3}/_{2}$
^{83}Kr	164	11.55	$^{9}/_{2}$	^{199}Hg	761.2	16.80	$^{1}/_{2}$
^{85}Rb	411.1	72.8	$^{5}/_{2}$	^{201}Hg	308	13.2	$^{3}/_{2}$
^{87}Rb	1393.2	27.2	$^{3}/_{2}$	^{203}Tl	2433	29.5	$^{1}/_{2}$
^{87}Sr	184.5	7.02	$^{9}/_{2}$	^{205}Tl	2457	70.5	$^{1}/_{2}$
^{89}Y	208.6	100	$^{1}/_{2}$	^{207}Pb	889.9	21.1	$^{1}/_{2}$
^{91}Zr	400	11.23	$^{5}/_{2}$	^{209}Bi	684.2	100	$^{9}/_{2}$
^{93}Nb	1040.7	100	$^{9}/_{2}$				

Eqn. (3) defines the condition for nuclear magnetic resonance. The values of γ_0 (in units of Hz G^{-1}) are listed in Table 1. Thus, when the field strength H_0 of the laboratory magnet is known, the NMR frequency for the given nucleus can be calculated simply by multiplying together γ_0 and H_0. For protons at field strengths of 9400, 14 092, and 23 450 G, the resonance frequencies are 40, 60, and 100 MHz respectively, for ^{31}P nuclei in a 14 092 G field μ_0 = 24.4 MHz, etc. Condition (3) was obtained on the basis of quantum concepts. It is interesting that the classical treatment leads to exactly the same resonance condition. Let us consider a magnetic dipole moment μ in a field H_0. According to Larmor's theorem[12], the dipole μ will precess around the direction of H_0 at a frequency

$$\nu_0 = \frac{\gamma}{2\pi} H_0,$$

where γ is the gyromagnetic ratio of the dipole. When an additional small magnetic field H_1 is applied at right angles to H_0 in the plane of the vectors $\vec{\mu}$ and H_0, the dipole is subjected to a force which tends to alter the angle θ between $\vec{\mu}$ and H_0. When the field H_1 remains in the plane of the vectors $\vec{\mu}$ and H_0 for an unlimited time (synchronisation of the Larmor precession of the vector $\vec{\mu}$ and the rotation of the additional field H_1), the angle θ will change significantly, i.e., in other words, the application of an external field H_0 leads to a marked change in the nuclear magnetisation of the specimen. On the other hand, if the rates of rotation of μ and H_1 do not coincide, and field H_1 will not affect appreciably the overall magnetic moment of the specimen. Next it was found that $\gamma/2\pi = \gamma_0$, i.e. on the basis of Larmor's theorem, we obtain the same resonance condition as from quantum considerations.

The above discussion based on vectors enriched our ideas about NMR: in order to induce resonance, electromagnetic radiation must be circularly polarised and the magnetic vector H_1 must rotate in a plane perpendicular to the vector H_0. In practice a rotating magnetic field is created as a component of a linearly oscillating field: an electric field at a frequency ν_0 is applied to the coil of the circuit tuned to the same frequency; the axis of the coil is positioned at right angles to a permanent magnetic field H_0. It is well known that a field $2H_1 \sin 2\pi\nu_0 t$ varying sinusoidally with time may be regarded as a superposition of two fields $H_1 \sin 2\pi\nu_0 t$ rotating in opposite directions. One of these components gives rise to NMR and the other hardly interacts with the specimen.

IV. NUCLEAR MAGNETIC RELAXATION

The above resonance conditions indicate merely the possibility of the phenomenon but do not guarantee that it will occur. Both groups of discoverers of NMR [13,14] were extremely worried about the difficulties associated with the relaxation processes in the system of nuclear spins. In fact, having carried out an experiment in which the specimen is exposed to quanta of the required magnitude, we stimulate transitions between the magnetic energy levels. Then the probability of transitions from a lower to an upper level (absorption of energy) w^+ and transitions from an upper to a lower level w^- are equal: $w^+ = w^-$. If the populations of the lower and upper levels are identical, the same number of nuclei would pass from the lower to the upper level and conversely per unit time and NMR would not be observed at all.

It was found that within the spin system energy exchange processes take place very effectively and it may be assumed that the system is in thermal equilibrium at a certain temperature (spin temperature), which, generally speaking, is not equal to the temperature of the specimen T. This implies that the attainment of thermal equilibrium within the spin system takes place many powers of ten faster than processes involving energy exchange between the spin system and its surroundings.

In this case the populations of the upper (n_2) and lower (n_1) nuclear magnetic energy levels will not be equal; according to the Boltzmann distribution law, their ratio is

$$\frac{n_2}{n_1} = \exp\left(-\frac{2\mu H_0}{kT_s}\right). \tag{4}$$

If it is assumed that $T_S \simeq T$, then in a field $\geqslant 10^4$ G, we have for protons

$$\frac{n_2}{n_1} \simeq 1 - \frac{2\mu H_0}{kT}. \tag{5}$$

This small difference between the populations is in fact responsible for the occurrence of NMR: w^+n_1 and w^-n_2 nuclei undergo transitions per unit time from below upwards and from above downwards respectively; it is clear from the foregoing that $w^+n_1 > w^-n_2$, i.e. power is absorbed from the radiofrequency field H_1 by the system of nuclear spins. In the absence of some external process which acts in the opposite sense, the field H_1 equalises the populations of the nuclear magnetic levels after a finite time interval and absorption ceases. Such a situation is called saturation.

Regardless of the state of aggregation of the specimen (liquid, gas, or solid), the substance containing nuclear magnetic moments is called a "lattice".

Since nuclear magnetic resonance is observed in practice (and has actually become one of the principal physical research methods in chemistry!), we must conclude that there exists an effective process which returns the spin system to thermal equilibrium with the lattice. Such a process is called spin–lattice relaxation.

On complete saturation, $n_2 = n_1$. Eqn. (5) shows that formally this implies an exceptionally large increase in the temperature of the spin system: $T_S \to \infty$. According to the Second Law of Thermodynamics, the energy exchange process between the heated spin system and the lattice, which is, for example, at room temperature, then takes place in only one direction, from the hot to the cold object, i.e. there must be spin–lattice relaxation.

Indeed simple considerations show that the temperature equalisation process between the spin system and the lattice takes place exponentially:

$$\Delta n_0 - \Delta n_t = (\Delta n_0 - \Delta n_a)\, e^{-t/T_1},$$

where Δn_0 is the difference between the populations of the nuclear magnetic energy levels at $T_S = T$, Δn_1 the difference between the populations observed at time t, Δn_a the initial difference between the populations, and T_1 the time constant or simply the spin–lattice relaxation time.

The physical cause of the spin–lattice relaxation in diamagnetic specimens is the thermal fluctuation of the local magnetic field of the specimen. Bloembergen[15] showed that one can isolate from the thermal vibration spectrum a component with a frequency ν_0 which corresponds to a randomly varying magnetic field in the specimen; this gives rise to transitions between nuclear magnetic energy levels, and is in fact responsible for the lowering of the spin temperature T_S.

These fluctuating local magnetic fields are also one of the causes of spin–spin relaxation, which is responsible for the rapid attainment of the spin temperature T_S. Spin–spin coupling can take place without energy exchange with the external medium. This is the so called "flip-flop" process, in which two interacting nuclei change orientations simultaneously in an external field. Since they do not require an expenditure of energy, such processes can occur very rapidly. They restrict significantly the lifetime of the nucleus in a fixed state and make an appreciable contribution to the line width observed for solids.

In liquid and solid specimens magnetic nuclei are separated by distances of the order of 1 Å and therefore any nucleus is in a local field $\mu r^{-3} \simeq 10$ G, which upsets the resonance condition (3) obtained for an isolated nucleus. This infringement is not very serious if resonance is observed in strong fields; its effect is that NMR is not observed at a single rigorously defined frequency ν_0 but over a range of frequencies $\Delta\nu_0$. The width of this range depends on the effectiveness of the averaging of the local field under the action of thermal motion. In crystals, where the nuclei do not change places,

$$\Delta\nu_0 \simeq \frac{H_{\text{loc}}}{\gamma_0} \simeq 10\,\text{kHz}.$$

This implies that, when the precession phases of two nuclear magnetic moments coincide at any instant but their resonance frequencies differ by 10 kHz, then after only 10^{-4} s their phases will diverge. The time required for the loss of "phase memory" is called the spin–spin relaxation time; in contrast to the spin–lattice relaxation time, it is denoted by T_2. It follows from the foregoing considerations that the time T_2 is closely related to the NMR line width. One of these relations has already been used implicitly. If $\Delta\nu_0$ is the line width, then $T_2 = (\Delta\nu_0)^{-1}$. On the other hand, when the NMR line has the form described by the function $g(\nu)$ and its area is constant, the amplitude $g(\nu)_0$ should fall as a consequence of line broadening. For this reason, there should be a direct proportionality between the NMR line amplitude and the spin–spin relaxation time:

$$T_2 = k\,[g(\nu_0)].$$

Below it will be shown that $k = 0.5$.

For crystals, the NMR lines are broad and $T_2 \leqslant 10^{-4}$ sec. At the same time the spin–lattice relaxation in diamagnetic crystals is very ineffective; T_1 may reach 10^4 s and more. Thus T_2 is smaller by a factor of tens of millions than T_1. This marked inequality ensures, firstly, the validity of the concept of the spin temperature, and, secondly, the possibility of experiments with *negative* values of T_S.

After the specimen has been placed in a magnetic field H_0, equilibrium nuclear magnetisation will be attained after a time interval which is several times longer than the spin–lattice relaxation time T_1. If, observing certain precautions[16], the direction of the field H_0 is then rapidly reversed, the populations of the nuclear magnetic energy levels are also reversed: the upper unfavourable level will contain more nuclei than the lower favourable level. In accordance with Eqn. (5), this means that the absolute spin temperature $T_S < 0$. It is quite clear that a spin system with a negative absolute temperature is essentially much "hotter" than a spin system in a state of saturation, for which the temperature was considered to be infinitely high. Experiments with negative spin temperatures have served as a starting point for purposeful research, which culminated in the creation of masers and lasers.

However, the simple concepts in nuclear magnetic relaxation employed by Bloch, who gave the first quantitative description of the phenomenon of nuclear magnetic resonance, are more important for the purposes of the present review.

V. BLOCH EQUATIONS

Let us consider the formulation of an NMR experiment in a specific form. In order to describe the phenomenon, rectangular coordinates are introduced with the z axis directed along the lines of force of the magnetic field, the y axis is vertical (the coil giving rise to the radiofrequency field H_1 is also as a rule directed along the vertical axis), and the x axis is perpendicular to the yz plane.

Bloch's approach consists in a detailed examination of the components M_X, M_Y, and M_Z of the nuclear magnetisation of the specimen. It is simplest to elucidate the behaviour of the longitudinal component M_Z. If there were no spin–lattice relaxation ($T_1 \to \infty$), then M_Z would be constant, since the Larmor precession of the nuclear magnetic moments around the direction of the magnetic field does not affect their z-projections, i.e. it does not alter their sum either: $dM_Z/dt = 0$.

The question now arises of the changes occurring in the presence of relaxation. We already know that spin–lattice relaxation equalises the temperatures of the spin system and the lattice. If at a temperature T we have a corresponding equilibrium nuclear magnetisation and at some instant the magnetisation M_Z deviates from M_0 for any reason, spin–lattice relaxation should ensure an exponential return of M_Z to M_0, the time constant of this process being T_1. The mathematical form of the situation outlined above is evident:

$$\frac{dM_z}{dt} = -\frac{M_z - M_0}{T_1}. \tag{6}$$

The fate of the other two components of magnetisation, M_X and M_Y, is somewhat more complex. In fact, even in the absence of spin–lattice relaxation one cannot assume that these components are constant, since we have the Larmor precession. By exact analogy with the equations for the motion of a top, we must write

$$\frac{dM_x}{dt} = \omega_0 M_y \quad\text{and}\quad \frac{dM_y}{dt} = -\omega_0 M_x.$$

We have already spoken of the short period of phase memory, which is characteristic of a nuclear spin system. Mention was also made of the energy transitions between the nuclear magnetic moments, which do not affect the overall energy of the system. From the standpoint of the classical vector model, such processes involve changes in M_X and M_Y without changing M_Z. Thus, for a given overall nuclear magnetisation M_Z, deviations of M_X and M_Y are possible; clearly, such a distinction need be introduced only when the characteristic time T_2 for this transverse (spin–spin) relaxation is not equal to T_1. When $T_2 \neq T_1$, the equations for the transverse components must be written in the form

$$\begin{aligned} \frac{dM_x}{dt} &= \omega_0 M_y - \frac{M_x}{T_2}, \\ \frac{dM_y}{dt} &= -\omega_0 M_x - \frac{M_x}{T_2}. \end{aligned} \tag{7}$$

Eqns. (6) and (7) are known as the Bloch equations.

VI. NMR LINE FORM FOR LIQUIDS AND GASES

In order to make any useful deductions from the Bloch equations, it is necessary to consider the factors responsible for the deviations of the components M_X, M_Y, and M_Z from their equilibrium values. We are principally interested in the electromagnetic wave having quanta $h\nu_0$, with the aid of which the NMR phenomenon is in fact observed. The transitions stimulated by these quanta actually give rise to the difference between the populations of the energy levels at the given temperature, which in practical terms implies changes in M_X, M_Y, and M_Z. In the analysis of Eqns. (6) and (7) one should speak not of the quanta $h\nu_0$ but of the magnetic field of the coil, with a current generated by a radiofrequency oscillator at a frequency ν, which is close to ν_0. This weak magnetic field $H_1 \sin 2\pi\nu t$ is added geometrically to the external magnetic field H_0.

When account is taken of the field H_1, Bloch's equations become markedly complicated. A natural method of simplifying the equations is to introduce new variables in which the radiofrequency field H_1 is at rest. In other words we introduced an observer "sitting" at the end of the vector H_1 and undergoing tens of millions of revolutions per second in this imaginary centrifuge. For such an observer, Bloch devised new components ($\omega = 2\pi\nu$) instead of the mutually perpendicular nuclear magnetisation components M_X and M_Y:

$$\begin{aligned} u &= M_x \cos\omega t - M_y \sin\omega t, \\ v &= -M_x \sin\omega t - M_y \cos\omega t. \end{aligned} \tag{8}$$

In Eqns. (8) u is the component of the magnetisation of the specimen varying in phase with H_1 and v is the component displaced by 90° relative to H_1. When the u and v components are employed, Bloch's equations become

$$\begin{aligned} &\frac{du}{dt} + \frac{u}{T_2} + (\omega_0 - \omega)v = 0, \\ &\frac{dv}{dt} + \frac{v}{T_2} - (\omega_0 - \omega)u + \gamma H_1 M_z = 0, \\ &\frac{dM_z}{dt} + \frac{M_z - M_0}{T_1} - \gamma H_1 v = 0. \end{aligned} \tag{9}$$

Eqns. (9) have a wide variety of consequences, but, from our point of view, the most important are their steady-state solutions corresponding to the case where M_Z = const., u = const., and v = const., i.e. to rotation of u and v synchronised with the vector H_1 and to a constant z-component of the nuclear magnetisation. All three derivatives of Eqn. (9) are then zero and we obtain three equations in three unknowns: u, v, and M_Z. By solving these equations, it is easy to derive the following formulae:

$$\begin{aligned} u &= \frac{\gamma H_1 T_1 T_2 (\omega_0 - \omega) M_0}{1 + T_2^2(\omega_0 - \omega)^2 + \gamma^2 H_1^2 T_1 T_2}, \\ v &= -M_0 \cdot \frac{\gamma H_1 T_2}{1 + T_2^2(\omega_0 - \omega)^2 + \gamma^2 H_1^2 T_1 T_2}, \\ M_z &= M_0 \cdot \frac{1 + T_2^2(\omega_0 - \omega)^2}{1 + T_2^2(\omega_0 - \omega)^2 + \gamma^2 H_1^2 T_1 T_2}. \end{aligned} \tag{10}$$

To elucidate the significance of these results, we shall consider the case where the oscillator producing H_1 is tuned exactly to the NMR frequency: $\omega = \omega_0$. From Eqn. (10), we obtain for exact resonance ($u = 0$)

$$v = -\frac{M_0 \gamma H_1 T_2}{1 + \gamma^2 H_1^2 T_1 T_2} \quad\text{and}\quad M_z = \frac{M_0}{1 + \gamma^2 H_1^2 T_1 T_2}.$$

We now compare these results with the quantum characteristics of NMR which are also already known. Clearly the v component describes the absorption of the energy of the electromagnetic wave incident on the spin system. The lower longitudinal magnetisation M_Z compared with the equilibrium value M_0 (before the spin system is exposed to the quanta $h\nu_0$), due to the presence in the denominator of the term $\gamma^2 H_1^2 T_1 T_2$, can be reasonably related to saturation.

Consequently the expression for v in Eqn. (10) describes the NMR absorption line shape. In physics this is known as a Lorentzian line. A second important result is a quantitative estimate of the saturation effect. In fact, when $\gamma^2 H_1^2 T_1 T_2 \ll 1$, saturation does not affect the NMR line form. Evidently, in the absence of saturation the amplitude of the NMR signal is directly proportional to the radiofrequency field strength H_1. It is frequently important to achieve the maximum amplitude of the NMR signal. However, it is clear from Eqn. (10) that the maximum amplitude is achieved at the expense of an appreciable broadening of the magnetic resonance line. On further increase of the radiofrequency field strength, saturation is fully shown: the signal shows a simultaneous decrease of its amplitude and broadening.

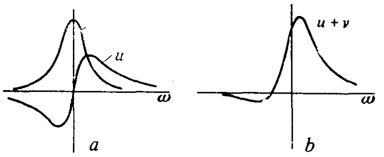


Figure 1. *a*) Absorption (*v*) and dispersion (*u*) signals; *b*) sum of absorption and dispersion signals.

The practical conclusion is that, in order to attain maximum resolution, it is necessary to employ minimum values of H_1 compatible with adequate sensitivity. The somewhat indefinite nature of this recommendation reflects the necessity to seek a compromise, the adequacy of which in each particular case depends on the skill of the operator.

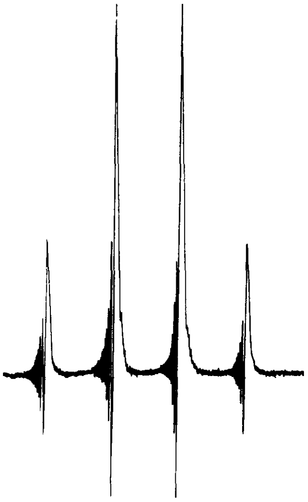


Figure 2. Quartet of the CHO proton in acetaldehyde. With a resolution of about 3×10^{-9}, slow pass conditions are not fulfilled even at a sweep rate of 0.05 Hz s^{-1}; RYa-2305 spectrometer.

It follows from Eqn. (10) that, apart from the absorption signal (the *v* component), there exists also another component of the NMR signal (the *u* component) in phase with the radiofrequency field H_1. The form of this signal is shown in Fig. 1*a*. When the NMR spectrometer is not accurately tuned, the signal recorded may contain a fraction of the *u* component or the so called dispersion signal. An example of such incorrect tuning is presented in Fig. 1*b*. Evidence of this type of error by the operator is revealed by the passage of the signal through the zero line.

It is important to note that the Lorentzian line should be symmetrical about the resonance frequency ω_0. The maintenance of this symmetry in high-resolution NMR spectra is difficult, since it can be achieved only by fairly slow sweep through the NMR line.

In the most frequently encountered design of the NMR spectrometer the spectrum is recorded by a slow linear variation (sweeping) of the magnetic field H. Usually this is done with the aid of special sweep coils. It would appear that there are no obstacles to varying the current in the sweep coil within any desired limits. However, we then encounter the problem of the stability of the high-resolution spectrometer. Therefore in practice there exists for each spectrometer an optimum sweep rate for which a reasonable compromise is achieved between the requirements of optimum resolution and adequate stability of the resonance conditions. For the vast majority of NMR spectrometers at present in use, this compromise is achieved for the narrowest NMR signals at the expense of a more or less serious infringement of the slow sweep conditions. Appropriate analysis of the complete Bloch equations[8] shows that the absorption signal symmetry is then distorted; the passage through the NMR line is accompanied by distinct transient processes (Fig. 2). In the American literature these oscillations have been called "wiggles". The existence of wiggles sometimes leads to misunderstanding in the estimation of the resolution achieved and interpretation of the spectra. Sometimes instead of "wiggles" the term "ringing" is used. This is a very graphic term. The system of nuclear spins is similar to an unusually sensitive resonator. A slow pass resembles the stroking of a bell, but when the bell is struck, it rings! For solids, Eqn. (10) does not hold (see Section XIV).

VII. HIGH AND LOW RESOLUTION

We have now acquired sufficient information to explain quantitatively the origin of the terms "high" and "low" resolution which are popular in NMR spectroscopy. The resolving power of spectroscopic apparatus is limited by the width $\Delta\nu$ of the line recorded at a frequency ν (Fig. 2). The width is measured in different ways; one of the usual definitions is that of the distance between the points at a height equal to half of the line amplitude. It is clear from Eqn. (10) that $|v_{\max}| \simeq M_0\gamma H_1 T_2$ when saturation effects are not observed. On substituting in Eqn. (10) the particular value $v_1 = \frac{1}{2}M_0\gamma H_1 T_2 = v_{\max}/2$ and neglecting saturation as before, we find that the NMR line width is $\Delta\nu = 1/\pi T_2$. Experiments showed that pure diamagnetic liquids give rise to a line with a width of 0.1–0.2 Hz. Consequently, for such lines $T_2 \simeq 1$ s. At operating frequencies of 60 and 100 MHz lines as narrow as this ensure a resolution $\Delta\nu/\nu \simeq 10^{-9}$. This is the maximum resolution achieved at the present time in nuclear magnetic resonance; for a long time nuclear magnetic resonance was a "world champion" among spectroscopic research methods. In the Mössbauer effect [nuclear gamma resonance (NGR)] discovered ten years ago resolutions up to 10^{-16} are achieved but the actual quanta which have to be employed in the Mössbauer effect are 10^{10} to 10^{11} times larger than in nuclear magnetic resonance. Therefore the NMR method remains unsurpassed as regards the details which can be distinguished with its aid in the energy structure of matter. The boundary separating high and low resolution is of course arbitrary. In proton magnetic resonance (PMR) of organic liquids a resolution ranging from $(1-2) \times 10^{-8}$ to $(2-5) \times 10^{-9}$ is usually achieved. One begins to regard the resolution as unquestionably low when $\Delta\nu/\nu > 10^{-6}$. Estimates of the quality of resolution in the range 10^{-6}–10^{-8} depend on which end of the range is approached: the resolution is regarded as high in experiments with solids, viscous liquids, and liquid crystals, and low in those with non-viscous liquids.

The role of the viscosity η was established in a classical study by Bloemberger et al.[17], who showed that the spin–lattice relaxation time T_1 depends on η. T_1 varies within wide limits when the ratio $\eta/T(°K)$ is altered; this variation has a minimum in the vicinity of $\eta/T(°K) = 1$ P deg^{-1}. The minimum value of T_1 is in the range 10^{-2}–10^{-4} s. For such rapid spin–lattice relaxation, the lifetime of each nucleus in the upper energy level is correspondingly very short. The indeterminacy principle predicts that the restriction of the lifetime Δt will widen the nuclear magnetic energy levels, i.e. will increase the width $\Delta\nu$ of the NMR line, since the indeterminacy product $\Delta\nu\Delta t \simeq 1$. Therefore for the minimum values of T_1, $\Delta\nu \simeq 10$ kHz, i.e. we enter the region of low-resolution NMR. In non-viscous liquids and gases $T_1 \simeq T_2$. Thus, if we follow the fate of the NMR line due to a particular specimen on cooling from the gaseous state to the liquid and crystal states, the very narrow peaks become increasingly broader as the temperature is reduced and the viscosity increases; after crystallisation of the specimen, when $\Delta\nu \geqslant 10$ kHz, the time T_2 remains unchanged on further increase of $\eta/T(°K)$, while the spin–lattice relaxation time increases, which results in the previously described situation, typical for solids, where $T_1 \gg T_2$.

VIII. THE CHEMICAL SHIFT

Almost all the quantities which we introduced in the discussion of the nature of nuclear magnetic resonance were independent of the chemical properties of the specimen. Chemical properties reflect a wide variety of structural features of the electron cloud of the molecule. We have to show how the electronic structure affects the resonance conditions of the magnetic nuclei in the atoms constituting the molecule investigated.

The simplest case is the nuclear magnetic resonance of atomic hydrogen. According to Eqn. (3) and the data in Table 1, the resonance conditions for a proton correspond to $\nu_0 = 4257.7\,H_0$ (Hz). The question arises how the resonance frequency ν_0 varies under the influence of the spherical 1s electron shell surrounding each proton. The answer to this problem comes from the theory of diamagnetism[18]. When a magnetic field H_0 is applied to our hypothetical specimen, a circulating electric field is induced in the electron shell of the atom, and according to Faraday's law this is proportional to the rate of variation of the magnetic field dH/dt. Under the influence of this field, the momentum associated with the electron shell alters and the rate of its variation is proportional to dH/dt. As a result, the total change in momentum is independent of the rate of increase of the magnetic field and is simply proportional to the square of the radius of the orbit in which electron circulation takes place and to the steady magnetic field strength. The increased momentum of the s electron generates a proportionate magnetic moment which, according to the Lenz law, gives rise to a magnetic field opposed to H_0. Thus the nuclei of hydrogen atoms in a magnetic field H_0 are in fact exposed to the field

$$H_{\text{eff}} = H_0(1-\sigma), \qquad (11)$$

where σ is the diamagnetic screening constant.

For the purpose of subsequent exposition, it is important to emphasise that the greater is the absolute value of σ the smaller is H_{eff}. This is an obvious consequence of the negative diamagnetic susceptibility of our specimen: $\chi < 0$. Suppose that the specimen investigated contains two types of protons with screening constants σ_1 and σ_2. Then the corresponding effective fields are $H_1 = H_0(1-\sigma_1)$ and $H_2 = H_0(1-\sigma_2)$. If the spectrometer operates at a fixed frequency ν_0, then, in order to observe the NMR of the first nucleus, it is necessary to apply to the specimen the "resonance" field

$$H_{\text{res}_1} = \frac{\nu_0}{\gamma_0(1-\sigma_1)} \simeq \frac{\nu_0}{\gamma_0}(1+\sigma_1),$$

and the resonance of the second nucleus will be "seen" in the field

$$H_{\text{res}_2} = \frac{\nu_0}{\gamma_0}(1+\sigma_2) = H_0(1+\sigma_2).$$

Consequently the greater is the diamagnetic screening the stronger must be the resonance field; in other words, an increase in screening displaces the NMR signal towards stronger fields. The difference, on the magnetic field scale, between the relevant signals is

$$\Delta H = H_{\text{res}_2} - H_{\text{res}_1} = H_0(\sigma_2 - \sigma_1).$$

Evidently the chemical shift ΔH is proportional to the strength of the magnetic field employed in the apparatus. This is an important factor to which we shall frequently return later.

In order to compare the spectra recorded in different magnetic fields, one usually employs a dimensionless relative chemical shift:

$$\frac{\Delta H}{H_0} = \sigma_2 - \sigma_1. \qquad (12)$$

Thus, the intervals between the signals of chemically non-equivalent nuclei observed in the NMR spectra are determined directly by the diamagnetic screening constants. The calculations and estimates of these constants are important for high-resolution NMR spectroscopy. The structural interpretation of chemical shifts is very valuable in modern chemistry.

In successful cases the chemical shifts observed in the NMR spectra indicate directly the number of non-equivalent groups of atoms and the relative signal intensities yield an unambiguous estimate of the numbers of atoms in the corresponding groups. In many cases such information is sufficient to determine the structure of the molecule. However, the diamagnetic screening constants σ are susceptible also to a more profound treatment.

1. Interpretation of Chemical Shifts

The value of σ for the hydrogen atom was calculated for the first time by Lamb[19]. This quantity can be simply estimated. The diamagnetic moment induced in the atom is

$$\mu_d = -\frac{ne^2}{6mc^2} H_0 \langle r^2 \rangle, \qquad (13)$$

where e is the electronic charge, m the electronic mass,

$\langle r^2\rangle$ the mean square of the radius of the electronic orbit, and $n = 1$ for the hydrogen atom. The magnetic field set up by the moment μ_d at the centre of the electronic orbit is

$$H_d \simeq \frac{\mu_d}{r^3} \simeq \frac{ne^2}{6mc^2}\langle r^{-1}\rangle H_0.$$

The ratio of H_d and H_0 gives an estimate of the screening constant:

$$\sigma = \frac{ne^2}{6mc^2}\cdot\frac{1}{\langle r\rangle}. \qquad (14)$$

By substituting the values of e, m, and c and assuming that $\langle r\rangle = 0.5\times10^{-8}$ cm, we obtain $\sigma_H \simeq 10^{-5}$. By a rigorous calculation, Lamb found $\sigma_H = 2\times10^{-5}$. Thus the magnetic field at the nucleus of the hydrogen atom is smaller by 20 p.p.m. than the external field H_0. If small changes in n are postulated (equivalent in our estimate to changes in electron density at the atom considered), the screening is directly proportional to such changes. If Eqn. (14) gave an exhaustive description of the magnetic screening of nuclei, proton NMR would be an ideal method for the measurement of the distribution of electron density in organic molecules. However, this is not so.

The calculation of σ for the hydrogen molecule (H_2) proved to be much more difficult. This is quite reasonable: here the problem loses spherical symmetry, which significantly complicates the physical nature of the magnetic screening. In the molecule it is necessary to consider the screening of a given nucleus as the sum of the following contributions: (a) the diamagnetic contribution due to the spherical component of the electron cloud centred at this nucleus and (b) the magnetic fields set up at this point by the magnetic circulation of other electrons. The first contribution is described by an equation of type (14) and always reduces the external field H_0. The magnetic fields set up by other electrons can be of either sign; if they add to the external fields, such a contribution is called "paramagnetic". We shall consider this problem in somewhat greater detail. If the molecule under consideration has an electron cloud with a non-zero overall orbital momentum L and a spin moment S, the energy of the molecule in the ith state will be[3]

$$\varepsilon_i = \varepsilon_i^{(0)} - \frac{ehL_z}{4\pi mc}H_0 - \frac{ehH_0}{2\pi mc}S_z + \frac{e^2H_0^2}{6mc^2}\Sigma\langle r_i^2\rangle,$$

where L_Z and S_Z are the projections of the corresponding moments on the direction of the magnetic field H_0 and $E_i^{(0)}$ is the energy of the molecule in the absence of a magnetic field. We shall not consider a molecule with true paramagnetism and throughout subsequent exposition it will be assumed without additional stipulation that the electron shells are filled—all possible states with both positive and negative projections of the moments on the z axis are occupied: $L = 0$ and $S = 0$, i.e. there is no paramagnetism in our specimens in the true sense of the word. The last term in the expression for the energy E_i is responsible only for diamagnetism and the "paramagnetic" contributions to the magnetic field, acting on the given atomic nucleus, arise only because the electron cloud of the molecule is not spherical. The magnetic screening in ^{31}P, ^{19}F, and similar heavy atoms is complicated by the fact that the orbital moment L does not become identically zero; as a result, a large paramagnetic component appears in the screening constant. This will be treated in greater detail below.

If two hydrogen atoms are placed at a small distance from one another and are "forbidden" to form a chemical bond, the screening constant of one atomic nucleus will be independent of the diamagnetic circulation in the electron shell of the neighbouring spherical atom: the orbital moment of the 1s shell is zero ($l = 0$) and the spin moment in this model treatment is neglected in view of the above decision to disregard paramagnetic molecules. The question then arises of the origin of the "paramagnetic" contribution to the screening of the protons in the H_2 molecule. The answer is given below.

2. Magnetic Anisotropy

The covalent H–H bond has axial symmetry—its electron cloud may be approximately represented by an ellipsoid of rotation. Evidently, in contrast to the case where a spherical atom is placed in a magnetic field, the intensity of induced diamagnetic currents will vary for different orientations of the half-axis a of this ellipsoid, which is directed along the bond relative to the constant magnetic field H_0. Moreover the deviations of the electron cloud from the cylindrical form lead to the appearance of Van Fleck paramagnetism[3], i.e. the susceptibilities become

$$\chi_i = \chi_{di} - \chi_{pi} = \alpha_i\chi_{di};\ i = x, y, z.$$

Therefore the magnetic susceptibility χ_l for $a \parallel H_0$ is not equal to the susceptibility χ_t for $a \perp H_0$. Consequently the deviations from spherical symmetry should make the magnetic susceptibility anisotropic: the longitudinal susceptibility χ_l is not equal to the transverse susceptibility χ_t.

When the molecule participates in thermal motion, it assumes all possible orientations relative to H_0 and the time-average magnetic moment of the bond considered (or group of atoms) is not zero. The following quantity is a measure of the anisotropy of the magnetic susceptibility of an n-electron shell[13]:

$$\Delta\chi = \chi_l - \chi_t = \frac{ne^2}{4mc^2}(\alpha_l\langle r^2\rangle_l - \alpha_t\langle r^2\rangle_t);\ 0 \leqslant |\alpha| \leqslant 1. \qquad (15)$$

According to the definition (15), $\Delta\chi$ is a magnetic dipole. It is easy to establish a relation between the anisotropy of the magnetic susceptibility of the given bond $\Delta\chi$ and the change in the screening of the given nucleus $\Delta\sigma$ which arises under the influence of $\Delta\chi$. McConnell[20] showed that

$$\Delta\sigma = \frac{\Delta\chi}{3R^3}(3\cos^2\theta - 1), \qquad (16)$$

where R is the distance from the centre of the dipole $\Delta\chi$ to the given nucleus and θ is the angle between the axis of the anisotropic bond and R. It is important to emphasise that in many cases (C=O, C=C, and other bonds) $\langle r_t^2\rangle$ has two values: $\langle r^2\rangle_x$ and $\langle r^2\rangle_y$, and therefore, strictly speaking, for such bonds it is necessary to introduce two values of the magnetic anisotropy: $\Delta\chi_x$ and $\Delta\chi_y$.

Thus a classification of the model forms of electron shells and the corresponding magnetic susceptibilities may be proposed (Table 2; $ne^2/4mc^2 = k$).

Table 2 shows that in the general case it is virtually impossible to calculate $\Delta\chi$ (the values of α_i are determined by the wave functions of excited molecular states).

Quantum-mechanical calculation[21] yields a screening constant $\sigma(H_2) = 23\times10^{-6}$ for the H_2 molecule; the local screening of each proton by "its" electron gives $\sigma_{loc} = 28\times10^{-6}$ and the "paramagnetic" contribution is $\sigma_n = -5\times10^{-6}$. The accuracy of this calculation is not very great, but on its basis and in combination with Lamb's data one may assert, firstly, that the 1*s* electron, distributed around a given proton, is responsible for a screening effect of about 25 p.p.m. in the molecule and, secondly, that the deviations from spherical symmetry of the electron shell can give rise to a 20% change in the local screening. Thus in proton NMR the dominant contribution to screening comes from the proton's "own" electron and the changes of σ under the influence of the anisotropy of the magnetic susceptibility of the neighbouring bonds are smaller by a factor of ten. The effect of the magnetic anisotropy can be of either sign. This is caused, firstly, by the fact that, as the angle θ varies, the factor $3\cos^2\theta - 1$ changes sign in the vicinity of $\theta_0 = 54°44'$. Therefore, when $\Delta\chi > 0$, the correction $\Delta\sigma$ calculated by Eqn. (16) is positive (shift to a stronger field) for $\theta = 0$ and negative (shift to a weaker field) for $\theta = 90°$. Secondly, $\Delta\chi$ can be of different signs. It is then extremely important to agree exactly on the significance of the terms "positive $\Delta\chi$" and "negative $\Delta\chi$".

Table 2.

Form of electron shell	$-\chi_z$	$-\chi_x$	$-\chi_y$	$\Delta\chi$
Ellipsoid	$\alpha_z k\langle r^2\rangle_z$	$\alpha_x k\langle r^2\rangle_x$	$\alpha_y k\langle r^2\rangle_y$	$k(\alpha_z\langle r^2\rangle_z - \alpha_x\langle r^2\rangle_x)$ $k(\alpha_z\langle r^2\rangle_z - \alpha_z\langle r^2\rangle_y)$
Circular cylinder	$k\langle r^2\rangle_z$	$\alpha_x k\langle r^2\rangle_x$	$\alpha_x k\langle r^2\rangle_y$	$k(\langle r^2\rangle_z - \alpha_t\langle r^2\rangle_t)$
Ring (one-dimensional)	kR^2	0	0	kR^2
Sphere	$\frac{3}{2}k\langle r^2\rangle$	$\frac{3}{2}k\langle r^2\rangle$	$\frac{3}{2}k\langle r^2\rangle$	0

Experiment shows that misunderstandings frequently arise in this problem, associated with the differences between the traditional concepts in magnetochemistry and those which have arisen in NMR spectroscopy. Let us consider some examples. In the hypothetical measurement of the magnetic susceptibility of an acetylene single crystal we found that the anisotropy of the diamagnetic susceptibility is positive, i.e. the diamagnetic susceptibility χ_l measured along the triple bond is higher than the diamagnetic susceptibility χ_t measured in a perpendicular direction. But the diamagnetic susceptibility is *negative*. Therefore, strictly speaking, we are dealing with positive anisotropy of negative magnetic susceptibility, i.e. $\Delta\chi < 0$. However, the NMR method is used almost exclusively to investigate diamagnetic properties and for acetylene one usually assumes that $\Delta\chi > 0$. Accordingly, Eqn. (16) predicts a shift to stronger fields for the acetylene proton located on the triple bond axis ($\theta = 0$), which is in fact observed. Because the distance R is short, this shift is very considerable and sets the upper limit to the effect of magnetic anisotropy: $\Delta\sigma(C{\equiv}C) \simeq 4 \times 10^{-6}$. For single and double bonds, the anisotropy of diamagnetic susceptibility is negative, i.e. $\Delta\chi < 0$; accordingly, the NMR signals of nuclei on the bond axis and within a cone with an angle of 54°44′ at the apex are shifted towards weaker fields. A striking case of positive diamagnetic anisotropy is provided by benzene and similar aromatic molecules. The 6π electrons of benzene circulate in a ring of conjugated bonds, the average radius of which is close to 1.4 Å. Using Table 2 (annular current), we obtain $\chi_l \simeq 100 \times 10^{-30}$. Consequently for benzene $\Delta\chi = 100 \times 10^{-30}$ (per molecule) or $\simeq 60 \times 10^{-6}$ (per mole). It is interesting that this rough estimate agrees satisfactorily with the results of the measurements of the static magnetic susceptibility of benzene. Calculation by Eqn. (16) shows that such anisotropy displaces the signal of its "own" protons (i.e. protons in the plane of carbon atoms at a distance $R = 2.48$ Å from the centre of the molecule) by about 2×10^{-6} towards weaker fields. This is the so called "aromatic shift". It is frequently also called the shift due to annular currents. In full agreement with the foregoing, the annular current in benzene can displace the signals of "alien" protons towards stronger fields, when these protons are located in a conical region the axis of which is normal to the plane of the molecule. Thus in pure liquid benzene the proton magnetic resonance (PMR) signal is displaced approximately by 0.6×10^{-6} towards stronger fields relative to a 1% solution of benzene in carbon tetrachloride.

In ferrocene—a sandwich compound of iron with two C_5H_5 rings—the NMR signals of the cyclopentadienyl protons are displaced towards stronger fields by 3.3 p.p.m. relative to benzene[6]. This shift permits an unambiguous choice in favour of the calculation by Shustorovich and Dyatkina[22], according to which, and in contrast to Dahl and Ballhausen[23], there is a negative charge on the C_5H_5 ring of ferrocene (since the molecule is neutral as a whole, a double positive charge is localised at the Fe atom). The conclusion of Dehn and Mulay[24] that 4.8 electrons circulate in each C_5H_5 ring, i.e. that iron has a negative charge appears to contradict the finding of Shustorovich and Dyatkina[22]. The magnetic susceptibilities of ferrocene are $\chi_z = -162 \times 10^{-6}$, $\chi_x = -104 \times 10^{-6}$, $\chi_y = -108 \times 10^{-6}$, and $\Delta\chi = 56 \times 10^{-6} \simeq \Delta\chi_{\text{benz}}$. The conclusion that iron has a negative charge arose as a result of the application to ferrocene of the annular current model (Table 2). In fact, if one assumes that $\Delta\chi = kR^2$ and remembers that $R_{C_5H_5} < R_{C_6H_6}$ and also that two C_5H_5 rings are responsible for $\Delta\chi$, it is found that the number of electrons in the rings is reduced compared with the initial value $n = 5$. However, it is evident from the comparison of the values of χ_z and $\chi_\perp$ for ferrocene with Table 2 that the estimate of kR^2 gives a value of χ_z which leads to $n \simeq 20$, i.e. all the π electrons of the molecule contribute to the longitudinal susceptibility. The charge on the rings cannot be estimated by assuming that $\Delta\chi = kR^2$.

Hence it follows that the dipole $\Delta\chi$ of the real magnetic anisotropy of ferrocene is localised at the centre of the Fe atom and has very little effect on the screening of the C_5H_5 protons, i.e. here $\theta \simeq 60°$ and the angular factor in Eqn. (16) is close to zero. Thus, despite the conjugation of the C_5H_5 rings, the annular current effect in ferrocene is appreciably weaker, i.e. the corresponding PMR signal should be displaced towards stronger fields. The estimates quoted above show that this gives rise to approximately half the shift which needs to be explained. The other half of the observed shift is due to the *negative* charge of the rings, which confirms the view of Shustorovich and Dyatkina: the metal behaves not as an acceptor but as an electron donor in relation to the C_5H_5 rings.

Here it is appropriate to recall yet again that the positive anisotropy of the diamagnetic susceptibility of benzene, ferrocene, and acetylene molecules corresponds exactly to the negative anisotropy of the magnetic susceptibility of the same molecules. In many literature sources the second magnetochemical sign convention is employed; the McConnell formula is then written in the form

$$\Delta\sigma = \frac{\Delta\chi}{3R^3}(1 - 3\cos^2\theta).$$

In the interpretation of the PMR spectra the considerations described above make it possible in most cases to achieve a satisfactory understanding of the experimental data.

3. Paramagnetic Screening in Heavy Atoms

For heavier atoms, the calculation or qualitative treatment of σ involves considerable difficulties. One may regard it as a general rule that σ increases in parallel with the atomic number, i.e. there is an increase in the frequency interval ν_0 in which the NMR signal of nuclei of a given kind may be observed in a given field H_0.

It must be emphasised that, for ^{19}F, ^{31}P, and similar atoms, one can no longer regard diamagnetic screening as the main contribution to the observed chemical shift. In the discussion of the screening in the hydrogen atom and in the H_2 molecule the absence of an orbital momentum in the *s* electron shell plays an important role. For *p*, *d*, and other electrons, the orbital momentum is not zero, i.e. these electrons give rise to a strong magnetic field at the atomic nucleus. The strength of this field is directly proportional to the magnetic moment of the electron (10^{-20} erg $Gauss^{-1}$) and is inversely proportional to the cube of the average distance between the corresponding electron and the nucleus. For fluorine, the average distance of the $2p$ electron from the nucleus is 0.25 Å, i.e. the magnetic field which it sets up amounts to hundreds of thousands of oersteds. This is tens of times more than the typical values of H_0 in NMR spectrometers and therefore it would appear that ^{19}F NMR should be observed at frequencies many times higher than $\gamma_F H_0$. In reality, when F atoms are bound in molecules, the intramolecular electric fields force the *p* electrons to precess and the so called "freezing" of the orbital motion of the $2p$ electron takes place[3,25]; the magnetic field of the $2p$ electrons at the ^{19}F nucleus is close to zero. In a magnetic field H_0 the orbital momentum is partly "unfrozen" and the *p* or *d* electrons have a very powerful influence on the screening of the nucleus and are responsible for the paramagnetic contribution to σ. For ^{19}F, the diamagnetic term $\sigma_d \simeq 10^{-5}$ and $\sigma_p \simeq -20 \times 10^{-4}$. Thus the chemical shifts of ^{19}F and ^{31}P are largely determined by the paramagnetic contribution to the screening due to the spherically asymmetric electron orbits.

4. Chemical Shift Scales

In the measurement of the PMR chemical shifts standard chemical shift scales are employed. Tetramethylsilane (TMS), which has a very high value of σ, is most used as an internal standard; for the vast majority of substances, the NMR signals of protons occur in weaker fields than the TMS signal. In the so called δ scale the position of the TMS signal is assumed to be zero and the shifts to weaker fields are treated as positive; the shift is measured in parts per million (p.p.m.). The higher is the numerical value of δ, the weaker the screening of the corresponding proton. This is a disadvantage of the δ scale.

The parallel variation of the screening constant and the numerical value of the chemical shift is maintained in the τ scale, where the reference point is also the TMS signal but its position has been arbitrarily and quite unjustifiably assumed to be 10 p.p.m. Consequently the zero of the τ scale corresponds to $\delta = 10$ p.p.m.; evidently

$$\delta = 10 - \tau$$

or

$$\tau = 10 - \delta.$$

A disadvantage of the τ scale is the change in the sign of τ for shifts with $\delta > 10$ p.p.m., characteristic of acids and protons involved in strong hydrogen bonds. The negative signs of τ is physically quite meaningless. On the other hand, the negative sign of δ indicates either a powerful effect of the magnetic anisotropy of the molecule or an unusually effective concentrations of electron density at the corresponding chemical bond. Possibly, the most convenient would be a scale (we shall call it the τ^* scale) in which the TMS signal would be at 25 p.p.m.: on this scale the value of τ^* could be roughly identified with the electron density at the corresponding hydrogen atom.

In order to elucidate the significance of the symbols introduced and to learn how to employ them correctly, we shall consider an example. The PMR signal of the methyl group in ethyl is usually displaced by 1.25 p.p.m. towards weaker fields relative to the TMS signal. Consequently on the δ scale this shift is $\delta(CH_3) = 1.25 \times 10^{-6} = 1.25$ p.p.m. and on the τ scale it is $\tau(CH_3) = 8.75 \times 10^{-6}$. Such notation is sometimes inconvenient in the context of a given paper and a different procedure is resorted to: the scale designation is written as a multiplier of the shift, i.e. the shift of the methyl group on the δ scale is written

$$\sigma(\mathrm{TMC}) - \sigma(\mathrm{CH_3}) = \delta(\mathrm{CH_3}) = 1.25 \times 10^{-6} = 1.25\,\delta.$$

Here the symbol δ on the right-hand side has the significance

$$\delta = \frac{\sigma(\mathrm{TMC}) - \sigma(\mathrm{X})}{10^6\,|\,\delta(\mathrm{X})\,|} \equiv 1 \times 10^{-6},$$

i.e. $\delta = 1$ p.p.m. reckoned from the tetramethylsilane signal. Thus the phrases "the methyl group has a shift $\delta(CH_3) = 1.25 \times 10^{-6}$", "the methyl group has a shift $\tau(CH_3) = 8.75 \times 10^{-6}$", "the PMR of the methyl group was observed at 1.25 δ", and "the position of the peak due to methyl protons is at 8.75 τ" have in practice the same significance. Sometimes for brevity the multiplier 1×10^{-6} = p.p.m. is omitted and the chemical shift is written in the form $\delta(CH_3) = 1.25$.

IX. PRINCIPAL EMPIRICAL RELATIONS IN CHEMICAL SHIFT SERIES

The chemical shift is an important parameter of a high-resolution NMR spectrum. Impressive experimental data on the chemical shifts in the NMR of ^1H, ^{19}F, ^{31}P, and certain other nuclei have now accumulated. The chemical shifts in high-resolution PMR have assumed particularly great importance in the structural analysis of organic compounds, organic derivatives of the elements, and inorganic compounds. A typical PMR chemical shift diagram is presented in Fig. 3. Extensive compilations of the chemical shifts of protons and other nuclei can be found in monographs[5,6,9,10]. One of the first such compilations was published in this journal[26].

Handbooks dealing with compounds investigated by the NMR method and compilations of chemical shifts[27,28] are of great assistance in day to day work. Since the number of investigations with active employment of NMR reaches several thousand per year, a complete grasp of this stream of results can be achieved only with the aid of the card indexes published by several firms[29,30].

The following comments may be made on the PMR chemical shift diagrams. The PMR signals of transition metal hydrides occur in the strongest fields (the negative part of the δ scale). The nature of these extremely high shifts has been frequently discussed but its causes are still not clearly understood. The simplest qualitative explanation is based on the high electron-donating activity of

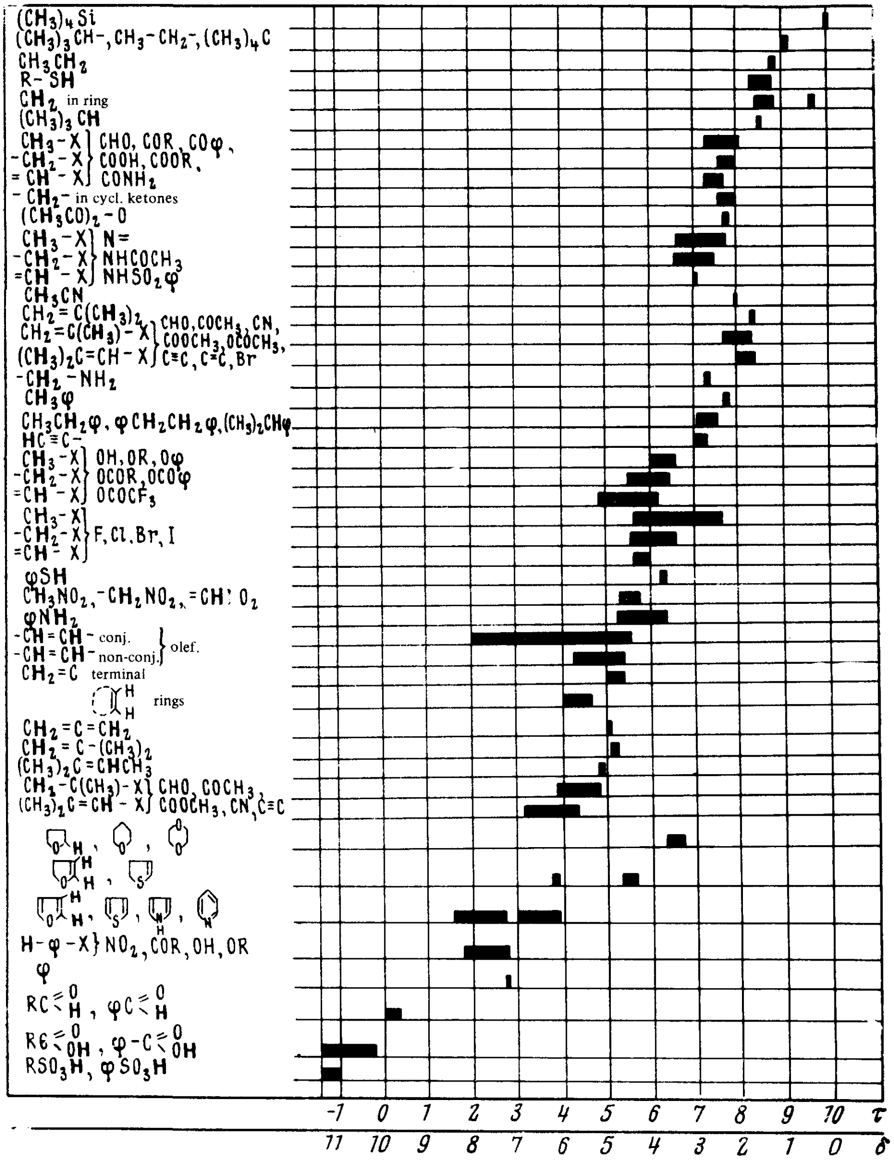


Figure 3. Diagram of NMR chemical shifts of protons.

transition metals and the tendency towards the formation of a helium type electron shell in the hydride hydrogen atom.

In the vicinity of the zero of the δ scale are the signals of the methyl groups attached to germanium and silicon atoms. The signals of cyclopropane and the terminal groups of fairly long ($n > 5$) alkane molecules are located between zero and unity on the δ scale. Methyl groups in ethyl and similar radicals give rise to a signal in the vicinity of 1.25. Methylene groups in the same radicals can give rise to PMR signals in the range $1 \leqslant \delta \leqslant 4$, depending on the properties of the atoms to which the radicals are attached; in certain organometallic compounds the CH_2 and CH_3 signals change places: the signal of the CH_2 protons occurs in stronger fields. Olefinic protons give rise to resonance peaks in the region $4 \leqslant \delta \leqslant 6.5$. Signals of hydroxyls and similar groups can be very markedly displaced under the influence of solvents which modify the intermolecular hydrogen bonds. In the absence of a hydrogen bond, the PMR of OH protons is in the vicinity of 2δ, very strong intermolecular bonds displace the signal to 10δ, and finally chelate protons give signals in the vicinity of 18δ, which is characteristic of extremely strong acids. However, this cannot be interpreted directly as implying the "stripping" of the chelate proton. Neutral aromatic molecules give signals in the region $6.5 \leqslant \delta \leqslant 8.0$. The signal of the aldehyde group is usually observed in the range $8 \leqslant \delta \leqslant 10$. It is possible to observe a satisfactory correlation between the donor-acceptor properties of substituents and the chemical shifts. As stated in the preceding paragraph, electron-donating and electron-accepting substituents displace the signal towards stronger and weaker fields respectively.

As already mentioned, the range of ^{31}P and ^{19}F chemical shifts is much wider than the brief interval corresponding to changes in the screening of protons. The NMR chemical shifts of ^{19}F and ^{31}P are less characteristic than the PMR shifts. As a rule structural conclusions are arrived at on the basis of a detailed spectrum, taking into account the spin–spin interaction. One discusses largely, not the absolute values of the shifts, but the changes under the influence of a suitable selected series of substituents[6,9].

X. SPIN–SPIN COUPLING

Five years after the discovery of NMR, Proctor, Gutowsky, and coworkers[31] observed a characteristic splitting in the NMR signals from many chemical compounds. This discovery was made immediately after this group of investigators succeeded in constructing a magnet with a field homogeneity of the order of 10^{-7} (exceeding by a power of ten the homogeneity of the magnetic fields in the best spectrometers previously available). It was then found that the NMR signals previously incorrectly attributed to chemically different atoms show further splitting into two and more components when the resolving power of the apparatus is increased. The principal feature of these multiplets proved to be that their splitting was independent of the magnetic field H_0. This finding demonstrated unambiguously a fundamental difference between the nature of the splitting and the chemical shift [see Eqn. (12)]. Simple relations observed in the study of the symmetry and the number of components in these new details of NMR spectra showed that the reason for the complication is indirect interaction of the nuclear magnetic moments via bonding electrons located between the atoms to which these nuclei belong.

To illustrate the mechanism of this interaction, we shall turn to the HD molecule. The reason why we are not discussing the spin–spin coupling in the H_2 molecule will be made clear below. The nucleus with a spin of 1/2 then interacts magnetically only with the electron shell of its "own" atom. The direct dipole–dipole effect of the magnetic moment of the electron μ_e on the magnetic moment of the nucleus μ_n in a liquid specimen will be largely averaged out by the thermal motion of the molecule and contact interaction[3] which is proportional to the density of the s electrons of the nucleus, plays the main role. Spin–spin coupling is therefore transmitted only via bonds which have non-zero s character.

Suppose that the HD molecule is in the ground state: two electrons are in the bonding orbital. The coupling of the nuclear and electronic magnetic spin moments in the H atom makes the antiparallel orientation of these moments more favourable than the parallel orientation. The antiparallel orientation of the electron spins in the HD molecule does not require further justification: this is a consequence of the existence of a covalent bond. Consequently the electron in the D atom, for which the mechanism of the coupling between the electronic and nuclear spins is the same as in the H atom, endeavours to orient the nuclear spin of the deuteron antiparallel to its own and hence antiparallel to the spin of the proton, i.e. the sign of the coupling between the nuclei is positive. Theory and experiment[33] have shown that the reversal of the sign of the spin–spin coupling is also possible: situations occur where the mechanism discussed leads to parallel orientation of the magnetic moments of the interacting nuclei.

As a result of the presence of the spin–spin coupling in the HD molecule, the NMR signal of deuterium ceases to be a singlet line. In simple words, the factor which orients the magnetic moment of the nucleus is the magnetic field. As has been frequently mentioned, protons have a spin of 1/2, i.e. are capable of being oriented in the field in two ways: along the field and in opposition to it. We also know that the populations of these states differ at room temperature by several tens of p.p.m. This difference is quite sufficient to detect the NMR signal with the aid of modern electronics. However, its intensity can be measured in the most favourable case only with an accuracy of several thousand p.p.m. Therefore in practice in half of the molecules of the specimen the deuterium nuclei will be subjected to the field

$$H'_{\text{eff}} = H_0(1-\sigma) + H_{ss},$$

while in the other half the magnetic field at the deuterons will be

$$H''_{\text{eff}} = H_0(1-\sigma) - H_{ss}.$$

Consequently the signal of the relevant nucleus will be converted into a doublet with equal component intensities. The distance between the doublet components is $2H_{SS}$ gauss. Since at present precise measurements of magnetic fields are made by determining accurately the NMR frequency[6], it was reasonable to characterise the spin–spin coupling by a constant measured on the frequency scale (not in gauss but in hertz). The value of $2H_{SS}$ measured in hertz units is called the spin–spin coupling constant and is denoted by J. For the HD molecule, J = 43 Hz.

The signal due to the second nucleus of the molecule is of course also a doublet with the same distance between the components. Table 1 shows that it is very difficult to observe the doublets simultaneously: owing to the considerable difference between the magnetic moments of the H and D nuclei, the resonance in a given field H_0 occurs at frequencies which differ by a factor of almost seven in the two cases. Therefore in the HD molecule the total NMR spectrum consists of two doublets the distance between the centres of which exceed by six powers of ten the doublet splitting. In the nomenclature adopted this spectrum is of the type AX: the designation of nuclei by letters from different ends of the alphabet is a symbolic representation of the fact that $\nu_A - \nu_X = \Delta\nu \gg J_{AX}$, i.e. the difference between the resonance frequencies of these nuclei is many times greater than the degree of spin–spin coupling between them.

XI. THE NUMBER OF LINES IN THE SPECTRUM

We established that the NMR spectrum of an AX system with two nuclei having spins of 1/2 consists of four lines—a doublet of doublets. It is not difficult to extend the considerations dealt with in the previous section to an AM...P...Z system of n non-equivalent nuclei with spins of 1/2. If each of the $n-1$ neighbouring nuclei is linked to the nucleus under consideration by spin–spin coupling, then, by numbering the neighbours in order of decreasing coupling we find that the nearest neighbour splits the signal of the given nucleus into a doublet and each component of this doublet becomes a doublet itself as a result of the interaction with the second neighbour, etc. Thus the signal of the given proton becomes a multiplet consisting of 2^{n-1} components. There will be as many multiplets as there are nuclei in the system, i.e. altogether in the spectrum of a system of n interacting nuclei there will be

$$m = n \times 2^{n-1} \tag{17}$$

peaks.

Eqn. (17) gives the multiplicity of the PMR spectrum when the distances between the multiplets exceed greatly the splitting within them, i.e. the chemical shifts $\nu_0\delta_{ik}$ exceed approximately by a power of ten the corresponding spin–spin coupling constants:

$$\nu_0\delta_{ik} \geqslant 10J_{ik}. \tag{18}$$

If condition (18) holds for each pair of nuclei, then the corresponding spectrum is called a first-order spectrum. Eqn. (17) gives the maximum multiplicity for such spectra.

A decrease in the number of lines in a first-order spectrum may be caused by some kind of equivalence of the nuclei. We shall consider only two principal types: chemically and magnetically equivalent nuclei. Chemically equivalent nuclei are those with identical screening (identical chemical shifts). According to the laws of quantum mechanics, spin–spin coupling within a group of chemically equivalent nuclei cannot be detected. This in fact is the reason for our choice of the HD molecule as a model for the discussion for the mechanism of spin–spin interaction: the chemical equivalence of the protons in the H_2 molecule precludes the observation of a powerful (J = 280 Hz) spin–spin coupling. Therefore, when p nuclei have the same chemical shift, then, instead of $p \times 2^{n-1}$ lines, this group gives only one line, which is split into $2^{(n-p)-1}$ components when there is different spin–spin coupling between the remaining nuclei of the system and each nucleus within the group of the chemically equivalent nuclei. Thus the multiplicity of the spectrum is then significantly reduced.

Further simplification or, the so called degeneracy of the spectra, can occur due to fortuitous equality of certain spin–spin coupling constants or when there are multiple relations between them. Then two or more peaks coincide.

Apart from chemical equivalence, there is also a possibility of magnetic equivalence of the nuclei. A group of chemically equivalent nuclei is said to be magnetically equivalent when each of them undergoes the same spin–spin interaction with any nucleus of another group of nuclei. Naturally, under these conditions the second group also consists of magnetically equivalent nuclei.

The methyl and methylene protons of the ethyl group may be regarded as constituting the most widely known case of magnetic equivalence. For any hindered conformation of the ethyl group, methyl protons, for example, would have the same chemical shifts but would undergo different interactions with the protons of the methylene group, i.e., while maintaining their chemical equivalence, they would be magnetically non-equivalent.

The rapid rotation of the methyl group around a single C–C bond leads to the averaging of the spin–spin interaction constant, and in the presence of sufficiently strong magnetic fields the ethyl group gives rise to a PMR spectrum of the type A_2X_3. It is easy to establish the form of the spectrum. Owing to the equality of the constants, the signal of the methyl group instead of being a doublet of doublets becomes a triplet with intensity ratios of 1 : 2 : 1, since the central peaks coincide. The spectrum of the methylene protons instead of comprising eight (2^3) equal peaks will consist of a quadruplet with a binomial intensity distribution 1 : 3 : 3 : 1. It is easily seen that the sum of the relative intensities is equal to the corresponding spin multiplier 2^{n-1} in Eqn. (17). This is an additional illustration of the fact that binomial multiplets are only a very special case of spin–spin splitting in high-resolution PMR spectra.

When the chemical shifts diminish, there is as a rule an appreciable increase in the number of lines in the spectrum compared with the multiplicity predicted by Eqn. (17). The reason is the occurrence of the so called combination lines. In the examination of the scheme which led to formula (17) it was suggested that only pure transitions take place between the energy levels formed. Thus the A transition is one in which the state of only the A nucleus is altered. However, in many-spin systems there is a possibility also of transitions in which there is a simultaneous change in the state of several nuclei. Thus in three-spin systems there is a possibility of a transition from the situation ↑↓↓ to ↓↑↑. Usually the intensities of these lines are low, but for $\nu_0\delta \leqslant J$ the combination transitions lead to a sharp increase in the number of lines. To illustrate this, the table taken from Braier et al. is quoted[33].

n	2	3	4	5	6	7
m_{min}	4	12	32	80	192	448
m_{comb}	0	3	24	130	690	2555
m_{max}	4	15	56	210	792	3003

Such a large number of lines causes significant difficulties in the interpretation of the spectra: the individual multiplets may overlap and the assignment ceases to be unambiguous. Frequently in the spectra of many-spin systems the lines are so close to one another that instead of individual peaks a common outline is observed. Under these conditions, differing sets of parameters can lead to virtually identical spectra. The calculation of the spectrum should give a set of parameters (chemical shift δ_i and spin–spin interaction constant J_{ik}) corresponding unambiguously to the observed spectrum. Such a calculation is a typical quantum-mechanical problem. For a system of n nuclei with spins of 1/2, the number of energy levels is 2^n, i.e. the secular equation for a two-spin system is of the fourth degree and the equation for a three-spin system is of the eighth degree. In fact the symmetry properties of the spin systems make it possible to reduce significantly the degree of the secular equation. Thus for a two-spin system, the secular equation becomes

$$\begin{vmatrix} H_{11}-E & 0 & 0 & 0 \\ 0 & H_{22}-E & H_{23} & 0 \\ 0 & H_{32} & H_{33}-E & 0 \\ 0 & 0 & 0 & H_{44}-E \end{vmatrix} = 0, \tag{19}$$

i.e. the problem reduces to the solution of two linear equations and one quadratic equation. Fig. 4 presents the spectrum of an AB system, i.e. a two-spin system with a chemical shift $\nu_0\delta_{AB}$ close in magnitude to the spin–spin coupling constant J_{AB}. The solution of Eqn. (19) leads to the result

$$\nu_0\delta_{AB} = \sqrt{\Delta_{14}\,\Delta_{23}}; \qquad A_1 : A_2 = \Delta_{23} : \Delta_{14}. \tag{20}$$

It is important to note that, in contrast to a system AX, in the analysis of a system AB the spectrum yields directly only the value of J_{AB} and the chemical shift is obtained only as a result of the calculation. For more complex systems, none of the NMR spectral parameters can be obtained by direct measurement of any interval between the peaks.

The complex spectra of many-spin systems are analysed on electronic computers[34] and also with the aid of binary and multiple resonance methods[9]. Eqn. (20) shows that the distance between the two inner components of the spectrum of the AB system is appreciably smaller than the chemical shift $\nu_0\delta_{AB}$. As a result of this phenomenon, in the case of small shifts the multiple set of lines in the spectrum frequently merges into one peak, which reduces the reliability of the interpretation. All these difficulties are largely obviated when the operating frequency of the spectrometer is increased: the increase of the chemical shifts is then accompanied by a narrowing of the spin multiplets due to the disappearance of the combination lines; both factors tend to simplify the spectrum up to the limiting case of a set of doublets of equal intensity.

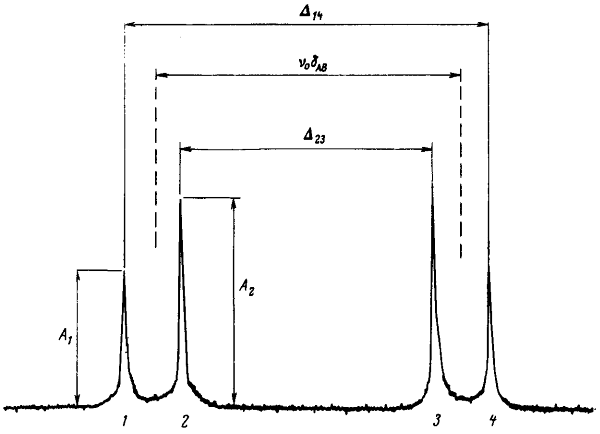


Figure 4. Spectrum of an AB system.

It is not difficult to calculate the frequency at which a given spectrum will become such a simple set of doublets. Suppose that $\delta_{\min}$ is the minimum chemical shift and $J_{\max}$ the maximum spin–spin coupling constant. Then the width of the spin multiplet will be approximately $2J_{\max}$ and for the spectrum to be simple the following condition must be fulfilled:

$$\nu_0\delta_{\min} \geqslant 20J_{\max}$$

If simple spectra are considered necessary for $\delta_{\min} \simeq 10^{-8}$ and $J_{\max} \simeq 10$ Hz (typical values for monoalkylbenzenes), then the required frequency is $\nu_0 = 2 \times 10^{10}$ Hz. This exceeds by a factor of one hundred the maximum value of ν achieved by 1968.[35] The above estimate clearly illustrates the principal trend in the design of NMR apparatus: a steady increase in the strength of the magnetic fields employed and in the corresponding values of ν_0 (proportional to them).

It is important to note that, apart from simplifying the spectra, an increase in ν_0 greatly improves the sensitivity. This is because an increase in ν_0 entails an increase in the spacing between the nuclear magnetic levels. At the same time there is also an increase in the size of the quantum absorbed by the specimen and in the difference between the populations of the upper and lower levels. In practice the sensitivity increases in proportion to ν_0^n, where the power exponent is in the range $1 \leqslant n \leqslant 2$.

XII. PRINCIPAL EMPIRICAL RELATIONS IN SPIN–SPIN COUPLING CONSTANT SERIES

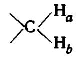
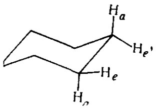
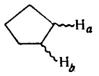
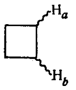
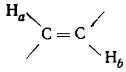
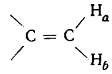
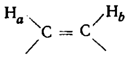
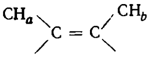
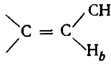
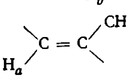
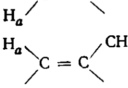
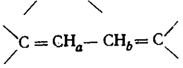
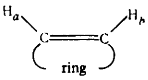
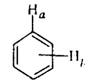
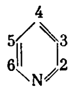
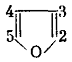
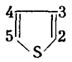
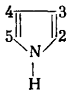
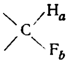
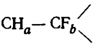
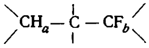
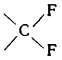
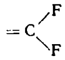
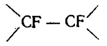
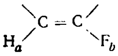
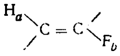
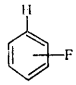
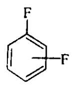
The experimental values of the constants J are very useful in studies on the structures of complex organic compounds. In contrast to the chemical shifts, these values depend little on the nature of the solvent, the concentration of the test substance, etc. The conclusions arrived at with the aid of the spin–spin coupling constants are distinguished by high reliability.

Table 3 lists the values of J for saturated organic compounds. Only individual items in this table need to be commented upon. The change in the sign of the *gem* constant (row 1) with the valence angle was predicted theoretically by Karplus[32] and soon confirmed experimentally by the double resonance method[36]. The high values of the axial–axial constant (row 4) constitute one of the principles underlying the conformational studies of substituted cyclohexanes and similar problems in more complex compounds[37]. In those cases where the splitting of the hydroxyl proton signal indicated in row 8 is observed experimentally, it indicates unambiguously the absence of proton mobility; the disappearance of the multiplet structure of the signal permits the measurement of the rate of proton exchange (see Section XIII).

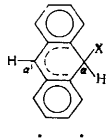
The constants J_{ab} for unsaturated compounds are given in rows 10–26 of Table 3. Here the most interesting finding appears to be the theoretically predicted[38] rule $J_{trans} > J_{cis}$, which has always been confirmed experimentally. This rule is invaluable in the study of the stereochemistry of the reactions of olefinic hydrogen atoms[39]. It is a special case of the dependence of J_{ab} on the angle between the half-planes containing the bonds CH_a and CH_b, investigated by Karplus[38]. This relation also constitutes a useful method for stereochemical investigations in most cases where the C–C bond is intermediate between a single and a double bond[40]. The useful relations in the series of conjugated cyclic compounds do not require further comment.

The interaction constants $J(^{13}C-H)$ play a major role in structural analysis by the NMR method. If the principal carbon isotope carbon-12 had a magnetic moment the ^1H NMR spectra would have been much more complex than is actually observed. Fortunately only the nucleus of carbon-13, the natural concentration of which is 1.1%, has a spin of 1/2. Therefore when the sensitivity of the spectrometer is enhanced, the proton resonance spectra show the so called ^{13}C satellites: doublet signals due to molecules in which the light carbon isotope is replaced by the heavy isotope. In the centre of this spin–spin doublet there is a signal two hundred times more intense and corresponding to protons joined to carbon-12. It has been found that the $J(^{13}C-H)$ splitting makes it possible to distinguish clearly the hybridisation of the carbon atom to which the given proton is linked. According to Muller and Pritchard[41], the values of $J(^{13}C-H)$ for methane, ethylene, and acetylene are respectively 125, 156, and 250 Hz. These three points together with the origin of coordinates (fourth point) lie quite accurately on a straight line when the $J(^{13}C-H)$ values are plotted against the amount of s character. This observation gave rise to an extensive literature. One may quote as a good example the work in

Table 3. Spin–spin proton coupling constants (from data issued by the Varian Company).

No.	Type	J_{ab}, Hz	J_{ab}, Hz typical
1		from +5 to -30	from —12 to —15
2	$CH_a - CH_b$ (free rotation)	6—8	7
3	$CH_a - \overset{\mid}{\underset{\mid}{C}} - CH_b$	0—1	0
4	 $a - a'$ $a - e'$ $e - e'$	6—14 0—5 0—5	8—10 2—3 2—3
5	 (*cis* or *trans*)	0—7	4—5
6	 (*cis* or *trans*)	6—10	8
7	 (*cis* > *trans*)	2—8	3—5
8	$CH_a - OH_b$ (no exchangc)	4—10	5
9	$CH_a - \underset{\underset{C}{\Vert}}{OH_b}$	1—3	2—3
10	$=CH_a-\overset{\overset{O}{\Vert}}{CH_b}$	5—8	6
11		12—18	17
12		0—3	—2
13		6—12	10
14		0—3	1—2
15		4—10	7
16		from—0.5 to —3.0	—1.5
17		from—0.5 to —3.0	—2
18		9—13	10
19	($H_a - C \equiv CH_b$	from—2 to —3	
20	$-CH_a - C \equiv C - CH_b -$	2—3	
21	 3-memb. 4-memb. 5-memb. 6-memb. 7-memb.	0—2 2—4 5—7 8—11 10—13	
22	 *J* (*ortho*) *J* (*meta*) *J* (*para*)	6—10 1—3 0—1	9 3 ~0
23	 *J* (2—3) *J* (3—4) *J* (2—4) *J* (3—5) *J* (2—5) *J* (2—6)	5—6 7—9 1—2 1—2 0—1 0—1	5 8 1.5 1.5 1 ~0
24	 *J* (2—3) *J* (3—4) *J* (2—4) *J* (2—5)	1.3 (?) —2.0 3.1—3.8 0—1 1—2	1.8 3.6 ~0 1.5
25	 *J* (2—3) *J* (3—4) *J* (2—4) *J* (2—5)	4.9—6.2 3.4—5.0 1.2—1.7 3.2—3.7	5.4 4.0 1.5 3.4
26	 *J* (1—2) *J* (1—3) *J* (2—3) *J* (3—4) *J* (2—4) *J* (2—5)	2—3 2—3 2—3 3—4 1—2 1.5—2.5	
27		44—81	
28		7—13	
29		0	
30		200—300	
31		7—80	
32		0—25	
33		1—8	
34		12—40	
35		*o* 6—10 *m* 5—6 *p* 2	
36		*o* 20 *m* 0—7 *p* 0—12	

which it was shown unambiguously on the basis of the values of the $J(^{13}C-H)$ constants that in the molecule of dihydroanthracene[42]



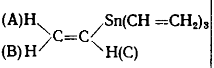
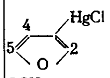
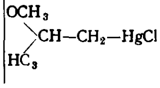
the α-atom of the benzene ring is sp^3-hybridised:

$$J_\alpha(^{13}C-H)=127\,Hz,\quad J_{\alpha'}(^{13}C-H)=163\,Hz.$$

Measurements of the constants for the spin–spin coupling between protons and ^{29}Si, $^{117(119)}Sn$, Pb, $^{203(205)}Tl$, and ^{199}Hg nuclei are widely used in the chemistry of organometallic compounds. Typical values of these constants are listed in Table 4. An interesting example of the importance of these data is provided by the work of Nesmeyanov et al.[43] It was found that in the spectrum of C_5H_5Tl the signal due to the cyclopentadienyl protons is a narrow singlet with a chemical shift typical for compounds of this type without the slightest trace of spin–spin interaction with thallium nuclei.

At the same time Table 1 shows that thallium has no non-magnetic isotopes and it is evident from Table 3 how strong the spin–spin J(Tl–C–H) interaction usually is. The singlet nature of the PMR signal of C_5H_5Tl indicates complete exclusion of the spin–spin coupling. This is important evidence confirming the generally accepted view[44] concerning the mechanism of the spin–spin coupling, to which the Fermi contact interaction makes the main contribution. Such interaction is non-zero only when there is an appreciable electron density at both nuclei. Only s electrons can come into contact with the nucleus and therefore when the chemical bond involves pure p or d states, the absence of spin–spin interaction is to be expected. Univalent thallium forms a bond with the cyclopentadienyl ring via a $6p$ electron and the admixture of the s state to this chemical bond from thallium does not exceed 10^{-3} according to the data of the experiment quoted, since otherwise signs of splitting in the PMR signal would have been noticeable. Similar observations were made in the study of organophosphorus compounds. The constant $J(^{31}P-C-H)$ for tricoordinate phosphorus in the fragment $^{31}P-CH_2$ is several times smaller than for pentacoordinate phosphorus, which can be reasonably related to the tendency towards lone pair formation and the corresponding decrease of the s character of the $P^{III}-C$ bond.

Table 4. Metal–proton spin–spin coupling constants.

No.	Type	J(M-H), Hz	No.	Type	J(M-H), Hz
1	SiH_4	202	9	$Sn(CH_3)_4$	54
2	SiH_3F	229	10	$Sn(CH_3)_3Cl$	60
3	SiH_3I	240	11	$Sn(CH_3)_2Cl_2$	71
4	SiH_2F_2	282	12	$Sn(CH_3)Cl_3$	100
5	$SiHF_3$	381	13	$^{205}Tl(CH_3)_3$	251
6	$Si(CH_3)_4$	~6	14	$^{205}Tl(C_2H_5)_3$	$J(Tl-CH_2)=198$ $J(Tl-CH_3)=396$
7	$^{119}Sn-(CH_2-CH_3)_4$	$J(SnC-H_3)=\pm 71$ $J(Sn-CH_2)=\pm 32$			
8		$J(Sn-H_A)=91$ $J(Sn-H_B)=183$ $J(Sn-H_C=98$	15		$J(Hg-H_2)=40$ $J(Hg-H_4)=75$ $J(Hg-H_5)=28$
			16		$J(Hg-H_\alpha)=223$ $J(Hg-H_\beta)=338$ $J(Hg-H_\gamma)=0$

Spin–spin interaction with nuclei which have spins $I > 1/2$ leads to appreciable changes in the NMR spectra. Apart from a magnetic moment, such nuclei also have a quadrupole electric moment. The interaction of the nuclear quadrupole moment with an inhomogeneous electric field fluctuating as a result of thermal motion, which must exist in the specimen, leads to rapid reorientation of the nucleus, i.e. constitutes an additional mechanism of nuclear magnetic relaxation. Depending on the contribution of this mechanism, the spin–spin multiplets associated with the nuclei participating in the interaction with the quadrupolar nucleus can be either altogether "diffuse", or significantly broadened, or can comprise a set of sharp peaks of virtually the normal type.

The contour of the signals obtained is sometimes unexpectedly freakish. We may quote several examples. The simplest[45] is provided by deuterium exchange in 2-methylpentane; the 1,2-methyl protons in $(CH_3)_2-CH-(CH_2)_2CH_3$ give rise to a distinct doublet with a splitting of 6.62 Hz. In 2-deutero-2-methylpentane $(CH_3)_2-CD-(CH_2)_2CH_3$ the signal due to the $(CH_3)_2$ group proved to be a triplet with intensity ratios of 1 : 1 : 1 and a splitting of about 1 Hz. The form of this signal demonstrates unambiguously that deuterium is precisely in the position indicated. The ratio of the spin–spin interaction constants $J(CH_3-CD)/J(CH_3-CH) = 0.1512 \pm 0.008$, which agrees well with the ratio $\gamma_D/\gamma_H = 0.1535$.

^{14}N nuclei also have a spin $I = 1$, i.e. should give rise to 1 : 1 : 1 triplets. However, the high magnetic moment leads to an even more effective quadrupole relaxation of the ^{14}N nuclei; these nuclei execute such rapid transitions that the width of the signals of the protons linked to ^{14}N via a spin–spin interaction also increases markedly. Then the PMR signal is sometimes absent altogether. Thus in formamide the signals of the NH_2 protons are clearly visible only on saturation of the ^{14}N resonance[46].

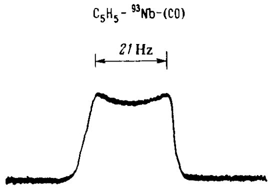


Figure 5. PMR signal of cyclopentadienyl protons in cyclopentadienylniobium tetracarbonyl.

It is important to emphasise that for ^{14}N the 1 : 1 : 1 ratios indicate only the integral line intensities. The observed pattern is altered by the different peak widths: the outer lines of the triplet correspond to levels with a shorter lifetime and therefore they are 40% wider and correspondingly lower than the central peak.

^{11}B and ^{35}Cl are typical examples of nuclei with a spin $I = 3/2$. In accordance with the possible number of states of the 3/2 spin in a magnetic field, such nuclei should give rise to a quartet. Indeed the ^{19}F NMR signal of the B–F group in 3-fluorobarene proved to be a quartet with intensity ratios of 1 : 1 : 1 : 1, all the peaks having approximately the same integral intensity and width. The NMR spectra of compounds with spin–spin coupling between the ^1H, ^{19}F, ^{31}P, and ^{35}Cl nuclei do not show this type of pattern: the quadrupole relaxation of the nuclei obliterates the multiplet and a single averaged peak is observed. The ^{93}Nb nucleus has a spin $I = 9/2$. Spin–spin coupling with such a nucleus leads to the formation of a decaplet all the components of which have the same integral intensity. However, in a multilevel system of this kind the probability of transitions is such that the extreme peaks of the multiplets are longest-lived and hence have the highest amplitude[47]. A typical spectrum is presented in Fig. 5. Evidently quadrupole relaxation in the Nb nucleus leads to a broadening of the multiplet components such that only a characteristic outline with maxima at the edges remains. After dividing the distance between the maxima by the number of intervals between the peaks, we obtain an approximate estimate $J(Nb-C-H) \simeq 2$ Hz.

XIII. CHEMICAL EQUILIBRIUM AND CONFORMATIONAL TRANSITIONS

Nuclear magnetic resonance proved to be a very sensitive and reliable method for detecting tautomeric equilibria, prototropy and exchange processes, intramolecular motion, etc. The reasons for the effectiveness of the method for these phenomena have already been given in essence when discussing the question of the magnetic equivalence of the methyl and methylene protons in the ethyl group. If the rate of a process whereby a given nucleus is transferred from a situation A to a situation B is high compared with the frequency range $\Delta\nu_{AB}$ which separates the ν_A and ν_B peaks in the spectrum, the effective field acting upon the nucleus becomes averaged. Therefore instead of two peaks only one is observed and its width is close to the natural width of the NMR line, i.e. is determined by the spin–spin relaxation time T_2. By reducing the temperature, it is possible to ensure that the residence time τ in each state (let $\tau_A = \tau_B = \tau$) is comparable to T_2. This leads to a broadening of the observed peak. Further retardation of the process leads to the "spreading" of the line over the entire frequency range $\Delta\nu$, and, when the latter is sufficiently wide, the line becomes virtually unobservable. Finally, when the given process ceases completely, two distinct peaks with frequencies ν_A and ν_B will of course arise in the spectrum and their width will again be determined by T_2. When the temperature is raised somewhat relative to the point corresponding to such "freezing out" of the exchange process, we yet again note signs of broadening of the peaks: the new widths, as in the previously discussed case of the other end of the temperature range, will be $T_2^{-1} + \tau^{-1}$. All these processes can be described mathematically in detail with the aid of Bloch's equations. However, for the purpose of the present review, the overall pattern of the changes with temperature observed in the NMR spectra of certain systems has been outlined adequately above.

The simplest example of the equilibrium of the type described is the keto–enol tautomerism, the study of which by nuclear magnetic resonance revealed a number of fundamental facts. Here the starting point was the investigation of acetylacetone[48], which at room temperature proved to be a mixture of the keto- and enolic forms in proportions of 4 : 1. It is important to stress that the detection of tautomers and the measurement of their concentration can be achieved with the aid of NMR much more reliably than by any other method, since each form is associated with a particular set of lines. Thus the enolic form of acetylacetone and similar compounds is characterised by the formation of a strong intramolecular hydrogen bond; a six-membered ring system of conjugated bonds is formed. In such systems there is a very marked shift of the hydroxyl proton signal towards weaker fields: from 13 to 20 p.p.m. on the δ scale. The signal of the methylene protons of the keto-form is displaced approximately by 10 p.p.m. towards stronger fields; the two signals can be very reliably distinguished. In more complex molecules there is a tendency for the enolic form to predominate at low temperatures. Thus 4-acetoacetylphenyl ether[49] shows no signs of the presence of the keto-form up to 100°C and only in the melt at 150°C does the ketone content reach 20%. The rate of interconversion of the equilibrium forms is low, since the corresponding peaks of the OH and CH_2 protons are broadened by no more than 1 Hz. These data provide a rough estimate of the height of the barrier inhibiting the ketone $\rightleftharpoons$ enol interconversion. It is significant that the estimate based on the Arrhenius equation, which is invariably invoked in all more accurate investigations in this field, is $\nu = \nu_0 \exp(-U/kT)$. Here the frequency ν_0 can be reasonably compared with intermolecular vibrations, i.e. is close to 10^{13} Hz. In other words ν_0 is the number of attempts at bond dissociation. The observed frequency ν of the ketone $\rightleftharpoons$ enol transitions represents the number of successful attempts at overcoming the barrier inhibiting the transition from one tautomeric form to another. For high-resolution NMR spectra, the observed frequency may be assumed to be $\nu \simeq 1$ Hz. Thus, let us suppose that at a low temperature in the absence of equilibrium $\nu = 0$ and the line width is > 1 Hz. Then the specimen is heated to a temperature T_C at which the line broadens approximately by 1 Hz due to the limited lifetime of a given tautomer. Under these conditions, the barrier is

$$U = kT_c \ln 10^{13} \simeq 55T_c, \tag{21}$$

where U is the height of the barrier in cal mole^{-1} and T_C the temperature on the Kelvin scale. For 4-acetoacetylphenyl ether, Eqn. (21) gives $U \simeq 20$ kcal mole^{-1}. It has been shown[50] that the accuracy of this estimate is ±3 kcal mole^{-1}.

As a rule, owing to the reduced strength of the hydrogen bond, the keto-enol tautomeric process is accompanied by prototropy, which leads to an additional temperature dependence of the hydroxyl proton NMR line width[51].

The prototropy also obeys the Arrhenius equation, in which the frequency factor and the activation energy can be readily determined from the NMR spectra recorded at different temperatures. In fact, an increase in line width of the order of 1–2 Hz can be readily detected in PMR spectra at low temperatures. This means that, for an activation energy $\Delta E \simeq 2$ kcal mole^{-1} which is frequently encountered, one can observe with certainty at a temperature of about 200°K proton exchange processes with a frequency factor $\nu_0 = e^5 = 140$ Hz. It is quite impossible to observe such weak processes by other methods.

An extensive literature has been published on the problem of *cis*- and *trans*-enolisation. A rigorous experimental examination of this problem proved to be possible only with the aid of NMR. A series of investigations by Kabachnik and coworkers[52,53] made it possible to study the kinetics and mechanism of the conversion of a *trans*-enol into the *cis*-enol. It was demonstrated convincingly that in solutions the *cis*-enol is more favoured by energy factors than the *trans*-enol.

In organometallic chemistry NMR made it necessary to postulate new types of tautomerism. Thus cyclopentadienyl derivatives of germanium and silicon show an unusual pattern of temperature changes in their NMR spectra. A single narrow signal due to the protons of the cyclopentadienyl ring accompanied by narrow ^{13}C satellites with a splitting of the completely normal kind is observed at high temperatures, while at low temperatures the typical pattern of cyclopentadiene involved in σ-addition is obtained. The question arises how to represent the structure of such a molecule in the intermediate temperature range where the form of the PMR spectrum clearly indicates that the protons of the cyclopentadienyl ring participate in a dynamic process, which averages out the immediate environment. At least two explanations can be proposed. A widely held view is that of Piper and Wilkinson[54], according to which at high temperatures there is rapid metallotropic migration along the perimeter of the cyclopentadienyl ring, at low temperatures the rate of this migration is vanishingly small, and in the range corresponding to the dynamic process the rate of migration is comparable to the chemical shift between the signals of protons involved in sp^2- and sp^3-hybridisation. In other words, according to Piper and Wilkinson, a change of temperature alters only the quantitative measure of the observed phenomenon: the sharp difference between the high-temperature and low-temperature PMR spectra may be accounted for by a more or less fortuitous factor: at high temperatures the rate (frequency) of migration is greater than the chemical shift, while at low temperatures it is lower.

Another explanation is almost self-evident: one can relate the narrow singlet arising at high temperatures to centrosymmetric addition of the cyclopentadienyl ring to the metal (C_{5v}-bonding). Then the intermediate temperature range corresponds to a sandwich–σ-bond transition in which the interconversion of the σ and C_{5v} molecules (tautomerism) takes place, its rate diminishing as the temperature is reduced, in parallel with the increasing concentration of the σ-molecules. When the temperature is reduced sufficiently, only the stable σ molecules remain in solution.

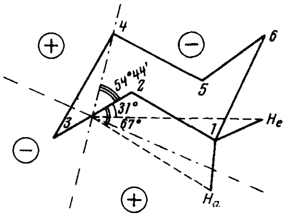


Figure 6. Location of the axial (H_a) and equatorial (H_e) protons in cyclohexane relative to the C_2-C_3 bond in different screening zones.

In principle nuclear magnetic resonance permits a valid choice between the two explanations of the experimental data.

The most widely known example of conformational changes observed with the aid of NMR is provided by the cyclohexane spectrum. The axial and equatorial hydrogen atoms in this molecule are located in different ways relative to the dipole associated with the magnetic anisotropy of the C_2-C_3 bond (Fig. 6). Therefore at low temperatures, at which this molecule may be regarded as rigid, the PMR spectrum is a doublet: the axial protons are screened to a greater extent and their signal is displaced towards weaker fields by 0.2×10^{-6}. On raising the temperature, the inversion of the cyclohexane ring begins and the PMR doublet signal is gradually converted into a singlet, in accordance with the laws already described. At room temperature the rate of inversion is relatively low and the cyclohexane signal is significantly broadened. The shift Δ_{ae} between the signals of the axial and equatorial protons and the available information about molecular geometry permit the calculation of the magnetic anisotropy of the C–C bond. The data thus obtained are significantly more accurate than the estimates of magnetic anisotropy based on magnetochemical concepts[55]. Nuclear magnetic resonance is one of the most effective methods for the investigation of conformations and there is an extensive literature on its application in this field[37,56–58].

XIV. STUDIES ON CRYSTAL STRUCTURES

High-resolution nuclear magnetic resonance is very actively employed in organic chemistry. Until recently low-resolution NMR was largely employed in inorganic chemistry and yielded a number of first class results concerning the fine details of the crystal lattice structure and also the details of thermal motion in the solid state, which are quite unobtainable by other methods.

Diffusion and vibrations of crystallised water molecules[59], the mechanism of the ferroelectric transition[60], the retarded motion in molecular crystals[61], and the exact determination of the coordinates of light atoms[62] are typical examples of problems successfully investigated by low-resolution NMR.

NMR chemical shifts in the solid state are difficult to observe: they are usually hundreds and thousands of times smaller than the observed line width. In Section VI it was already stated that in solids $T_1 \gg T_2$, in contrast to liquids where $T_1 \simeq T_2$. This inequality is caused both by higher values of T_1 and lower values of T_2 compared with the liquid state.

The decrease of the spin–spin relaxation time T_2 implies that the energy exchange processes in the nuclear spin system are very rapid. This entails a corresponding increase in line width. The increase of the spin–lattice relaxation time T_1 implies a sharp reduction in energy transfer from the nuclear spin system to the lattice. In other words, the magnetic nuclei form in the crystal lattice a highly isolated physical system; heat exchange between the lattice and the nuclei is strongly hindered. Therefore it is possible to introduce the concept of the spin temperature (see Section IV). The NMR line form for the crystal cannot be predicted in the general case. Bloch's equations are inapplicable to solids for a simple reason. They have been formulated essentially for a single nucleus and the problem of line form in the spectra of solids must be treated on the basis of statistical laws. In fact, the random motion of molecules in a liquid or gas leads to complete averaging of the intermolecular contribution to the local magnetic field; for an exact description of the phenomenon of nuclear magnetic resonance, it is quite sufficient to take into account only the phase differences between the magnetic moment of an arbitrary nucleus and the vector of the rotating magnetic field H_1 applied to the specimen.

On the other hand, in a solid the radiofrequency field H_1 is much smaller than the local magnetic field H_{loc} caused by the mutual effects of the nuclear magnetic moments fixed in the crystal. Therefore the line form cannot be a function of only H_1 and simple parameters such as T_1 and T_2; it depends fundamentally on the detailed distribution of the nuclear magnetic moment in the crystal structure and in a rigorous approach requires the examination of the specimen as a whole. The difficulties in the theoretical treatment of this problem have not as yet been overcome.

However, Van Vleck[63] showed that, when the crystal structure of the specimen is known, it is possible to find certain numerical characteristics of the line form—the so called moments. If the deviation of the magnetic field from the condition of exact resonance is denoted by the symbol h, the line form is described by a function $g(h)$. It is easy to show that $g(h)$ is symmetrical relative to the point $h = 0$. The nth order moment of the function $g(h)$ is defined as

$$\Delta\overline{H^n} = \int_{-\infty}^{+\infty} g(h)\, h^n dh. \tag{22}$$

Since the function $g(h)$ is even, all the odd moments ($n = 1$, 3, 5) become zero and only the even moments need to be calculated. The Van Vleck formula is most widely used in practice for the calculation of the second moment:

$$\Delta H^2 = \frac{9}{4}\cdot\frac{1}{N}\mu^2\sum_{k}^{n}\sum_{i} r_{ik}^{-6}(3\cos^2\theta_{ik} - 1)^2, \tag{23}$$

where r_{ik} is the distance between the ith and kth nuclei in the unit cell, n the number of types of crystallographically non-equivalent nuclei in the unit cell, and θ_{ik} the angle between the direction of the constant magnetic field H_0 and r_{ik}.

Comparisons of Eqns. (22) and (23) shows that NMR permits a structural analysis whereby the coordinates of the magnetic nuclei can be determined with high accuracy. The analysis can be carried out by the method of trial and error[64]. Suppose that we have a hypothetical structure A_1 in which specific trial values can be attributed to the distances r_{ik} and the angles θ_{ik}. Then, for any orientation of the single crystals in the field H_0, it is possible to calculate by Eqn. (23) the second moment $\Delta\overline{H}^2_{1c}$. Having recorded the real NMR signal for the same orientation of the crystal, it is possible to evaluate by Eqn. (22) the experimental value ΔH^2_{1e}. When the two numbers are highly inconsistent, it is necessary to revise the hypothetical structure, i.e. to employ for the calculation a new structure A_2, etc. until in the pth stage of the procedure satisfactory agreement between $\Delta\overline{H}^2_c$ and $\Delta\overline{H}^2_e$ is obtained. McCall and Hamming[62] showed that the process described permits the determination of 15 independent structural parameters for a triclinic structure. With increase in the symmetry of the structure, the number of independent parameters is of course smaller and in the simple cubic structure it reduces to a single parameter—the lattice constant. Therefore McCall and Hamming suggested, instead of the method of trial and error, a direct procedure for the structural analysis of single crystals by the NMR method: not more than 15 (depending on the symmetry of the crystal) measurements of the second moment are made. According to Eqn. (23), this set of numbers leads to 15 (or less) equations with 15 unknowns. The solution of this set permits, in principle, the determination of all the required structural parameters. However, Lundin and coworkers[60] and Dereppe et al.[64] showed that the McCall algorithm is unstable relative to unavoidable experimental errors and its practical application does not yield unambiguous results; practically useful conclusions can be derived only by improving the method of calculation significantly. Kitaigorodskii[65] stated that the NMR method can be very useful in the concluding stages of the X-ray diffraction analysis of single crystals. It has been shown[66] that, in order to arrive at a sufficiently reliable result, it is necessary to alter significantly the method of measurement and the experimental values of the second moment must be evaluated by an electronic computer. The accuracy of the structural analysis of single crystals by the NMR method would be indisputable if a rigorous theory of the NMR line shape for solids were available. Provotorov[67] has obtained important results in studies in this direction. Unfortunately it is not yet possible to give a rigorous theoretical explanation even of the almost self-evident fact of the rapid "decay" of the wings of the lines (at distances 2–3 times greater than the line width at half height). The creation of a theory predicting the behaviour of the line, if only at the wings, would convert the low-resolution NMR method into a regular method for improving the accuracy of the results of the X-ray structural analysis of crystals containing hydrogen and fluorine.

In many cases the magnetic nuclei in the crystal form physically isolated pairs or triplets. These cases have been examined by Pake[68] and Powles and Gutowsky[69] respectively. A typical example of the existence of isolated pairs is provided by water of crystallisation. Here the NMR signal proved to be a doublet in which the distance between the components is given by

$$\Delta H = \frac{3}{2}\gamma\hbar r^{-3}(3\cos^2\theta - 1),$$

where the notation has the same significance as in Eqn. (23). For water molecules, $r = 1.5$ Å and $\Delta H_{\max} \simeq 20$ G. Methyl groups are a typical example of nuclear triplets isolated in the crystal. It has been shown[70] that methyl groups at rest separated by distances greater than 3 Å give rise to a complex multiplet spectrum, the form of which changes with the orientation of the single crystal in the magnetic field.

The magnitude of the splitting observed in the spectrum of an isolated group may depend markedly on temperature. The explanation is that, when internal motions arise in the specimen, there is a possibility of additional averaging of the local field at the nucleus under consideration; when the motion is sufficiently rapid, instead of the multiplier $3\cos^2\theta - 1$ having a particular value, it is necessary to calculate its average value over the reorientation period. As in the discussion of the analogous questions in Section XIII, here one must regard as "sufficiently rapid" those motions whose rate exceeds significantly the interval between the observed multiplet components expressed in frequency units. Thus a broad NMR signal is observed for a rigid lattice (low temperatures), while at a high temperature the higher rate of internal motions appreciably diminishes the distance between the components of the NMR signal. A smooth structureless NMR line also consists of separate component pairs. Therefore on raising the temperature, with the consequent appearance of fairly rapid internal motions in the crystal, the single broad NMR line becomes narrower.

The events described are fully analogous to the changes occurring in high-resolution NMR spectra associated with chemical exchange (see Section XIII) but with the difference that the distances between the components and their width in the low-resolution spectrum are greater by a factor of several thousands, since their origin is different. Therefore, as the internal motions are "unfrozen", the characteristic changes in the low-resolution spectrum occur at frequencies $\nu_c \simeq 10^3-10^4$ Hz and not approximately 1 Hz as in the high-resolution spectra. Such a marked change in critical frequencies leads to an appreciable modification of the coefficient in Eqn. (21). If T_c is the temperature at which the width of the low-resolution signal begins to change, the height of the corresponding energy barrier is approximately[50]

$$U(\text{cal mole}^{-1}) = 37\ T_c\,(^\circ\text{K}). \tag{24}$$

A somewhat higher accuracy may be achieved by using a more complex expression:

$$U = kT_c \times 2.5\,\lg\frac{n}{\Delta}\sqrt{\frac{kT_c}{2J}}, \tag{25}$$

where n is the multiplicity of the barrier, Δ the NMR line width for $T \leqslant T_c$, J the moment of inertia of the molecule with respect to the reorientation axis, and k the Boltzmann constant.

This formula does not entail a greater experimental complexity—it is only necessary to consider additional information about the specimen. An explanation of the validity of the strikingly simple formulae (21) and (24) also follows from the form of Eqn. (25): all the parameters describing the structure of the specimen in a specific form are included in the logarithmic term and, when reasonable assumptions are made about the range of their variation, their effect on the final result is small.

The method described by Levich et al.[17] is widely used in the calculation of energy barriers; it requires extremely laborious experiments and frequently leads to contradictory results due to the inadequate accuracy of the measurements.

The sensitivity of broad-band NMR for slow motions led to the discovery in a number of crystals of unexpected displacements and reorientations of large molecules[71]. A word of warning against a common error is appropriate here. The results of the experiments are expressed in terms of curves representing the variation of the width and the second moment of the line with temperature. At certain temperatures these curves show distinct jumps, corresponding to changes by a factor of several units, which are sometimes interpreted as sudden "unfreezing" of a particular type of internal motion. In fact these points correspond to only one type of event: the frequency of the motion under consideration, which varies smoothly with temperature, becomes equal to the width of the NMR line (or the distance between its components); a real phase transition can coincide only fortuitously with the jump in the temperature variation of the NMR line width.

If the crystal has a rigid lattice, in which the thermal motion is confined to small oscillations about equilibrium positions, the NMR line width hardly changes up to fusion, where the width diminishes by a factor of tens of thousands and a high-resolution spectrum is produced. In crystals containing fluorine the chemical shifts are sometimes so great that in modern apparatus (with a field $H_0 = 23\,400$ Oe) they can be observed also in crystals, i.e. in broad-band spectra[72].

XV. PROSPECTS FOR THE IMMEDIATE FUTURE

The question arises of the way in which the NMR method will develop further and the contribution which such development may make to chemistry. It is risky to attempt an answer to these questions but certain trends in present day developments are so clear that their extrapolation to the immediate future and beyond is quite valid.

As in any physical method, the experimental technique is of decisive importance. The available working frequencies, i.e. the strength of the magnetic field H_0, will continue to increase. Electromagnets with a ferromagnetic 28 200 gauss core (120 MHz for protons) and superconducting 51 200 gauss solenoids (220 MHz for protons) are now used in practice. One may expect that "ordinary" (with iron) 35 000 gauss magnets (150 MHz for protons) and highly strengthened fields in iron-free solenoids will be produced. The advantages of such developments were dealt with in adequate detail in Sections VIII and X. Briefly, these involve an increase in the sensitivity and reliability of the method, since the spectra will be simpler. The range of applications will be extended. However, devices with powerful and ultrapowerful magnetic fields will remain rare and will be available only to large complex research centres.

A second important trend in the development of instrumentation will be miniaturisation and improvement in the reliability and simplicity of operation as well as a reduction in price of NMR spectrometers for every day analytical investigations in the chemical laboratory. The results already achieved in 1968 by the firms Perkin-Elmer (P-12 spectrometer), Varian (T-60 spectrometer), and JEOL ("Minimar" spectrometer) show that the construction of a simpler and more reliable NMR spectrometer, no more expensive than the present day gas–liquid chromatographs, is quite realisable.

The automation of analytical investigations by the NMR method constitutes an extremely important task. This is part of the general problem of the automation of research. The Varian and JEOL companies have achieved decisive advantages in this field. It has been shown that in the near future one may expect a large scale employment in chemical research of automated analytical laboratories comprising mass spectrometers, NMR and infrared spectrometers, and other essential devices, the sequence and conditions of the operation of which (including the most complex types of techniques) will be specified by computing and controlling devices, in accordance with the problem formulated by the chemist and based on the fundamental physical relations specified in the program for the device and also on the results of previous solutions of similar problems. The creation of such automated systems will free qualified specialists from routine day to day analyses and will reduce to a minimum the likelihood of an erroneous assignment of spectral lines, will greatly enhance the labour productivity of chemists specialising in synthesis and also spectroscopists. At present the range of applications of high-resolution NMR is somewhat restricted by the requirement of a low viscosity of the specimen. Here revolutionary changes are close at hand. Waugh and coworkers[73,74] showed that it is possible to devise a system where pulses of a radiofrequency field H_1 are applied to the specimen in such a way that the dipole–dipole interaction of the nuclei in the crystal lattice will be reduced to zero with a decrease of the chemical shift by a factor of only $\sqrt{3}$. Consequently it will be possible to obtain the NMR spectra of solids. It is found that the resolving power of the NMR method for solids will be even greater than for liquids and for crystals of ultimate purity may reach $10^{-11}-10^{-12}$. The consequences of the large scale employment of this technique by chemists and physicists are difficult to assess; there is no doubt that important discoveries will be made, which will have the most far-reaching influence on both quantum chemistry and the physics of the solid state.

The pulse technique also requires the obligatory application of computers for the interpretation of results. Pulse NMR spectrometers will be increasingly used also in kinetic liquid-phase investigations. The studies described in Section XIII on the kinetics of slow chemical reactions were made using conventional NMR spectrometers. A pulse spectrometer allows the recording of the spectrum tens and hundreds of times faster and thus gives rise to the possibility of investigating fairly rapid processes. This brief list of the immediate prospects for the NMR method shows that its importance in chemistry will increase. The converse influence is also evident—namely the requirements of chemical laboratories to a large extent determine the range of interests of specialists developing the theory of the NMR method and improving its technique. Experience obtained in the "old" branches of spectroscopy shows that such mutual enrichment can continue for many decades. Predictions for such a long period must necessarily be rather vague.

One may also hope that the logic underlying the theoretical concepts will be enriched and their power will be enhanced; such a favourable course of events may occur following the joint interpretation of the vast and occasionally overlapping experimental data accumulated in various branches of radiospectroscopy (NMR, NQR, ESR), in studies based on the Mössbauer effect, β-spectroscopy, optical spectroscopy, etc.

The following are the simplest examples of such overlapping: information on electron density $|\psi(0)|^2$ at the nucleus obtained from experiments on the Mössbauer effect and measurements of the spin–spin coupling constants the nuclei of the same metals in NMR spectroscopy; data on the magnetic anisotropy of bonds accumulated by the NMR method and information concerning the deviations of these bonds from spherical symmetry obtained by the NQR method; rigorous linear relations between the spin–spin coupling constants and chemical shifts and between spin–spin coupling constants and acidity; correlation between NMR chemical shifts and the vibration frequencies of the corresponding bonds; comparison of NMR chemical shifts with those in β-ray spectra. These and many other facts constitute a wide range of experimental parameters, which may serve as a basis for the creation of a reliable theoretical apparatus which will predict exactly even the exceptionally small effects measured in NMR spectroscopy which play such an important role in chemistry.

The significantly many-sided nature of the tasks which arise in attempts at a rigorous treatment of problems of the chemical bond shows that success in the development of the theory may be achieved using the empirical facts indicated above within the framework of the technique based on finite Fermi systems [75].

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Institute of Organic Derivatives
of the Elements,
USSR Academy of Sciences,
Moscow

U. D. C. 541.151

Preparative Aspects of the Radiation Chemistry of Organic Compounds

I.V.Vereshchinskii

This review attempts to examine the preparative possibilities inherent in the use of ionising radiation, largely for the synthesis of organic compounds which are difficult to obtain or which are obtained for the first time.
The bibliography includes 86 references.

CONTENTS

I. INTRODUCTION

The first attempts to employ ionising radiation for the preparation of compounds more complicated than the initial components were made in the earliest days of radiation chemistry. The pioneer investigations of the radiation-induced synthesis of organic compounds were made in the 1950's. The wider availability and the improvement of the sources of ionising radiation led to a real possibility of a radiation-chemical synthesis of organic compounds not only on the laboratory scale but also on a preparative scale. However, preparative radiation-chemical synthesis is still not widely used. To some extent this is probably because organic chemists specialising in syntheses are still unaccustomed to regard this method as normal; on the other hand, the attention of chemists specialising in radiation chemistry is concentrated either on the study of the mechanism of radiation-chemical reactions or on devising large scale radiation-chemical technical processes.

Radiation-chemical syntheses are usually performed by irradiating liquid mixtures or solutions of organic compounds. The effects of ionising radiation are much more various and complex than those occurring in photochemical reactions†. Ionising radiation affects all the mixture components non-selectively, the radiation energy absorbed being distributed in proportion to the mole (more precisely electronic) fraction of each component. Frequently, particularly in those cases where aromatic compounds are present, effects occur which involve charge transfer from one component to another.

The general characteristic features of radiation-induced synthetic processes are as follows.

1. The feasibility of carrying out the process at temperatures as low as required; this makes it possible to increase the yield of the desired product by increasing the solubility of the gaseous components of reaction mixtures and to decrease the contribution of degradative and resinification processes by creating conditions suitable for the preparation of thermolabile compounds.

2. Absence from reaction mixtures of impurities due to added catalysts or initiators or their decomposition products.

3. Ease of inertialess regulation of the process and the possibility of altering very rapidly the dose rate or of stopping the process.

4. Lower fire risk and explosion risk, since the processes can be carried out under conditions far from the inflammation or detonation limits of the reaction mixtures.

Radiation-induced preparative synthesis has many specific advantages over photochemical synthesis: (1) the process can be carried out in highly coloured, opaque, turbid, or inhomogeneous systems; (2) the constancy of the radiation energy absorbed in the reaction space is ensured regardless of the formation on the vessel walls of a screening film or scale; (3) the harmful selective effect of light on reaction products having a high molar extinction coefficient in the spectral region close to the incident light is eliminated.

The radiation-chemical yields‡ of the products of the radiation-chemical synthesis may vary widely depending on the nature of the radiation-chemical process and its conditions. They are particularly high in the case of radiation-chemical initiation of chain reactions where the effect of radiation is virtually limited to the initiation stage, since for low absorbed doses the role of other radiation-chemical reactions is negligible [1,2].

When irradiating liquid-phase systems for preparative purposes, it is most convenient to employ cobalt-60

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†The characteristics, phenomenology, and the theory of radiation-chemical processes have been described in a number of monographs [1-5].

‡The radiation-chemical yield is the absolute number of species (molecules, ions, free radicals, etc.) formed in the chemical system on absorption of 100 eV of the energy of ionising radiation. It is denoted by the symbol G. The radiation-chemical yield, sometimes called the energy yield, is an important quantitative characteristic of radiation-chemical reactions. The yield is calculated from the relation $G = 10^2\ \Delta c/D$, where Δc is the absolute change in concentration, i.e. the absolute number of species referred to unit volume or unit mass, and D is the dose absorbed in electron-volts referred to the same unit volume or unit mass. An extensive compilation of G values has been made.

γ-radiation. A very important factor in such cases is the impossibility, in principle, of the generation of induced radioactivity in the object irradiated. The high penetrating power of the γ-radiation from the cobalt-60 isotope makes it possible to carry out synthetic reactions in both glass and metallic apparatus without a significant decrease of the dose rate in the object irradiated.

A number of isotopic devices of various designs have been constructed at scientific establishments and have been described in a monograph[7] and in technical papers[8-14]. MRKh-γ-100 apparatus, designed for radiation-chemical research, is manufactured on industrially[13].

In radiation-induced synthetic reactions with low radiation-chemical yields, it is desirable to employ electron accelerators. However, the relatively low penetrating power of accelerated electrons requires the use of fairly thin inlet windows or membranes in the irradiation vessels and virtually excludes the possibility of experiments at elevated pressures. Additional difficulties are associated with the intense heating of the irradiated system as a result of the absorption of a considerable amount of radiation energy and the complexity of thermostatic devices.

II. RADIATION-INDUCED SYNTHESIS OF HALOGENO-SUBSTITUTED HYDROCARBONS

The liquid-phase radiation-induced chlorination of 1,1,1,5-tetrachloropentane leads to the synthesis of highly chlorinated polychloropentanes[15-17]:

$$C_5H_8Cl_4 \rightarrow C_5H_7Cl_5 \rightarrow C_5H_6Cl_6 \rightarrow C_5H_5Cl_7 \rightarrow C_5H_4Cl_8 \rightarrow C_5H_3Cl_9 \rightarrow C_5H_2Cl_{10}.$$

The radiation-chemical yield of polychloropentanes diminishes with increasing extent of chlorination. Each succeeding chlorine atom is introduced into the polychloropentane molecule with greater difficulty than the previous one. The increase in the number of chlorine atoms diminishes the polarisability of the C–H bond, while the influence of the inductive effect increases, consequently the attack by chlorine on the C–H bond becomes the slowest stage. When the process was carried out under mild conditions at low temperatures (less than 120°C), a number of polychloropentanes were isolated from the reaction mixture and identified. Decachloropentane, the isomers of which probably have the structural formulae $CCl_3CHClCHClCCl_2CCl_3$ and $CCl_3CCl_2CH_2CCl_2CCl_3$, was synthesised for the first time. The isomer isolated is a white crystalline substance with a camphor smell[18].

The synthesis of tetrabromoxylene by radiation-induced bromination of xylene is also a multistage reaction with a parallel-consecutive mechanism[81].

In contrast to radiation-induced chlorination and bromination processes in which free chlorine or bromine participates, the radiation-induced fluorination is an indirect reaction. Studies on the radiolysis of fluorohydrocarbons showed that the radiolytic stability of the C–F bond is comparable to the radiolytic stability of bonds in hydrocarbons, but the radiation-chemical yields of the fluorohydrocarbon radiolysis products are somewhat lower than for hydrocarbons.

Fluorohydrocarbons have been used as fluorinating agents to form new fluorine–carbon bonds or to introduce fluorine-containing groups and also as components of mixtures subjected to ionising irradiation.

In sealed-tube experiments with γ-irradiation of benzene–carbon tetrafluoride mixtures, fluorobenzene and α-trifluorotoluene were synthesised in approximately equal amounts[19]:

$$C_6H_6 + CF_4 \rightarrow C_6H_5F + CHF_3,$$
$$C_6H_6 + CF_4 \rightarrow C_6H_5CF_3 + HF.$$

The radiation-chemical yield increases with the carbon tetrafluoride content in the mixture and is independent of temperature in the range investigated. The maximum value $G(C_6H_5CF_3) = 1.3$ was obtained in a mixture containing 37 wt.% CF_4. In CF_3Br–C_6H_6 mixtures $G(C_6H_5F)$ increases from about 0.22 to about 1.5 with increase of temperature from 27° to 250°C, while $G(C_6H_5CF_3)$ remains approximately 2.

It has been suggested that the radiolytic reactions of fluorohydrocarbons take place both by an ionic and a radical mechanism. The ionic intermediate, for example CF_3^+, acts upon the C–F bond; radical processes take place simultaneously.

In the radiolysis of two-component mixtures of CF_4, SiF_4, BF_3, and C_2F_6 with benzene, nitrobenzene, or toluene, fluorine-containing compounds were synthesised[20]. In the CF_4–$C_6H_5NO_2$ mixture the yield of *m*-fluoronitrobenzene increases linearly with the electronic fraction of CF_4 and is independent of irradiation temperature. In the radiolysis of toluene-containing mixtures, trifluoromethyl derivatives are mainly formed.

The radiation-induced synthesis of ethyl bromide from gaseous ethylene and hydrogen bromide is the first industrial radiation-chemical synthetic process[21]. The reaction is carried out in ethyl bromide solution, the composition being chosen so that ethylene and hydrogen bromide are largely consumed during passage through the irradiation zone. The reaction is carried out at –2°C and a dose rate of about 40 rad s^{-1}. The chain reaction is initiated by bromine atoms produced by the radiation. The radiation-chemical yield reaches 3.9×10^4.

The competitiveness of the radiation-induced process depends to a considerable degree on the relative costs of anhydrous hydrogen bromide used in the radiation-chemical synthesis and of 48% hydrobromic acid employed in the "usual" chemical reaction with ethyl alcohol:

$$C_2H_5OH + HBr \rightarrow C_2H_5Br + H_2O.$$

The water formed carries away an appreciable amount of the hydrogen bromide dissolved in it.

The radiation method, which permits the synthesis of ethyl bromide from simple starting materials, virtually without side products, has advantages over other synthetic methods such as initiation with peroxides or reaction with aluminium bromide.

The addition of HBr to various α-olefins ranging from propene to octene has been investigated at temperatures between –79° and 25°C. The addition takes place predominantly contrary to the Markovnikov rule and leads to the formation of primary bromoalkanes (up to 90% of products). The radiation-chemical yield is about 10^3 in the gas phase and about 10^5 in the liquid phase[22].

The preparative synthesis of 1-bromo-2-chloro-1,1,2-trifluoroethane, used as an inhalation anaesthetic, is also an example of radiation-induced hydrobromination of halogeno-substituted ethylene:

$$F_2C{=}CFCl + HBr \rightarrow BrF_2C{-}CHFCl.$$

The reaction is performed at temperatures between –70° and +20°C over a wide range of dose rates, from 0.5 rad h^{-1} to 15 Mrad h^{-1}, and pressures up to 20 atm. The yield of the desired product reaches 89% of theoretical[23].

III. RADIATION-INDUCED SYNTHESIS OF ORGANIC SULPHIDES AND DISULPHIDES

The addition of butanethiol to pent-1-ene resulted in the synthesis of the corresponding dialkyl sulphide[24]:

$$RSH + CH_2{=}CHR' \rightarrow RSCH_2CH_2R'.$$

The reaction was carried out in cyclohexane solution under the action of X-rays; n-butyl pentyl sulphide was formed in 75–95% yield, G reaching 8×10^4.

Disulphides may be obtained from substituted mercaptans. The introduction of an OH group into the mercaptan molecule reduces significantly its radiation stability and gives rise to the possibility of the preparative synthesis of substituted disulphides. While in the γ-irradiation of ethanethiol the yield of decomposition products does not exceed 5, on irradiation (at a dose rate of 0.8×10^{15} eV ml^{-1} s^{-1}) of β-hydroxyethanethiol, G reaches 400. Crystals of the disulphide[25] $HOCH_2CH_2SSCH_2CH_2OH$ are isolated from the reaction mixture in yields up to 70%.

IV. RADIATION-INDUCED SYNTHESIS OF NITROGEN-CONTAINING ORGANIC COMPOUNDS

Among the radiation-induced syntheses of nitrogen-containing compounds, it is necessary to consider primarily the processes which result in the formation of compounds with C–N bonds.

1. Syntheses Based on Nitrogen Oxides

The reactions with nitrogen oxides have been little investigated to date. The trapping of unstable products by nitrous oxide, widely used in radiation-chemical experiments, has not found preparative application.

Among reactions with nitric oxide, the radiation-chemical synthesis of nitroso-derivatives of halogeno-substituted methane and ethane is of preparative interest. They are obtained by irradiating carbon tetrachloride (or chloroform, bromoform, trichloronitromethane, trichloroethane) with a stream of electrons (dose 10^8 rad) at room temperature in the presence of a stream of NO (15 litre h^{-1}).[26,27] The CCl_3 or CH_3CCl_2 radicals formed by radiolysis react with NO:

$$\dot{C}Cl_3 + NO \rightarrow CCl_3NO$$

or

$$CH_3\dot{C}Cl_2 + NO \rightarrow CH_3CCl_2NO.$$

$G(CCl_3NO)$ is in the range between 4.4 and 6.0; the chemical yield is 50% at 10% conversion: $G(CH_3CCl_2NO) = 0.5$. In the reaction with chloroform, dichloronitrosomethane was synthesised together with dichloroformaldoxime:

$$CHCl_3 \rightarrow \dot{C}HCl_2 + \dot{C}l$$
$$\dot{C}HCl_2 + NO \rightarrow CCl_2{=}NOH \rightarrow HCCl_2NO$$

This new compound, stable only at low temperatures, is obtained with $G = 0.5$ and a chemical yield of 20%.

The synthesis of dimeric nitrosobenzeneiron tricarbonyl, obtained by γ-irradiation of a benzene solution of nitrobenzene and iron pentacarbonyl, has been described[28]:

$$C_6H_5NO_2 + Fe(CO)_5 \rightarrow C_6H_5NO_2Fe(CO)_4 + CO,$$
$$2C_6H_5NO_2Fe(CO)_4 \rightarrow [C_6H_5NOFe(CO)_3]_2 + 2CO_2.$$

2. The Addition of Acetonitrile to Unsaturated Compounds

The addition of acetonitrile to olefins under the action of ionising radiation takes place fairly successfully[29], in contrast to photochemical addition sensitised by acetone or benzophenone. Sealed-tube experiments with a considerable excess of acetonitrile in an argon atmosphere lead to the formation of addition products (Table 1).

Table 1. Radiation-chemical yields of products of addition of acetonitrile to unsaturated compounds under the action of cobalt-60 γ-radiation, (dose rate 3.84×10^5 rad h^{-1}).

Olefin	Product	Yield, %	*G*
Hex-1-ene	heptyl cyanide	35	1.2
Hept-1-ene	octyl cyanide	36	1.2
Oct-1-ene	nonyl cyanide	45	1.2
Dec-1-ene	undecyl cyanide	40	1.2
Dodec-1-ene	tridecyl cyanide	42	1.2
Cyclopentene	cyclopentylacetonitrile	38	1.2
Cyclohexene	cyclohexylacetonitrile	45	1.2
Cyclo-octene	cyclo-octylacetonitrile	47	1.2
Cyclodecene	cyclodecylacetonitrile	43	1.2
Cyclododecene	cyclododecylacetonitrile	35	1.1
Norbornene	norbornylacetonitrile	65	1.7
Norbornadiene	nortricyclylacetonitrile	60	1.6
Benzene	benzyl cyanide	10–15	0.2

Table 2. Radiation-induced synthesis of diamines[31,32] by γ-irradiation in the absence of air (dose $\simeq 10^{21}$ eV ml^{-1}).

Initial amine	Diamine synthesised	Radion-chemical yield, *G*
Diethylamine	*meso*-* and racemic* *NN*-diethylbutane-2,3-diamine	0.77
Triethylamine	*meso*-* and DL-2,3-di(diethylamino)-butane	2.9
Trimethylamine	*NNN'N'*-tetramethylethylenediamine	2.5
N-Methyldiethylamine	*meso*-*NN*-diethyl-*N'N'*-dimethylbutane-2,3-diamine* *NNN'N'*-tetraethylethylenediamine 1-diethylamino-2-ethylmethylamino-propane*	0.5
1-Methylpiperidine	1,2-dipiperidinoethane	0.37
	meso-1,1'-dimethyl-2,2'-dipiperidyl*	0.75
	1-methyl-2-(piperidinomethyl)piperidine*	0.39
Benzylamine	*meso*-stilbenediamine	2.76
	N-Benzylidenebenzylamine	0.11
t-Butylamine	*NN'*-di-t-butylformamidine*	0.026
	2-amino-1-t-butylamino-2-methylpropane*	0.025
	2,5-dimethylhexane-2,5-diamine	0.008

*Synthesised for the first time.

The addition takes place exclusively contrary to the Markovnikov rule:

$$RCH{=}CH_2 + CH_3CN \rightarrow RCH_2CH_2CH_2CN.$$

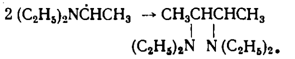
Nitriles, products of the addition of the CN radical to olefins, are also formed in low yields (2–3%).

3. Synthesis of Amines and Radiation-induced Amidation

Under the action of γ-radiation, aliphatic and aromatic amines enter into reactions not involving C–N bonds. As a result of the removal of a hydrogen atom from the α-position, radicals are formed which dimerise to form diamines[30–33].

The following reactions take place with mono-, di-, and trialkylamines in which all the alkyl groups attached to the same nitrogen atom are identical:

$$(C_2H_5)_2NCH_2CH_3 \rightarrow (C_2H_5)_2N\dot{C}HCH_3 + H,$$



$$2\,(C_2H_5)_2N\dot{C}HCH_3 \rightarrow \underset{(C_2H_5)_2N\quad N(C_2H_5)_2.}{CH_3CHCHCH_3}$$

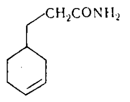
If the irradiation of amines results in the formation of radicals of various compositions and structures, then the set of diamines (dimerisation products) becomes more complex (Table 2). The low *G* in the case of t-butylamine is due to the absence of a hydrogen atom in the α-position relative to the nitrogen atom. The radiolysis gives rise to the radicals $CH_2C(CH_3)_2NH_2$ and $(CH_3)_3CNH$.

Table 3. Yields and radiation-chemical yields of diene amidation products[37].

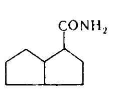
Initial diene	Addition product	Yield, %	*G*
4-Vinylcyclohexene	I	35	3
1,5-cyclo-octadiene	II	50	3.5
Norbornadiene	III	75	5

Attempts at radiation-induced synthesis of quaternary ammonium salts containing a phenyl group from aryl halides were unsuccessful[34]. Trialkylamines react with aryl halides to form trialkyl- or dialkyl-ammonium salts ($G < 7$), but this reaction is of no preparative interest.

The amidation of olefins by formamide under the action of γ-radiation or as a result of a photochemical reaction initiated by acetone leads to the synthesis of 1 : 1 addition products. The high chemical yield makes both methods suitable for synthetic purposes[35]. In contrast to the addition to olefins, photochemical addition of formamide to dienes with formation of 1 : 1 products takes place with a low yield[36]. Under the action of γ-radiation, the addition to dienes occurs with an appreciable yield (Table 3) and may be used for synthetic purposes.



(I)



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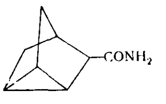


(III)

Carbamoyl radicals $CONH_2$ are formed as a result of the direct action of radiation on formamide, while the diene, the concentration of which in the reaction mixture is low, is little affected by the radiolytic processes.

V. RADIATION-INDUCED SYNTHESIS OF ORGANOPHOSPHORUS COMPOUNDS

Several trends have now been established in the field of radiation-induced synthesis of compounds with C–P bonds. The radiation-chemical reactions of aliphatic or cyclic hydrocarbons with phosphorus trichloride or its alkyl-(cycloalkyl)-substituted derivatives, leading to the synthesis of compounds of the type $RPCl_2$ and $RR'PCl$, constitute a large group of processes. Reactions involving addition of PCl_3 to unsaturated compounds constitute another group. The use of γ-irradiation has led to interesting preparative possibilities based on the introduction of aryl groups R into quaternary phosphonium salts $[RP(R')_3]Hal$ and phosphonic acid esters $RP(O)(OR')_2$.

1. Synthesis of Alkyl(cycloalkyl)-substituted Phosphorus Trichloride Derivatives

The reactions of phosphorus trichloride with a number of aliphatic and cyclic hydrocarbons have been investigated[38,39]. The main products of the synthesis are alkyl- or cycloalkyl-phosphorus dichloride—the products of the substitution of a chlorine atom by a hydrocarbon group. When the alkyl(cycloalkyl)-substituted derivatives are used as the initial phosphorus compounds, disubstituted derivatives[38] and various compounds with a more complex structure are formed (Table 4). The synthesis is carried out in simple glass apparatus in an inert gas at atmospheric pressure and room temperature, the hydrogen chloride evolved being passed through an absorber. A finely dispersed orange deposit, the amount of which is proportional to the dose absorbed, is formed as a side product. This deposit is the product of the decomposition of tetrachlorodiphosphine P_2Cl_4 and is a polymeric substance of variable composition: $R(H_2)ClP_n$, where n = 20–30.

A reaction mechanism involving the participation of free radicals and excited molecules of the initial components has been proposed:

$$RH \rightarrow R^{\cdot} + H^{\cdot},$$
$$PCl_3 \rightarrow {}^{\cdot}PCl_2 + Cl^{\cdot},$$
$$H^{\cdot} + PCl_3 \rightarrow HCl + {}^{\cdot}PCl_2,$$
$$Cl^{\cdot} + RH \rightarrow HCl + R^{\cdot};$$
$$R^{\cdot} + {}^{\cdot}PCl_2 \rightarrow RPCl_2,$$
$$R^{\cdot} + R^{\cdot} \rightarrow R_2,$$
$$R^{\cdot} + Cl^{\cdot} \rightarrow RCl,$$
$${}^{\cdot}PCl_2 + {}^{\cdot}PCl_2 \rightarrow P_2Cl_4$$

and also

$$RH^{*} + PCl_3 \rightarrow HCl + RPCl_2,$$
$$PCl_3^{*} + RH \rightarrow HCl + RPCl_2.$$

Table 4. Yields of organophosphorus compounds synthesised under the action of γ-radiation[39].

Initial hydrocarbon	Initial phosphorus compound	Molar ratio	Dose absorbed, eV, ml^{-1}	Compound synthesised	B.p. (*p*, mmHg)	d_4^{20}	n_D^{20}	Yield, mole litre^{-1}
Cyclopentane	PCl_3	1.0:1.2	3.4x10^{20}	cyclopentyldichlorophosphine*				0.5
Cyclohexane	PCl_3	1.0:1.2	5.0x10^{20}	cyclohexyldichlorophosphine				0.5
Cyclohexane	cyclo-$C_6H_{11}PCl_2$	1.3:1.0	5.0x10^{20}	dicyclohexyldichlorophosphine*	T. m.p.23°	—	—	0.05
	PCl_3 and cyclo-$C_6H_{11}PCl_2$			dicyclohexylchlorophosphine				0.2
–		1.0:1.3	5.0x10^{20}	cyclohexenyltetrachlorodiphosphine*	130—135 (0.5)	1.4582	1.5865	0.2
n-Hexane	PCl_3	1.0:1.2	4.0x10^{20}	isohexyldichlorophosphine				0.5
			5.6x10^{21}	hexenyltetrachlorodiphosphine*	111—120 (0.5)	1.3205	1.5402	0.2
n-Hexane	$C_6H_{13}PCl_2$	1.0:1.0	5.0x10^{21}	dihexylchlorophosphine*	105—113 (0.2)	0.959	1.4862	0.2
n-Heptane	PCl_3	1.0:1.2	4.0x10^{20}	isoheptyldichlorophosphines				0.6
n-Octane	PCl_3	1.0:1.2	4.0x10^{20}	iso-octyldichlorophosphines*				0.6

*Compound synthesised for the first time.

The reaction mixtures consist mainly of $RPCl_2$, R_2PCl, and $R'(PCl_2)_2$, the proportions of which depend on the dose absorbed. The fraction of R_2PCl and $R'(PCl_2)_2$ in the reaction mixture increases with the dose. This suggests that these compounds are formed largely from alkyldichlorophosphines

$$RPCl_2 \rightarrow R'PCl_2 + H^{\cdot} \text{ or } \rightarrow R\dot{P}Cl + Cl^{\cdot},$$
$$R'PCl_2 + {}^{\cdot}PCl_2 \rightarrow Cl_2PR'PCl_2,$$
$$R\dot{P}Cl + RH \rightarrow R_2PCl + H^{\cdot},$$
$$R\dot{P}Cl + R^{\cdot} \rightarrow R_2PCl.$$

The radiation-induced synthesis of higher dichlorophosphines, various dialkylchlorophosphines, and other compounds based on them is of considerable preparative interest, since chemical methods for their preparation via organomercury, organocadmium, and organomagnesium compounds or by oxidative chlorophosphonation using a fast stream of oxygen are relatively complex and the yield is low.

In the radiation-induced synthetic reactions described above phosphorus trichloride is the main phosphorus-containing starting material. Another possible version of the synthetic reaction is based on the use of free (elemental) white phosphorus and alkyl chlorides as reactants. When solutions of white phosphorus in carbon tetrachloride are γ-irradiated, a number of products are formed[40], the yields of which depend significantly on temperature (Table 5).

Table 5.

Temp., °C	Radiation-chemical yield, G						
	Red P	PCl_3	CCl_3PCl_2	C_2Cl_6	Polymer $(CCl_2)_n$	consumption	
						CCl_4	P
25	22	1.4	4.5	3.1	1	10	28
130	<0.5	9.5	41	3.1	12	100	51

From the point of view of the preparation of compounds with a C–P bond, the synthesis of trichloromethylphosphorus dichloride is of greatest preparative interest. There are competitive reactions involving the formation of red phosphorus and low-molecular-weight products, which show different temperature dependences. While at room temperature red phosphorus is formed preferentially, at temperatures above 100°C the products are almost exclusively PCl_3 and CCl_3PCl_2. The mechanism of the reactions involves the addition of free radicals R, formed by the radiolysis of CCl_4, to dissolved P_4 phosphorus species:

$$R^{\cdot} + P_4 \rightarrow RP_4 \quad (R = CCl_3 \text{ or } Cl).$$

Further reactions of this adduct lead either to the formation of a red phosphorus polymer[41] or to the synthesis of low-molecular-weight products:

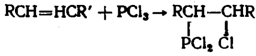
$$RP_4 + CCl_4 \rightarrow RP_4Cl + {}^{\cdot}CCl_3.$$

The activation energy for this chain propagation reaction is 8.2 kcal $mole^{-1}$.

Interesting preparative possibilities arise when red phosphorus activated by radiation and containing terminal CCl_3 groups is treated with chlorine, bromine, or other reagents which rupture P–P bonds[40]. When such activated phosphorus was dissolved in bromine, the previously unknown trichloromethylphosphorus dibromide CCl_3PBr_2 was synthesised.

2. Synthesis of Products of Addition of Phosphorus Trichloride to Unsaturated Hydrocarbons

Whe mixtures of liquid olefins with phosphorus trichloride are irradiated, radical-chain addition takes place:



$$RCH{=}HCR' + PCl_3 \rightarrow \underset{PCl_2}{RCH}{-}\underset{Cl}{CHR'}.$$

Olefins which do not show a tendency towards polymerisation by a free-radical mechanism (cyclo-olefins, n-olefins) give rise mainly to 1 : 1 addition products (Table 6)—α-chloroalkylphosphorus dichlorides; telomerisation products are formed with other types of olefin[42,43].

Table 6. Yields and radiation-chemical yields of products of addition of phosphorus trichloride to unsaturated hydrocarbons (irradiation with cobalt-60 γ-rays at room temperature).

Initial hydrocarbon	Hydrocarbon : PCl_3 (vol.%)	Dose absorbed, eV, ml^{-1}	Substance synthesised	Yield, mole $litre^{-1}$	G*, mol./ /100 eV	Refs.
Cyclopentene	1:2**	$7\cdot10^{18}$	$(cyclo\text{-}C_5H_8Cl)PCl_2$	0.6		44
	1:1				173	43
Cyclohexene	1:2**	$8.2\cdot10^{18}$	$(cyclo\text{-}C_6H_{10}Cl)PCl_2$	0.6		44
	1:1				240	43
	1:2**	$1.2\cdot10^{22}$	$cyclo\text{-}C_6H_9PCl_2$	0.8		44
		$1.0\cdot10^{22}$	$(cyclo\text{-}C_6H_9ClPCl_2)$ $PCl(cyclo\text{-}C_6H_9)$	0.07		44
Cycloheptene	1:1		$(cyclo\text{-}C_7H_{12}Cl)PCl_2$		103	43
Hept-1-ene			$CH_3(CH_2)_4CHClCH_2PCl_2$			45
Hept-2-ene			$CH_3(CH_2)_3CHClCHPCl_2CH_3$			45
Hept-3-ene			$CH_3(CH_2)_2CHClCHPCl_2CH_2CH_3$			45
Pent-1-ene	1:1		$CH_3(CH_2)_2CHClCH_2PCl_2$		278	43
Hex-1-ene	1:1		$CH_3(CH_2)_3CHClCH_2PCl_2$		192	43
Dec-1-ene	1:1		$CH_3(CH_2)_7CHClCH_2PCl_2$		89	43
Oct-2-ene	1:1		$CH_3(CH_2)_4CHClCHPCl_2CH_3$		252	43
Isobutene	1:1		$CH_3(CH_3)CClCH_2PCl_2$		430	43
			$(CH_3)_2CPCl_2CH_2Cl$		270	43
2-Ethylbutene	1:1		$(C_2H_5)_2CClCH_2PCl_2$		195	43
2-Methylbut-1-ene	1:1		$C_2H_5(CH_3)CClCH_2PCl_2$		245	43
2-Methylbut-2-ene	1:1		$(CH_3)_2CClCH(CH_3)PCl_2$		350	43

*Dose rate 7×10^{-3} r h^{-1}.
**Molar ratio.

To elucidate the optimum conditions for the radiation-chemical synthesis of the 1 : 1 addition product, the accumulation of chlorocyclohexyldichlorophosphine (CCHDCP) was investigated as a function of three principal parameters: temperature in the range 33–140°C, dose rate in the range between 1.5 and 55 rad s^{-1}, and the proportions of the initial components in the reaction mixture[44].

The linear variation of the yield of CCHDCP with the dose absorbed is observed only at low conversions. When the dose absorbed and hence the conversion is high, the reaction product (CCHDCP) accumulates and the proportions of the components begin to differ appreciably from the optimum values. The effective activation energy was determined from the temperature variation of the radiation-chemical yield as 5.9 kcal $mole^{-1}$. The rate of accumulation of CCHDCP is proportional to the square root of the dose rate and the order of the reaction with respect to each component is unity.

The radical-chain addition of PCl_3 to cyclohexene is described by the following mechanism:

$$PCl_3 \rightarrow {}^{\cdot}PCl_2 + Cl^{\cdot},$$
$$C_6H_{10} \rightarrow {}^{\cdot}C_6H_9 + H^{\cdot},$$
$$C_6H_{10} + {}^{\cdot}PCl_2 \rightarrow {}^{\cdot}C_6H_{10}PCl_2,$$
$$C_6H_{10}PCl_2 + PCl_3 \rightarrow ClC_6H_{10}PCl_2 + {}^{\cdot}PCl_2.$$

Chain termination takes place by the reactions:

$$\cdot PCl_2 + \cdot PCl_2 \rightarrow P_2Cl_4,$$
$$\cdot C_6H_{10}PCl_2 + \cdot PCl_2 \rightarrow PCl_2C_6H_{10}PCl_2,$$
$$\cdot C_6H_{10}PCl_2 + \cdot C_6H_{10}PCl_2 \rightarrow (C_6H_{10}PCl_2)_2.$$

When the dose rate is high, alkenyldichlorophosphine and alkyldichlorophosphine are formed, probably due to disproportionation and dehydrochlorination reactions.

Very similar kinetics were observed in the study of the radiation-chemical addition of phosphorus trichloride to linear mono-olefins, in liquid and gaseous phases[45]. The formation of two isomers of the main product and the increased reactivity of the olefins on displacement of the double bond from a terminal carbon atom to an inner carbon atom has been explained by postulating the formation in the initiation stage of a bridge-type dichlorophosphinealkyl radical.

The radiation-chemical yields of chloroalkyldichlorophosphines, reaching 10^4 mol./100 eV, suggest that γ-initiated reactions of phosphorus trichloride with unsaturated compounds could be successfully carried out on a larger scale[46,47].

3. Synthesis of Phosphonium Salts from Aryl Halides

While the synthesis of phosphonium and other quaternary 'onium salts from alkyl halides takes place readily on heating, the synthesis of 'onium salts from aryl halides is fairly complicated. γ-Irradiation of mixtures containing halogeno-substituted aromatic hydrocarbons has proved a very effective method for the synthesis of a number of quaternary phosphonium salts (Table 7). The radiation-chemical yields of arsonium salts are much lower and stibonium salts are formed with a negligible G.

The radiation-chemical synthesis has the following characteristic features: (1) a pronounced dependence of G of the 'onium salt on the mole fraction of the aryl halide in the mixture; the maximum is displaced towards higher contents of the aryl halide; (2) a significant increase in the percentage incorporation of triphenylphosphine on addition to the reaction mixture of various types of solvent; the curves relating the percentage incorporation to the amount of added solvent show a tendency towards saturation.

A mechanism with participation of positive ions and electrons derived from the solvent (S) has been proposed for dilute solutions:

$$S \rightarrow S^+ + e^-,$$
$$S^+ + (C_6H_5)_3P \rightarrow S + (C_6H_5)_3P^+,$$
$$e^- + C_6H_5Br \rightarrow C_6H_5 + Br^-,$$
$$(C_6H_5)_3P^+ + C_6H_5 \rightarrow (C_6H_5)_4P^+.$$

4. Synthesis of Phenylphosphonates

Trialkyl phosphites react with alkylhalides to form dialkyl esters of alkylphosphonic acid (Arbuzov rearrangement):

$$P(OR')_3 + RHal \rightarrow RP(O)(OR')_2 + R'Hal.$$

A similar thermal reaction cannot be achieved with aryl halides, but the use of γ-radiation allows the preparative synthesis of a number of phenyl phosphonates (Table 8).

The data presented in Table 8 show that the radiation-chemical yields of phenyl phosphonates are a maximum when iodobenzene is used as one of the reactants. In this case other characteristics of the reaction are a decrease of G proportional to the square root of the dose rate and a negative temperature coefficient of the reaction rate.

Table 7. Properties and yields of quaternary 'onium' salts synthesised under the action of cobalt-60 γ-radiation (dose rate 6×10^3–8×10^5 r h^{-1}).[48,49]

Starting materials	Mole %	Phosphonium salt	G	Rel. incorp. of phosphine(arsine)		M.p., °C properties of substance
				%	Dose × 10^{-7}, r	
Chlorobenzene Triphenylphosphine	76 24	$[P(C_6H_5)_4]Cl$	1.4	15	25	274-278 white crystals
Bromobenzene Triphenylphosphine	73.5 26.5	$[P(C_6H_5)_4]Br$	3.4	43	25	286-294 white crystals
Iodobenzene Triphenylphosphine	91.7 8.3	$[P(C_6H_5)_4]I$	6.5	78	5.6	335-343 transparent needles
Fluorobenzene Triphenylphosphine	90 10	$[(C_6H_5)_4P]F$	0.2	2.1	5.6	277-282 white needles
1,3-Dichlorobenzene Triphenylphosphine	90 10	$[(C_6H_5)_3PC_6H_4Cl]Cl$	2.0	80	10	207-208 white crystals
1,4-Dichlorobenzene Triphenylphosphine	71.5 28.5	$[(C_6H_5)_3PC_6H_4Cl]Cl$	3.9	90	20	157-158 white crystals
1,4-Dibromobenzene Triphenylphosphine	79.7 20.3	$[(C_6H_5)_3PC_6H_4Br]B$	5.1	25	2	134-150 white crystals
1-Chloro-4-iodobenzene Triphenylphosphine	74.8 25.2	$[(C_6H_5)_3PC_6H_4Cl]I$	4.4	55	3.5	219-222 yellow crystals
p-Chlorotoluene Triphenylphosphine	92 8	$[(C_6H_5)_3PC_7H_7]Cl$	2.0	21	6	215-223 white crystals
o-Chlorotoluene Triphenylphosphine	85 15	$[(C_6H_5)_3PC_7H_7]Cl$	1.4	3	1.6	260-262 white crystals
o-Bromotoluene Triphenylphosphine	85 15	$[(C_6H_5)_3PC_7H_7]Br$	2.4	7	1.6	228-237 white crystals
p-Bromotoluene Triphenylphosphine	64 36	$[(C_6H_5)_3PC_7H_7]Br$	2.1	41	4	228-237 white crystals
1-Chloronaphthalene Triphenylphosphine	82 18	$[(C_6H_5)_3PC_{10}H_7]Cl$	0.3	4	14	288-291 white crystals
1-Bromonaphthalene Triphenylphosphine	82 18	$[(C_6H_5)_3PC_{10}H_7]Br$	1.0	23	14	243-248 white crystals
2-Bromothiophen Triphenylphosphine	80 20	$[(C_6H_5)_3PC_4H_3S]Br$	6.2	13	1.2	250-253 yellow crystals
Bromobenzene Tributylphosphine	78 22	$[(C_6H_5)P(C_4H_9)_3]Br$	5.8	13	2.3	162-164 white crystals
Iodobenzene Tributylphosphine	78 22	$[(C_6H_5)P(C_4H_9)_3]I$	2.1	13	4	151-152 white lustrous crystals
Chlorobenzene Triphenylarsine	92 8	$[(C_6H_5)_4As]Cl$	0.06	2.5	19	256-260 white crystals
Bromobenzene Triphenylarsine	92 8	$[(C_6H_5)_4As]Br$	0.25	5.5	7.5	272-281 elongated colourless needles
Iodobenzene Triphenylarsine	88 12	$[(C_6H_5)_4As]I$	0.08			228-230 dark-red crystals
Bromobenzene Triphenylstibine	90 10	$[(C_6H_5)_4Sb]Br$	~0.005	—	25	212-218

Table 8. Yields of phenyl phosphonates synthesised under the action of cobalt-60 γ-radiation (dose rate 2.6×10^5 r h^{-1}).[50]

Starting materials	Mole %	Phosphonate synthesised	G	Dose × 10^{-7}, r	B.p., °C
$(CH_3O)_3P + C_6H_5F$	50:50	$C_6H_5P(O)(OCH_3)_2$	0.25	9.5	247
$(CH_3O)_3P + C_6H_5Cl$	50:50		2.6	5.8	
$(CH_3O)_3P + C_6H_5Br$	50:50		4.9	5.4	
$(CH_3O)_3P - C_6H_5I$	50:50		250	0.1	
$(C_2H_5O)_3P + C_6H_5Br$	50:50	$C_6H_5P(O)(OC_2H_5)_2$	4.0	8.0	267
$(C_2H_5O)_3P + C_6H_5I$	50:50		28	0.6	
$(iso\text{-}C_3H_7O)_3P + C_6H_5I$	50:50	$C_6H_5P(O)(O\text{-}iso\text{-}C_3H_7)_2$	11	0.7	—
$(CH_3O)_3P + p\text{-}ClC_6H_4I$	70:30	$(CH_3O)_2P(O)C_6H_4Cl$	68	0.6	264—268
$(CH_3O)_3P + p\text{-}BrC_6H_4CH_3$	70:30	$(CH_3O)_2P(O)C_7H_7$	2.5	1	262—265
$(CH_3O)_3P + m\text{-}C_6H_4Cl_2$	70:30	$(CH_3O)_2P(O)C_6H_4Cl$	1.9	1.5	265—268
$(CH_3O)_3P$ + 2-bromothiophen	50:50	$(CH_3O)_2P(O)C_4H_3S$	9.7	1	248—255

It has been suggested that the process has a chain mechanism:

$$\cdot C_6H_5 + P(OR)_3 \rightarrow C_6H_5P(OR)_3,$$
$$C_6H_5P(OR)_3 + C_6H_5I \rightarrow [C_6H_5P(OR)_3]^+I^- + \cdot C_6H_5.$$

The quasi-phosphonium salt formed as a result of the addition of an iodine atom to a phosphorus(IV) free radical breaks down with formation of the desired product:

$$[C_6H_5P(OR)_3]^+I^- \rightarrow C_6H_5P(O)(OR)_2 + RI.$$

Quadratic chain termination can occur via reactions of the phenyl radicals with one another or with intermediate phosphorus-containing radicals. The rate of the processes is probably determined by the formation of the quasi-phosphonium salt, which depends on the strength of the C–H bond in the aryl halide, the electron affinity of the halogen, and the solvation of the ions produced.

VI. RADIATION-INDUCED SYNTHESIS OF ORGANOTIN COMPOUNDS

The radiation-chemical synthesis of organotin compounds of the type R_2SnBr_2 and R_3SnBr is based on the reaction of an alkyl bromide RBr with metallic tin under the action of γ-radiation. The synthesis of dibutyltin dibromide (DBTDB) have been most thoroughly investigated[51–56]. The compound was synthesised in a bench-type apparatus and described by Miretskii et al.[56] n-Butyl bromide with a purity of 99% and tin powder containing not less than 99.5% of tin were employed. The experiments were performed mainly at 85–90°C and atmospheric pressure with vigorous stirring. The average absorbed dose rate was about 100 rad s^{-1}.

The interaction of n-butyl bromide with tin in the presence of γ-radiation is fairly selective, the main product being DBTDB and a certain amount of tributyltin bromide and stannous bromide.

One of the characteristics of the radiation-chemical synthesis of DBTDB is the induction period. Application of various techniques led to the discovery of the optimum conditions for the reaction under which there is virtually no induction period. The introduction into the reaction mixture of various compounds activating the reaction, for example n-butyl alcohol or water, proved to be highly effective[57].

The study of the parameters of the reaction occurring virtually without an induction period led to the discovery of its principal macrokinetic features[58]. A very important factor in the radiation-chemical process proved to be temperature. The effective activation energy determined from the kinetic curves for the accumulation of DBTDB in the range 20–95°C proved to be 12 kcal $mole^{-1}$. The rate of formation of DBTDB is proportional to the square root of the dose rate in the range 175–2.5 rad s^{-1}.

The formation of DBTDB probably involves a chain mechanism. This is suggested by the following findings: (1) the radical-chemical yield reaches 10^3–10^4 mol./100 eV at a high conversion; (2) the reaction system shows characteristic behaviour on introduction of activating species; (3) the rate of reaction depends on the square root of the dose rate. When irradiation is stopped, the reaction ceases immediately, but recommences at the previous rate after the source of radiation is reintroduced. An additional piece of evidence in favour of a chain mechanism is provided by observations of the effect of inhibiting additives on the rate of formation of DBTDB. Special experiments showed that oxygen in the reaction system or the introduction of electron-accepting additives such as benzoquinone, hydroquinone, or *m*-dinitrobenzene cause appreciable inhibition of the reaction. The author of the review suggested the following probable mechanism for the chain process, the principal feature of which is that all the chain-propagation stages take place on the surface of tin.

Initiation:

$$RBr \rightarrow R^{\cdot} + Br^{\cdot},$$

and (or)

$$RBr + e \rightarrow R^{\cdot} + Br^{-}.$$

Chain propagation:

$$R^{\cdot} + Sn \rightarrow RSn,$$
$$RSn + RBr \rightarrow R_2SnBr,$$
$$R_2SnBr + RBr \rightarrow R_2SnBr_2 + R^{\cdot}.$$

Chain termination:

$$R^{\cdot} + Br^{\cdot} \rightarrow RBr,$$
$$R^{\cdot} + R^{\cdot} \rightarrow R_2,$$
$$R_2SnBr + Br^{\cdot} \rightarrow R_2SnBr_2,$$
$$Br^{\cdot} + Br^{\cdot} \rightarrow Br_2.$$

The formation of tributyltin monobromide and $SnBr_2$ may involve the reactions

$$R_2SnBr + R^{\cdot} \rightarrow R_3SnBr,$$
$$Br^{\cdot} + Sn \rightarrow SnBr,$$
$$SnBr + RBr \rightarrow SnBr_2 + R^{\cdot}.$$

The study of the radiation-induced synthesis of DBTDB homologues (from C_3 to C_9) showed that the macrokinetic features of all the reactions are very similar, dialkyltin dibromides being formed with fairly high radiation-chemical (500–1000 mol./100 eV) and chemical (80–85%) yields[59]. The synthesis of a number of dialkyltin dibromides in appreciable amounts permitted the determination for the first time of their physical constants (Table 9).

Table 9. Properties of dialkyltin dihalides synthesised by the radiation-chemical method[59].

Dialkyltin dibromide	n_D^{20}	d^{20}	M.p., °C
$(C_3H_7)_2SnBr_3$	1.5480	1.87	43
$(C_6H_{13})_2SnBr_2$	1.5270	1.537	8.3
$(C_7H_{15})_2SnBr_2$	1.5230	1.4720	20.5
$(C_8H_{17})_2SnBr_2$	1.5180	1.4157	20.2
$(C_9H_{19})_2SnBr_2$	1.5147	1.383	20.1

The radiation-chemical synthesis of dialkyltin dibromides has a number of useful characteristics: it is a single-stage selective process, the desired product is formed in high yield, there is no fire or detonation risk, and the process is readily controlled.

VII. RADIATION-INDUCED SYNTHESIS OF OXYGEN-CONTAINING COMPOUNDS

The radiation-induced oxidation of hydrocarbons at moderate temperatures is of no interest from the standpoint of the selective synthesis of oxidation products because of the lack of selectivity and low radiation-chemical yield of the products.

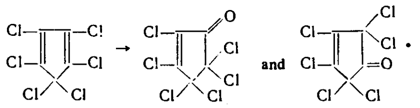
The oxidation of halogeno-olefins, in particular chloroethylenes, is of definite importance for the synthesis of valuable organic substances used as intermediates for various syntheses. Laboratory studies established that liquid tetrachloroethylene is oxidised by gaseous oxygen to tetrachloroepoxyethane and trichloroacetyl chloride on γ-irradiation at temperatures in the range 20–120°C.[60] The oxidation was carried out in a bench-type radiation-chemical apparatus[61] with a linear radiation source located coaxially in the reaction space, the average dose rate in the apparatus being about 100 rad s^{-1}. The flow rate of gaseous oxygen at atmospheric pressure was 1–2 litre min^{-1} per litre of the tetrachloroethylene taken for oxidation (with vigorous stirring of the reactants). The process was carried out in batches at 120°C and above, the duration of a single operation being 5–10 h. Trichloroacetic acid obtained by the radiation-chemical method is 4–5 times cheaper than the acid usually obtained by the oxidation of chloral with a mixture of nitric and sulphuric acids[62].

Liquid trichloroethylene is oxidised by gaseous oxygen to dichloroepoxyethane and dichloroacetyl chloride on γ-irradiation. Trichloroepoxyethane was obtained for the first time; 146 g of trichloroethylene treated with a stream of oxygen for 150 min at a flow rate of 0.3 litre min^{-1}, heated to 72°C, and exposed to γ-radiation (dose rate 0.4 rad s^{-1}) gave a mixture containing 60% of trichloroepoxyethane[63]. The optimum parameters for the synthesis of the acid chloride using the bench-type apparatus mentioned above at an average dose rate of about 25 rad s^{-1} are as follows: oxidation at 50–60°C at atmospheric pressure of oxygen flowing at a rate of 1–2 litre min^{-1} per litre of trichloroethylene. The process is carried out in batches and the duration of the oxidation is about 10 h.

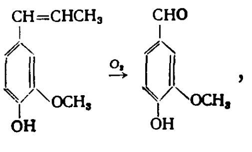
The radiation-chemical synthesis of trichloroethylene oxidation products has considerable advantages. Firstly, the cost of methyl dichloroacetate obtained from the acid chloride is approximately three times smaller than that of the product obtained by the usual chemical synthesis via chloral[64].

The radiation-induced oxidation of chloroethylenes and tetrafluoroethylene[65], leading to the synthesis of carbonyl fluoride COF_2, epoxytetrafluoroethane $(CF_2)_2O$, and a liquid polyperoxide $(-CF_2-CF_2-O-O-)_n$ is a typical chain process with an appreciable radiation-chemical yield.

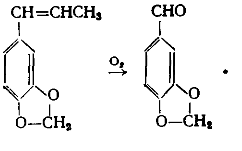
The radiation-chemical oxidation of hexachlorocyclopentadiene leads to the synthesis of hexachlorocyclopentenone[66]:



The radiation-chemical oxidation involving a double bond in the α-position relative to an aromatic ring is highly selective[67–70]. Thus vanillin was synthesised by the radiation-chemical oxidation of isoeugenol:



and heliotropin was obtained from isosafrole:

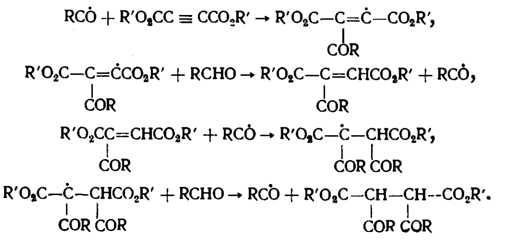


The addition of aldehydes to acetylenedicarboxylate esters has not been described previously[71]. On γ-irradiation in evacuated tubes (dose rate 4 × 10^5–4.5 × 10^5 rep h^{-1}) at 22°C, butyraldehyde, isobutyraldehyde, and acetaldehyde add to dimethyl- or diethyl-acetylenedicarboxylates with formation of diacylsuccinates (Table 10).

Table 10.

Starting materials	Dose absorbed, 10^6rep	Addition product	Yield, %	G, mol./100 eV
Butyraldehyde (0.264 M) Dimethyl acetylene-dicarboxylate (0.06 M)	10.4	dimethyl 2,3-dibutyryl-succinate	23	54
Acetaldehyde (0.30 M) Dimethyl acetylene-dicarboxylate (0.072 M)	18.8	dimethyl 2,3-diacetyl-succinate	31	54
Acetaldehyde (0.304 M) Diethyl acetylene-dicarboxylate (0.072 M)	18.8	diethyl 2,3-diacetyl-succinate	2	46
Isobutyraldehyde (0.225 M) Diethyl acetylene-dicarboxylate (0.051 M)	17.4	diethyl 2,3-di-isobutyryl-succinate		

The addition takes place by a free radical mechanism:



$$RCHO \rightarrow R\dot{C}O + H,$$
$$R\dot{C}O + R'O_2CC \equiv CCO_2R' \rightarrow R'O_2C-\underset{\displaystyle COR}{\underset{|}{C}}=\dot{C}-CO_2R',$$
$$R'O_2C-\underset{\displaystyle COR}{\underset{|}{C}}=\dot{C}CO_2R' + RCHO \rightarrow R'O_2C-\underset{\displaystyle COR}{\underset{|}{C}}=CHCO_2R' + R\dot{C}O,$$
$$R'O_2\underset{\displaystyle COR}{\underset{|}{C}}C=CHCO_2R' + R\dot{C}O \rightarrow R'O_2C-\underset{\displaystyle COR}{\underset{|}{\dot{C}}}-\underset{\displaystyle COR}{\underset{|}{C}}HCO_2R',$$
$$R'O_2C-\underset{\displaystyle COR}{\underset{|}{\dot{C}}}-\underset{\displaystyle COR}{\underset{|}{C}}HCO_2R' + RCHO \rightarrow R\dot{C}O + R'O_2C-\underset{\displaystyle COR}{\underset{|}{CH}}-\underset{\displaystyle COR}{\underset{|}{CH}}--CO_2R'.$$

VIII. RADIATION-INDUCED SYNTHESIS OF ORGANOSILICON COMPOUNDS

The addition of silanes to ethylene under the action of radiation leads to the formation of telomerisation products[72]. In the gas phase methylsilane and dimethylsilane form 1 : 1 and 1 : 2 telomers. For a silane : : ethylene ratio of 3 : 1 at 50°C the radiation-chemical yields are $G(CH_3CH_2CH_2SiH_3) = 38$ and $G(CH_3CH_2CH_2SiH_2CH_3) = 15$. At temperatures close to 250°C $G(CH_3CH_2CH_2SiH_3)$ reaches several hundreds. The mechanism of the telomerisation chain reaction is evidently ionic.

Under the action of γ-radiation, triphenylsilane adds to the double bond of oct-1-ene and cyclohexene[73]. Irradiation for 63 h of a mixture of 0.15 M triphenylsilane and 0.05 M octene in a sealed tube in an atmosphere of nitrogen at 65°C at a dose rate of 810 000 rep h^{-1} leads to the synthesis of 1-octyltriphenylsilane (700 mg) and hexaphenyldisiloxane (210 mg). A mixture of triphenylsilane and cyclohexene gives triphenylcyclohexylsilane and hexaphenyldisiloxane.

The addition of chlorosilane olefins takes place readily under the action of ultraviolet light[74]. When mixtures of various ethylene derivatives with trichlorosilane, dichlorosilane, methyldichlorosilane, or ethyldichlorosilane were exposed to ionising radiation, a large number of compounds were synthesised, some for the first time[75,76]. The telomerisation reaction takes place at a temperature not exceeding 120°C.

The preparative possibilities of the method, which permits the synthesis of the compounds $R'SiCl_2$ and $R'R'SiCl_3$ from fluoro-olefins $C_nH_{2n-m}F_m$ are illustrated in Table 11, where certain compounds synthesised for the first time are listed.

Table 11. Fluorine-containing chlorosilanes obtained by radiation-induced synthesis[75].

Starting materials	Product of synthesis	d^{20}	n_D^{20}	B.p., °C/mmHg	Percentage utilisation of starting materials	G, mol/100 eV
$C_3F_6 + HSiCl_3$	$(C_3HF_6)SiCl_3$	1.6170	1.3610	84/756.5	95	190
$C_3F_6 + H_2SiCl_2$	$(C_3HF_6)_2SiCl_2$	1.7202	1.3413	160	80	100
$C_3F_6 + CH_3HSiCl_2$	$(C_3HF_6)CH_3SiCl_2$	1.4610	1.3338	94/749	85	225
$C_3F_6 + C_2H_5HSiCl_2$	$(C_3HF_6)C_2H_5SiCl_2$	1.4342	1.3710	110—112/752	95	180
$C_2F_4 + HSiCl_3$	$(C_2HF_4)ClSiCl_2$	1.5138	1.3645	--	11	1.6

The chain reaction is initiated by $SiCl_3$ radicals formed from trichlorosilane under the action of radiation:

$$HSiCl_3 \rightarrow H^{\cdot} + {}^{\cdot}SiCl_3\,,$$

$$RCH{=}CH_2 + {}^{\cdot}SiCl_3 \rightarrow R\dot{C}HCH_2SiCl_3,$$

$$R\dot{C}HCH_2SiCl_3 + HSiCl_3 \rightarrow RCH_2CH_2SiCl_3 + {}^{\cdot}SiCl_3.$$

The reactions with other substituted chlorosilanes takes place similarly.

The CH_3 and C_6H_5 groups in methylphenyldichlorosilane and dimethylchlorosilane can be chlorinated by the radiation method[77].

Another method for synthesising a number of organosilanes involves the condensation of unsubstituted and alkyl(aryl)-substituted chlorosilanes $(R'R'')_nSiHCl_{3-n}$, the molecule of which must contain a mobile hydrogen atom, with alkyl and aryl halides[79-82]:

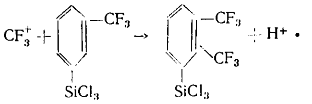
$$(R'R'')_nSiHCl_{3-n} + RCl \rightarrow (R'R'')_nSiRCl_{3-n} + HCl\,.$$

The reaction results in the introduction of a new group R into the chlorosilane molecule. A large series of chlorosilanes containing a wide variety of substituents was synthesised in this way with appreciable radiation-chemical yields (Table 12). The condensation reaction takes place at a temperature not exceeding 360°C. It has been established that the radiation-chemical synthesis of chloroperfluoroalkyl(aryl)-silanes takes place at lower temperatures than the synthesis of non-fluorinated alkyl(aryl) chlorosilanes[82].

An interesting example of the radiation-induced synthesis of fluoroaryl-substituted chlorosilanes is provided by the preparation of trichloro-2,3-di(trifluoromethyl)phenylsilane, which has not been described previously[83]. Irradiation of evacuated sealed tubes with a mixture of equal volumes of $\alpha\alpha\alpha$-trifluorotoluene and tetrachlorosilane at an average dose rate of 87 rad s^{-1} resulted in the synthesis of the desired product with $G \simeq 3$. The set of processes leading to the synthesis may include the following radical and ionic reactions:

$$SiCl_4 \rightarrow {}^{\cdot}SiCl_3 + {}^{\cdot}Cl\,,$$

$$R_FH \rightarrow \begin{cases} {}^{\cdot}R_F + H^{\cdot} \\ Ph^{\cdot} + {}^{\cdot}CF_3 \\ {}^{\cdot}CF_3^+ + {}^{\cdot}C_6H_5 + e^- \end{cases},$$



Although the data presented in the review are unquestionably fragmentary, there is hardly any doubt that preparative radiation-induced synthesis of many organic compounds is the simplest and the most rational procedure.

Table 12. Radiation-chemical synthesis of substituted chlorosilanes[81].

Chlorosilane	Aryl halide	Component ratio	Temp., °C	Product of synthesis	G
$HSiCl_3$	C_6H_5Cl	1:1	175	$C_6H_5SiCl_3$	300
$HSiCl_3$	p-$C_6H_4Cl_2$	1:3	170	p-$C_6H_4(SiCl_3)Cl$	100
$HSiCl_3$	p-$C_6H_4Cl_2$	2:1	300	p-$C_6H_4(SiCl_3)_2$	100
$HSiCl_3$	o-$C_6F_4Cl_2$	4:1	250	o-$C_6F_4(SiCl_3)_2$	60
$HSiCl_3$	1,2,4-$C_6H_3Cl_3$	1.2:1	175	$C_6H_3Cl_2(SiCl_3)$	70
CH_3SiHCl_2	C_6H_5Cl	1:2	300	$CH_3(C_6H_5)SiCl_2$	300
$C_6H_5SiHCl_2$	C_6H_5Cl	1:1	300	$(C_6H_5)_2SiCl_2$	150
$(CH_3)_2SiHCl$	p-$C_6H_4Cl_2$	4:1	300	p-$C_6H_4[Si(CH_3)_2Cl]Cl$ p-$C_6H_4[Si(CH_3)_2Cl]_2$	80 87
$(CH_3)_2SiHCl$	m-$C_6H_4Cl_2$	4:1	300	m-$C_6H_4[Si(CH_3)_2Cl]Cl$	80
$CH_3(C_6H_5)SiHCl$	p-$C_6H_4Cl_2$	2:1	300	p-$C_6H_4[SiCH_3(C_6H_5)Cl]_2$	20
$(C_6H_5)_2SiHCl$	p-$C_6H_4Cl_2$	2:1	300	p-$C_6H_4[(C_6H_5)_2SiCl]_2$	15

Together with the preparative radiation-induced synthesis described above, carbonylation, carboxylation, hydroxylation, nitration, and nitrosation reactions, synthesis of glycols, reactions involving the addition to olefins of telogens such as, for example, alcohols, aldehydes, mercaptans, etc. (see the relevant reviews[84-86]), occurring under the action of radiation, are also known. One cannot exclude the possibility that in certain cases some of the reactions enumerated may find preparative applications.

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Karpov Physicochemical Institute,
Moscow

U.D.C. 550.41

Advances in Organic Geochemistry

S.M.Manskaya

Two research fields embraced by the concept "organic geochemistry" are discussed. The first includes works on the abiogenic formation of organic compounds and the second deals with studies on the phenomena involving the formation and transformations of fossil organic matter and its importance in geochemical processes. This branch of geochemistry has been defined by certain Soviet investigators as "geochemistry of organic matter".

The present review deals with modern studies on aminoacids, carbohydrates, lipids, porphyrin structures, carotenoids, aromatic compounds of the type of lignin, and flavonoids in contemporary and ancient deposits in connection with problems of petroleum and coal formation.

On the basis of the investigations described, the author of the review believes it to be possible to define the future tasks in the geochemistry of organic matter and rational procedures for carrying them out.

The bibliography includes 111 references.

CONTENTS

1. PRINCIPAL FIELDS OF RESEARCH IN ORGANIC GEOCHEMISTRY

The branch of geochemistry under consideration (organic geochemistry) has been treated in a number of symposia[1,2] comprising papers of a fairly wide variety of types. Some of these are devoted to problems of organic cosmochemistry—the abiogenic formation of organic compounds. Others deal with modern concepts concerning the organic materials in coals, petroleum, and petroleum-bearing rocks. Reports on organic cosmochemistry and on the investigation of organic structures in coals and petroleum, scarace organic substances, and paleontological specimens were presented at the Fourth International Congress on Organic Geochemistry (Amsterdam, September, 1968). It is noteworthy that both natural phenomena characterised by the concept "organic geochemistry" gave rise to two different fields of geochemical research.

In the Soviet literature these two fields are fairly clearly distinguished. The first includes work on the abiogenic formation of organic compounds associated with organic cosmochemistry and problems of the origin of life. The second deals with studies on individual stages in the formation of fossil organic matter and its importance in geochemical processes. This branch of geochemistry has been defined by some Soviet investigators as "geochemistry of organic matter"[3,4].

In the present review it is necessary to consider in the first place the principal features of the first field: the abiogenic formation of organic compounds, the origin of life on earth, and the creation of the biosphere in which fossil organic matter was formed.

Meteorites are important objects for the investigation of organic matter of abiogenic origin. At present numerous data are available, showing the extraterrestial abiogenic nature of the organic material of meteorites[5,6]. A high-molecular-weight of carbon compound with a condensed aromatic structure has been isolated from carbonaceous chondrites[7].

The primary cold matter of the earth's mantle resembles the rocky meteorites. As a result of the rise of the earth's temperature due to radioactivity, readily fusible substances evolved from the earth's mantle in liquid and gaseous forms and formed its outer shells: aqueous (the ocean) and gaseous (the atmosphere)[8-10].

In his monograph Vinogradov[11] describes the probable situation on the earth's surface before the formation of the biosphere. The amount of oxygen in the atmosphere was negligibly small at that time and there was no ozone screen. Life could develop only in the water of the ocean where it was protected from cosmic radiation. Biogenic synthesis was probably preceded by radiogenic and photogenic formation on the earth of complex organic molecules. Oparin's theory of the origin of life[12] is based on the hypothesis of an abiogenic synthesis of primary organic molecules. Oparin and his coworkers performed numerous experiments whereby it was possible to synthesise under laboratory conditions biologically important compounds from ammonia, methane, and formaldehyde under the action of ultraviolet rays and radioactive emission[13-15]†. Aminoacids and nucleotides were synthesised in this way. The abiogenic synthesis of adenosine triphosphoric acid (ATP)—the principal source of energy in all present day organisms—from polyphosphates was achieved under the action of short-wavelength ultraviolet light. Oparin postulates the existence of an enormous number of catalysts which were responsible for the occurrence of a wide variety of reactions in prebiological systems (protobionts).

Nicotinamide adenine dinucleotide (NAD^+) is a universal hydrogen-transfer agent in the living cell. Its presence has been established in all present day organisms; microbes, plants, and animals. It is suggested that NAD^+ was first formed in an early stage of the evolution of organic matter. Similar universal catalysts were also other coenzymes and to an even greater extent enzymes with exclusive specificity and enormous catalytic activity. Thus the enzyme hexokinase accelerates the reaction of ATP with glucose by a factor greater than 10^{11} and alcohol dehydrogenase accelerates the oxidation of alcohol by a factor greater than 10^9. The principal components of all

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[†] Similar experiments were carried out for the first time by Miller [S. Miller, J. Amer. Chem. Soc., 77, 2351 (1955)] [Editorial Note].

these enzymes are proteins. The specificity of enzymes is associated with a strictly ordered arrangement of the aminoacid residues in the polypeptide chain and a definite packing of this chain in the protein molecule. In this connection there arose the hypothesis of the formation in the course of evolution of a "molecular-matrix" apparatus with the properties of polynucleotides[16,17]. Further development of the primary hydrocarbon systems was an important stage in the generation of life.

According to Oparin's concepts (Ref. 14, p. 56), "a characteristic feature of life is that it is not simply scattered in space but consists of individual very complex systems separated from the outer environment (organisms), which continuously interact with the external medium and the internal structure of which is extremely well adapted to their prolonged existence, continual self-renewal, and spontaneous reproduction under the given conditions of the universe surrounding them".

Vinogradov[11] believes that the formation of complex organic compounds in the water of the ocean, which led to the appearance of organisms, resulted in the first profound transformation in the composition of the ocean and the entire hydrosphere, in the atmosphere, and in many processes occurring on the earth's surface. The mechanism of photosynthesis, which includes the reduction of water with liberation of free oxygen, arose in the course of the evolution of the simplest organism. This led to the accumulation of oxygen in the atmosphere and the formation of the ozone screen so that life became possible not only in water but also on dry land.

Boichenko[18] points out the role of the metal-containing oxido-reductases in the evolution of photosynthesis. With the appearance of manganese in the chloroplast lipids, the oxidation-reduction potential necessary for the evolution of oxygen was attained. The biosphere was at one time investigated on a wide front by Vernadskii[19,20], who found that organisms should be investigated in relation to the medium where they lived or live, i.e. in relation to the earth's crust. This led to a new geochemical problem—the study of the chemical composition of living matter, i.e. the average chemical composition of living organisms in relation to geochemical processes occurring in the earth's crust. A new branch of geochemistry—biogeochemistry—also arose.

The role of organisms or living matter in geochemical properties was studied by Vinogradov[21] on a large amount of material. The elementary chemical composition of sea organisms was determined taking into account their evolutionary development and position in the system of nomenclature. Subsequently the effect of the medium on the elementary composition of organisms was elucidated[22].

Koval'skii[23], who studied the effect of the medium (chemical elements) on metabolism in organisms, concluded that the biochemical or physiological mechanisms of adaption to geochemical conditions are important factors in the evolutionary process. It is suggested that the microelements concentrated by plants may accumulate in structural components of the cells (nuclei, mitochondria, ribosomes) and influence the occurrence of mutations.

As a result of the development of living matter in the biosphere, the products of the decomposition of the organisms, which gave rise to fossil organic matter, also began to accumulate. Vinogradov states (Ref. 24, p. 4) that it is difficult to separate the geochemical role of living matter from the geochemical role of organic substances formed after the death of the organisms. The appearance of deposits of coal, petroleum, lime, and other organic rocks itself altered the face of the earth; later Vinogradov states (Ref. 24, p. 11) "...in order to elucidate the mutual effects in the organic substance—rock system, we must be able to distinguish the individual properties of particular organic molecules. This is why it is necessary to concentrate attention on and to intensify the study of the molecular composition of organic substances, the role of which in geological processes cannot be over-estimated".

New studies on the geochemistry of organic matter show investigations of individual organic compounds and methods of their conversion in natural processes may prove very useful for the solution of many geochemical problems.

Here we may include the following branches of geochemistry: (1) the study of the chemical composition of the organic matter of different types of peat and fresh and seawater deposits together with the biochemical processes occurring in them, which determine the initial stages in the formation of different types of coal and petroleum; (2) the study of the organic fraction of paleontological specimens in order to establish the phylogenetic differences and to elucidate the preservation conditions; (3) discovery of the organic structures responsible for the concentration of rare elements in caustobioliths and other natural materials.

In his examination of the principal problems of the chemical study of the world ocean, Zenkevich[25] attributed considerable importance to the investigation of organic matter. Starting with the postulate that "organic matter is a trigger actuating the diagenetic processes in sea deposits", Zenkevich believes that the first task to be performed is the study of the chemical composition of organic matter in oceanic water and deposits and the determination of the individual organic compounds.

Much serious work, described in symposia, monographs, and individual articles, has been done on the chemical balance of organic matter in the ocean and also on its composition. This includes the studies by Skopintsev[26,27] who developed the hypothesis that the bulk of the dead organisms of the plankton decomposes in the upper layer of the ocean. This hypothesis is confirmed by numerous data on the distribution in the sea of ammonia, nitrates, organic carbon, nitrogen, and phosphorus. Romankevich[28,29] followed the relations governing the distribution of organic carbon and nitrogen in the surface layer and in the bulk of the deposits in the Pacific Ocean. In the deep water part of the Pacific Ocean the degree of mineralisation of the organic matter of the phytoplankton in the water and on the surface of the bottom amounts to 99.93–99.99%.

As one moves away from the foot of the continental shelf to the central part of the ocean, the content of organic carbon and nitrogen in the deposits diminishes to minimal values (0.25% of organic carbon and 0.05% of nitrogen relative to the non-silicate and non-carbonate material of the deposits).

Lisitsyn[30] investigated the present day deposits in the Bering sea. The biomass of the phytoplankton in the Bering sea consists largely (90%) of diatomaceous algae. In this connection the distribution of silicon in the waters and deposits of this reservoir is of definite interest.

Much attention has been devoted to the study of the organic matter of present day and ancient sea and continental deposits in connection with the conditions governing the formation of petroleum. Veber[31] attributes particular importance to the study of bitumens in the organic matter of the deposits as a function of the conditions of their formation in the facies.

Rodionova[32] studied by biochemical-bitumenological analysis the composition of the hydrocarbons in more than 2000 rock specimens from the Devonian and Lower Carboniferous periods in the Volga-Ural petroleum- and gas-bearing region. The results of the chromatographic separation of the individual bitumen fractions enabled her to determine the distribution of hydrocarbons in the organic matter of rocks of different lithological composition and different geological ages.

2. STUDY OF INDIVIDUAL ORGANIC COMPOUNDS IN DIFFERENT STAGES OF THEIR CONVERSION INTO FOSSIL ORGANIC MATTER

The modern theory of the organic origin of petroleum is based on the following concepts: (1) the nature of the materials from which petroleum was derived; (2) the processes and conditions in the formation of petroleum; (3) the migration and accumulation of petroleum[33-35]. The principal compounds in petroleum are hydrocarbons of the methane, naphthene, and aromatic types. Hydrocarbons similar to those detected in petroleum have been found in all sedimentary rocks, ranging from ancient to contemporary deposits[36].

The majority of investigators agree with the hypothesis that the principal biochemical source of petroleum hydrocarbons are fats and fatty acids. Fats included in the group of lipids constitute a mixture of esters of glycerol (a trihydric alcohol) and high-molecular-weight fatty acids. The principal fatty acids entering into the composition of fats are palmitic $CH_3(CH_2)_{14}COOH$, stearic $CH_3(CH_2)_{16}COOH$ oleic $CH_3(CH_2)_7CH=CH(CH_2)_7COOH$, linoleic $CH_3(CH_2)_4CH=CHCH_2CH=CH(CH_2)_7COOH$, and linolenic $CH_3CH_2CH=CHCH_2CH=CHCH_2CH=CH(CH_2)_7COOH$.

All living organisms contained the enzymes (lipases) which catalyse the hydrolysis of fats with formation of glycerol and fatty acids. The decarboxylation of fatty acids in the course of their conversion into petroleum hydrocarbons might have occurred in the first place under the influence of bacterial enzymes and also under the action of physical factors—temperature and pressure.

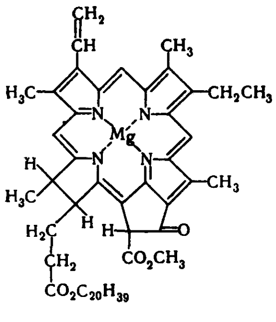
Abelson[37] devoted much attention to kerogen as the most probable source of petroleum hydrocarbons in the course of formation of petroleum from the decomposition products of the phytoplankton. He postulates also the possibility of a secondary transformation of kerogen (the insoluble fraction of the organic matter in ancient deposits). The fatty acids liberated after the death of the phytoplankton interact with other compounds or are acted upon by micro-organisms (depending on the conditions in the medium). In both cases they can serve as the starting material for the formation of petroleum hydrocarbons or an insoluble kerogen complex. The data obtained by Williams[38], who established a sharp decrease of the ratio of fat carbon to the total content of carbon in the organic matter of the deposits compared with its value in algae, are of interest in this connection. Williams determined this ratio as 0.3 for diatomaceous algae and 0.2 for mixed algae. In the organic matter from the deposits taken at a depth of 20 m the ratio is 0.08 and at a depth of 400 m it is 0.02. For the dissolved organic matter at depths of 20 and 400 m, the ratio is 0.004 and 0.003 respectively.

Brooks and Smith[39] determined the relative amounts of hydrocarbons with even and odd numbers of carbon atoms in living plants, coals with different degrees of metamorphism, in different types of petroleum, and in natural gas. They suggested that in many cases the same plants can serve as starting materials for the formation of both coal and petroleum, depending on the biochemical conditions and early diagenesis. Wood gave rise to the formation of humus coal, and small plant particles (leaves and others) containing large amounts of lipids may have been involved in the formation of lake or sea silt. Deposits of this type served as a source for the formation of petroleum. Characteristic differences in the composition of humus and sapropel types of fossil organic matter have been demonstrated[40,41].

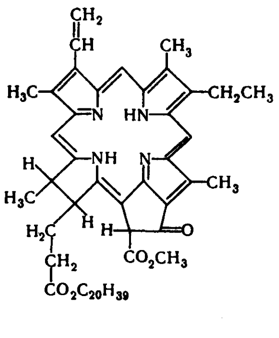
In the hypotheses concerning the genesis of petroleum considerable importance is attributed to pigments: chlorophyll and carotenoids. Porphyrin pigments of the type of chlorophyll were first detected by Treibs[42] in different types of petroleum, asphalts, and tars, which confirmed the theory of the organic origin of petroleum.

The products of the decomposition of chlorophyll and haemoglobin in natural materials have been extensively investigated at the present time and the possible pathways in their conversion into petroleum porphyrins have been demonstrated. Orr et al.[43] proposed a mechanism for the conversion of chlorophyll via a number of intermediates into the porphyrin structures of the deposits and petroleum. Among the intermediate decomposition products postulated in the mechanism, pheophytin and phaeophorbide, chlorophyll derivatives without magnesium, have been detected in deposits.

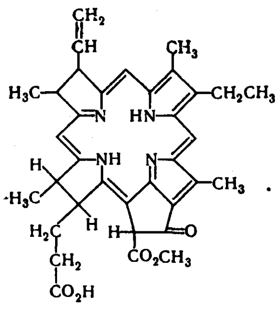
Studies on the organic matter of the present day deposits in the Pacific Ocean, taken from various depths (from 30 to 7500 m), established that chlorophyll decomposition products predominate markedly over unchanged chlorophyll[28]:



chlorophyll a

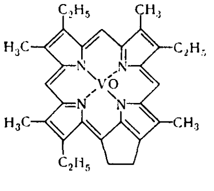


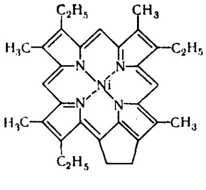
phaeophytin a

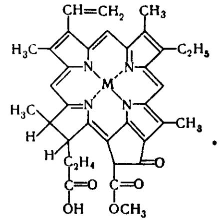


phaeophorbide a

Hodgson et al.[44] demonstrated in model experiments the conversion of phaeophytin and its derivative chlorene into petroleum porphyrins. In sedimentary rocks and in hydrocarbon accumulations porphyrins are encountered mainly in the form of vanadium or nickel complexes. There exists the hypothesis that pigments having the porphyrin structure with a metal atom in the ring (chlorophyll with magnesium, haemin with iron) lose the metal in the subsequent reactions of the organic material. Metal-free porphyrins are encountered in fossil organic matter fairly rarely—probably the interaction of vanadium or nickel with the free porphyrins is relatively rapid:

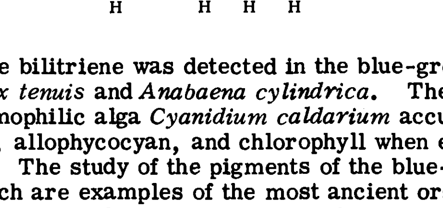

V-porphyrin


Ni-porphyrin


Metal-chlorene

Hodgson et al.[45] investigated the distribution of porphyrins and chlorene in polycyclic aromatic compounds in 250 specimens of soils, deposits, and sedimentary rocks of different ages, ranging from the early Precambrian period up to the present day. Ni- and V-porphyrins were detected in all the specimens, which indicates their wide distribution in sedimentary formations. They are found mainly in fine-grained clastic sea rocks with ages ranging from the Tertiary to the Precambrian periods. Chlorenes are encountered predominantly in contemporary deposits and in soils. Fe-Porphyrins have been found in a small number of specimens. Hodgson and coworkers extracted Fe-porphyrin from gilsonite with the aid of methanesulphonic acid and then obtained it in the form of free porphyrin. This enabled them to investigate on models the interaction of porphyrin with nickel, copper, cobalt, zinc, and both divalent and trivalent iron and to obtain complexes of these compounds.

In connection with the importance of the study of porphyrin structures in the geochemistry of organic matter, mention should be made of the pigments in the blue-green and purple algae. These are phycocyans, allophycocyans, and phycoerythrins—complexes of proteins and plant bile pigments. Bile pigments are regarded as derivatives of porphyrins—tetrapyrroles with an open chain. An example of such a pigment is bilitriene which has a blue-green colour:



The blue bilitriene was detected in the blue-green algae *Tolypothrix tenuis* and *Anabaena cylindrica*. The unicellular thermophilic alga *Cyanidium caldarium* accumulates phycocyan, allophycocyan, and chlorophyll when exposed to light[46]. The study of the pigments of the blue-green algae, which are examples of the most ancient organisms on earth, can provide new data for the characterisation of the Precambrian kerogen, recently investigated by Hoering[47]. Paleobotanists demonstrated the existence of the blue-green algae in the Precambrian period[48].

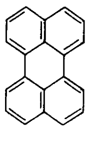
Chlorophyll in green plant leaves is always accompanied by yellow pigments—carotenoids, which belong to the group of isoprenoids. Carotenoids can be divided into two classes: (1) hydrocarbons (carotenes) and (2) xanthophylls—oxygen-containing derivatives of carotenes.

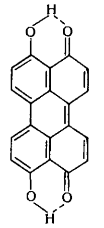
Vallentyne[49,50] investigated the carotenoids from fresh and sea water deposits; he succeeded in isolating carotenoids from fresh water deposits 20 000 years old. Data on the content of carotenoids in the waters and deposits of the Pacific Ocean were obtained by Romankevich[28].

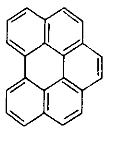
Kojama et al.[51] investigated plant pigments (chlorophylls and carotenoids) in lake deposits by paper chromatography and spectrophotometry. They established that both the total pigments and their individual fractions decrease in the deposits on the bottom on going from surface to deeper layers.

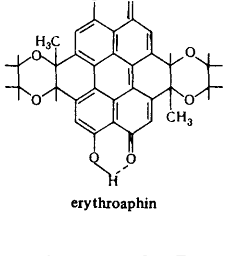
The study of perylene, a polycyclic aromatic hydrocarbon ($C_{20}H_{12}$) consisting of five rings, is of interest. It has been detected in the distillate from crude petroleum, in present day deposits, and in ancient sedimentary rocks[52]. It has been suggested that biogenic pigments are a source of perylene and other polycyclic aromatic compounds[53,54]. A likely biological precursor of perylene may be the widely distributed quinone, similar to 4,9-dihydroxyperylene-3,10-quinone, isolated from the Ascomycete *Daldinia concentrica*[55]. Another quinonoid pigment similar to perylene—erythroaphin—has been isolated from insects of the family Aphididae[56].

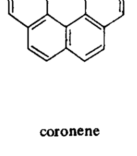
The reduction of these pigments results in the formation of 1,12-benzoperylene and coronene together with perylene:


perylene


4,9-dihydroxyperylene-3,10-quinone


1,12-benzoperylene


erythroaphin


coronene

Recent investigations by Douglas and coworkers[57,58], who studied isoprenoid and other hydrocarbons and pigments in coorongite and torbanite and also in the algae *Botryococcus braunii* from which these deposits were formed, are of considerable interest.

In the last 10–15 years the attention of investigators was attracted to the determination of the decomposition products of proteins and carbohydrates in various waters, present day deposits, and organic matter of sedimentary rocks[59,60]. The publication of a large number of papers on this question can be accounted for, on the one hand, by the biochemical importance of these compounds in living organisms, and, on the other hand, by the relative ease of their determination in fossil organic matter.

The variation of the qualitative composition of aminoacids with preservation conditions, the composition of rocks with which they are mixed, and the geological age of rocks has been investigated. Siliceous shale and argillaceous minerals contain appreciable amounts of aminoacids[60,61]. It has been suggested that the presence in rocks of certain thermostable aminoacids be used as a geological thermometer[62].

Studies on the preservation of aminoacids in the skeletal residues of organisms are of great interest. Abelson[62,63] isolated aminoacids from ancient trilobites of the Ordovician period and peptides from shells and bony residues of the Pleistocene period buried in asphalt. Jones and Vallentyne[59] isolated from the fossil shells of *Mercenaria mercenaria* (Pleistocene), after dissolution of the mineral component, 0.3 g of periostracum fibres—the organic fraction of the shells. The set of aminoacids in this fraction proved to be close in composition to that of the conchiolin of present day shells. Florkin[64] quotes the chemical composition of a typical mother-of-pearl conchiolin found in the fossil shells of the Eocene period (about 60 million years old).

Examples are known of the preservation under geological conditions of collagen and protein characteristic of vertebrate animals and detected in fossil bony residues, horns, teeth, and fish scale[65]. There has been a remarkable discovery of protein of the collagen type in the mummified skin of a fossil amphibian, the geological age of which corresponded to the Lower Permian period (about 200 million years ago)[66].

In most studies on fossil organic matter and the pathways followed in its formation, the carbohydrate content in various natural materials was investigated together with the determination of the aminoacids. The literature on this question has been collected in monographs and reviews[3,67,68]. The studies of Swain and coworkers[69], who determined the monosaccharides in the hydrolysates of fossil residues (Devonian–Permian period) of 25 plant species, are striking. They succeeded in revealing the evolutionary change from the algal polysaccharide rich in galactan to a polysaccharide of the cellulose type characteristic of cordaites.

In many geochemical processes associated to some extent with organic matter, humic substances play a notable role. The term humic substances is not fully defined even when applied to their most thoroughly investigated representatives—humic acids. It is believed that the dark-coloured humic acids are polymeric compounds which dissolve in dilute solutions of alkali and are readily reprecipitated by aqueous acid solutions. Chemically humic acids are characterised as a heteropolycondensate with a high reactivity owing to the presence of active functional groups.

The information about soil humic acids and their chemical composition and properties available at present is extensively described in Kononova's monograph[70]. Humic acids in peat constitute the basis of the organic component of human coal. Humic acids are present in the non-compacted deposits of sea and continental origin constituting in some cases more than 50% of the total organic matter in the rock[60,71].

Humic acids may be formed from various organic compounds which enter into the composition of the living population of soils, peats, and silts and which are liberated after the death and breakdown of the organisms. The presence of phenolic components and also nitrogen-containing groupings is characteristic of humic acid. One of the sources of phenolic compounds in humic acids may be their synthesis by micro-organisms from carbohydrates[72,73].

Among phenolic compounds which participate in the formation of humic acids, the most important role belongs to lignin. Lignin is widely distributed in all plants with a vascular system and a mechanical tissue. The involvement of land plant lignins in the formation of soil and peat humic acids is confirmed by the detection of lignin structures in the two materials[74,75].

The role of lignin has been decisive in the formation of the organic component of humus coal and lignites. Brefer[76,77] justly regards lipids and lignins as the most important organic compounds participating in the formation of present day and ancient deposits.

The fundamental outline of the aromatic structure of lignin and the pathways of its formation from photosynthetic products have now been largely elucidated[78]. The complex polymeric lignin molecule is constructed of compounds of the phenylpropane series.

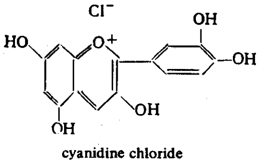
After the death of plants under natural conditions, lignin is acted upon by biological and physicochemical factors in the medium. Under the influence of these factors, depolymerisation processes, i.e. partial rupture of bonds between individual monomers, takes place in the lignin on the one hand and on the other secondary condensation processes occur[79]. The composition of humic acids may include both individual lignin monomers as well as its larger units and also secondary condensed aromatic structures.

The possible pathway of the biological breakdown of lignin and its participation in the formation of humic acids is indicated in the mechanism presented below.

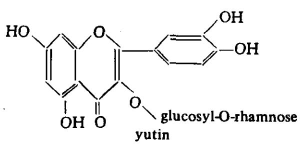
The mechanism shows the sequence of reactions in the biological breakdown of lignin to the monomers. Further reaction leads to the decomposition of the side chain—demethylation and oxidation with formation of protocatechuic acid. Structures of the hydroxy-*p*-benzoquinone type are readily formed from protocatechuic acid in natural processes. The interaction of aromatic lignin structures with nitrogen-containing compounds in the formation of humic acids takes place, according to current hypotheses, after the demethoxylation and oxidation of the aromatic components to quinones[80].

New studies on aromatic soil pigments[81,82], in which the P_g fraction (green pigment) is regarded as a perylene derivative, are of considerable interest. A close genetic relation between these pigments and humic acids is suggested.

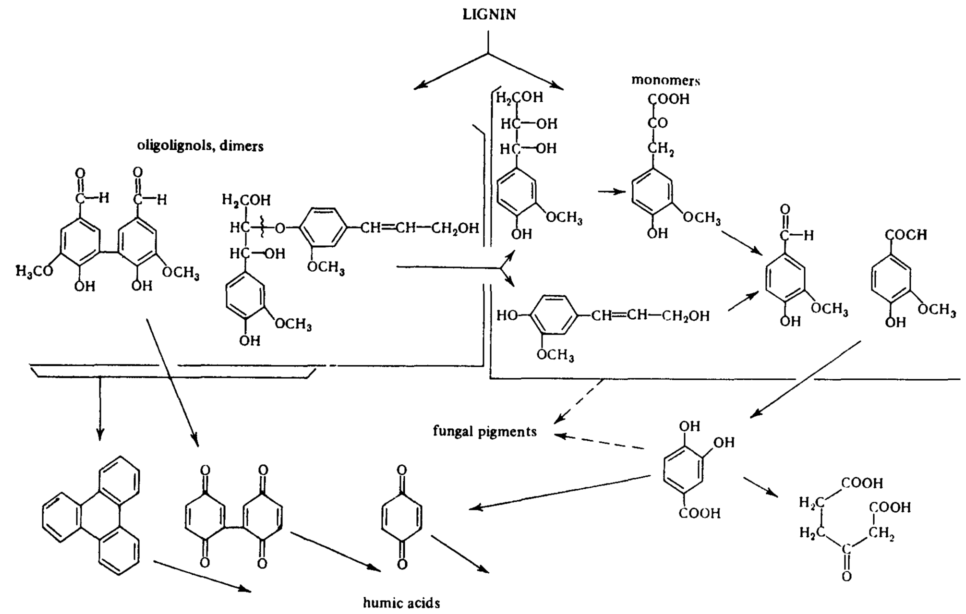
Flavonoids are included among the phenolic compounds fairly widely distributed among plants and undoubtedly participating in natural processes. Flavonoid pigments are a group of water-soluble phenolic glycosides the principal structural unit of which is the flavone skeleton $C_6-C_3-C_6$. Compounds of the type of anthocyanin, which are responsible for the wide variety of raspberry-red and violet tints in various parts of plants, and yellow pigments of the rutin type are known to be present among them:



cyanidine chloride



yutin .



Mechanism of the possible geological breakdown of lignin and its participation in the formation of humic acids.

In plants, flavonoids and lignin are genetically related in their biosynthesis via common precursors, which are phenylalanine and cinnamic acid[83]. Flavonoid pigments are characteristic mainly of higher plants and few are known among spore-bearing plants[84]. Bendz et al and coworkers[85,86] isolated from the green moss *Bryum cryophylum O. Mårt* two anthocyanin pigments. These workers isolated from the cell walls of the sphagnum moss *Sphagnum magellanicum* and *Sphagnum nemoreum* a pigment which they characterised as a copolymer of a flavonoid of the anthocyanin type and lignin structures.

The detection of phenolic acids and flavonoid pigments in the pollen of various plants is of great interest[87,88]. The colour of the pollen ranging from pale-yellow to dark-brown, in various plant species depends on the presence of two types of pigments: flavonoids and carotenoids. Inglett et al.[89] determined in the ether-soluble fraction of pollen tars, hydrocarbons, sterols, and fatty acids. In the alcoholic fraction of defatted pollen they found nitrogen-containing components and about 20 flavonoids including rutin and quercetin.

Lunden[90] reviewed briefly the studies on the chemical composition of the pollen of various plants. Free amino-acids, polypeptides, and proteins have been found in the pollen of the majority of plants.

Considerable amounts of nucleoproteins and deoxyribonucleic acids have been detected. Among carbohydrates, starch, cellulose, pentosans, and reducing sugars were discovered. Lactose was detected in the pollen of *Forsythia*—for the first time in a plant material.

Pollen flavonoids have been separated by chromatography and their spectra have been investigated in the same way as those of chlorophyll and carotenoids.

Fatty acids were isolated from the pollen of five conifer species and analysed by gas–liquid chromatography. Oleic, linoleic, palmitic, and stearic acids were found[91]. The ash content of pollen is 1–7%, potassium predominates in the ash (20–45%), there is frequently much silicon (2–10%), and manganese and titanium have been detected.

After the elimination of fats, proteins, and water-soluble material from pollen, a fairly large amount of non-extractable substances remains in the test samples. In certain pine species between 20 and 57% of such substances were found in the pollen. In the past century these substances were called "pollenins" and the exceptional strength of the outer coats of pollen grains was explained by their presence. Pollenins frequently combine with cutin, also a little investigated substance, which impregnates the outer cell walls of the epidermis of leaves and plant stalks. Matic[92] investigated cutin from the leaves of the agave and concluded that it is a polyester of acids containing 16 and 18 carbon atoms in an unbranched chain and 2 or 3 hydroxy-groups.

In the 1930's pollenin from the pollen of conifers and sporopollenins from the spores of lycopodium were isolated by Zetzsche and Vicari[93]. These substances are resistant to the action of concentrated solutions of alkali and many acids but are oxidised on heating with nitric or chromic acids and alkaline permanganate. Zetzsche et al.[94] isolated sporopollenin preparations from tasmanite and Chulkovo brown coal of the Moscow Basin. The first preparation, which they called tasmanin, had the composition $C_{90}H_{134}O_{15}(OH)_2$ and the second, called bothrodendrin, had the composition $C_{90}H_{111}O_{12}(OH)_9$. Descriptions of these interesting studies have been included in monographs on the chemistry of coal[95,96] but until recently they were not developed any further. The presence of sporopollenins in exine (the outer coat of pollen grains) is responsible for the morphological stability of pollen grains, which made possible the widely familiar spore and pollen analysis. Chemical studies on fossil pollen significantly supplement the microscopic observations. Recently Brooks and Shaw[97] investigated the sporopollenins from rocks of different ages. They believe that the older forms of kerogen are identical in many respects with sporopollenin formed from deposited spores. They believe that the fossil sporopollenins are polymers of carotenoids and their esters, present in the pollen of the initial plants.

They present data on the isolation of aromatic acids from the sporopollenins as a result of alkaline treatment: *p*-hydroxybenzoic, *m*-hydroxybenzoic, protocatechuic, and vanillic.

The information presented above on the chemical composition of present day and fossil pollen suggests the presence in sporopollenins of condensed structures formed from flavonoid compounds and compounds of the lignin type. Their determination in small amounts is quite feasible[98].

3. THE ROLE OF ORGANIC MATTER IN THE MIGRATION AND CONCENTRATION OF CHEMICAL ELEMENTS

Numerous data are now available confirming the importance of organic matter in the migration and concentration of chemical elements[3]. The detection in the organic matter in rocks or in paleontological residues of the decomposition products of highly polymerised natural compounds (aminoacids, aromatic structural units of lignin and flavonoids, and compounds with porphyrin structures) enables us to postulate not only the individual stages in the reactions of these compounds but also the possible conditions for their interaction with metals. Earlier the various ways in which uranium, germanium, vanadium, molybdenum, copper, gold, and other elements accumulated in the organic matter of sedimentary rocks were characterised by the present author[3]. An example of such a process is the distribution of germanium and other metals in fossil coals. Ratynskii and Glushnev[99] noted an increased zinc and lead content in fractions of coal material having the minimal density and relatively rich in components of the exine group (pollen and spores). Their experimental investigations led to a quantitative assessment of the bond between a number of metals and the organic component of the coal material. The following affinity series was established: Ge > W > Ga > Be > Nb > Mo > Sc > Y > La > Zn > Pb.

Earlier Ratynskii and Shterenberg[100] established that germanium is concentrated in the vitrain fraction of coal. The vitrain fraction of coal is formed mainly as a result of natural transformations of polymeric lignin molecules. Structures containing ortho-hydroxyquinonoid groupings responsible for the accumulation of germanium and other rare elements in the organic matter of coals at the peat stage of their formation can be readily formed from lignin in natural processes[101].

It has been noted[102] that the enhanced concentrations of rare elements (germanium, uranium, vanadium, and others) in coal inclusions are associated with plant tissues in fossil wood and bark. It is known that the chemical compositions of the cell walls in the bark and wood of present day plants and also the compositions of extractable substances differ considerably[103]. In this connection it is important to elucidate which of these compounds were involved in the formation of coal inclusions and the concentration of rare elements in them.

It is noteworthy that the organic content of silicon-impregnated inclusions in coal strata known as coal balls, large opal-containing lens-shaped discs found in brown coals[104], has not been investigated. Only isolated chemical studies on mineralised plant residues have so far been made.

An organic fraction in an amount of 0.1–0.2% has been isolated (and investigated) from silicon-impregnated wood of conifers (Cretaceous) and stalks of a lycopodium species—genus Lepidodendropsis (*Lepidodendropsis kazachstanica Senk*, Devonian period)[105]. After alkaline nitrobenzene oxidation, small amounts of aromatic aldehydes derived from lignin were discovered in the organic fraction. Knoche and Ourisson[106] extracted with a benzene–methanol mixture an organic fraction (3 mg) from argillaceous inclusions in sand deposits containing residues of the horsetail *Equisetum brongniarti*. Chromatography on silica gel of the extract led to the determination of the following compounds: n-tricosane, n-pentacosane, and n-nonacosane, which are characteristic of the present day horsetail *Equisetum sylvaticum*.

Recently data have been published characterising the mutual effects of the organic matter and the mineral components in sedimentary rocks and paleontological residues. One may include here the studies on the formation of framboids with participation of sulphate-reducing bacteria: these investigations have been reviewed critically by Kizil'shtein[107]. It was found that the aminoacid composition of shell conchiolin differs in the mineralised and non-mineralised layers[108].

Long et al.[109] showed experimentally that montmorillonite minerals act as acid catalysts in the condensation of aromatic compounds to cyclic structures. The observations on present day organisms are of interest. Thus Werner[110] established appreciable differences in the nucleoside-phosphate metabolism of the diatomaceous alga *Cyclotella cryptica* cultivated in a medium with and without $Si(OH)_4$. Drum[111] observed the formation and distribution of opal in the cell walls of the birch when birch twigs were kept in sodium metasilicate solution for 12–24 h.

The study of reactions of this type may prove useful for the elucidation of the form in which chemical elements are combined with fossil organic matter.

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The results of modern investigations presented in this review suggest the future tasks in the geochemistry of organic matter and rational methods for their fulfilment. One of such tasks is the study of the individual organic compounds in present day and ancient deposits, in fossil coals and coal inclusions, and in the organic fraction of mineralised plant and animal residues. It is essential to investigate it in greater depth lipids, porphyrin structures and carotenoids and aromatic compounds of the type of lignin and flavonoids in the course of their biosynthesis in present day organisms. The knowledge of the accompanying enzymic reactions and the intermediates formed will help elucidate the transformations of these compounds in the course of their conversion into fossil organic matter.

One may expect that studies of this kind will lead to the discovery of new possibilities for elucidating the nature of complex natural formation such as kerogen, land and sea humus, and sporopollenins.

The next important task is to establish the specific structures of the organic compounds responsible for the concentration of rare elements in the organic matter of peats, coals, and shale. Experiments on models play a significant role in the solution of this problem.

No less important is the investigation of organic compounds in paleontological residues. The chemical study of paleontological specimens by modern microchemical and physical methods will help discover new aspects of the evolution and phylogeny of organisms. Another aim of studies of this kind is to elucidate the geochemical and paleoclimatic conditions in which the residues of the organisms were preserved and their chemical composition was transformed. The study of the corresponding organic compounds is phylogenetically similar present day organisms is one of the ways in which this problem may be solved.

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Vernadskii Institute of Geochemistry and
Analytical Chemistry, USSR Academy of
Sciences, Moscow

U. D. C. 543.544

Advances in the Thin-layer Chromatography of Inorganic Ions

M.P.Volynets and A.N.Ermakov

The review deals with studies published during 1960-1967 and partly in 1968 on the applications of thin-layer chromatography. Much attention has been devoted to the description of specific procedures which improve the efficiency of the method. Possible applications of the method in inorganic and analytical chemistry have been noted. The bibliography comprises 228 references.

CONTENTS

I. INTRODUCTION

Thin-layer chromatography (TLC) on plates, which has been fairly widely used in organic chemistry, has found increasing application in inorganic chemistry starting in the 1960's. This is demonstrated by the increase in the number of publications. Thus one paper dealing with the application of thin-layer chromatography in inorganic chemistry was published in 1960, four papers were published in 1962, about twenty papers in 1965, thirty papers in 1966, and more than sixty papers in 1967.

The scope of thin-layer chromatography and in many cases some of its advantages over other methods for the separation and concentration of microamounts of substances are responsible for its vigorous development together with other effective methods such as extraction, column chromatography, etc. The method may be used to separate and identify from several tens of microgrammes to tenths and sometimes hundredths of a microgramme of complex mixtures.

The universality and simplicity of the method and the clear-cut separation after a short period of analysis make thin-layer chromatography (in combination with sensitive analytical methods) suitable for the solution of many problems involving the determination of microgramme amounts of elements.

Although in the last three years many publications on inorganic thin-layer chromatography have appeared, adequate reviews are not available. The wide scatter of the publications is a considerable inconvenience to readers. A number of monographs[1-7], apart from describing the principle of the method and the experimental technique, discuss mainly the applications of thin-layer chromatography in organic analysis. These publications deal very briefly and by no means exhaustively with data on inorganic thin-layer chromatography and the specific thin-layer chromatographic procedures for inorganic ions are not indicated. There are a number of reviews on inorganic thin-layer chromatography[8-16] but they are not sufficiently comprehensive.

We hope that our attempt to give as far as possible a complete review of studies on inorganic thin-layer chromatography between 1960 and 1967 inclusive (partly in 1968) and to deal with the principal trends, possibilities, and applications of the method for the analysis of inorganic ions will prove useful to readers, particularly now when the interest in this method by chemists increases steadily, as shown by the widening of the range of its applications and the increase in the number of relevant publications from year to year.

In the present review we shall only describe briefly the principle of the method and the experimental technique, because these problems have been thoroughly dealt with in the books and reviews mentioned above. In each section we shall note the characteristic procedures which enhance the effectiveness of inorganic thin-layer chromatography.

The experimental technique is as follows. Small amounts of the test solutions (of the order of 1–5 μl) are placed at the starting point on a thin layer of sorbent covering a plate. The plate is dried and the edge below the starting line is immersed in a mobile solvent contained in a hermetically sealed chamber. As the solvent moves along the layer of sorbent, the ions of the elements are separated in accordance with the partition coefficients under the given conditions. The position of the solvent front line is noted and after the plate has been dried the zones containing the elements are detected by spraying with solutions of appropriate reagents which give rise to colour or luminescent reactions with the elements to be detected. When radioactive elements are separated, radiometry and radioautography are employed.

The quantitative characteristic of the position of the substance in a chromatogram is its R_f value (the ratio of the distance between the starting line and the centre of the spot to the distance between the starting line and the solvent front line). The R_f value is characteristic of a given compound on a given sorbent in a given system, and depends on a number of conditions: experimental method, purity and moisture content of the sorbent, thickness of the layer, purity of the solvent, amount of substance deposited, duration of separation, etc, (see Ref. 6, p. 7). Therefore in order to obtain reproducible R_f values, it is necessary to perform experiments under rigorously standardised conditions. The standard conditions recommended by Stahl for thin-layer chromatography[17] are quoted below: (1) plate dimensions 200 × 200 mm and 200 × 100 mm; (2) thickness of dry layer 0.1–0.3 mm; (3) plates stored in a closed vessel over silica gel; (4) distance from the starting line to the lower edge of the plate 15 mm and to the side edge 10 mm; (5) distance traversed by the solvent (distance between the starting line and the solvent front line) 100 mm; (6) chamber saturated with solvent vapour (chamber closed by a ground lid and walls lined with strips of filter paper wetted with the mobile phase; (7) plate immersed in the solvent to a depth of 0.5 cm; (8) elution temperature 18–25°C; relative humidity of air 40–65%; (9) standard sorbents; (10) careful purification of the solvents; (11) size of sample of 0.1–1% solution 1–5 μl.

Since not all these conditions are observed in practice, the R_f values quoted in the literature may differ and the R_f values quoted in the Tables below must be regarded only as a comparative characteristic of the separation of ions of the elements.

II. QUALITATIVE INORGANIC THIN-LAYER CHROMATOGRAPHY

1. SEPARATION OF CATIONS

Alkali and Alkaline Earth Elements

A number of studies have been made on the separation of these elements[18-28]. Solutions of the acetates[5,18], sulphates[18], nitrates, chlorides[20-22,24-26], and polyiodides[27] of alkali and alkaline earth elements are deposited on the sorbent layer. The time taken by the solvent front to rise to a height of 10 cm varies from 10 to 120 min, depending on the composition of the mobile phase. Initially various investigators employed silica gel without added gypsum. Mixtures of methanol, ethanol, and propanol with acetic acid and also with addition of acetylacetone and other complex-forming substances have been used as a mobile phase[18-21]. However, under these conditions a clear separation was not achieved.

Best results are obtained on cellulose[22,23] and corn starch[26]. The R_f values for cations in the chromatography of individual specimens and their mixtures are usually the same. These methods make it possible to separate and detect 1×10^{-8}–5×10^{-9} equiv. of each of the test cations, i.e. smaller amounts than in paper chromatography. On cellulose, it is possible to separate any alkaline earth element from mixtures with others when its relative content in the mixture is as low as 1 : 500. Magnesium may be separated[23] not only from large amounts of beryllium, calcium, strontium, and barium but also from iron, titanium, cobalt, nickel, zinc, zirconium, cadmium, antimony, and bismuth.

It has been noted that the method involving the use of heteropolyacids as sorbents[20] is unsuitable for the rapid separation of alkali metals. However, on oxinegermanododecamolybdate, using 0.01 M NH_4NO_3, it proves possible to separate caesium from other alkali metals and also from yttrium, ruthenium, zirconium, niobium, and strontium.

A mixture of cellulose with zinc hexacyanoferrate(II), which is selective in relation to alkali metal ions[24], has been used for the rapid (16 min) separation of sodium, potassium, rubidium, and caesium. Rapid separation of these elements is achieved when 0.2 M ammonium nitrate is used as a mobile solvent.

Alkali metals are also satisfactorily separated on other inorganic ion exchangers, for example, on thin layers of crystalline zirconium and titanium phosphates. The latter is the best sorbent for the separation of alkali metals, particularly sodium and potassium[25].

In the separation of elements of this group considerable difficulties arise in connection with the detection of the alkali metals on the chromatogram. It is very difficult to choose a sensitive reagent giving a colour or luminescent reaction under these conditions. Sometimes solutions of violuric acid are employed[18,21] but this does not always yield good results. Therefore alkali metals are frequently identified radioautographically[20,24,25]. Alkaline earth metals are detected by illumination with ultraviolet light after spraying the plate with a solution of 8-hydroxyquinoline[22,26].

Transition Elements

The majority of studies[19,26,28-56], on inorganic thin-layer chromatography have dealt with the separation of mixtures of transition elements in different combinations. The sorbents most frequently employed are silica gel[19,29-33,36-40,42,43,48,49,52,53] and cellulose[34,46,50,54], and also alumina[37,45,51], starch[26,35,41], etc. Mixtures of compounds of the elements separated are deposited on the plate in the form of solutions of the chlorides or nitrates[31,33-37,40,41,43,52,54], sulphates[38], and sometimes various complexes[29,30,37,46,49,53]. The mobile phases employed to separate transition elements are extremely varied. In many cases acetone[19,26,35,39,41,42,46,48,51,52], various alcohols (ethanol, methanol, butanol, and others)[30,34,36,39,42,44,45,53], inorganic acids[31,32,36,50,54], organic acids[28,30], etc., are used as one of the components. The duration of chromatography ranges from 10–30 to 120–180 min. The choice of the reagent for detection is determined by the composition of the mixture to be separated. Rubeanic acid is used to identify copper, cobalt, nickel, and platinum[30,38,51], 8-hydroxyquinoline is used to determine zinc, cadmium, iron, mercury, chromium, and aluminium[33,34,35,39,40], ammonium sulphide is used for cadmium, iron, bismuth, copper, lead, mercury, and silver[26,36,41], dithizon is used for lead, silver, and mercury[40], and stannous chloride is used for rhenium, noble metals[45,51,52], and others. Elements separated in the form of chelate complexes are detected on the chromatogram by their intrinsic colour[29,37,41,49]. The separation of various combinations of transition elements has been described: iron, nickel, cobalt, copper, manganese, chromium, silver, zinc, cadmium, aluminium, and mercury[19,26,27-42]; titanium, zirconium, thorium, scandium, UO_2^{2+}, and niobium[43]; vanadium, molybdenum, tungsten, and rhenium[44,45,54]; niobium and tantalum[47]; noble metals[48-53].

Certain characteristic features and procedures in the thin-layer chromatographic method used to separate this group of elements may be indicated. For example, in order to improve the separation of 1-nitroso-2-naphthoxides of iron, nickel, cobalt, and copper, repeated chromatography has been employed with the aid of two solvent systems[29]; iron(III) and cobalt are separated in a solvent containing pentyl alcohol and, when the plate is placed in a system containing dioxan, copper, iron(II), and nickel are separated.

Two-dimensional chromatography has been used successfully[35] to separate iron, aluminium, and chromium and zinc, cobalt, manganese, and nickel.

The method of circular chromatography on a thin layer of sorbent usually gives a clearer separation than on paper. The zones of different elements consist of sharply outlined concentric rings. Thus noble metals are very readily separated on a layer of alumina[51]. Hashmi and Adil[51] succeeded in obtaining by this method about fifteen chromatograms on a 10 × 20 cm plate, the formation of each taking about 2 min. Mercury, copper, cadmium, nickel, and zinc have been separated by circular chromatography on a thin layer of silica gel impregnated with dithizon[42]. The solutions analysed are deposited at the centre of the plate and the mobile solvent (mixture of acetic acid and acetone) is supplied from a dropping funnel at the point of deposition. The dithizonates of these cations form coloured rings in the chromatograms.

A number of transition metals have been separated by thin-layer chromatography of their complexes with dithizon (silver, gold, palladium, and yttrium)[49], 1-nitroso-2-naphthol (cobalt, nickel, manganese, and iron)[37], thiocyanate complexes (zinc, copper, cadmium, cobalt, and nickel)[30], and others.

An interesting procedure involving precipitation thin-layer chromatography has been used[33] to separate copper, iron, and cobalt on a layer of silica gel 0.2 mm thick containing 14% of 8-hydroxyquinoline as the reagent precipitating the metals. The zones of the different elements consist of discrete bands, the content of a particular element being estimated approximately from the width of the band.

Recently thin-layer chromatography on ion exchangers has been increasingly employed, liquid anion exchangers (high-molecular-weight amines and salts of quaternary ammonium bases)[31,54], with which silica gel or cellulose are impregnated, being used particularly extensively. It is best when the carrier is inert with respect to the impregnating phase. Aqueous acid solutions are usually employed as eluents. It has been shown that, by varying the concentration of the acid in the eluent and the type of ion exchanger, it is possible to achieve satisfactory separation of a wide variety of mixtures of inorganic ions. Apart from liquid anion exchangers, anion exchangers such as Amberlite CG-400[28], Dowex-1, and DEAE-cellulose[46,55] and the cation exchangers Amberlite CG-120[28] and Dowex-50[55,56] are used in thin-layer chromatography.

In thin-layer chromatography with phase reversal, which is employed fairly frequently—in particular also for the separation of transition metals, the carrier is usually silica gel. The stationary phase is most often tributyl phosphate (TBP) (solutions in ethyl ether[32], benzene[43], and carbon tetrachloride[50]). Nickel–copper–silver–zinc–iron, cobalt–copper–silver–zinc–iron (mobile phases—aqueous acid solutions)[32], niobium–tantalum (mobile phase—solution of ammonium thiocyanate in a mixture of oxalic and 6 *N* hydrochloric acids)[47], rhodium–ruthenium–palladium–gold (mobile phase—2 *N* hydrochloric acid)[47], etc. mixtures have been separated on such sorbent layers. Solutions of di-(2-ethylhexyl)phosphoric acid (D2EHPA) and tri-iso-octylamine (TIOA)[33] are also employed as stationary phases, which in this case function also as cation- and anion-exchangers respectively. Erbium–holmium–terbium–gadolinium, europium–lanthanum, yttrium–strontium (D2EHPA), and zinc–cobalt–manganese (TIOA) mixtures have been separated on resins impregnated with these reagents.

Non-transition Elements

Certain non-transition elements (bismuth, antimony, cadmium, arsenic, tin, selenium, tellurium, and thallium) have been separated from one another and from transition elements in a number of investigations[28,34,36,57-63], where sometimes the same procedures were employed as in the separation of transition elements, for example separation of the complexes[58], thin-layer chromatography on the ion-exchange resins Amberlite CG-400 and CG-120[28], etc.

The sorbents used to prepare the thin layers were of a wide variety of types: silica gel[59,61,63], kieselguhr[57], cellulose[34-58], starch[60], and ion-exchangers[28]. The mobile solvents in partition thin-layer chromatography frequently include alcohols (ethanol, propanol, and butanol) or ketones [acetone, hexone (4-methyl-2-pentanone—Ed. of Translation), ethyl methyl ketone, and others] and various acids (hydrochloric, nitric, acetic, and tartaric). Selenium and tellurium are separated with a solution of TBP in benzene. Solutions of ammonium fluoride (for arsenic, iron, and bismuth)[28] or sodium chloride (for arsenic, cadmium, and barium)[28] are used as eluents in ion-exchange processes on resins. The duration of the chromatographic process is as usual 10–180 min.

Colour reactions of the elements with dithizon[57,60] and ammonium sulphide[36,57] are used for identification. Arsenic, antimony, and tin separated in the form of dithizonates are identified by their intrinsic colour[58].

The groups of elements for which methods of separation have been developed are listed below: bismuth, antimony, cadmium, arsenic, lead, mercury, and thallium[57]; arsenic, antimony, and tin[34,58-60]; arsenic, iron, and bismuth[28]; arsenic, cadmium, and barium[28]; selenium and tellurium[61-63]; bismuth from lead, cadmium, copper, and nickel and lead from cadmium, nickel, and copper[66].

Lanthanides

The separation of lanthanides which have similar properties is one of the most complex problems in analytical chemistry. Difficulties increase when it is necessary to separate ultrasmall amounts of the elements. In this case it is helpful to employ together with paper chromatography also thin-layer chromatography, which permits the separation and identification of submicrogramme amounts of lanthanide mixtures. A number of papers have been published on the methods for the separation of lanthanides[64-69]. Various two- and multi-component mixtures of lanthanides can be separated by thin-layer chromatography. The chromatographic separation process terminates after 10–180 min. The zones containing the separated elements can be successfully located with Arsenazo III[69] and 8-hydroxyquinoline[64,66] and also radiometrically[64,65,68].

Di-(2-ethylhexyl)phosphoric acid (D2EHPA) is widely used for the separation of lanthanides. The high separation factor for lanthanides achieved when they are extracted by D2EHPA led to studies on partition chromatography involving the application of this acid either as a mobile solvent or as the stationary phase on various carriers: silica gel D for thin-layer chromatography[66], a copolymer of poly(vinyl chloride) and poly(vinyl acetate)[64], and others. In experiments by the phase reversal method the sorbent layer is impregnated with D2EHPA dissolved in a mixture of carbon tetrachloride and ethyl ether[64] or in butanol[65]. It cannot be dissolved in toluene, since the sorbent layer impregnated with such a solution cracks.

The technique of horizontal thin-layer chromatography can also be employed at 60–80°C.[64] The mobile phase in the phase reversal method is usually hydrochloric or nitric acid solution at different concentrations. Elements with a high atomic number migrate more slowly than those with a low atomic number at any constant acidity. With increasing acidity of the eluent, the rate of migration of the lanthanides down the plate increases also. The ion-exchange mechanism of the interaction between lanthanides and the sorbent has been noted[67].

Elution with nitric acid leads to better results in some cases, more clearly outlined spots being obtained, which is probably due to rapid equilibration in the system nitric acid–D2EHPA. It is suggested that the introduction of complex-forming substances into the mobile phase should also improve the separation of difficult mixtures.

To improve the separation of lanthanides, the repeated elution procedure employed; it improves, in particular, the separation of cerium and praseodymium[66]. The separation of lanthanides is best carried out on as thin a sorbent layer as possible, with a high content of D2EHPA[67]. Three-component and four-component mixtures of elements can be separated by this method (for example: lanthanum–praseodymium–samarium; terbium–gadolinium–erbium[64]; lanthanum–cerium–praseodymium–samarium; lanthanum–cerium–neodymium–samarium; praseodymium–samarium–gadolinium; neodymium–samarium–gadolinium; samarium–europium–gadolinium; gadolinium–terbium–dysprosium; terbium–dysprosium–holmium–erbium; terbium–dysprosium–holmium–yttrium; holmium–erbium–ytterbium; holmium–yttrium–ytterbium[66]; and others).

The separation of mixtures of a large number of lanthanides may be achieved by increasing the sorbent layer capacity, by altering the thickness of the sorbent layer, and by using two-dimensional chromatography (in two mutually perpendicular directions). Thus by one-dimensional chromatography with a thickened sorbent layer (500 μm against 250 μm usually employed) with 12 ml of D2EHPA + 34 ml of n-butyl alcohol applied to 30 g of silica gel, it is possible to separate up to 5 elements of the cerium and yttrium groups: lanthanum–cerium–praseodymium–samarium–europium (mobile solvent—0.5 *N* hydrochloric acid); terbium–dysprosium–holmium–erbium–ytterbium (4 *N* nitric acid)[66]. In two-dimensional chromatography with the same eluents and with deposition of mixtures of substances at two points on the left-hand and right-hand edges of the plate, it is also possible to separate five elements of the yttrium group (7 μg of an ytterbium–erbium–holmium–dysprosium–terbium mixture at each spot) and four elements of the cerium group (35 μg of a lanthanum–cerium–neodymium–samarium mixture at each spot[67]).

D2EHPA can also be used as a mobile phase[65,68]. One then uses silica gel, without the addition of gypsum, impregnated with buffer solutions or acids (perchloric acid gives more reproducible results than hydrochloric acid). The mobile phase, a solution of D2EHPA in carbon tetrachloride, is first equilibrated with the stationary phase. Since D2EHPA is itself very strongly adsorbed on silica gel, two solvent fronts are formed, the first being due to the migration of carbon tetrachloride along the plate. When dilute solutions of D2EHPA are employed, the second front lags appreciably behind the first. Therefore 1 M D2EHPA solutions are employed in order to avoid this phenomenon.

It was found that, when the mixtures of substances to be analysed by the phase reversal method are deposited on the plate in the form of aqueous solutions, the pH of the stationary phase alters and 5–10% of the lanthanide (detected with the aid of radioactive isotopes) remains at the site of deposition in the chromatographic experiments. Therefore it is best to employ solutions of mixtures in organic solvents. This procedure yields spots which are usually symmetrical. "Tails" and jagged spots are rarely encountered. The spots which migrate with the solvent front are very narrow which permits the separation of up to five components (cerium–samarium–europium–gadolinium–terbium and promethium–samarium–europium–gadolinium–terbium) when, for example, 0.15 M perchloric acid is used as the stationary phase and 1 M D2EHPA in carbon tetrachloride as the mobile phase. Lanthanum and cerium are separated with 0.01 M perchloric acid as the stationary phase and heavy lanthanides (lutetium–ytterbium–thulium) are separated using 1.75 M perchloric acid and 0.5 M D2EHPA[68]. In the separation of lanthanides and in the removal of impurity elements from them solutions of DBP in benzene (1 : 1 and 1 : 10)[69] have been employed as the mobile phase in addition to D2EHPA; under certain conditions, it proved possible to separate with their aid cerium(IV)–thorium–UO_2^{2+}, neodymium–UO_2^{2+}, neodymium–praseodymium, cerium(III)–cerium(IV), europium(II)–europium(III), and other mixtures which are normally difficult to separate.

Non-lanthanide impurities (iron, copper, nickel, calcium, mercury, and zinc) in amounts between 10^{-1} and 10^{-2}% have been detected in mixtures of lanthanides[69] using acetone as the mobile solvent.

Actinides

It is of particularly great interest to employ the fast and highly sensitive thin-layer chromatographic method for the analysis of tracer amounts of radioactive elements, particularly short-lived isotopes. However, the number of studies in this field is still very limited[43,70–74].

The combination of thin-layer chromatography for the separation of elements with subsequent radioautographic recording of the spots on photographic (or X-ray) film has proved very successful in the detection of submicroamounts of radioactive elements. At the same time it is possible to employ colour or luminescent reagents[71–74]. The rapidity and simplicity of analysis by this method, the clear-cut separation, and the clarity of the results are the advantages of this procedure compared with other micromethods. Silica gel is usually employed as a carrier for the stationary phases.

In experiments with uranium ores and in the treatment of irradiated nuclear fuel selective separation of uranium from as large a number of other ions as possible is of great importance. It is therefore not fortuitous that several thin-layer chromatographic studies concerning this problem have been made[43,70–72], since the method is very rapid and economical. It has proved possible[72] to separate uranium on a sorbent layer consisting of silica gel and cellulose and fixed with starch from 55 cations (including the most important cations—uranium decomposition products). The mobile solvent was a mixture of hexone [4-methyl-2-pentanone (Ed. of Translation)], and TBP saturated with 4.7 *N* nitric acid. Separation from thallium proved to be impossible under these conditions.

Selective separation of uranium(VI) from a mixture with iron, nickel, cobalt, and zinc in sulphuric acid solution has been achieved using tri-iso-octylamine. This liquid amine has been particularly effective in experiments by the phase reversal method designed to separate uranium from molybdenum, cobalt, nickel, zirconium, thorium, and other elements[71]. In connection with the development of studies on the synthesis of new transplutonium elements, the problem of the separation of microamounts of the transplutonium elements from the main bulk of uranium or plutonium and also from the fission products is of undoubted interest. The possibility of the separation of microgramme amounts of uranium and plutonium from tracer amounts of americium and curium by thin-layer chromatography on silica gel using a mixture of TBP and benzene as the mobile solvent has been demonstrated[73].

The extraction of plutonium and its separation from uranium and other elements present at the same time by the thin-layer chromatographic method proposed by Volynets and Milyukova[74] can be usefully carried out in studies on solutions of complex composition with high β- and γ-activity when it is desirable to work with minimal volumes for reasons of safety. In the system 3 M nitric acid–23% solution of TBP in Synthin it is possible to separate quantitatively by this method plutonium(IV) and plutonium(VI) from plutonium(III). By combining the partition of plutonium(IV) in the systems 3 M nitric acid–23% TBP solution in Synthin and 1 M perchloric acid–23% TBP solution in Synthin with a single pass of the mobile phase, it is possible to separate quantitatively plutonium from uranium, lanthanides, zirconium, nickel, lead, copper, chromium, and iron and to determine radiochemically its amount in the spot with an error of ±10–15%. The duration of analysis of 0.03 ml of the initial solution is 60–90 min.

Heterovalent Forms

One of the interesting fields of application of the thin-layer chromatographic method is the separation of elements in various valence states. Studies have been made on the separation by this method of the heterovalent forms of mercury, arsenic, antimony, chromium, selenium, tellurium, iron, plutonium, cerium, and europium (Table 1). Usually the separation is very clear-cut. Silica gel fixed to the plate with starch or gypsum is most often employed as a sorbent.

Complete and Systematic Analysis of Cations

Some of the studies on inorganic thin-layer chromatography deal with the behaviour of large groups of cations and anions under particular conditions[78–86]. The chromatographic behaviour of many ions has been studies on thin cellulose or silica gel layers impregnated with both neutral organophosphorus compounds (TBP, tri-n-octylphosphine oxide, and others[81,83]) and liquid ion exchangers (amines, alginic acid, etc.), using solutions of hydrochloric, nitric, sulphuric, hydrobromic, hydriodic, thiocyanic, perchloric, and other acids[71,80,82,84,85].

The separation of a number of cations and anions having similar properties by thin-layer chromatography on organic and inorganic ion exchangers (Dowex-1 × 10, Dowex-50, Chelex 100, zirconium hydroxide, and others) has been described[87]. The effects of the composition of the eluents on the chromatographic behaviour of a large group of cations on cellulose have been investigated[86,88].

Methods for the separation of a wide variety of numerous combinations of elements have been suggested on the basis of such systematic studies and the determination of the differences in the behaviour of ions.

For qualitative semimicroanalysis, it has been suggested that 40 cations and 19 anions be detected by circular thin-layer chromatography with a duration of analysis, including the time required for the preparation of the solution to be analysed, of 2–3 h (duration of chromatographic process 2 min).

The principles governing the choice of sorbents and solvents for optimum chromatographic separation have been

Table 1. Heterovalent forms

Elements separated	Initial solution	Sorbent	Mobile solvent	Method of detection	R_f	Duration of separation, min	Refs.
Hg^{II} and Hg^{I} As^{V} and As^{III} Sb^{V} and Sb^{III}		silica gel + starch	butanol + benzene + 1 N HNO_3 + 1 N HCl (50:46:2.6:1.4)				19
Cr^{IV} and Cr^{III}	$^{51}CrCl_3$ $Na_2^{51}CrO_4$	Al_2O_3 + gypsum	Na_2SO_4 and Na_2CO_3 solution	radiometry	Cr^{III} (0.0); Cr^{VI} (0.60)	120	75
Te^{VI} and Te^{IV} Se^{VI} and Se^{IV} Cr^{VI} and Cr^{III}		silica gel	isobutyl methyl ketone, ethyl acetate; n-butyl acetate				63
As^{V} and As^{III}	solutions of As_2O_3 in NaOH and of $Na_2HAsO_4.7H_2O$ in water	silica gel + gypsum	acetone + 15 M H_3PO_4 (50:1)	$SnCl_2$ solution followed by 5% solution of $Na_2S_2O_3$	As^{III} (0.0); As^{V} (1.0)	20	76
Fe^{II} and Fe^{III}		ditto	acetone + 5 (or 10)% 1 N $HClO_4$	0.1% methanol solution of pyridylazonaphthol	Fe^{II}(~0.65 or ~0.75); Fe^{III}(~0.1 or ~0.3)		77
ditto	1-nitroso-2-naphthoxides in chloroform	silica gel D + Al_2O_3 D (1:1)	benzene	intrinsic colour	Fe^{II} (0.0); Fe^{III} (0.50)		37
Pu^{III} and Pu^{IV}; Pu^{VI}	solutions in 3 N HNO_3	silica gel + starch impregnated with 3 N HNO_3	TBP + synthin (23:77)	radioautography; radiometry; 0.1% solution of Arsenazo III	Pu^{III} (0.0) Pu^{IV} and Pu^{VI}—with solvent front	60–90	74
(1) Ce^{III} and Ce^{IV} solution of NH_4Cl added at point of deposition)	nitric acid solutions	silica gel + starch	(1) TBP + benzene (1:10)	0.1% aqueous solution of Arsenazo III; $NH_4OH + H_2O_2$ (4:1)		30–90	69
(2) Eu^{II} and Eu^{III} ($MgSO_4$ solution added at point of deposition)			(2) water				

Table 2. Anions

Elements separated	Initial solution	Sorbent	Mobile solvent	Method of detection	R_f	Duration of separation, min	Refs
F^-, Cl^-, Br^-, I^-	1 M solutions of NaF, NaCl, KBr, and KI	silica gel + gypsum	acetone + butanol + conc. $NH_4OH + H_2O$ (65:20:10:5	1% ethanol solution of Bromocresol Red; 1% ammonium-alkali soln. of $AgNO_3$; 0.1% soln. of zirconium-alizarin lake in HCl	$Fe^- > Cl^- > Br^- > I^-$	30—40	93
F^-, Cl^-, Br^-, I^-, CN^-, SCN^-, N_3^-, $Fe(CN)_6^{3-}$ $Fe(CN)_6^{4-}$	solutions of potassium and sodium salts of the anions	silica gel	(1) 1-butanol + 1-propanol + di-n-butyl amine (45:45:10); (2) 1-butanol + benzylamine (90:10); (3) 1-propanol + $CHCl_3$ + benzylamine (60:30:10)	with suitable reagents in visible and ultraviolet parts of spectrum	$I^- > SCN^- > Br^- > Cl^- >$ $> N_3^- > Fe(CN)_6^{3-} >$ $> Fe(CH)_6^{4-} > CN^- >$ $> F^-$	55—95	94
F^-, Cl^-, Br^-, I^-	0.5% aqueous salt solutions	MN-300 cellulose	acetone + water (4:1)	0.1% ethanol solution of dichlorofluorescene and $AgNO_3$; ultraviolet light	R_f values increase with atomic weight of anions and are almost independant of cations		95
ClO_4^-, ClO_3^-, ClO_2^-, BrO_3^-, IO_3^-	0.1 M solutions of sodium salts	Al_2O_3G + Kieselguhr G (1:1)	butanol + acetone + conc. NH_4OH + water (8:10:2:1)	solution of anilinium phthalate in butanol	$ClO_4^- > ClO_3^- > BrO_3^- >$ $> ClO_2^- > BrO_3^- > IO_3^-$	40—50	96
F^-, Cl^-, Br^-, I^-, IO_3^-, BrO_3^-, ClO_3^-		silica gel + gypsum	acetone + ethyl methyl ketone + 14% NH_4OH (30:20:5)		$I^- > Br^- > Cl^- > F^-$; $ClO_3^- > BrO_3^- > IO_3^-$		97
(1) I^-, Br^-, Cl^-, (2) PO_4^{3-}, $P_2O_7^{4-}$; (3) AsO_3^- , AsO_4^{3-}; (4) $HCOO^-$, CH_3COO^-, ClO_3^-, BrO_3^-. IO_3^-; CN^-,SCN^-,$Fe(CN)_6^{4-}$, $Fe(CN)_6^{3-}$		(1) MN-300 cellulose + Dowex 1 x 10 in OH-form (2) cellulose + Biorex-5 in Cl-form; (3) ditto (4) " zirconium hydroxide	(1) 1 M $NaNO_3$ (2) 1 M $NaNO_3$ (3) 2 M NaCl (4) 2 M NaCl and 3 M NaCl				87
F^-, Cl^-, Br^-, I^-; ClO_4^-, ClO_3^-, BrO_3^-, IO_3^-	0.1 M solutions of alkali metal salts of anions	corn starch	acetone + 3 *N* NH_4OH (7:3)	2% solution of $AgNO_3$ (Cl^-, Br^-, I^-) and 1% solution of KI in 0.1 M HCl (ClO_3^-, BrO_3^-, IO_3^-) 1% ethanol solution of Bromocresol Red (F^-); 0.05% solution of Methylene Blue (ClO_4^-)	I^- (0.78); Br^- (0.60); Cl^- (0.40); F^- (0.04); ClO_4^- (0.82); ClO_4^-(0.97); ClO_4^-(0.82); BrO_3^- (0.53); IO_3^-(0.06)	90	98
PO_4^{3-}, $P_2O_7^{4-}$, PO_3^{3-}, PO_2^{3-}	0.1 M solutions of sodium salts	silica gel + starch	methanol + conc. NH_4OH + 10% trichloroacetic acid + water (50:15:5:30)	1% solution of $(NH_4)_2MoO_4$ and 1% solution of $SnCl_2$ in 10% HCl	$PO_3^{3-} > PO_3^{3-} > PO_4^{3-} >$ $> P_2O_7^{4-}$	50—60	99
Phosphates	1-2% solutions of phosphates	cellulose + collodion	solutions based on dioxan	solution of Na_2MoO_4 followed by reducing solution		75	100
ditto	1-2% solutions of sodium triphosphates	cellulose + collodion	methanol + dioxan	solutions of $(NH_4)_2MoO_4$ and others		75	101
Polyphosphates	0.1 M solutions of Na_3PO_4, $Na_4P_2O_7$, and $Na_5P_3O_{10}$	silica gel	methanol + NH_4OH + $CCl_3COOH + H_2O$ (15:15:5:65)	1% solution of $(NH_4)_2MoO_4$, 1% solution of $SnCl_2$ in 10% HCl			102
ditto		cellulose	menthol (isopropyl alcohol) or dioxan + 10% aqueous solution of CCl_3COOH + 98% CH_3COOH or 25% NH_3 solution and water				103
Sulphates and polythionates	1% solutions of potassium and sodium salts of corresponding acids	silica gel + starch	methanol + 1-propanol + conc. NH_4OH + water (50:50:5:10); methanol + dioxan + conc. NH_4OH + water (30:60:10:10)	0.1 M ammoniacal solution of $AgNO_3$ and 0.1 % solution of Bromocresol Green in dil. ammonia	$S_5O_6^{2-} > S_4O_6^{2-} > S_3O_6^{2-} >$ $> S_2O_6^{2-} > S_2O_3^{2-}$; $S_2O_8^{2-} > SO_3^{2-} >$ $> S_2O_3^{2-} > SO_4^{2-}$	45	104
NO_2^-, $S_2O_3^{2-}$, CrO_4^{2-}, N_3^-, CN^-, SCN^-, BO_3^-, S^{2-}, AsO_3^{3-}, AsO_4^{3-}, NO_3^-, SO_4^{2-}, PO_4^{3-}	1 M solutions of sodium and potassium salts of anions; boric acid	corn starch	acetone + 3 M NH_4OH (1:4)	1% solution of KI in 0.1 *N* HCl (NO_2^-, $S_2O_3^{2-}$, CrO_4^{2-}); $FeCl_3$ solution (N_3^-, CN^-, SCN^-) 0.1% solution of Congo Red (BO_3^{3-}); 0.2 *N* solution of $AgNO_3$ (S^{2-}, CrO_4^{2-}, AsO_3^{3-}, AsO_4^{3-}), etc.	$SCN^- > NO_3^- > NO_2^- >$ $> N_3^- > S_2O_3^{2-} > S^{2-} >$ $> SO_4^{2-}$; $CrO_4^{2-} > BO_3^{3-} >$ $> AsO_4^{3-} > PO_4^{3-} >$ $> AsO_3^{3-} > CN^-$	90	105

described[89]. The most compact and in practice most convenient graphical presentation of the results has been adopted, for example, in Refs. 82, 83, and 90.

The present author believes that the value of such systematic studies consists in the fact that, on the basis of known R_f data, it is possible to choose rapidly the conditions for the separation of many mixtures of elements in the solution of specific problems. Thus Brinkmann et al.[82] demonstrated in a series of qualitative separations the suitability of the recorded R_f values for analysis by thin-layer chromatography in hydrochloric acid solutions on liquid anion exchangers (nickel–cobalt–manganese–zinc, nickel–cobalt–copper–manganese–iron, aluminium–indium–gallium, aluminium–titanium–uranium–iron, aluminium–uranium–iron–zirconium, copper–cadmium–lead–bismuth–mercury, lead–bismuth–tin–cadmium, zinc–cadmium–lead, arsenic–antimony–tin, arsenic–antimony–bismuth, and many two-component mixtures have been separated). Naturally, the separation should be carried out under standard conditions.

2. SEPARATION OF ANIONS

After the thin-layer chromatographic layer had been successfully applied in inorganic analysis for the separation of cations, studies began on its employment for the separation of anions. The thin-layer chromatography of a number of inorganic anions has been investigated[91,92]. Halides and pseudohalides, halogen oxy-acids, phosphates, sulphates, polythionates, and others have been separated by this method (Table 2).

Cellulose, starch, and silica gel are usually employed as sorbents. Ion-exchange resins have also been used to separate chlorine-36, bromine-82, and iodine-131.[55]

In the separation of anions the mobile solvents should be more polar than in the separation of cations because anions are less solvated and have a lower capacity for the formation of solvate systems with solvents other than water[93,94]. Usually systems containing methanol, acetone, water, and ammonium hydroxide are employed in the separation. Only iodides show a tendency to migrate also in non-polar solvents.

Among special procedures used to separate anions, mention should be made of *precipitation chromatography* for the separation of I^-, Br^-, Cl^-, and PO_4^{3-} on silica gel powder impregnated with silver nitrate as the precipitant[107] and *two-dimensional chromatography* of mono-, di-, and tri-phosphoric acids on a thin layer of cellulose[108]. The following mixtures of radioactive anions have been successfully separated: Cl^-, SO_4^{2-}, and PO_4^{3-};[109] Cl^-, ClO_2^-, ClO_3^-, and ClO_4^-;[106] I^-, IO_3^-, and TeO_3^{2-}.[110]

In the study of halides it was established that the R_f values increase with the atomic weight of the anion and are almost independent of the cation. The separation of halides from cations on cellulose is due to a cation-exchange process. In thin-layer chromatography on cellulose (in contrast to paper chromatography) there is a possibility of complete separation of cations from anions due to the larger area of contact and the larger number of exchange steps per unit length.

Phosphates cannot be separated on a sorbent layer fixed with gypsum since insoluble calcium phosphate is formed. Usually in such cases the sorbent is fixed with starch. Whereas on paper the separation of condensed phosphates with $n = 1–8$ and $n > 8$ is possible over a period of 16 h, thin-layer chromatography takes 1 h.

The possibility of separating and detecting micro-amounts of twenty inorganic anions has been investigated[92].

3. THIN-LAYER CHROMATOGRAPHY OF COMPLEX COMPOUNDS

As already mentioned earlier, certain elements have been separated in the form of complexes[111]. Thus, when suitable mobile solvent systems were selected, it proved possible to separate the dithizonates of arsenic, antimony, and tin[58], cadmium, copper, cobalt, mercury, manganese, nickel, zinc, lead, and bismuth[112,113], silver, gold, palladium, and platinum[49], 1-nitroso-2-naphthoxides of cobalt, nickel, manganese, and iron[29,37], diethyldithiocarbamates of chromium, manganese, iron, cobalt, copper, zinc, silver, cadmium, mercury, lead, calcium, magnesium, bismuth, tin, and antimony[114,115], cyanide complexes of iron[116,117], certain Complexonates, in particular those of cobalt, rhodium, and platinum[53], cobalt(II) and cobalt(III), manganese(II) and manganese(III)[116,117], acetylacetonates of iron, cobalt, and chromium[116,117], and other complexes. The square planar complexes of platinum(II) and palladium(II) have been separated by thin-layer chromatography[118].

The use of the thin-layer chromatographic method for the fine separation of geometrically isomeric complexes, namely the *cis- trans*-isomeric complexes of cobalt[119,120] and platinum[121], is of great interest. The purity of the preparations may be determined and the hydration and hydrolysis of these complexes may be investigated by thin-layer chromatography. The stoichiometric composition of palladium(II) complexes with certain phosphorus-containing organic compounds has been studied[122]. The composition of the palladium(II) phosphorodithioate complex has been determined as 1 : 1 by thin-layer chromatographic versions of the isomolar series and molar ratio methods.

The examples quoted above evidently do not exhaust the possibilities of thin-layer chromatography in studies on complexes, but the rate of development of studies in this field is still inadequate.

4. THIN-LAYER CHROMATOGRAPHY AND RADIOCHEMICAL METHODS

Since thin-layer chromatography permits the separation and identification of small amounts of substances, this micromethod constitutes a good auxiliary procedure in radiochemistry. With its aid, it is possible to separate also inactive substances labelled with radioactive isotopes. The recording in some way (radiometry, radioautography) of the emission by the components separated on the chromatogram constitutes an excellent, highly sensitive method for their detection.

The possibility of a rapid chromatographic process and of recording particle tracks in thick-layer emulsions makes the method attractive for the separation and detection of short-lived isotopes. The principle of the separation of inactive and active substances is the same. The studies on thin-layer chromatographic radiochemical analysis have been reviewed[123].

Thin-layer chromatography and the radiochemical method may be combined in two versions[124]: (1) radioactive substances are separated on a plate and then determined; (2) inactive substances separated on a plate are converted into active substances and then determined. In the latter case one may use in principle either the so called method of radiochemical reagents or irradiation with neutrons. Both these methods are still relatively little employed because of technical difficulties. When the chromatogram is irradiated with neutrons, the impurities contained in the sorbent are also activated and interfere. The method of radiochemical reagents also imposes certain requirements: the sorbent must be inert and the excess reagent must be readily removed. Because of these requirements, the radiochemical reagent method has limited applicability. Mercury, copper, and cadmium separated on a plate have been determined by treatment with $H_2{}^{35}S$ prepared in a special apparatus from $ZN^{35}S$ and 2 *N* sulphuric acid[124].

The methods for the separation of radioactive substances are more numerous. They are all largely associated with the separation of mixtures of elements produced by radioactive breakdown. For example, thorium-234 (decomposition product) has been separated by thin-layer chromatography on silica gel in 25 minutes from small amounts of uranyl nitrate with the aid of a mixture of solvents consisting of ether, water, and TBP[109]. Chlorine-38, sulphur-35, and phosphorus-32, produced by irradiation of ammonium chloride with neutrons[109], can be successfully separated. The elements are detected in the chromatogram radiometrically and are identified by their half-lives.

In studies by thin-layer chromatographic and radiometric methods of the chemical behaviour of sodium pyrophosphate and sodium salts of chlorine acids (solid specimens and solutions) during neutron activation[106], higher phosphates were not detected among the reaction products and only $P_2O_7^{4-}$, PO_4^{3-}, and PO_3^{3-} were separated and identified. The presence of cations (copper, zinc, and magnesium) had a catalytic effect on the cleavage of pyrophosphate on irradiation and influenced the quantitative ratios of various forms. After irradiation of the solid salts and solutions of NaCl, $NaClO_2$, $NaClO_3$, and $NaClO_4$, the radioactivity of Cl^- ions was found to be maximum in all cases. The addition of Cu^{2+} ions increased the extent of formation of chloride.

Examples of the separation of microamounts of two- and multi-component mixtures of radioactive substances without a carrier, which are of interest for radiochemists ($^{140}Ba-^{140}La$, $^{133}Ba-^{133}Cs$, $^{47}Ca-^{47}Sc$, Sr–Y, $^{72}Zn-^{72}Ga$, $^{95}Nb-^{182}Ta$, $^{95}Zr-^{95}Nb$, $I^--IO_3^--TeO_3^{2-}$, $SO_4^{2-}-PO_4^{3-}$, etc.) have been quoted[110]. The positions of the zones containing various elements were established automatically with the aid of a counter and a pen recorder.

In order to follow the separation of the test elements, radioactive isotopes may be introduced into the solution and their emission can be used to investigate by radiometric and radioautographic methods the distribution of the mixture components on chromatograms, as was done, for example in Refs. 69, 125, 126, and others.

For radioautographic detection of spots, use is usually made of an X-ray film, which remains in contact for a specified time with the chromatographic plate and is then developed in the usual way. A semiquantitative visual analysis and photometric quantitative measurements may be made on the basis of the intensity of the blackening of the spots under the influence of the radioactive emission.

5. ELECTROPHORESIS OF INORGANIC IONS

One of the promising trends in the development of the thin-layer chromatographic method is thin-layer electrophoresis. A description of the equipment for and technique of electrophoresis in a thin layer of carrier may be found, for example, in Refs. 127–131. Electrophoresis in a thin layer of carrier (both low- and high-voltage) differs little in experimental technique and apparatus employed from paper electrophoresis but does have a number of characteristic features: the layer of carrier on the plate may be impregnated with a larger amount of electrolyte than paper and because of this the electric field may be applied for longer periods (without risk of rapid drying of the layer), which in turn increases the effectiveness of the separation. The absence of a fibrous structure in the carrier eliminates diffusion-dependent spreading of the spots, so that the zones of the elements separated are more compact than in paper electrophoresis and the separation is more clear-cut. Owing to the greater capacity of the carrier layer compared with paper much greater amounts of the substances may, if necessary, be deposited for separation without the formation of diffuse spots. This is very important in the analysis of highly pure specimens where it is necessary to separate very small amounts of impurities. As a result, it is possible to achieve a much greater analytical sensitivity than in paper electrophoresis.

The possibility of varying the carrier is another advantage of inorganic thin-layer electrophoresis. Acetylcellulose[132] and cellulose[131], quartz sand[129], starch[133], heteropolyacid salts[134], kieselguhr[131], silica gel with starch[135,136] or with gypsum[137], a mixture of Teflon and cellulose[138], and photographic gelatine[139] have been used as carriers in this method.

Various mixtures of cations and anions can be satisfactorily separated by thin-layer electrophoresis (Table 3).

The separation of elements by electrophoresis is based on the difference in the stabilities of the complexes formed by the ions of the elements with a complex-forming agent (electrolyte) and in the case of alkali metals on the different degrees of association of the ions with the electrolyte anions[140].

The association constants of alkali[141] and alkaline earth[142] metal ions have been determined by the electromigration method from the mobilities.

Combination of thin-layer electrophoresis with thin-layer chromatography in two-dimensional separation has not been described in inorganic analysis but may prove to be useful.

III. QUANTITATIVE INORGANIC THIN-LAYER CHROMATOGRAPHY

The thin-layer chromatographic method for the separation and concentration of ultramicroamounts of substances is particularly important when combined in a rational manner with quantitative methods for the determination of the separated components. While inorganic thin-layer chromatography is widely used for a qualitative characterisation of chemical mixtures, the quantitative applications of this method have been described in a comparatively small number of publications and mainly in recent years. The method of quantitative microanalysis with the aid of thin-layer chromatography is employed in two versions: analysis after removal from the sorbent of the separated components and direct determination on the plate[143–145].

1. DETERMINATION OF SUBSTANCES AFTER ELUTION FROM THE ADSORBENT

In this case the substance to be determined is first removed from the adsorbent by elution with a suitable solvent from the zone on the plate where it was localised.

Table 3. Thin-layer electrophoresis

Elements separated	Carrier	Electrolyte	Potential gradient, V cm^{-1}	Duration, min	Method of detection	References
Rb and Cs	quartz sand	3.5×10^{-3} M solution (w.r.t.W) of ammonium paratungstate	19	18	radiometry	129
Ditto	ditto	0.34 M $K_4Fe(CN)_6$ + 0.052 M KNO_3	8.5	30	ditto	140
Li, Na, K, Rb, Cs	silica gel G	NH_4Cl + HCl buffer solution (pH 2.18) in 1 : 2 propylene glycol–water mixture	circular electric field with a potential of 400–500 V and a current of 40–45 mA		spraying with colour and luminescent reagents	137
Na, K, Rb, Cs	heteropoly acid salts	0.001–0.1 M NH_4NO_3	50	20	radioautography	134
Lanthanides	acetylcellulose (cellogel)	0.2–0.8 M solution of α-hydroxy-isobutyric acid	40–70	~30	radiometry, radioautography	132
	cellulose	1.1 M solution of α-hydroxy-isobutyric acid, pH 2.4	60 (cooling to -10°)	120	ditto	138
32 cations	ditto	0.1 M solution of α-hydroxy-isobutyric acid	50	20	spraying with 1% ethanol solution of 8-hydroxyquinoline, NH_3 vapour, u.v.light	131
20 cations	silica gel + starch	0.15 M citric acid solution	1200 V/30 cm	20	spraying with suitable reagent	135
33 cations and 13 anions	kieselguhr	0.05 M solution of lactic acid (cations); 0.1 *N* NaOH (anions)	13–45	from 2 to 5	radiometry	130
IO_3^- and IO_4^-	Alabaster (Ignited gypsum)	0.05 M $(NH_4)_2CO_3$	300–400 V/30 cm	90–120	radiometry	128
20 anions	silica gel S–HR and starch	0.05 M Na_2CO_3	1000 V/30 cm	20	colour reactions	136

Usually the sorbent is scraped off along the outline of the spot and then transferred to the elution vessel. In the resulting solution the substance is determined by one of the sensitive (usually instrumental) methods, for example spectrophotometrically, polarographically, etc. Precautions must be taken to prevent losses in the transfer of the sorbent on the one hand and to ensure complete extraction on the other. The effect of impurities which are also eluted from the sorbent is screened off by using selective and specific methods for the determination of the relevant element.

This method is more time consuming than direct determination on the chromatogram, is more complex, and may involve certain losses of the substance but at the same time it allows determination of the isolated components by highly sensitive and accurate micromethods. To reduce the errors in this version of quantitative thin-layer chromatography, special devices are employed to elute the substances from the chromatographic zones[146–148].

Two methods have been described for the isolation of the components from the layer of adsorbent by additional elution[149]. In the first method after elution of the mixture in a vertical direction the adsorbent layer is dried, part of the adsorbent around the spots (visible in ultraviolet light) is removed, and a pentagon cut out from ashless filter paper is placed on the adsorbent near the spot. The plate with the adsorbent and the paper is covered by glass and with the aid of a paper bridge horizontal elution with a fast-acting eluent, which displaces the components from the adsorbent to the upper part of the paper pentagon, is carried out. The part of the paper containing the substance is cut off and the substance is extracted with a suitable solvent. In the second method the additional elution from the adsorbent layer containing the spots is carried out in an open chamber with a fast-acting eluent. The substance is concentrated in a small part of the layer which is then scraped off the plate. The substance is extracted from this part of the adsorbent by the usual methods.

The substances eluted from the adsorbent in one way or another are determined by different procedures. In some investigations[150–153] microgramme amounts of nickel, uranium, cobalt, and bismuth were determined spectrophotometrically with morpholine-N-dithiocarbonate after their separation from other elements of the $(NH_4)_2S$ or H_2S groups on cellulose powder. Condensed phosphates have been determined as phosphomolybdenum blue[101] after elution from a layer of cellulose powder.

In the analysis of the components of semiconductor alloys, gold was determined[154] (after separation of other elements) by oscillographic inversion polarography.

After removal from the plate of the section of sorbent containing the substance to be determined, the latter can be determined with fairly high accuracy without elution. For this purpose, thin-layer chromatography is combined with reflection spectroscopy. The separation is usually carried out on cellulose or silica gel layers. After the detection of the element with the aid of a suitable reagent, the layer with the spot is taken off the plate, ground carefully in an agate mortar to a homogenous mixture, and placed in the reflection cell of a spectrophotometer. Usually between 0.05 and 6–10 μg of the test substance is determined with a relative error of ±2–6%. For example, the following substances have been determined by this method: aluminium, bismuth, cadmium, chromium, cobalt, copper, iron, lead, manganese, mercury, nickel, silver, tin, and zinc[155]; chromium[156]; iron, nickel and cobalt[157]; copper, nickel, and zinc[158].

Very high sensitivity was achieved in the determination of uranium in minerals using activation analysis[159]. Uranium separated quantitatively from impurities on a thin layer of silica gel was carefully transferred from the plate together with the sorbent into a polyethylene bag and was irradiated in a reactor with a neutron stream (1.7×10^{12} neutron $cm^{-2}s^{-1}$) for 30 min. The amount of uranium in the sample was determined from the activity of the neptunium-239 formed from the uranium. A calibration curve relating the area of the neptunium-239 peak at 106 keV to the amount of uranium in the sample was first obtained. The activity was measured 4 h after irradiation.

The sensitivity of the method is 0.02%.

Mass spectrometry is used for the analysis of small amounts of a substance sorbed on a thin layer[160]. The specimen in a thin glass capillary with a sealed end is put in the chamber of the mass spectrometer so that after the evacuation and heating (150–200°C) of the source the sorbed substance is evaporated and enters the electron beam of the source. In this way it is possible to analyse all substances stable at a given temperature and having a vapour pressure $> 10^{-7}$ mmHg.

2. DIRECT DETERMINATION ON THE PLATE

Since sharply outlined small spots of the separated substances are usually obtained in thin-layer chromatography, the components can be successfully determined directly on the chromatogram. This procedure is very rapid. The plotting of calibration curves under rigorously identical conditions lowers the error resulting from the possible non-uniform distribution of the substance in the thickness of the layer. At any rate, we believe that the error in such determination should not exceed the error due to the losses of the substance in the elution process.

Direct determinations on the plate can be carried out by various procedures: (1) by a semiquantitative method involving the visual comparison of the size and colour intensity of the spots with the dimensions and colour of a spot formed in the chromatography of known amounts of the substance; (2) quantitatively from the accurately measured area of the spot; (3) by photometric investigation of the spot (in some cases in ultraviolet light); (4) by measuring the emission of radioactive substances, etc.

In a direct quantitative determination it is particularly necessary to standardise carefully the conditions of the chromatographic processes (uniformity of the thickness of the sorbent layer and its grain size, its purity, and its moisture content, identical times taken by the solvent to traverse the plate, deposition of exact volumes of the solvent, saturation of the chamber with solvent vapour, controlled amounts of the reagent required for development, temperature, etc.).

Some of these procedures will now be considered.

Determinations from the Area of the Spot

The technique of this method is simplest, no special apparatus is required, and the determination is fairly rapid. The content of the substance in the spot is calculated on the basis of the fact that the logarithm of the weight of the substance is a linear function of the square root of the spot area[143].

In this case it is possible to make determinations using a calibration plot (which is best constructed on the basis of data obtained on the chromatographic plate used in the analysis of the test specimen) or by the method of additions (calculation by a formula). An advantage of the second procedure is that it does not require the plotting of a calibration graph and is more accurate.

The spot areas are determined with a planimeter or by superimposing a sheet of transparent paper on the layer outlining the spots, and measuring the areas of the resulting figures by placing the outlines against millimeter paper.

For example, chromic acid has been determined by the method described (from the area of the spot)[161]. The linear relation between the amount of chromic acid and the area of the coloured spot was found to hold in the range 50–300 μg of CrO_3. The error of the determination was ±6%.

The method has been used to analyse mixtures of potassium and magnesium acetates[143] and also for the determination of 1–7 mg of PO_4^{3-} per litre in the presence of chloride ions and 1–5 mg ml^{-1} each of I^-, Br^-, and Cl^-, when these were present simultaneously, after separation of the anions by thin-layer precipitation chromatography[107].

Densitometric Method

After the development of the spots on the chromatograms with colour reagents, the substances are determined from calibration plots with the aid of special devices (densitometers) using a linear relation between the dimensions and colour intensity of the spot on the one hand and the amount of the element contained in it on the other[162].

Nickel, cobalt, copper, lead, manganese, chromium, mercury, zinc, bismuth, iron, barium, and strontium have been determined in this way[163]. In the determination of 0.1–3.2 μg of the element the possible error is in the range between 0.2 and 2.1%. Densitometric measurements on a chromatogram with the aid of a chromoscan [chromoscope? (Ed. of Translation)] have been made after separation of microgramme amounts of iron, nickel, and cobalt[164].

A special device described by Pataki and Kunz[165] may be used for a direct quantitative determination on thin-layer chromatograms of spots containing fluorescent substances.

The Radiochemical Method

Spots containing radioactive substances are scanned directly on the chromatograms with the aid of special apparatus whereby the content of the given element may be found from the distribution of radioactivity on the plate. An example of the application of this method[166] is the determination of $^{125}I^-$.

3. ANALYSIS OF NATURAL AND TECHNICAL MATERIALS BY THIN-LAYER CHROMATOGRAPHY

Very few studies have so far been made in this field. In many cases when the weight of the test objects is very small, the chromatographic micromethod for the separation of elements in combination with highly sensitive methods for the subsequent quantitative determination proves to be very promising. The simplicity and rapidity of the method make it suitable for large scale analysis.

Analysis of Natural Objects

The thin-layer chromatographic method combined with densitometric determination of the elements directly on the chromatogram may be used to analyse the magnetic fraction of cosmic dust (the iron–nickel–cobalt system)[164]. The weight of the specimen analysed (cosmic spheres found in the region where the Tunguska meteorite fell) was 3–10 μg. The separation was carried out on a thin layer of KSK silica gel fixed with starch. The mobile solvent was a 99 : 1 mixture of acetone and 3 *N* hydrochloric acid. The duration of the chromatographic process was 15–20 min. The elements were detected by spraying with solutions of rubeanic acid and 8-hydroxyquinoline. The average relative error of the determination at the 0.95 confidence limit was ±22% for iron, ±15% for nickel, and ±9% for cobalt.

Thin-layer chromatography has been used for the qualitative analysis of sulphide ores and minerals[167], as well as for the quantitative determination of tellurium in minerals containing mercury (cinnebar)[126], using TBP-benzene mixture (3 : 7) to separate tellurium from Hg, Au, Sb, As, and Bi. Microgramme amounts of tellurium were determined spectrophotometrically with bismuth II after elution from the sorbent; for a 100 mg sample the accuracy was within ± 10%.

The possibility of semiquantitative analysis of water (including natural water) under field conditions using microcrystalline cellulose as a sorbent has been investigated[168]. The mobile solvent for the separation of the cations was a solution of Complexon(III) [sodium salt of EDTA (Ed. of Translation)] in dilute nitric acid to which was added dioxan and antipyrine or a solution of *sym*-collidine in nitric acid. A mixture of ethanol, pyridine, water, and concentrated ammonia was used to separate the anions. After spraying with a suitable reagent, calcium (10 mg ml^{-1}), magnesium and iron (1 μg), aluminium (0.02 μg), manganese (0.3 μg), Cl$^-$ (5 μg), SO$_4^{2-}$ (20 μg), PO$_4^{3-}$ (25 μg), F$^-$ (5 μg), NO$_3^-$ (10 μg), and SO$_3^{2-}$ (100 μg) were determined visually.

Analysis of Technical Materials

Thin-layer chromatography has been used[154] to separate microgramme amounts of components of semiconductor alloys based on lead, tin, and indium. The following mixtures have been separated on a thin layer of silica gel fixed with starch using various eluents: lead–gallium; lead–antimony; lead–tin; tin–zinc; tin–gallium; tin–indium; tin–gold; tin–arsenic; indium–aluminium. The possibility of a quantitative determination of the elements (after elution from silica gel) by oscillographic inversion polarography has been demonstrated for gold. In this determination the standard deviation was 2.8%.

In the analysis of technical preparations of lanthanides (neodymium and yttrium oxides) by thin-layer chromatography, non-lanthanide impurities (iron, copper, mercury, zinc, and calcium) were detected when their content in the lanthanide mixture was 10^{-2}–10^{-1}%.[69]

Thin-layer chromatography can be conveniently employed in the analysis of highly pure materials at the stage of separation where the main bulk of the interfering elements has already been separated by some other procedure. This was done, for example, in the determination of 10^{-3}–10^{-5}% of lanthanides in highly purified uranyl nitrate[125]. The initial salt sample taken for analysis weighed 0.05–5 g. The main bulk of uranium (90–95%) was separated by preliminary extraction and the final separation of milligramme amounts of uranium and microgramme amounts of lanthanide impurities was achieved by repeated ascending thin-layer chromatography on silica gel with a mobile solvent consisting of a 5 : 95 TBP–benzene mixture. The sum of lanthanides remaining at the starting point after elution from silica gel was determined spectrophotometrically with Arsenazo III or Arsenazo M. The standard deviation was about 5–8%.

IV. POSSIBLE APPLICATIONS OF THIN-LAYER CHROMATOGRAPHY IN ANALYTICAL AND INORGANIC CHEMISTRY

On the basis of our own experience and the literature, we believe that the rapid and simple thin-layer chromatographic method will be used in future in combination with sensitive quantitative analytical methods (luminescence analysis, spectrophotometry, polarography, radiography, mass-spectrometry, etc.) and in different versions (partition, ion-exchange, precipitation, multi-dimensional, and gradient chromatography, thin-layer electrophoresis, etc.) for the following purposes: (1) as a method for the separation and concentration of substances and the analysis of various natural and industrial micro-objects using samples down to 10^{-5}–10^{-6} g (minerals, inclusions, articles produced in semiconductor engineering and electronics, etc.); (2) for the rapid separation and identification of short-lived radioactive elements (for example transplutonium elements) with radioautographic detection of the elements on a thick layer of emulsion; (3) as a rapid control method for the determination of the purity of preparations at different stages of the purification of substances (probably largely with a sensitivity of 10^{-2}–10^{-3}%); (4) in a preparative version for the separation of milligramme amounts of elements free from specified impurities (for example in the preparation of standards); (5) for the investigation of the chromatographic behaviour of compounds of metal ions in different valence states (in particular in the study of the disproportionation of elements); (6) for the investigation of problems of complex formation, the mechanism and kinetics of sorption, many other theoretical questions, etc.

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During the preparation of this review for the press, a number of studies were published, the most interesting of which are listed below.

Transition elements: iron–copper, cobalt–copper, iron–cobalt, and cobalt–lead mixtures have been separated by thin-layer chromatography[169]; the glycinate complexes of cadmium, cobalt, copper, nickel, platinum, and zinc have been separated on cellulose layers[170]; chromium, iron, zinc, and nickel have been separated on carboxymethyl- and DEAE-cellulose[171]; manganese and mercury[172], the noble metals[173–179], and rhenium, molybdenum, tungsten, and vanadium[180–182] have been separated; zirconium has been isolated and separated from scandium, yttrium, thorium, uranium, and the lanthanides[183]; cations of analytical groups III and IV have been separated by thin-layer ion-exchange and precipitation chromatography[184].

Non-transition elements: microgramme amounts of indium have been separated from iron, aluminium, gallium, and titanium on cellulose layers[185]; arsenic, antimony, and tin have been separated in the form of pyrrolidinedithiocarbamates[186]; arsenic, antimony, and bismuth[187] and selenium and tellurium[188,189] have been separated.

Lanthanides and actinides: scandium, yttrium, the lanthanides, thorium, and uranium have been separated[190,191].

Heterovalent states: tellurium(IV) and tellurium(VI)[192] and arsenic(III) and arsenic(V)[193] have been separated; the separation of iodine in various states of oxidation has been achieved[194].

Systematic thin-layer chromatography: a number of studies have been made on the systematic thin-layer chromatography of many cations[195–201].

Anions: the sorption behaviour of twenty seven inorganic anions has been investigated[202]; the behaviour of halides[203] and phosphates[204] has been studied.

Radiochemistry: a number of papers have been published on the combination of thin-layer chromatography and radiochemistry[280–210].

Thin-layer chromatography of complexes: the separation of various cations in the form of complexes has been described—as glycinates[170], pyrrolidinedithiocarbamates[186], diethyl dithiocarbamates[211], complexes with salicylaldoxime[212], diketonates[213,214], pyridylazonaphthoxides[215,216], EDTA complexes[217], and others[218–220].

Quantitative thin-layer chromatography: spectrophotometric determination of iron[221,222]; densitometric determination of zinc[223,224]; determination of aluminium, beryllium, and chromium[225]; determination of metal ions in water[226]; analysis of minerals[227].

Thin-layer electrophoresis: this has been used to separate iodine in different states of oxidation[194] and the mixtures[228] ^{90}Sr–^{90}Y and ^{212}Rb–^{212}Bi.

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Vernadskii Institute of
Geochemistry and Analytical
Chemistry, USSR Academy
of Sciences, Moscow

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The Structure of Hydrazones

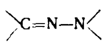
Yu.P.Kitaev, B.I.Buzykin, and T.V.Troepol'skaya

The review surveys the present state of research on the conformation, isomerism, and intramolecular interactions of molecules of the immense class of organic compounds containing a hydrazone group. A list of 221 references is included.

CONTENTS

I. INTRODUCTION

Compounds whose molecules contain the hydrazone grouping



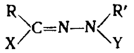
$$>C=N-N< \qquad (I)$$

belong to the huge class of azomethines and are distinguished from other members of this class (imines, oximes, etc.) by the presence of two interlinked nitrogen atoms.

Being very readily available substances, hydrazones have found wide application in synthetic chemistry for the preparation of compounds of most diverse structure, and in analytical chemistry for the identification and isolation of carbonyl compounds, and for the detection of a large number of metal cations. Their application has been reported as plasticisers and stabilisers for polymers, polymerisation initiators, antioxidants, etc. However, the most valuable property of hydrazones is, perhaps, their great physiological activity. Among them are found herbicides, insecticides, nematocides, rodenticides, and plant growth regulators. The value of hydrazones in fighting tuberculosis is well known. Substituted hydrazones have been found to exhibit spasmolytic activity, hypotensive action, and activity against leukaemia, sarcomas, and other malignant neoplasms. The possibility is being investigated of using substituted hydrazones for the treatment of schizophrenia, leprosy, and other illnesses.

An attempt is made in the present review to consider on a uniform basis compounds in which the hydrazone group (I) is present in an open chain, and only the outermost atoms of the system can form part of rings. For convenience we shall henceforward term the nitrogen atom in the azomethine group the imine nitrogen, and the other atom the amine nitrogen.

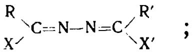
The triatomic hydrazone group is characteristic of a large number of organic compounds of the type



$$\begin{matrix} R \\ X \end{matrix}\!\!>C{=}N{-}N\!<\!\!\begin{matrix} R' \\ Y \end{matrix} \qquad \text{(II)}$$

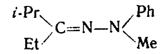
where R, R′, X, and Y can vary widely. We will use the term "hydrazones" as a general name for compounds having the structure (II). When R′ = Y = H we have "unsubstituted hydrazones"; when R′ = Alk(Ar, Az) and Y = H, "alkyl(aryl, acyl)hydrazones", and when R′ = Alk (Ar, Alk, Alk) and Y = Alk(Ar, Ar, Az) "dialkyl(diaryl, alkylaryl, acylalkyl, etc.)hydrazones"; and also with X = H we have an "aldehyde hydrazone", with X = Alk, Ar, Az a "ketone hydrazone", and so on. If R′ = NH_2CO the compounds (II) are semicarbazones, and if R′ = NH_2CS they are thiosemicarbazones. Dihydrazones of α-dicarbonyl compounds are usually termed "osazones".

Where X = Hal, NO_2, OAlk, OAr, the compounds are α-halogeno-hydrazones† or α-nitro(alkoxy, aryloxy)-hydrazones; when X = N : NR they are formazans, X = NHNHR hydrazidines, X = NH_2, NHR, NRR′ amidrazones; and with X = OH, SH hydrazides and thiohydrazides are formed. Furthermore, R′ and Y may together constitute the residue of a carbonyl compound, in which case the structure (II) acquires the form (III), and compounds of this class are termed "azines":



$$\begin{matrix} R \\ X \end{matrix}\!\!>C{=}N{-}N{=}C\!<\!\!\begin{matrix} R' \\ X' \end{matrix} \;; \qquad \text{(III)}$$

with R = R′ and X = X′ they are symmetrical, or simply azines of the carbonyl compounds (aldazines, ketazines); and when R ≠ R′ and X ≠ X′ we have mixed azines. Thus in naming the hydrazone we first state the name of the carbonyl compound and then name the substituents attached to the nitrogen atom together with the word "hydrazone", e.g. ethyl isopropyl ketone methylphenylhydrazone‡



$$\begin{matrix} i\text{-Pr} \\ \text{Et} \end{matrix}\!\!>C{=}N{-}N\!<\!\!\begin{matrix} \text{Ph} \\ \text{Me} \end{matrix} \;. \qquad \text{(IV)}$$

In present-day chemical literature there is an increasing tendency to name hydrazones more briefly and independently—aromatic arylhydrazones (II: R = R′ = Ar; X, Y = H or Ar), aliphatic arylhydrazones (II: R = Alk; R′ = Ar; Y = H or Ar; X = H or Alk), aldhydrazones (R′ = X = Y = H), ketohydrazones (R and X = Ar, Alk, etc.; R′ = Y = H), keto-acylhydrazones (R and X = Ar, Alk, etc.; R′ = Az; Y = H), etc.—although a special nomenclature has not yet been developed.

It is undoubtedly impossible to give in a single paper an exhaustive review of the literature on the structure and the chemistry of hydrazones, and therefore the authors have not pursued this aim. However, the absence of generalisations of the numerous fresh results on the structure of hydrazone molecules has led us to make an attempt at a systematic discussion. Still, individual aspects of the structure and especially the chemistry of certain types of hydrazones have already been considered many times in special reviews [1-18] or incidentally in reviews concerned mainly with other classes of compounds [19-26].

Henceforward we shall usually give references to papers in which earlier results are often critically discussed. The large number of publications on various aspects of the chemistry of hydrazones makes it necessary to examine separately the structure, the chemical properties, methods of preparation, and the application of hydrazones.

II. GENERAL INFORMATION

Unsubstituted hydrazones, alkylhydrazones and certain arylhydrazones, and azines of simple aliphatic aldehydes and ketones are colourless or very slightly coloured liquids possessing a characteristic odour [4,27,28]. The boiling point rises with increase in the molecular weight of R, X, R′, or Y (II). Alkylhydrazones having a branched carbon chain possess lower boiling points than their analogues having a straight chain. The phenylhydrazones of aromatic and heterocyclic aldehydes and ketones are solids, mostly slightly coloured. Several arylhydrazones, especially the 4-nitro- and 2,4-dinitro-derivatives, have a well-developed crystal structure and sharp melting points, so that they are convenient for identifying carbonyl compounds. Carbazones, semicarbazones and thiosemicarbazones, and sometimes azines are used for this purpose.

Unsubstituted hydrazones, alkylhydrazones and certain arylhydrazones, and azines are bases, forming salts with acids. Increase in the electron-acceptor character of R′ and Y is accompanied by a fall in basic strength, p-nitrophenylhydrazones being acidic substances [29]. 2,4-Dinitrophenylhydrazones are weak acids, in which the value of pK_a varies with the nature of R and X [30].

Crystallographic analysis indicates [31-33] that the grouping $>C{=}N{-}N<$ in hydrazones possesses a planar structure, although the coplanarity may break down in certain sterically hindered molecules [31]. The length of the C=N bond in hydrazones depends on the nature of the substituents R, R′, X, and Y, varying between 1.27 and 1.35 Å [31-33], which somewhat exceeds the values of 1.24 [34] and 1.255 Å [35] for aliphatic imines, in which the order of this bond is closer to 2. [35] The presence of a lone pair of electrons on the amine nitrogen atom in hydrazones, capable of conjugation with π-electrons, leads to a decrease in the order of the C=N bond and hence an increase in its length. In 1966 Bayer and Häfelinger [35] correlated the stretching frequences ν with the carbon–nitrogen bond length l and also order p (Fig. 1), which provided a fairly easy method for estimating the variation in length and order of the bond with change in the character of the substituents [14].

Although Bayer and Häfelinger's constructions involved certain assumptions, they yield results which agree quite well with calculations [14] of the bond order by the LCAO-MO method. On the basis of spectroscopic data the latter method of calculation gives estimates of 1.80–1.90 for the order of the C=N bond in hydrazones [9,14].

Less attention has, of course, been paid to the length of the N–N bond in hydrazones, which varies between 1.38 and 1.41 Å [31-33], being rather shorter than in hydrazine (1.46 Å [36]). It is difficult to make any definite statement on the order of the N–N bond, since existing data are insufficient for valid comparisons and conclusions. Calculations by the LCAO-MO method show [9] that this bond order approximates to 1.2 in semicarbazones. The length of the N–C bond (between the amine nitrogen atom

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†σ-Halogeno-hydrazones are often termed "halogeno-hydrazides" or "hydrazones of acid halides".

‡A better and more succinct name would be "2-methyl-pentan-3-one methylphenylhydrazone" (Ed. of Translation).

and carbon in a substituent R′) is close[31-33] to the values for a C−N single bond (1.47 Å)[37], but it decreases, of course, when conjugation is present between the hydrazone group and the R′ or Y radical, and in methylglyoxal bisamidinohydrazone, for example, it is 1.35 Å.[32] The C=N−N angle is often close to the theoretical value (120°), although cases of substantial deviations are known. In methylglyoxal bisamidinohydrazone and in ribose *p*-bromophenylhydrazone, for example, this angle is 117° [31,32], but in anisaldehyde azine it is 111.2° [33]. Other angles in the hydrazone group are mostly close to the theoretical values, although the observed deviations differ with different types of hydrazones[31-33].

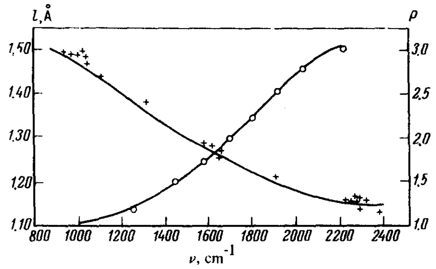


Figure 1. Variation of ν with *l* and *p* for the carbon-nitrogen bond[35].

Because of the specific character of the azines (III) coplanarity of the azine group may be destroyed by rotation of the imine fragments about the N−N bond (Fig. 2) [38,39]. Calculations based on dipole moments show that the angle of deflection of the planes of the imine fragments is $\theta = 60-70°$ in most aliphatic and alicyclic aldazines and ketazines. In benzylideneazine this angle $\theta = 20°$, whereas the molecule of the azine of salicylaldehyde is planar as a consequence of intramolecular hydrogen bonding[39].

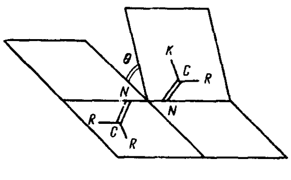
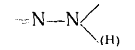


Figure 2. Conformation of azine grouping[39].

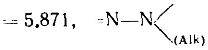
It is not possible to estimate the energies of the bonds in the hydrazone group, or to examine the effect of the structure of the molecule on them, since the literature does not contain the necessary data on the group as a whole, while available values of bond energies for the fragments are quite contradictory. The energy of the C=N bond has been given as 94, 132, and 139.5 kcal mole⁻¹ by Pauling, Palmer, and Syrkin respectively (see bibliography[34]). The energy of the N−N bond depends greatly on the nature of the radicals attached to the nitrogen atoms, and varies from 57 kcal mole⁻¹ in hydrazine to 22 kcal mole⁻¹ in hydrazobenzene[40], but has not been determined in hydrazones. This evidently applies also to the energy of the C−N bond in the hydrazone group; the values found for amines lie in the ranges 70−80 and 80−90 kcal mole⁻¹ in aliphatic and aromatic amines respectively[40]. Even from these data it can be concluded that the N−N bond is the weakest in the hydrazone group. The energy of internal rotation about the $=N-N\langle$ bond in the dialkylhydrazones of cyclic ketones appears from the nuclear magnetic resonance spectra to be ~11 kcal mole⁻¹ [41].

The group moment has not been determined for hydrazones, values for the individual bonds being used in the additive vectorial calculation of dipole moments[9,14,39,42,43]. The difference in electronegativity between carbon and nitrogen atoms causes polarisation of the C=N and N−C bonds in the direction of the more electronegative nitrogen atom. Values of μ for the C=N bond in the earlier papers—0.9, 2.40, 2.27, 2.5 D—are extremely contradictory[42,43]. From the dipole moments of aliphatic aldimines Everard and Sutton found that $\mu_{C=N} = 1.4-1.5$ D.[44] Kitaev and his coworkers[43] used the experimental dipole moments of various azomethines to obtain a mean value of 1.5 D. A monograph[45] gives the values $\mu_{C=N} = 1.4$ D, $\mu_{C-N} = 0.45$ D, and $\mu_{H-N} = 1.31$ D.

It is also fairly difficult to reach any conclusion on the group refraction, and calculations are based on values of *R* for the component atoms of the hydrazone group or on the bond refractions $R_D = 3.67$, 1.57, 1.99, and 1.76 for the C=N, C−N, N−N, and N−H bonds respectively[46]. Different authors give values of 8.205, 8.45, and 8.277 [4,46,47] for R_D of the group =N−N= in aliphatic ketazines. Kost and Grandberg[47,48] give such values as



$R_D = 5.871$,



$R_D = 6.245$.

for the hydrazone group in pyrazolines, which can be regarded as cyclic hydrazones.

Considerably more work has been done on the infrared spectra of hydrazones. The hydrazone group does not possess a characteristic absorption band, observations usually being based on that of the C=N bond, and with the monosubstituted compounds also on the N−H bond. Depending on the structure of the surrounding radicals, absorption of moderate intensity by C=N lies in the range 1570−1680 cm⁻¹ [9,14,27,28,35,39,49-75] (see Table 1), and the N−H stretching band in unsubstituted and monosubstituted hydrazones is located in the range 3150−3400 cm⁻¹ [9,43,53,59,69,72,76-78].

In the region of 1600 cm⁻¹ arylhydrazones show superimposition of the absorption frequency due to the azomethine group on that due to the aromatic ring[14,28,53,55,59]. If steric conditions in the hydrazone molecule do not prevent *p*−π conjugation, the frequency of the C=N bond shifts to longer wavelengths[14,28,39,58,61,62,69,70,73]. In alkylhydrazones the structure of the alkyl radicals has little effect on the C=N frequency, whereas the structure of the radicals in the carbonyl component has a substantial effect[69]. The C−N absorption band in hydrazones lies in its usual range, and is considered only in a complete interpretation of the spectrum[59,72]. In this connection the band in the range 1525−1550 cm⁻¹, which sometimes produces a different interpretation[54], has recently been assigned to N−H deformation vibrations alone or together with C−N vibrations[51,68,72].

Table 1.

No.	Type of hydrazone	Infrared $\nu_{C=N}$, cm^{-1}	Refs.	Raman $\nu_{C=N}$, cm^{-1}	Refs.	Ultraviolet λ, nm	Refs.
1	Unsubstituted hydrazones	1650	9,51	1645—1650	14,39,79,80	210—230,265—340	87,93
2	Alkylhydrazones	1650—1635	55,69	1640	80	230—245,270—350	55,87,93,94
3	Dialkylhydrazones	1570—1590 1590—1640	52,56 52,55,74	1650	79	210—250,260—320	55,87,93,94
4	Aliphatic aldazines and ketazines	1635—1665	14,39,49,51	1610—1630	14,39,79	205—210,210—215	84
5	Aromatic aldazines and ketazines	1610—1630	14,39,49,51,64	—	—	300—305,310—315	84
6	Arylhydrazones of aldehydes	1600—1610	14,53,59	1620—1630	14,80	250—275	28,57
7	Arylhydrazones of ketones	1635—1645	14,50,59,73	1630—1640	14,80	240—260,325—370	85
8	2,4-Dinitrophenylhydrazones	—	—	—	—	360—400	85,86,88,90
9	Alkylarylhydrazones	1610—1645	57,59	1635—1645	—	250—275	57
10	Acylhydrazones	1610—1630	63,72	—	14,80	225—230,320—325	76,92
11	Semicarbazones	1610—1670	14,51,58,60—62,72	1610—1660	9,14,81	220—250,260—330	87,89,91,96
12	Thiosemicarbazones	1610—1660	14,51,58	1610—1660	9,14,81	230—280,300—360	89,96,98
13	Bis- and tris-phenylhydrazones of vicinal di- and tri-carbonyl compounds	1630—1645	68	—	—	360—400*	88
14	*o*-Chloroarylhydrazones	1595—1670	65	—	—	235—240,350—375	65
15	*o*-Nitro(and sulpho)arylhydrazones	1590—1680	66,67	—	—	240—250,340—400	66,67,97
16	Formazans	1590—1610	75	—	—	220—290,280—450, 420—500	2,75

* Bis-2,4-dinitrophenylhydrazones of α-dicarbonyl compounds.

Considerably less work has been done on the Raman spectra than on the infrared spectra of hydrazones. Lines attributable to C=N absorption occur in the range 1610–1660 cm^{-1} in the Raman spectra (see Table 1) [14,39,53,79-83]. These spectra enable absorption due to C=N in arylhydrazones to be distinguished from that due to the aryl ring system, which, as already mentioned, is not possible from the infrared spectra.

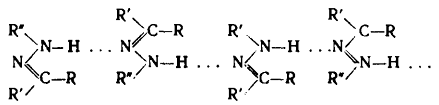
In the near ultraviolet hydrazones usually have two absorption bands, but sometimes a third may appear, or even only one band (Table 1) [14,28,49,57,65-67,76,84-98].

The presence of unsaturated groups capable of conjugation—in any radical of the hydrazone structure—results in a bathochromic shift in the absorption maximum (Table 1). The introduction of electron-acceptor substituents into the phenyl ring of the hydrazones of aromatic aldehydes and ketones has an analogous effect, which is most clearly developed with *para*-substitution[49,84,87,89,93-96,99]. Only a slight bathochromic displacement of λ_{max} but a very considerable increase in intensity of absorption occur[88] on passing from the mono- to the bis-2,4-dinitrophenylhydrazones of α-dicarbonyl compounds.

Nuclear magnetic resonance has been applied many times and extremely usefully to study of the structure of hydrazones[28,100-102]. Without discussing in detail the proton magnetic resonance spectra of hydrazones, we note merely that the chemical shift due to the aldehyde proton in the hydrazones of aldehydes (I: X = H) is τ = 3.2–3.8 ppm, and that due to the NH proton in monosubstituted and unsubstituted hydrazones is considerably more affected by surrounding groups[38,100-102].

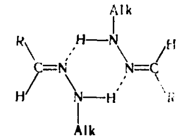
III. HYDROGEN BONDING

The presence of C=N and N–H groups in monosubstituted and unsubstituted hydrazones makes intermolecular hydrogen bonding possible. Several alkylhydrazones and phenylhydrazones are in fact associated in the liquid state, and in solutions molecules of the solvent are involved in the association[69,99-108]:

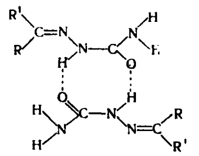


where R, R′ = Alk and R″ = Alk, C_6H_5. The stability of the resulting complexes depends both on the structure of the hydrazone and on the nature of the solvent. With phenylhydrazones, for example, the stability diminishes in the sequence of solvents—dimethyl sulphoxide > acetone > pyridine > nitrobenzene > chlorobenzene > isodurene[102].

It has been suggested that dimers are formed by intermolecular hydrogen bonding of the *syn*-form

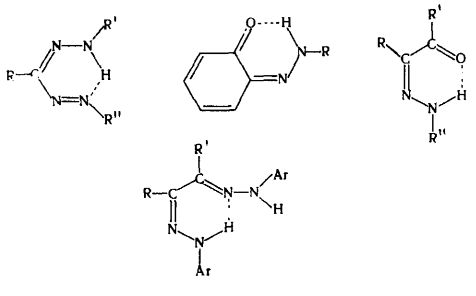


in solutions of the alkylhydrazones of aliphatic aldehydes[69]. The formation of dimeric together with linear association complexes is observed in solutions of semicarbazones



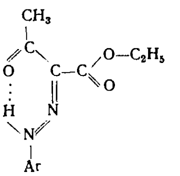
the former being the more stable[9].

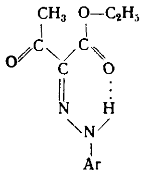
A strong intramolecular hydrogen bond is present in formazans[1,2,109], osazones[110], and monoarylhydrazones of *o*-quinones, semicarbazones, thiosemicarbazones, alkylhydrazones, and arylhydrazones of keto-acids[9,14,50,53,54,99], and in bisphenylhydrazones of α-dicarbonyl compounds[111]



where the hydrogen bond results in formation of a stable chelate system.

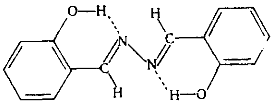
Arylhydrazones of ethyl αβ-dioxobutyrate are present in solutions as a mixture of roughly equal quantities of isomers containing an intramolecular hydrogen bond formed by the hydrazone proton with a keto-group or the ester grouping[99]: i.e. both possible alternatives





are realised in this case.

A hydrogen bond is formed in hydrazones also when a hydroxy-group is present and appropriately located in the carbonyl or hydrazine portion. Thus in the azines of *o*-hydroxybenzaldehydes a hydrogen bond is responsible for their luminescence[112], and also for the coplanarity of the atoms in the azine group[39]

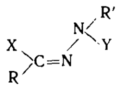


IV. ISOMERISM OF HYDRAZONES

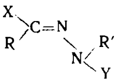
Hydrazones include examples of both stereoisomerism and structural isomerism, while in some cases tautomeric equilibrium of two or even three forms is observed. Isomerism of the skeleton and metamerism are due to the possibility of preparing hydrazones from both isomeric hydrazines and isomeric carbonyl compounds—to the possibility of wide variation in R, R′, X, and Y in (II)—and is of no special interest. Cases of stereoisomerism (geometrical and optical) and position isomerism in the hydrazone group (conversion into azo-compounds or into alkenylhydrazines), with the tautomeric equilibrium of the isomeric forms involved in these changes, are considerably more interesting. Quite often isomeric transitions and tautomeric equilibrium of the various forms of hydrazones are combined, which makes it more difficult to solve the problem.

V. GEOMETRICAL ISOMERISM

The geometrical isomerism of the hydrazones of aldehydes and unsymmetrical ketones is a particular case of isomerism in the $\rangle$C=N−Z system. By analogy with oximes, the isomer in which the substituted or unsubstituted amino-group and the hydrogen atom in the aldehyde derivatives (X = H) or the smaller radical in the ketone derivatives (X < R) are in the *cis*-position with respect to the C=N bond is usually termed the *syn*-isomer (V), and that in which they are in the *trans*-position the *anti*-isomer (VI)[11,100]:



(V) *syn*-isomer



(VI) *anti*-isomer

When R and X are complicated it is necessary, in order to avoid confusion, to indicate which isomer is regarded as *syn* and which as *anti*: this is sometimes effected by stating after the type of isomer the group which occupies the given position relative to the amino-group, e.g. the *syn*-phenyl isomer of acetophenone 2,4-dinitrophenylhydrazone[113].

Geometrical isomerism was postulated in hydrazones by analogy with oximes, and very many papers have been devoted to this question. However, some of the earlier papers must be treated with caution, and the designations α- and β-forms must be accepted for the compound having the lower and higher melting point respectively, since only in a few cases were geometrical isomers actually isolated[11,13].

The matter is complicated by the fact that many hydrazones, especially those containing a nitroaryl substituent, tend to exhibit polymorphism. Thus acetaldehyde *syn*-2,4-dinitrophenylhydrazone exists in four polymorphic modifications, having melting points of 145−146°, 157−158°, 160−161°, and 165−166°C respectively[13,101]. Polymorphism may be the reason for the appearance of different colours in a hydrazone, even if the two modifications have the same melting point and identical ultraviolet and infrared spectra. Only by means of X-ray examination has it been possible to establish that 1-phenylpropane-1,2-dione bis-2,4-dinitrophenylhydrazone, which crystallises from acetic acid as orange−yellow and from nitrobenzene as red needles, is present in different crystalline modifications[114].

Hydrazones are characterised also by phototropy. On standing in sunlight benzaldehyde phenylhydrazone acquires an orange−red colour, which disappears when kept in the dark for a long time. The loss of colour is slower than its appearance[11].

In addition, arylhydrazones are able to form mesomorphic phases. Transition of the phenylhydrazones of *p*-nonyloxy- and *p*-decyloxy-benzaldehydes into the nematic state takes place at 94−95° and at 91−92°C respectively, the transition from the nematic into the liquid state occurring at 97−98° and 93−94°C [115].

Many problems in the stereochemistry of hydrazones have been solved during recent years by the application of the most modern physical methods. The nuclear magnetic resonance spectra as well as the infrared and ultraviolet spectra are widely used for these purposes, but a combination of several methods has proved the most fruitful. The existence of geometrical isomers has been recorded in unsubstituted hydrazones[106], methyl-[27,107], dimethyl-[108,116], methylphenyl-[105,117], aryl-[11,77,102,113], and 2,4-dinitrophenyl-hydrazones[13,100,101,113,118,119], and in thiosemicarbazones[13,77,100,119-121], azines[122-126], acylhydrazones[127,128], formazans[1,2,109], *α*-nitroarylhydrazones[129], 2,4-dinitrophenylhydrazones of quinones[130], and arylhydrazones of *α*-dicarbonyl compounds[88,131].

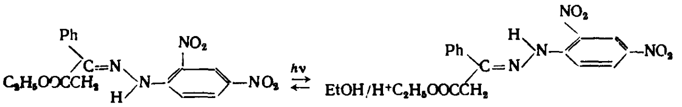
The *syn*-configuration of hydrazones is the more stable. If neither substituent attached to the amine nitrogen atom (R′ or Y) is a hydrogen atom, hydrazones of aldehydes (X = H) are formed, and exist solely in the *syn*-configuration not only in the solid but also in the liquid state and in solutions. A bulky substituent (R′ or Y) produces the same effect even by itself, but equilibrium between *syn*- and *anti*-forms can then be observed in solutions. Thus the dimethyl-, methylphenyl-, and 2,4-dinitrophenylhydrazones and the semicarbazones of aldehydes exist in the *syn*-configuration[101,105,108,119,120]. Equilibrium is slowly established in solutions of 2,4-dinitrophenylhydrazones and semicarbazones, but the process can be accelerated by adding a catalyst, e.g. sulphuric acid. The relative proportions of *syn*- and *anti*-forms depends on the nature of the solvent, as indicated by the following values from the nuclear magnetic resonance spectra of acetaldehyde 2,4-dinitrophenylhydrazone[101]:

in dibromomethane and nitrobenzene	2 : 1
in pyridine, acetone, and dimethylformamide	4 : 1
in tetramethylurea and dimethyl sulphoxide	7 : 1

The rate of isomerisation is fairly low, only a small quantity of the *anti*-isomer being formed during recrystallisation of the *syn*-isomer. This enables the *anti*-form to be isolated or at least enriched by fractional crystallisation of the equilibrium mixture. Acetaldehyde 2,4-dinitrophenylhydrazone containing 85% of the *anti*-isomer has been prepared[101] by crystallising the equilibrium mixture containing only 33%. The size of the radicals in the carbonyl component (R, X) also affects the position of equilibrium between the isomeric forms: when one of them becomes larger, the percentage of the *syn*-form increases. Branching of the carbon chain at the *α*-position relative to the hydrazone group displaces the equilibrium towards the *syn*-form more than does lengthening the straight chain by the same number of carbon atoms. The various hydrazones of isobutyl [?t-butyl] methyl ketone are present in the *syn*-form in any state[100,103,105-108] (see Table 2).

However, not all hydrazones form equilibrium mixtures in solution. Acetophenone phenylhydrazone is obtained in the *syn*-form, which is preserved in solution[102]. A hydrogen bond usually stabilises the *anti*-form[11].

One isomer can be converted into the other in various ways. The stable *syn*-2,4-dinitrophenylhydrazone of ethyl benzoylacetate (VII) obtained from the reaction passes, on prolonged illumination in benzene solution, into the labile *anti*-form (VIII), which can be changed back into the *syn*-form by heating an alcoholic solution in the presence of catalytic quantities of hydrochloric acid[132]:



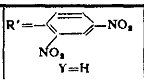
(VII) *syn*-isomer m.p. 161.5–163.5°C

(VIII) *anti*-isomer m.p. 121–121.5°C

A similar situation is found with *ω*-bromoacetophenone 2,4-dinitrophenylhydrazone[133].

Isomerisation of the geometrical forms of hydrazones can be caused not only by hydrochloric acid and irradiation but also by iodine, sulphur dioxide, hydrogen sulphide, yellow mercuric oxide, caustic potash, sodium ethoxide, sulphur, acetic and other acids, heating to the melting point, etc.[11,113]. Interconversion of the geometrical forms is observed also during the chemical reactions of bromination[116], acylation[134], saponification, and esterification[46]. The explanation of isomerisation during a reaction is that in the *anti*-isomer, for example, the mobility of the methine hydrogen atom (X = H) exceeds that in the *syn*-isomer, perhaps for steric reasons[116].

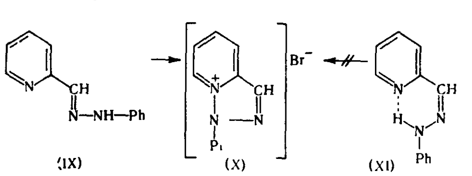
Table 2. Content (%) of *syn*-form of hydrazone of type (II) (liquid or in solution)[100-103,105-108].

R	X	R′=H Y=H	R′=CH$_3$ Y=H	R′=CH$_3$ Y=CH$_3$	R′=Ph Y=H	R′=Ph Y=CH$_3$	R′=  Y=H	R′=$-\overset{\displaystyle O}{\overset{\|}{C}}-NH_2$ Y=H
H	CH_3	51	73	100	65^a	100	100^b, 66^a	—
H	C_2H_5	64	83	100	89	100	100^b, 78^a	—
CH_3	C_2H_5	78	83	82	80	86	80^a	75^a
CH_3	$CH(CH_3)_2$	93	96	93	94	94	90^a	90^a
CH_3	$C(CH_3)_3$	100	100	—	100	100	100^a	100^a
CH_3	Ph	—	—	—	100^a	100^a	63^a	—

(*a*) In solution in dibromomethane or in chloroform.

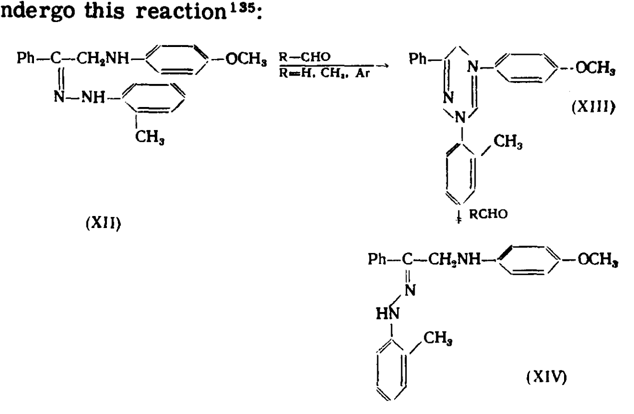
(*b*) In the initial stages (immediately after dissolution).

Although interconversion of the geometrical forms can be observed, it is not yet possible to establish chemically the structure of each form of a hydrazone. Pyridine-2-aldehyde *syn*-phenylhydrazone (IX) is converted by the action of *N*-bromosuccinimide into 1-phenyl-1,2-diaza-8-azoniaindene bromide (X), whereas the *anti*-isomer (XI), in which the atoms are more favourably arranged for ring closure, does not yield (X):



(IX) (X) (XI)

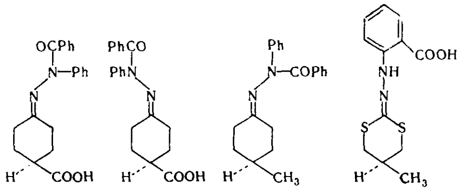
Nevertheless, *ω*-*p*-methoxyanilinoacetophenone *syn*-*o*-tolylhydrazone (XII) reacts with aldehydes to form triazine derivatives (XIII), whereas the *anti*-isomer (XIV) does not undergo this reaction[135]:



(XII) (XIII) (XIV)

Pearson et al.[136] suggested that geometrical isomers of hydrazones could be identified by their rearrangement into amides, but unfortunately this yields a mixture of amides, which makes the problem more difficult to solve. Khromov-Borisov[113] suggested the genetic relation with pyrazolone as a criterion for establishing the stereochemical structure of a hydrazone. In this case the corresponding pyrazolone must be hydrolysed, decarboxylated, or subjected to other reactions, which greatly limits the range of application, and furthermore introduces the possibility of isomerisation during such operations. The *anti*-structure was attributed[137] to one of the forms of the phenylhydrazone and the bisphenylhydrazone of benzil on the basis of their ability to form a complex with tin(IV) chloride.

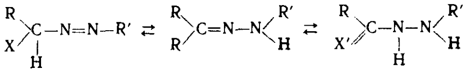
The hydrazones (XV), (XVII), and (XVIII) could be resolved into enantiomers[138], their optical activity being explained by molecular asymmetry, as is shown in the case of (XV) and (XVI):


(XV) (XVI) (XVII) (XVIII)

The hypothesis of these workers[138] (repeated by others[11,39]), that the third valency of the imine nitrogen atom in compounds (XV)-(XVIII) does not lie in the C=N plane, is inconsistent with the results of modern X-ray[31-33] and conformational analysis[39,120] of hydrazones. This is a case of atropoisomerism, resulting from the absence of a plane of symmetry in the isomeric forms.

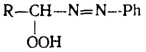
VI. ISOMERISM OF THE TYPE HYDRAZONE ⇌ AZO-COMPOUND

The molecular structure of monosubstituted hydrazones (II: Y = H) has been most often discussed in the literature. It is accepted that three forms—hydrazone (XX), azo-compound (XIX), and alkenylhydrazine (XXI)—are possible:


(XIX) (XX) (XXI)

It is well known that hydrazones and the isomeric azo-compounds are able to exist independently, and also that azoalkanes and arylazoalkanes can be converted into hydrazones[9,11,13,14,42,43,56-58,62,63,81,98,99,102,103,131]. Thus many examples are known of the conversion into hydrazones of azo-compounds formed by coupling arenediazonium salts with aliphatic compounds[20], and also in the Japp-Klingemann reaction[21,140,141]. Diarylazo-compounds, formed by coupling monosubstituted hydrazones with arenediazonium salts, change into formazans either spontaneously or under the influence of alkalis[142,143]. It has been reported that azoalkanes, arylazoalkanes, arylazosteroids, and other azo-compounds are converted into hydrazones under the influence of acids[141,144-146], alkalis[144,147,148], and free radicals[144]. Dondoni and his coworkers have shown[147] that the catalytic activity of tertiary amines in converting azo-compounds into hydrazones in benzene solution is proportional to their pK_a-value in water. Furthermore, the catalytic activity of the amines depends on the type of solvent, diminishing in the sequence—anisole > chlorobenzene > dioxan > benzene—in the case of triethylamine. Several workers[145,147] have observed also the spontaneous transformation of azo-compounds into hydrazones: thus on prolonged storage methylazobenzene rearranges into benzaldehyde methylhydrazone[145].

Considerably greater divergence of views among investigators has been found on the question of the isomerisation of hydrazones into azo-compounds (see Refs. 3, 11, 13, 14, 57, 144, 145, and 149-157 and references in these papers). Baly and Tuck's communication[154] on the possibility of the conversion of phenylhydrazones into phenylazoalkanes by the ultraviolet irradiation of their solutions was criticised by Stobbe and Nowak[155]. Soon after this Busch and Dietz[156] isolated, instead of the expected azo-tautomer, a product of the autoxidation of the phenylhydrazone, which has since been found[149-153,158] to be an azo-hydroperoxide

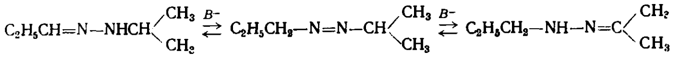

$$\underset{\displaystyle OOH}{\underset{|}{R-CH}}-N=N-Ph$$

(XXII)

The azo-hydroperoxide (XXII) differs from the azo-tautomer (XIX: X = H) in the presence of the HOO group attached to the carbonyl carbon, which, however, does not entail any great changes in the ultraviolet spectra of these compounds, studied for evidence of isomeric transitions. Therefore Grammaticakis[159] in 1948 and later O'Connor[57], both of whom used ultraviolet spectroscopy to study the changes undergone by arylhydrazones in solutions, reached the erroneous conclusion that the isomerisation hydrazone → azo-compound took place in solution. In fact, however, several investigations have shown[149-153,158] that autoxidation with formation of an azo-hydroperoxide (XXII) occurs under these conditions. O'Connor and Henderson's statement[152] that oxygen may not only take part in forming the hydroperoxide (XXII) but also catalyse the transition (XX) → (XIX) evidently requires verification, since repeated attempts to use this method to convert cyclohexanone phenylhydrazone into phenylazocyclohexane have been unsuccessful[13]. However, the possibility of the isomerisation of hydrazones into azo-compounds is supported by the formation of phenylazomethane when the product of the reaction between phenylhydrazine and formaldehyde is distilled in steam[154]. The use of alkali as catalyst for this reaction enables the azo-compound to be obtained as the main product[160].

Final confirmation of the isomerisation of hydrazones into azo-compounds has been given in a series of publications by Ioffe and his coworkers[28,145,161-163]. In 1965 they accomplished the isomerisation of alkylhydrazones of aliphatic aldehydes and ketones in the presence of an alkaline catalyst, the more volatile azo-compound being distilled off at the same time[161]. They later reported a series of such conversions[145,162], of alkylhydrazones of aromatic aldehydes[163] among others, and also the isomerisation of formaldehyde phenylhydrazone into phenylazomethane[28]. The rate of isomerisation of alkylhydrazones of aromatic carbonyl compounds is lower than that of aliphatic alkylhydrazones, evidently because the conjugated chain is considerably shorter in the latter than the chain of $\pi-\pi-p$ conjugation in the former molecules[163]. The possibility of the isomerisation (XX) → (XIX) is indicated also by the formation of diarylazo-compounds when arenediazonium salts are coupled with monosubstituted hydrazones[142,143]. Thus evidence for the isomerisation (XX) → (XIX) in the hydrazones is as indisputable as that for the isomerisation (XIX) → (XX). Only the phenylhydrazones of aliphatic carbonyl compounds have not yet proved capable of isomerisation, because of their tendency to Fischer cyclisation and nitrile cleavage[28], but even these difficulties can evidently be overcome by choosing appropriate conditions.

The occurrence of the isomeric transformations (XIX) → (XX) and (XX) → (XIX) indicated the possibility of the tautomeric equilibrium (XIX) ⇌ (XX). Numerous investigations have established that arylhydrazones, alkylhydrazones, semicarbazones, and thiosemicarbazones of aliphatic and aromatic aldehydes and ketones exist in the hydrazone form[9,11,13,14,18-20,38,42,56,58,81-84,102,144,145,149-151,158] and that the above tautomeric equilibrium is not established in the absence of a catalyst[157,162,163]. In 1967 Simon and Moldenhauer[157] noticed, while investigating hydrogen exchange in preparations labelled with tritium, that the equilibrium (XIX) ⇌ (XX) can be observed with phenylhydrazones and semicarbazones if alkali is added to their alcoholic solutions. From kinetic measurements the content of the azo-tautomer in an alkaline alcoholic solution of benzaldehyde phenylhydrazone has been estimated[107] as ~10^{-9}%. Ioffe[162,163] has shown that the content of the azo-form present in the equilibrium mixture in the presence of alkali is considerably higher with the alkylhydrazones of aliphatic and aromatic carbonyl compounds. The most probable explanation of this difference is the breakdown, on the isomerisation of benzaldehyde phenylhydrazone, in the length of the $\pi-\pi-p-\pi$ conjugation chain, which is absent in aliphatic alkylhydrazones[162]. The position of tautomeric equilibrium in alkaline solutions of alkylhydrazones depends on the structure of the substituents in both hydrazine and carbonyl portions of the hydrazone. The content of the azo-tautomer is greater in the alkylhydrazones of aldehydes than in those of ketones. Branching of the alkyl group of the hydrazine shifts the equilibrium towards formation of (XIX)[162]. Unsymmetrical azo-compounds can be obtained from various isomeric hydrazones, and three forms may then be present in equilibrium[157], for example[162]

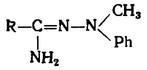


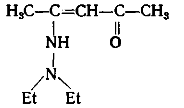
$$C_2H_5CH{=}N{-}NHCH\genfrac{}{}{0pt}{}{CH_3}{CH_3} \overset{B^-}{\rightleftarrows} C_2H_5CH_2{-}N{=}N{-}CH\genfrac{}{}{0pt}{}{CH_3}{CH_3} \overset{B^-}{\rightleftarrows} C_2H_5CH_2{-}NH{-}N{=}C\genfrac{}{}{0pt}{}{CH_3}{CH_3}$$

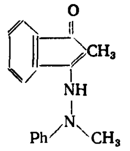
VII. ISOMERISM OF THE TYPE HYDRAZONE ⇌ ALKENYLHYDRAZINE

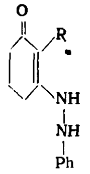
The concept of the hydrazone ⇌ alkenylhydrazine type of isomerism has considerable value for the interpretation of the mechanisms of certain reactions undergone by hydrazones, primarily the Fischer–Arbuzov reaction, and this isomerism has long been the subject of many investigations, very often being studied at the same time as the hydrazone ⇌ azo-compound isomerism. At an early stage Freer[164] drew attention to the ready oxidisability of some phenylhydrazones and the relative stability of others, and suggested that the former had an alkenylhydrazine structure; in confirmation he was able to establish differences in the chemical behaviour of the two groups of phenylhydrazones on reaction with oxygen, benzoyl chloride, etc. Subsequently the use of various chemical and physicochemical methods has shown that arylhydrazones, alkylhydrazones, disubstituted hydrazones, semicarbazones, thiosemicarbazones[9,14,56,58,102,103,157], and ω-methyl-ω-phenylamidrazones (XXIII)[165], as noted above, are present in the hydrazone form both in the solid state and in solutions. Quantum-chemical calculations have shown[96] that, for example, the semicarbazone form is energetically more advantageous than the alkenylhydrazine form by 15 kcal $mole^{-1}$. The hypothetical existence of the alkenylhydrazine form in solutions of arylhydrazones of aliphatic aldehydes and ketones, based on polarographic data[166], could not subsequently be confirmed[13,14].

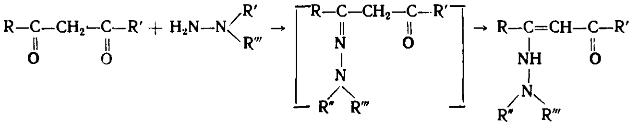
The alkenylhydrazine structure has been established for dialkylhydrazones (XXIV)[167], methylphenylhydrazones (XXV)[168], and monoarylhydrazones (XXVI)[11,169,170] of β-dicarbonyl compounds, derivatives of pentane-2,4-dione, cyclohexane-1,3-dione, indane-1,3-dione, 1-phenylpropane-1,3-dione, etc. The molten phenylhydrazone of ethyl acetoacetate is also regarded as having the alkenylhydrazine structure (XXVII)[170].


(XXIII)

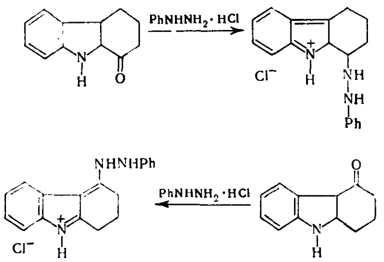

(XXIV)


(XXV)

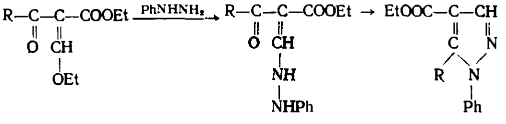

(XXVI)

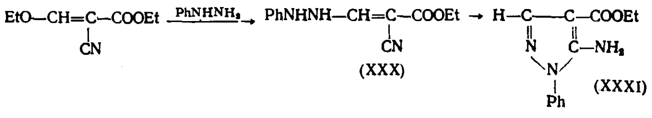

(XXVII)

The reaction of 1,2,3,4-tetrahydro-1(and 4)-oxocarbazoles with phenylhydrazine hydrochloride yields products, to which the alkenylhydrazine structure has been assigned on the basis of their infrared spectra[171]:

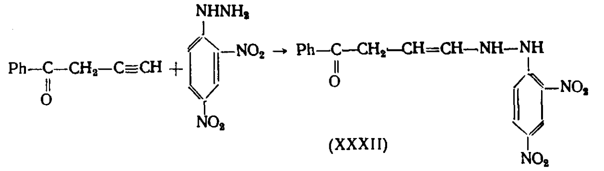


The alkenylhydrazine structure is possessed by the hydrazones of 5-formylbarbituric acids[172] and by compounds (XXVIII) and (XXX), which are prepared as follows[173-175]:

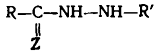

(XXVIII) (XXIX)


(XXX) (XXXI)

Alkenylhydrazines of type (XXVII) can sometimes be formed by the reaction of acetylene derivatives with arylhydrazines[176]:

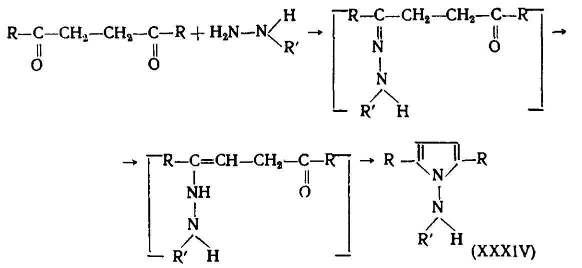

(XXXII)

Unsubstituted and β-substituted hydrazides and thiohydrazides of carboxylic acids


$$\mathrm{R{-}\underset{\underset{Z}{\|}}{C}{-}NH{-}NH{-}R'}$$
(XXXIII)

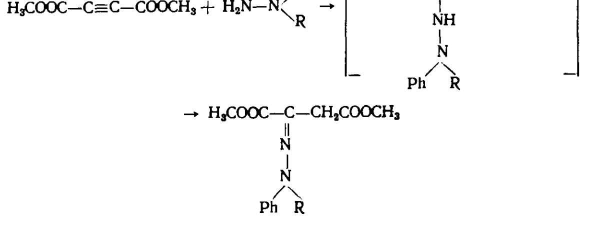
(where Z = O, S and R' = H, Alk, Ar, Az) represent a kind of alkenylhydrazine (cf. II, XX, XXI) in which the α-carbon atom has been replaced by a heteroatom.

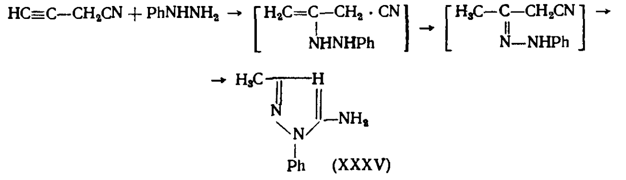
The possibility of the isomerisation hydrazone → alkenylhydrazine (XX → XXI) is suggested by the numerous examples of the formation of 1-aminopyrroles when γ-dicarbonyl compounds react with hydrazine hydrate and with the hydrazides of formic, acetic, benzoic, isonicotinic, phthalic, and other acids[11,177,178]:


(XXXIV)

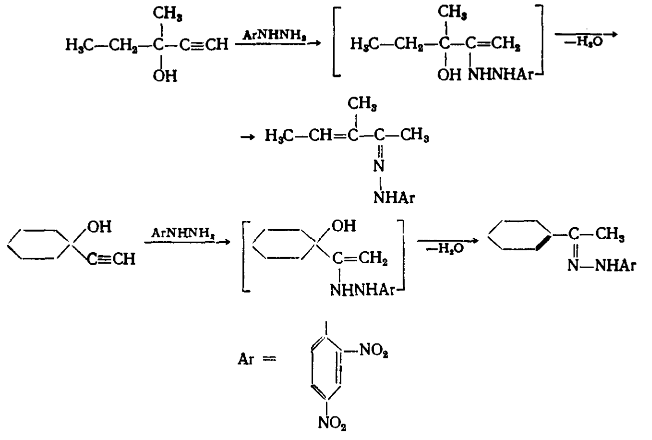
It is supposed that formation of the compounds (XXIV)–(XXVII) also passes through a hydrazone stage. The concept of the isomerisation (XX) → (XXI) is widely used in explaining the mechanism of the Fischer–Arbuzov preparation of indoles from arylhydrazones[5-7,15]. Similar isomerisation had been suggested earlier[179] to explain the formation of osazones from α-hydroxycarbonyl compounds and hydrazine derivatives, and has been confirmed by the most recent investigations[180].

Isomerisation of alkenylhydrazines into hydrazones (XXI → XX) can be observed when arylhydrazines react with acetylene derivatives. The alkenylhydrazines can be isolated only in certain cases (e.g. XXXII [176]), the reaction usually yielding arylhydrazones or products of their further conversion[11,181]:



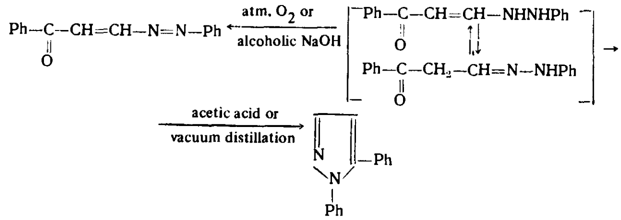

(XXXV)

With derivatives of prop-2-ynol the reaction is accompanied by dehydration[182]:

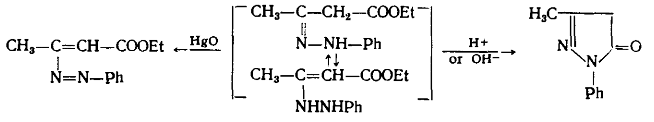


When heated in acetic acid the alkenylhydrazines (XXVIII) and (XXX) are converted into the corresponding pyrazole derivatives (XXIX) and (XXXI), which apparently involves an intermediate stage of isomerisation into the hydrazones[174,175].

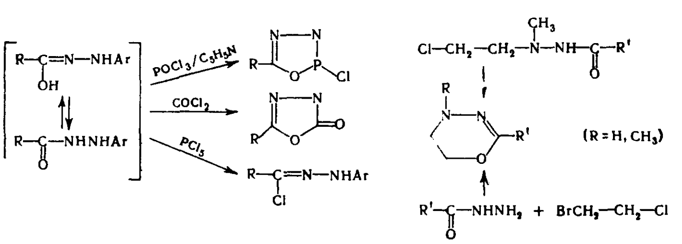
The possibility of the tautomeric equilibrium hydrazone ⇌ alkenylhydrazine (XX ⇌ XXI) is probably suggested by the dual reactivity of the arylhydrazones of β-dicarbonyl compounds and of the hydrazides, thiohydrazides, and hydrazones of certain heterocyclic compounds, e.g. pyrimidine derivatives, etc.[11,19,22]. Aryl hydrazones of β-dicarbonyl compounds (XXIV–XXVII): R″ = H) are converted by oxidants into azoalkenes, but when distilled or heated in acetic acid they are cyclised into pyrazole derivatives[11,169]:



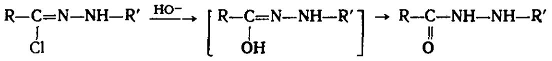
Similar behaviour is shown by the unstable phenylhydrazone of ethyl acetoacetate, obtained in ethereal solution from the ester and phenylhydrazine. When heated with mercury(II) oxide in alcohol it forms ethyl phenylazocrotonate, but in acid and alkaline media it cyclises into 3-methyl-1-phenylpyrazolone[183]:



There are numerous examples of reactions in which hydrazides, thiohydrazides, and diacylhydrazines behave as compounds having an α-hydroxy-hydrazone structure[11,19,22,184,185]:

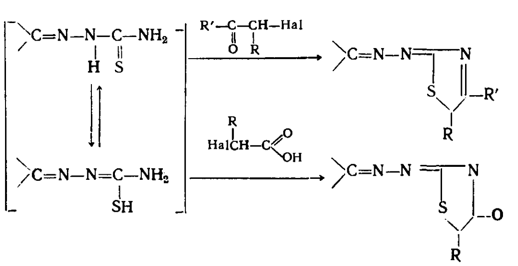


And conversely, the hydrolysis of α-halogeno-hydrazones results in separation of a hydrazide[11,186], instead of the α-hydroxy-hydrazone, which is also an example of the isomerisation (XX) → (XXI):



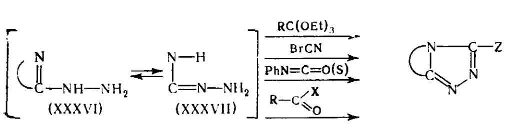
$$\underset{Cl}{\underset{|}{R{-}C}}{=}N{-}NH{-}R' \xrightarrow{HO^-} \left[\underset{OH}{\underset{|}{R{-}C}}{=}N{-}NH{-}R'\right] \rightarrow \underset{O}{\underset{\|}{R{-}C}}{-}NH{-}NH{-}R'$$

The widely known[187-194] condensations of thiosemicarbazides and thiosemicarbazones with α-halogeno-carbonyl compounds and α-halogeno-carboxylic acids to form thiazoline derivatives are based on their capacity for thione ⇌ thiol tautomerism[98], which in this case is a further variety of the hydrazone ⇌ alkenylhydrazine tautomerism:

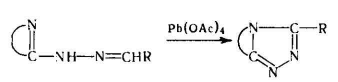


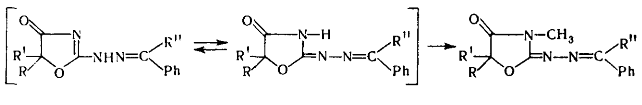
An analogous reaction is characteristic of selenocarbazide and selenocarbazones[195].

Examples of dual reactivity are widely known also with heterocyclic hydrazines containing the grouping (XXXVI) (cyclic amidrazones). They undergo not only reactions characteristic of the hydrazine structure but also reactions characteristic of the hydrazone form (XXXVII)[11,17,196]. Tautomerism of the given type is usually assumed[197]:



(X = Hal, OAlk, OH, OCOR); Z = R, NH$_2$, Ph, OH, SH)

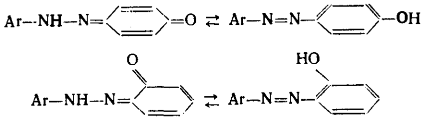




However, dual reactivity merely suggests the possibility of the transitions (XX) → (XXI) and (XXI) → (XX), but does not prove the establishment of tautomeric equilibrium, although the occurrence of tautomerism is very often deduced from this fact[5-7,11,15,140,198,199]. Although dual reactivity may be a consequence not of tautomerism but of migration of the reactive centre in the system, it is very likely that equilibrium is actually established in several cases. Thus Razumov et al.[200] have recently reported occurrence of the tautomerism (XX) ⇌ (XXI) in the hydrazides of phosphorylated carboxylic acids, and a paper already referred to[157] has reported establishment of the above tautomeric equilibrium in certain semicarbazones in alkaline alcoholic solutions, although it is very greatly displaced towards the hydrazone tautomer. But the above papers still do not permit any final or general conclusions to be drawn, and the question of the occurrence of the hydrazone ⇌ alkenylhydrazine tautomerism has not yet been finally settled.

VIII. OTHER TYPES OF ISOMERISM OF HYDRAZONES

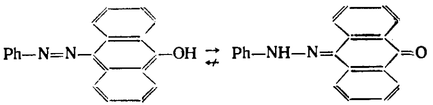
Prototropic isomerism of the quinone arylhydrazone ⇌ hydroxyazobenzene type, which is closely similar to the hydrazone ⇌ azo-compound type, has been known for a long time, widely studied, and discussed repeatedly[11,13,201,202]. Whereas the isomerisation (XX) ⇌ (XIX) involves 1,3-migration of a hydrogen atom, the isomerisation of arylhydrazones of quinones involves 1,7-migration of a proton in derivatives of *p*-benzoquinone and 1,5-migration in those of *o*-benzoquinone. In view of the above and several other peculiarities, this isomerism is usually considered individually, most often in relation to the structure of azo-dyes[202]. These changes were studied considerably earlier and in greater detail than the isomerism (XX) ⇌ (XIX). Detailed investigations have been made of the transitions (XXXVIII) → (XXXIX) and (XXXIX) → (XXXVIII), and also of cases of the tautomerism



(XXXVIII) (XXXIX)

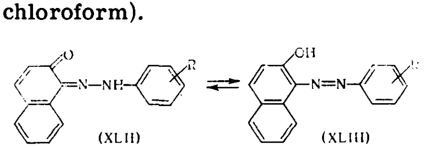
The numerous papers on this problem have been summarised in a review by Ershov and Nikiforov[25].

Whereas benzoquinone derivatives exist in the azo-form even in solution, certain substituted derivatives of naphthaquinone and anthraquinone exhibit a tautomeric equilibrium of the type (XXXVIII) ⇌ (XXXIX) in solution, and 10-phenylazoanthrol (XL) exists only in the hydrazone form (XLI) (see bibliography in Ref. 25):



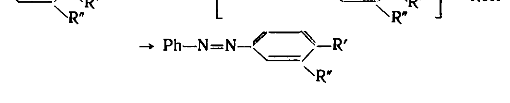
(XL) (XLI)

Substituents in both parts of the molecule have a substantial effect on the position of equilibrium. Accumulation of azo and hydroxyl groups in the quinone ring tends to shift the equilibrium towards the hydrazone form[25,203-205]. The influence of substituents in the phenyl ring of the hydrazine component on the position of the equilibrium (XXXVIII) ⇌ (XXXIX) is illustrated by Table 3[206] for the series 1-R-phenylazo-2-naphthol (solution in deuterated chloroform).



(XLII) (XLIII)

Derivatives of *p*-quinones react comparatively readily with substituted hydrazines, but the resulting hydrazones are converted under the reaction conditions into azobenzenes, with the loss e.g. of an alcohol molecule[207]:



Prototropic isomerism, closely similar to the alkenylhydrazine → hydrazone type of isomerism, was observed by Ioffe and Kochetov with allylhydrazones, which in the presence of alkalis are converted into mixed azines[208]:

$$\mathrm{AlkCH{=}N{-}NH{-}CH_2{-}CH{=}CH_2 \xrightarrow{HO^-} AlkCH{=}N{-}N{=}CH{-}CH_2{-}CH_3}$$

Another type of isomerism, in which the double bond migrates from the nitrogen atom into the aliphatic chain (beyond the α-position), was reported by Abramovitch and Spenser[53], though for cyclic hydrazones:

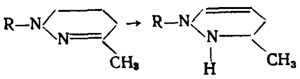
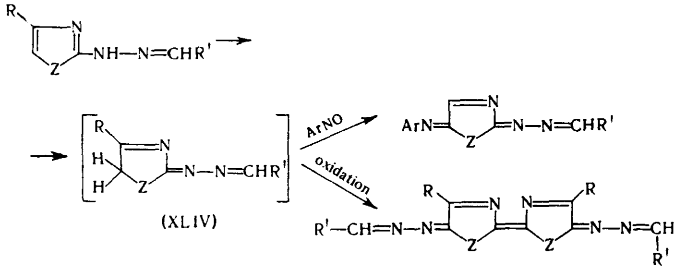


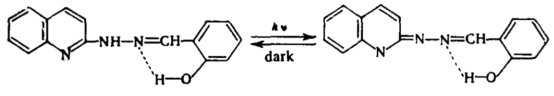
Table 3. Content of hydrazone form in the system (XLII) ⇌ (XLIII)[206].

R	(XLII), %	R	(XLII), %
4-CN	97	H	79
3-CN	91	4-HCl	78
3-Cl	81		
3-OMe	81	4-Me	69
3-Me	80	4-OMe	52

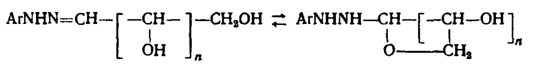
Thiazol-2-ylhydrazones[209] and selenazol-2-ylhydrazones[195] behave in certain reactions probably in the isomeric form (XLIV), which is formed by migration of a hydrogen atom from the hydrazone group to the 5-position in the ring:


(XLIV)

Wong and Bruscato[210] invoke analogous migration of a hydrogen atom into a heterocyclic ring to explain the photochromism of quinolylhydrazones, which had previously been explained[24] by hydrazone ⇌ azo-compound isomerisation:



Arylhydrazones of sugars exist in two isomeric forms: in the hydrazone (XLV) the carbohydrate radical has an open chain; the hydrazine (XLVI) contains the carbohydrate residue in a cyclic configuration[31,36,211-214]:

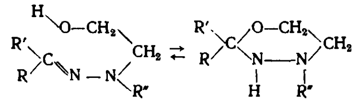


$$\mathrm{ArNHN{=}CH{-}\left[{-}\underset{OH}{CH}{-}\right]_n{-}CH_2OH \rightleftarrows ArNHNH{-}CH{-}\left[{-}CH{-}OH\right]_n}$$

(XLV) (XLVI)

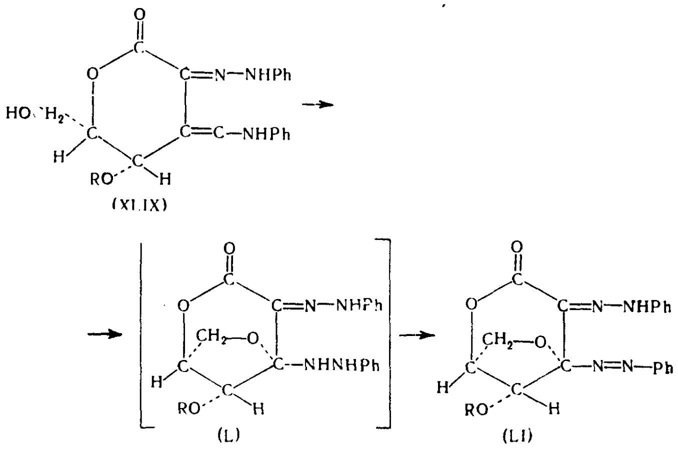
X-Ray examination indicates that ribose p-bromophenylhydrazone exists in the crystalline state in the hydrazone form[31], whereas arabinose p-bromophenylhydrazone is present in the hydrazine form[36], and many similar examples are known. Open-chain products are formed when (XLVI) is acylated[211]. This suggests that the isomerisation (XLVI) → (XLV) takes place, which is confirmed by a study of the polarographic behaviour of arabinose phenylhydrazone[212], this compound existing in the solid state in the form (XLVI). The tautomeric equilibrium (XLV) ⇌ (XLVI) may be established in solutions of the arylhydrazones of sugars, as is confirmed by spectral data[213,214].

Whereas the tautomerism (XLV) ⇌ (XLVI) is established in the hydrazones of sugars by addition at the C=N bond of a hydroxy-group present in the carbonyl component, Ioffe and Potekhin[215,216], simultaneously with Dorman[217], described a new type of ring–chain tautomerism, involving addition at the C=N bond in the hydrazone of a hydroxy-group present in the hydrazine component:


(XLVII) (XLVIII)

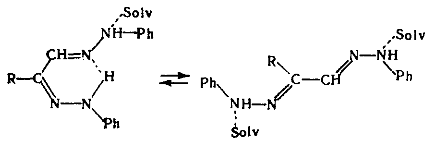
This tautomeric equilibrium is established both in solutions and in the pure substances (liquids) in the case of derivatives of aliphatic carbonyl compounds. Increasing the temperature, the polarity of the solvent, and the molecular weights of the radicals R and R′ and decreasing the molecular weight of R″ tend to increase the content of the hydrazone form (XLVII). Unsubstituted 2-hydroxyethylhydrazones (R″ = H)[215] and also the derivatives (XLVII) of aromatic aldehydes exist in the hydrazone form[216].

The conversion of (XLIX) into (LI) by the action of a periodate, described by El Khadem and El Ashry[218], is easily explained on the assumption that (L) is formed as an intermediate product:

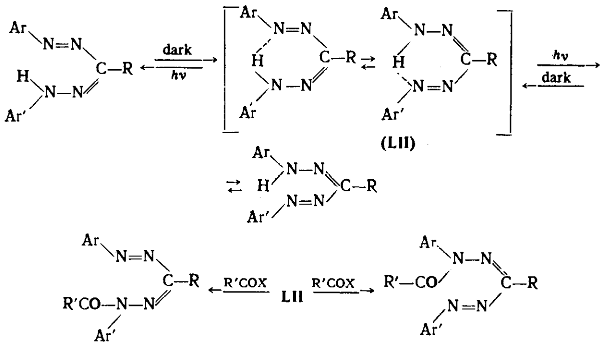

(XLIX)

(L) (LI)

Bisphenylhydrazones of α-dicarbonyl compounds are known to exist in a chelate form[110,111], which is present in solutions in equilibrium with the isomeric open-chain form[111]:



Formazans are in general capable of the interconversions indicated below, and a tautomeric equilibrium is apparently established in solution, as is indicated by the results of acylation, when both possible acylformazans are obtained from (LII)[1,2,10]:



IX. INTRAMOLECULAR INTERACTIONS

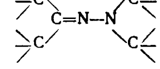
The presence of the grouping

$$\rangle C{=}N{-}N\langle \qquad \text{(I)}$$

makes hydrazones a convenient model for studying $\pi-p$ conjugation[9,14,27,28,39,56,59,60,70,79-85,93,94,163,219-221]. The chief condition for interaction to occur between the π-electrons of the C=N bond and the lone pair of electrons on the amine nitrogen atom is that the hydrazone fragment (I) should be planar[31-33], which permits appropriate orientation of the p- and π-orbitals. The development of the $\pi-p$ type of conjugation in the molecules of hydrazones has been observed in studies of the infrared[59,60,69,70], Raman[79,81,82], ultraviolet[84,85,93,94], and nuclear magnetic resonance[219] spectra and also the optical properties of these compounds[27,28,56,94,220,221]. When conjugation is present, the electronic spectra of hydrazones show a bathochromic shift in the band corresponding to the $\pi \rightarrow \pi^*$ transition[84,85,93,94]. In the vibrational spectra $\pi-p$ conjugation leads to a lowering of the C–N stretching frequency[59,60,70,79,81,82]; in such hydrazones the C–N frequency lies in the range 1590–1620 cm^{-1}, whereas in aliphatic imines it lies between 1650 and 1670 cm^{-1} [34]. The higher the degree of conjugation the larger is $\Delta\lambda$ or $\Delta\nu$. The simple mono- and di-alkylhydrazones of saturated and unsaturated aldehydes and the phenylhydrazone of formaldehyde show high exaltation of molecular refraction, which indicates a considerable degree of conjugation in these systems[27,28,56,220,221]. Whereas in unsaturated hydrazones and alkylhydrazones, in semicarbazones and thiosemicarbazones, $\pi-p$ conjugation occurs within the hydrazone group[27,81,82,94], in arylhydrazones the π-system of the benzene ring is involved in conjugation, $\pi-p-\pi$ conjugation now being observed[28,59,60,81], and in alkylhydrazones of aromatic and unsaturated aldehydes $\pi-\pi-p$ conjugation is present[56,94,163,220,221].

A specific effect of conjugation in hydrazones is an increase in intensity of the C=N absorption band in the Raman spectra on passing from unsubstituted hydrazones to alkylhydrazones[14] and an increase in the exaltation of molecular refraction on passing from mono- to di-alkylhydrazones of $\alpha\beta$-unsaturated aliphatic aldehydes[220]. These facts indicate an increase in degree of conjugation, which can be explained by a change in the hybridisation of the electron orbitals of the amine nitrogen atom in the hydrazone group. In unsubstituted hydrazones the hybridisation of this atom is close to sp^3, and the orbital of its p-electrons is not parallel to that of the π-electrons of the C=N bond, although partial overlapping is already possible. Substitution on the amine nitrogen changes the pyramidal configuration of its bonds into a planar arrangement, as a consequence of which the hybridisation of the nitrogen atom approaches sp^2, which increases the overlapping of p- and π-orbitals[14].

Steric hindrance is one factor affecting the degree of $\pi-p$ conjugation in the hydrazone group. A considerable diminution in the conjugation effect is noticeable in the methylphenylhydrazones of aldehydes[59], and conjugation of the given type is almost completely absent in the methylphenylhydrazones and dialkylhydrazones of ketones[60,93,94]. The reason for the decrease in and even complete absence of $\pi-p$ conjugation when an alkyl group is introduced into a monosubstituted hydrazone of a ketone is that, owing to steric hindrance, the grouping



cannot be planar, as is readily evident when the structure of these compounds is examined with Briegleb–Stuart models: the groups are deflected about the N–N bond, which destroys the appropriate orientation of π- and p-orbitals.

Kitaev and his coworkers[39] have remarked that in azines, in which a considerable conjugation effect had been reported earlier[79], the $\pi-p$ type of conjugation is more strongly developed than the $\pi-\pi$ type, as might have been expected from the planar structure of azine molecules (III). The deflection of the C=N groups about the N–N bond (Fig. 2) is confirmed by spectroscopic data[38,39,51] and by the results of an investigation of the structure of azines by means of the dipole moments[39]. The conditions for $\pi-\pi$ conjugation are destroyed by the deflection, and at a certain angle of rotation (θ = 60–70°) the π-orbitals of one C=N group become able to interact with the p-orbital of the nitrogen atom in the other C=N group[39].

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Arbuzov Institute of Organic and
Physical Chemistry, USSR Academy
of Sciences, Kazan

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Hexamethylphosphoric Triamide in Organic Chemistry

H.Normant

CONTENTS

I. INTRODUCTION

Chemists have recently being paying increasing attention to the effect of solvents on the occurrence of chemical reactions, especially the effect of dipolar aprotic solvents [1-5]. Among the latter the most interesting is the hexamethyltriamide of orthophosphoric acid $OP(N(CH_3)_2)_3$ (Hexametapol) or trisdimethylaminophosphine oxide. It is often denoted by the letters HMPA or HMPT†; the latter designation seems to be the better, since it reflects the triamide character of the compound. Recent publications on this solvent [6-8] refer in particular to its immense solvent power for a large number of organic and inorganic substances and macromolecular compounds, and also to its use as a copolymerisation catalyst.

The present Review presents data on the physical and chemical properties of hexamethylphosphoric triamide and its use as a reaction medium.

II. PHYSICAL AND PHYSICOCHEMICAL PROPERTIES

Triamides of orthophosphoric acid were obtained by Michaelis [9] by the reaction of phosphoryl chloride with excess of a secondary amine. When dimethylamine is used, this reaction yields the hexamethyltriamide of orthophosphoric acid:

$$O{=}PCl_3 + 6HNMe_2 \rightarrow O{=}P(NMe_2)_3 + 3Me_2\overset{+}{N}H_2Cl^-$$

When this reaction is conducted in an inert solvent, the first chlorine atom in the phosphoryl chloride molecule is easily replaced (exothermic process), but the system must be heated to effect substitution of the remaining two chlorine atoms. The hydrogen chloride liberated in the reaction is neutralised with sodium carbonate, ammonia, or other base, which diminishes the consumption of dimethylamine. After separation of the salts (dimethylamine hydrochloride, sodium carbonate, ammonium chloride) the filtrate contains HMPT, which is purified.

Hexamethylphosphoric triamide is a mobile, colourless liquid, which is miscible with water in all proportions. It forms complexes with chlorinated solvents [10], and can therefore be isolated from aqueous solutions of the latter. Table 1 gives partition coefficients for the amides—dimethylformamide (DMF), methylacetamide (MA), and HMPT—in mixtures of chloroform, methylene dichloride, and ethylene dichloride with water.

Table 1.

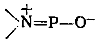
Compound	DMF	MA	HMPT
$CHCl_3$—H_2O	0.77	0.099	5.53
CH_2Cl_2—H_2O	0.57	0.088	2.07
ClC_2H_4Cl—H_2O	0.29	0.039	0.58

Hexamethylphosphoric triamide is miscible with polar and non-polar organic liquids, but not with saturated hydrocarbons (petroleum ether). It is an exceptional solvent for a large number of polymers [6], various gases [6], and a large number of inorganic salts [8]‡.

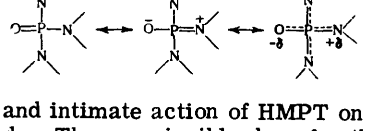
Hexamethylphosphoric triamide has a pyramidal structure [11]. The P–O bond may be more or less ionic or covalent in character in different molecules depending on the substituents [11,12]:

$$F_3P{=}O \qquad (Me_2N)_3\underset{\delta^+}{P}{=}\!{=}\underset{\delta^-}{O} \qquad Me_3\underset{+}{P}{-}\underset{-}{O}$$

In the HMPT molecule it is usually accepted that the P–O bond is 50% ionic, whereas the NPO bond can be represented as



Thus the following limiting structures



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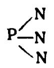
†The abbreviation HMPTA is also used in the literature.

‡Prolonged and intimate action of HMPT on the skin must be avoided. The permissible dose for the rat is 6 g kg^{-1}.

are suggested for the HMPT molecule. The symmetrical distribution of positive charge on the grouping



and the enhanced electron density on the oxygen atom confer both electron-acceptor and electron-donor character on the HMPT molecule.

The melting point of HMPT is 7.20°C, and its cryoscopic constant 6.93 ± 0.07.[14] It boils at 235°C (760mm)[15], 125°C (15 mm), 120°C (10 mm),[10] and 68–70°C (1 mm). The vapour pressure is very low at ordinary temperature (0.07 mmHg at 30°C),[17] and its temperature dependence has been published[18]. The density is $d_4^{20} = 1.0253$.[19] Values published for the refractive index are $n_D^{20} = 1.4582$[19] and $n_D^{25} = 1.4570$;[20] another publication[21] reports values measured by various methods at various wavelengths. The viscosity is 3.5 cS at 60°F.[15] The dielectric constant is $\epsilon_{20°} = 30$,[4] and its temperature dependence has been published[22]. The dipole moment $\mu = 4.31$ D;[13] however, values obtained for the pure liquid (5.37 D) and in benzene solution (5.54 D) differ greatly from this value[22].

Table 2.

Stretching vibration	Absorption band, μm
C—N	7.1—9.8
P—O	7.5—8.5
P—N	⩾ 13.9

The compound absorbs in the infrared[21] (Table 2). The frequency of the P–O bond is 8.7 μm.[23] The position of this band varies little[24] with the nature of the solvent: it occurs at 8.26, 8.32, 8.32, 8.30, and 8.28 μm in carbon tetrachloride, chloroform, pentachloroethane, 1,1,2,2-tetrachloroethane, and methylene dichloride respectively.

The enthalpy of formation from phosphoryl chloride and dimethylamine is $H_{f(gas)} = 114$ kcal mole^{-1}.[25]

The ^{31}P chemical shift in the nuclear magnetic resonance spectrum, relative to 85% orthophosphoric acid, is $\delta = 23.4$ ppm.[26]

1. Properties of Hexamethylphosphoric Triamide

The ability of a solvent to supply its pair of electrons to a compound AH (e.g. chloroform) can be assessed by various physicochemical methods, in particular by means of nuclear magnetic resonance[27]. For every solvent we can calculate the quantity $\delta_\infty(CHCl_3)$:

$$\Delta\delta_\infty(CHCl_3) = \delta_\infty - \delta$$

where δ_∞ and δ are obtained by extrapolating to infinite dilution solutions of chloroform in the given solvent and in an inert solvent (cyclohexane) respectively. The values in Table 3 were first determined by Martin[28], published later[29], and confirmed by another worker[4].

Infrared spectroscopy has yielded similar results. Increase in the basic strength of the solvent is accompanied by a considerable change in the C–Br frequency in aliphatic and unsaturated bromides. The same changes have been shown to occur with solvent–bromide interaction as with solvent–proton interaction[29,30].

Table 4 lists some characteristics of dipolar aprotic solvents. It is readily seen that, among the solvents included, HMPT has the lowest dielectric constant and the greatest basic strength. Because of its electric-donor power HMPT associates with organic and inorganic compounds.

Table 3.

Solvent	$\Delta\delta_\infty$	Solvent	$\Delta\delta_\infty$
Cyclohexane	0	Cyclohexanone	1.06
Dioxan	0.64	$OP(OC_4H_9)_3$	1.28
$P[N(CH_3)_2]_3$	0.68	DMF(dimetliylformamide)	1.30
Ether	0.70	DMSO (dimethyl sulphoxide)	1.34
Oxolan	0.80	TMU (tetramethylurea)	1.37
Acetone	0.94	HMPT	2.03

Thus HMPT is able to form various complexes with compounds containing a labile hydrogen atom. These include, besides chloroform[31], polyhalogenated ethanes[24]. Solvation occurs at the oxygen atom of the phosphoryl group, not at a nitrogen atom. Study of the infrared spectra enables these compounds to be arranged in the sequence of diminishing electron-acceptor power:

$$CHCl_3 > CHCl_2—CCl_3 > CCl_2H—CHCl_2 > CH_2Cl_2$$

The sequence

$$(Me_2N)_3PO > (EtO)_3PO > (EtS)_3PO > (PhS)_3PO > (Et_2N)_3PO$$

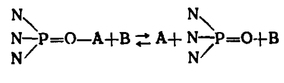
shows that the electron-donor character of HMPT exceeds that of the other phosphorus oxides, its homologue $((C_2H_5)_2N)_3PO$ coming at the end of the series[32].

Table 4.

Solvent	Dielectric constant ϵ	Dipole moment, D	Δj, ppm
DMF	36.7	3.90	0.78
DMSO	49	4.03	1.05
Ethylene glycol	95	4.86	0.41
Thiolan dioxide	44	4.7	0.78
HMPT	30	4.3—5.3	1.89

Acids, phenols, alcohols, aromatic amines, and glycols form stable crystalline complexes with HMPT (Table 5).[33] Among acids which form complexes with HMPT are nicotinic, isonicotinic, and *o*- and *m*-toluic acids. The toluidines (*ortho- meta-* and *para*) must be included with aniline; 1- and 2-naphthols and various chlorinated phenols must be included with phenol itself[34].

A complex formed by HMPT with a compound A containing a hydrogen atom can be broken down by a stronger acid B:

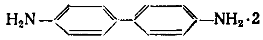


$$(N)_3P{=}O{-}A + B \rightleftarrows A + (N)_3P{=}O{+}B$$

This method can be used in the separation of acids; it has been employed to separate terephthalic acid from isophthalic acid[33].

A study has been made of the infrared spectra of the complexes formed by HMPT with ketones and with hydrogen halides. The association constant of HMPT with the latter compounds increases in the sequence—HBr < HCl < HF—whereas the acidity diminishes in this sequence, from hydrogen bromide to hydrogen fluoride[35].

Table 5.

Compound		M.p., °C
$C_6H_4(COOH)_2 \cdot 2$ HMPT	*ortho-* *meta-* *para-*	70 52 128
 $\cdot 2$ HMPT		152
$C_6H_5CH_2OH \cdot$ HMPT		10
$C_6H_5NH_2 \cdot$ HMPT		<0
 $\cdot 2$ HMPT		132
$C_2H_4(OH)_2$.2HMPT		—20

It has been reported[33] that HMPT forms complexes with various unsaturated hydrocarbons—$CH{:}CH$, $CH{:}C$, $CH_2{:}CH$, $CH{:}C.C_6H_5$, $CH_2{:}CH.CH{:}CH_2$, $CH_2{:}CH.C_6H_5$—but no information is available on the structure of these complexes.

Basic solvents are known to form complexes with Lewis acids, the complex being more stable the more basic the solvent: $(C_2H_5)_2O.BF_3$ < Oxolan.BF_3 < HMPT.BF_3. Examples of crystalline complexes of HMPT with certain Lewis acids are given below.

Complex	M.p., °C	Ref.
HMPT x BF_3	175	35
HMPT x $BClPh_2$	159-160	37
HMPT x $POCl_3$	170-180	
HMPT x $POBr_3$	165-180	

Table 6.

Metal	Complex	Anion
Ag	MSX	halide
Co, Ni, Mn, Fe^{II}, Cu^{II}	MS_2X_2	halide
Pb^{II}	MS_3X_2	halide
Mg, Zn, Cd	MS_4X_2	halide
Co, Ni, Mn, Fe^{II}	MS_4X_2	ClO_4^-
Cr^{III}, Fe^{III}	MS_6X_3	halide
Ti, Sn	MS_2X_4	halide

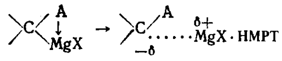
Crystalline complexes can be obtained also by the reaction of HMPT with certain metal salts. The infrared spectra and the dipole moments show that coordination with metal cations takes place at the oxygen atom in the phosphoryl group[13,38]. The number of solvent molecules involved in complex formation may vary. Neutral molecules of the type MS_2X_2 and ions of the type $[MS_4]^{2+}$ have a tetrahedral structure[13,38]. Table 6 gives the types of complexes formed with various metal salts.

Stable complexes of HMPT with thorium and uranium tetrachloride and tetrabromide have been obtained recently, and have proved to be more stable than analogous complexes with dimethyl sulphoxide[39]. Thus the more basic is a dipolar aprotic solvent, the more easily does it form complexes.

The stability of solvated organomagnesium compounds increases with increase in the basic strength of the solvent, and a more basic solvent can displace a less basic solvent from a solvate[36]:

$$2(C_2H_5)_2O.RMgX < 2\ \text{Oxolan}.RMgX < 2HMPT.RMgX.$$

Symmetrical organomagnesium compounds are soluble in HMPT.[40] Insoluble compounds RMgX.2HMPT are formed with RMgX, and very stable complexes $MgBr_2$.4HMPT with magnesium bromide[41]. Geminal organomagnesium compounds



(I) (II)

where A = OR[42] or Hal[43] are intramolecular complexes. Addition of HMPT favours stabilisation and increase in reactivity of the ionised form (II) formed from the carbenoid form (I). However, the rate of the double decomposition

$$CH_3.CH{:}CH.CH_2\text{-}Zn + CdCl_2 \rightleftharpoons CH_3.CH{:}CH.CH_2\text{-}Cd + ZnCl_2$$

decreases with increase in the basic strength of the solvent as the cadmium atom becomes more solvated[44]. Because of the immense solvating power of HMPT, organometallic compounds can be obtained by their direct reaction with metals; organocadmium compounds have been obtained in this way[45]. Among the saturated halogen compounds only the iodides have been studied. With unsaturated bromides HMPT forms complexes at 0°C. A complex of melting point 112°C, soluble in acetone, has been obtained from cadmium bromide and HMPT.

2. Use of Hexamethylphosphoric Triamide in Electrochemistry

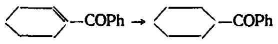
Little use has been made of HMPT as a solvent for electrochemical purposes. The literature contains no information on its application as solvent in polarography.

A voltametric study of HMPT has enabled a stable reference electrode of the Ag/Ag^+ type to be obtained. The electrical activity of HMPT depends considerably on the nature of the cation present and on the water content of the medium[46]; it has been studied in a medium containing sodium and lithium perchlorates with different quantities of water. The results indicate that HMPT differs greatly from other solvents[47,48]. It can also be used as a solvent for electrolysis. Metal salts which dissolve in it[49] undergo ionisation with the formation of ion-pairs, and perhaps dissociation with the formation of ions.

In some cases ionisation results in the formation of coloured anions (HMPT solvates anions weakly). Thus deeply coloured red solutions are formed on the dissolution in HMPT of certain organometallic compounds, e.g. $(C_6H_5)_3CM$, $(C_6H_5)_2CHM$, and $C_6H_5CH_2M$, where M represents an alkali metal or MgX. An ethereal solution of benzylmagnesium chloride is colourless, but a solution of the same compound in HMPT has the characteristic red colour of the benzyl anion[47,48].

It has not proved possible to electrolyse organometallic compounds in HMPT. However, inorganic salts can be electrolysed by using a soluble anode M and a platinum cathode (where MX = $MgBr_2$, which is soluble in ether as $2(C_2H_5)_2O.MgBr_2$; and MX = CaI_2).

The electrolytic reduction of an α-unsaturated ketone to a saturated ketone takes place in HMPT with an 80% yield[49]:



3. Polarity of Solvents

The term polarity in reference to dipolar aprotic solvents must be taken as implying various physical quantities (ϵ, μ, $\Delta\delta$, ...). The nucleophilic substitution

$$n\text{-}C_4H_9Br + N_3^- \rightarrow n\text{-}C_4H_9N_3 + Br^-$$

can be used for comparing solvents. The rate constant and the activation energy of this reaction conducted in HMPT indicate the exceptional role of this solvent (a high value of k and an abnormally low value of E are observed). Satisfactory correlation is obtained between the dependence of $\lg k$ on $1/\epsilon$ and on $\Delta\delta$ (ppm).[4]

The polarity of solvents can be expressed also in terms of semi-empirical parameters, such as the constant Z[50,51] or the parameter F[52]. According to the values of Z protic and dipolar solvents can be arranged in the sequence

CH_3OH, C_2H_5OH, t-C_4H_9OH, CH_3CN, $HCON(CH_3)_2$, $CHCl_3$, HMPT, Iso-octane

and according to the values of F in the sequence

CH_3OH, C_2H_5OH, t-C_4H_9OH, CH_3CN, HMPT, $HCON(CH_3)_2$, $CHCl_3$, Iso-octane

The above results show the "ambivalence" of HMPT.[52]

III. CHEMICAL PROPERTIES

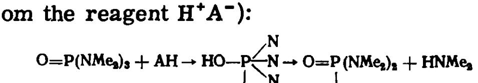
1. Action of Nucleophilic Reagents

Hexamethylphosphoric triamide exhibits considerable resistance to attack by nucleophilic reagents (unlike the amides of carboxylic acids, it does not undergo hydrolysis in alkaline media), and can itself be used as a nucleophilic and basic reagent.

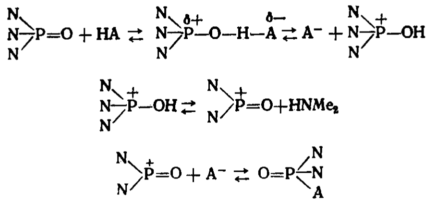
Various derivatives of the alkali metals can be obtained in HMPT. Alkali-metal hydroxides do not react with HMPT at 80°C, but do so at higher temperatures (110 to 120 °C). The inertness of HMPT towards nucleophilic reagents can be explained by great steric hindrance around the positively charged phosphorus atom.

2. Action of Electrophilic Reagents

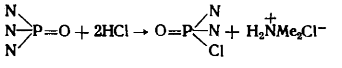
Protic acids and Lewis acids act vigorously on HMPT, with replacement of one or more dimethylamino-groups by A (from the reagent H^+A^-):



Because of the strongly developed basic character of the solvent, electrophilic reagents also form 1 : 1 complexes with it. These complexes, which are more or less stable, give various substitution products when heated. The mechanism of the reaction is assumed to be

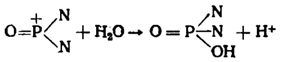


Dry gaseous hydrogen chloride reacts with HMPT according to the equation

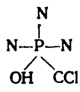


Further cleavage of P–N bonds does occur, but with great difficulty.

In aqueous media the dimethylamino-group is replaced by hydroxyl:



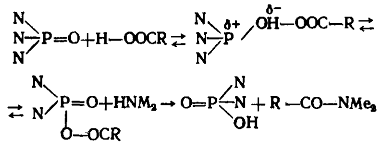
In acid media the rate of hydrolysis is of the same order as for the CO–$N(CH_3)_2$ bond[16]. The complex formed by HMPT with chloroform is unstable, and decomposes when heated. Among the reaction products HO–$P(N(CH_3)_2)_2$ has been identified[53] by nuclear magnetic resonance. According to the above scheme a pentacoordinated phosphorus derivative



should be present during the reaction, which seems improbable. Carboxylic acids yield stable complexes (1 : 1) with HMPT, their decomposition temperatures being 180–200°C. Transamidation[54]

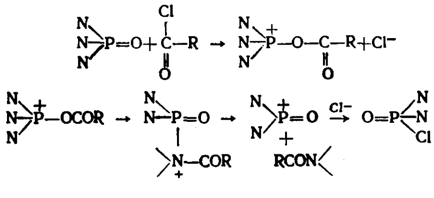
$$O{=}P(NMe_2)_3 + 3\,RCOOH \rightleftarrows O{=}P(OH)_3 + 3RCONMe_2$$

involves formation of a diamido-anhydride as an intermediate stage:



Similar reactions have been accomplished with aromatic, heterocyclic, and sulphonic acids. When the proportions of the reagents are HMPT : RCOOH = 1 : 3, orthophosphoric acid and the corresponding amides are formed[55].

Phenols, but not alcohols, form quite stable complexes§ in HMPT. The crystalline complexes of HMPT acid with chlorides $((CH_3)_2N)_3PO.OPCl_3$ decompose when heated, with replacement of a dimethylamino-group by chlorine:



(III)

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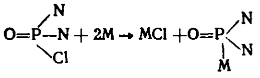
§The structure of these complexes has not been established.

The monochlorinated derivatives (III) can be obtained also (which is extraordinarily interesting) in the chlorides of inorganic acids (thionyl chloride, phosphoryl chloride)[56,57]:

$$2O{=}P(NMe_2)_3 + O{=}PCl_3 \rightarrow 3O{=}P(Cl)(NMe_2)_2$$
$$O{=}P(NMe_2)_3 + O{=}PCl_3 \rightarrow 2O{=}P(Cl)(NMe_2)_2$$

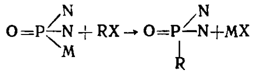
The monochlorinated derivatives can be used to prepare derivatives of the alkali metals[5,58]:



$$O{=}P(N)(N)Cl + 2M \rightarrow MCl + O{=}P(N)(N)M$$

(IV)

where M = Li, Na, K. The latter are in turn used for the preparation of various phosphoramides (V):



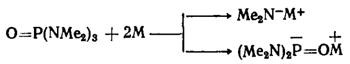
$$O{=}P(N)(N)M + RX \rightarrow O{=}P(N)(N)R + MX$$

(V)

The results of several reactions will be found in Refs. 58 and 59.

3. Action of Alkali Metals

Alkali metals interact with HMPT to yield two anions (via the radical-ions)—the dimethylamide anion (VI) and the phosphorodiamidite anion (VII):

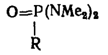


$$O{=}P(NMe_2)_3 + 2M \rightarrow Me_2N^-M^+ \quad (VI)$$
$$\rightarrow (Me_2N)_2\bar{P}{=}O\overset{+}{M} \quad (VII)$$

Saturated alkyl bromides react with HMPT to form tertiary amines (VIII) and phosphoramides (IX)

$RNMe_2$

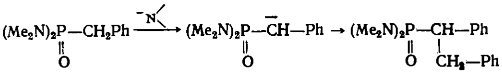
(VIII)



$$O{=}P(NMe_2)_2R$$

(IX)

Under these conditions benzyl chloride does not form the benzyl derivative (X), but yields the compound (XI):



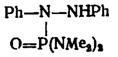
$$(Me_2N)_2P(O){-}CH_2Ph \xrightarrow{^-N\langle} (Me_2N)_2P(O){-}\bar{C}H{-}Ph \rightarrow (Me_2N)_2P(O){-}CH(CH_2{-}Ph){-}Ph$$

(X) (XI) (XII)

The benzyl derivative (X) can be obtained by the reaction between (IV) and benzyl chloride in a mixture of ether and benzene. Sodamide acts on the compound (X) in HMPT to give a good yield of (XII). This result indicates that, in a mixture of the two anions (VI) and (VII), the stronger base (VI) converts (X) into the carbanion (XI), which easily gives (XII).

The two anions formed by the interaction of HMPT with alkali metals are able to metallate weakly acidic hydrocarbons (triphenylmethane forms blood-red solutions); this phenomenon is not observed in benzene solution[60]. The base (VI) acts as a metallating agent, and is stronger than (VII). In fact, (IV) does not react with triphenylmethane even on heating. On the other hand, the conjugate acid $OPH(N(CH_3)_2)_2$, obtained as in Ref. 61, displaces triphenylmethane from its sodium salt.

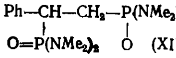
The compound (VII) gives various products with unsaturated systems. Azobenzene yields after hydrolysis the compound[62]



$$Ph{-}N(P(O)(NMe_2)_2){-}NHPh$$

(XIII)

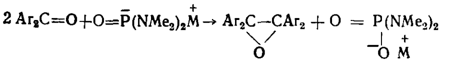
With phenylacetylene (or with β-bromostyrene) a twofold excess of (VII) gives the diphosphoramide[63]



$$Ph{-}CH(P(O)(NMe_2)_2){-}CH_2{-}P(O)(NMe_2)_2$$

(XIV)

The compound (VII) interacts with non-enolisable ketones to yield products in which the latter have condensed into epoxides[64]. In alkali-metal phosphites $MPO(OR)_2$ (sodium is the best cation) this reaction is possible also with aromatic aldehydes. No reaction occurs in non-polar solvents, but in HMPT a high yield is obtained[65]:



$$2Ar_2C{=}O + O{=}\bar{P}(NMe_2)_2\overset{+}{M} \rightarrow Ar_2C\overset{O}{-}CAr_2 + O{=}P(NMe_2)_2\bar{O}\overset{+}{M}$$

4. Hexamethylphosphoric Triamide as Catalyst

A few readily occurring reactions are known in which HMPT acts as a catalyst. Thus the formation of carbodiimides from isocyanates

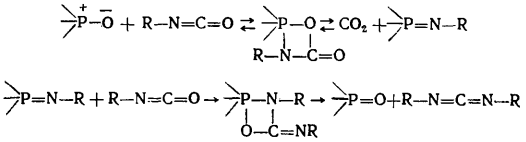
$$2R{-}N{=}C{=}O \rightarrow CO_2 + R{-}N{=}C{=}N{-}R$$

goes more rapidly, at a lower temperature, and with a better yield in the presence of small additions of HMPT[66,67] than of dimethyl sulphoxide (Table 7).

Table 7.

Solvent, mole	Phenyl isocyanate, mole	Temp., °C	Time, h	Yield, %
DMSO, 0.006	0.45	162–164	2.5	13
HMPT, 0.008	—	113–135	1.6	27

In the presence of HMPT phosphonimides are formed in similar reactions:



$$\rangle\overset{+}{P}{-}\bar{O} + R{-}N{=}C{=}O \rightleftarrows \rangle P(O){-}N(R){-}C{=}O \rightleftarrows CO_2 + \rangle P{=}N{-}R$$
$$\rangle P{=}N{-}R + R{-}N{=}C{=}O \rightarrow \rangle P(N{-}R){-}O{-}C{=}NR \rightarrow \rangle P{=}O + R{-}N{=}C{=}N{-}R$$

The rate of reactions involving exchange of radicals between trialkylborines and alk-1-enes

$$Bu_3B + CH_2{=}CH(CH_2)_7{-}CH_3 \rightarrow CH_2{=}CH{-}CH_2{-}CH_3 + Bu_2B(CH_2)_9{-}CH_3$$

is also increased by HMPT.[68] Chlorosilanes undergo disproportionation in the presence of 0.5–15% of HMPT at elevated temperature[69]:

$$2MeSiCl_2H \rightleftarrows MeSiCl_3 + MeSiClH_2$$

IV. USE OF HEXAMETHYLPHOSPHORIC TRIAMIDE AS ELECTRON-DONOR REACTION MEDIUM

A. FORMATION OF ANIONS AND METALLATION

Exchange between hydrogen and a metal yields anions or other organometallic compounds:

$$AH + MR \rightleftarrows RH + MA \text{ or } (M^+ + A^-)$$

The equilibrium is displaced to the right if AH is a stronger acid than RH, or if R^- is a stronger base than A^-. Table 8 gives an acidity scale for various compounds AH.

The solvent plays an important part in exchanges between hydrogen and a metal. Electron-donor solvents promote ionisation of the molecules AH and MR:

$$S_1 + \overset{\curvearrowright}{H-A} \rightleftharpoons (H^+, A^-)S$$

$$S_1 + \overset{\curvearrowright}{M-R} \rightleftharpoons (M^+, R^-)S$$

and yield solvated ion-pairs. If the dielectric constant of the solvent is sufficiently high, dissociation may occur:

$$(M^+, R^-)S \rightleftarrows (M^+ + R^-), S$$

in which the cations M^+ are strongly solvated, and the anions R^- are weakly solvated. Free anions are highly reactive in dipolar aprotic solvents, especially in HMPT, in which the electron-donor character is most strongly developed.

Table 8.

AH	pK_a	Solvent	pK_a
CH_4	50	NH_3 (liq.)	34
$PhCH(CH_3)_2$	37	$PhNH_2$	27
$Ph_2C=CHCH_3$	36	acetone	19
$PhCH_3$	37	t-C_4H_9OH	19
Ph_2CH_2	35	CH_3OH	16
Ph_3CH	33	H_2O	14
$HC\equiv CH$	26	H_2O	—
Fluorene	25	H_2O	—
Indene	21	H_2O	—
$PhC\equiv CH$	21	H_2O	—
Cyclopentadiene	17	H_2O	—

1. Alkoxide and Phenoxide Anions [70]

Alcohols and phenols which are relatively strong acids can interact with alkali-metal hydrides and amides in HMPT to yield more reactive unsolvated anions RO^- or ArO^- than when hydroxylated solvents are used. Similar reactions are possible with alcohols possessing little acidity (t-butyl and allyl alcohols) and with diols, from which diglycolates are formed. With acids the reaction products are alkali-metal salts RCOOM (the silver salt is an exception), which are converted into esters.

It is also noteworthy that very many alkali-metal salts possess extraordinarily high—sometimes unlimited—solubility in HMPT.

2. Anions of Amides [70]

Aliphatic amines are too weak acids to be converted into amides by alkali-metal hydrides and amides. I am aware of only one example of such a reaction—the formation of lithium methylamide [71]

$$CH_3NH_2 + MNH_2 \rightleftarrows CH_3NH-M + NH_3$$

Stronger organometallic bases are required for aliphatic amines. Arylamines ArNHR (R = H, Alk, Ar), indole, carbazole, and phenothiazine form sodium derivatives with sodium hydride or sodamide in HMPT at room temperature. Aniline may give the doubly charged anion $C_6H_5N^{2-}$; carboxyamides and amides can also react in the cold. The sodium derivatives of indole, acetanilide, and phthalimide are soluble without limit.

3. Carbanions of Hydrocarbons

The rate of exchange between hydrogen and a metal depends on the acidity of the hydrocarbon, the strength of the base, and the polarity of the solvent. The influence of these three factors will be examined in the following sections.

(*a*) Carbanions of alkynes. Organomagnesium compounds react with alkynes in HMPT in the cold [72]:

$$R-C\equiv C-H + i\text{-}PrMgCl \rightarrow R-C\equiv C-MgCl + C_3H_8$$

A similar reaction is possible with organozinc compounds [73]:

$$2\,Ph-C\equiv CH + Et_2Zn \rightarrow (Ph-C\equiv C)_2Zn + 2C_2H_6$$

The reaction takes place instantaneously in HMPT, in contrast to other polar solvents [73] (Table 9). The strength of the base plays an important part in such reactions [74]. Thus phenylacetylene (as also acetylene itself) does not react with sodium hydride in HMPT.

Table 9.

Solvent	Oxolan	DMF	DMSO	HMPT
Half reaction time at 50°C, s	129	270	200	8

In the presence of suitable bases alkynes undergo isomerisation: hept-1-yne yields a mixture of heptynes, the main component of which is the isomer hept-2-yne.

At room temperature the more basic alkali-metal amides form the alkynylides RC : CNa. It is noteworthy that acetylene and phenylacetylene, which form complexes with HMPT, do not give sodium derivatives in pure HMPT.

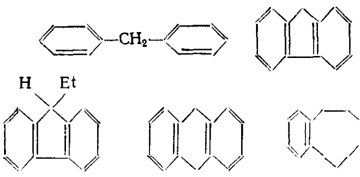
(*b*) Carbanions of triphenylmethane. In solvents of low polarity (ether, oxolan) triphenylmethane does not react with Grignard reagents to give compounds of the type $(C_6H_5)_3CM$ (where M = MgX). With isopropylmagnesium chloride in HMPT this reaction goes smoothly at 90°C. [75] Stable alkali-metal derivatives $(C_6H_5)_3CM$ (where M = Li, K, Na) can be obtained in HMPT from the corresponding hydrides and amides. In liquid ammonia metal amides form $(C_6H_5)_3CM$, but addition of ether decomposes them if M = Na, Li. In oxolan triphenylmethane cannot be metallated either by sodium hydride or by sodamide even at the boiling point of this solvent: stronger bases, e.g. $C_6H_5CH_2Na$, $CH_2:CHCH_2Na$, are necessary for the reaction [76].

Under similar conditions triphenylgermane can be converted into $(C_6H_5)_3GeM$.

In HMPT triphenylmethane is able to react with lithium aminoalkynylides [77]:

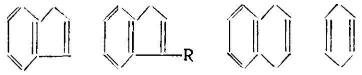
$$\rangle N-C\equiv C-Li + Ph_3CH \rightarrow \rangle N-C\equiv C-H + Ph_3CLi$$

(*c*) **Hydrocarbons of the diphenylmethane type.** Diphenylmethane and various hydrocarbons of related structure



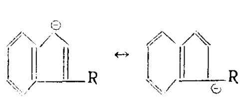
and metallated in HMPT medium[78]. Being less acidic than triphenylmethane, diphenylmethane undergoes exchange only with isopropylmagnesium chloride in HMPT. The reaction takes place at 100°C (red carbanion); on the other hand, it goes very readily at room temperature with the hydrides and still better with the amides of alkali metals. Formation of an organosodium compound is possible even in a less polar medium. Fluorene is able to give organomagnesium compounds at 135–140°C in xylene, and at 40°C in HMPT. Organozinc compounds can also be obtained in the latter solvent[73]. Dihydroanthracene can be metallated in good yield even in the cold both by isopropylmagnesium chloride and by sodium hydride. In HMPT in the cold dihydrodibenzocycloheptene is converted into a dark orange carbanion (at position 5).

(*d*) **Hydrocarbons of 1,4-diene structure**[72]. A study has been made of the compounds

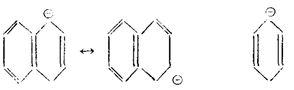


In solvents of low polarity indene reacts with ethylmagnesium bromide at 100°C to yield magnesium derivatives; with isopropylmagnesium chloride in HMPT a similar reaction takes place at only 30°C. Metallation with sodium hydride in HMPT can be accomplished at 0°C (exothermic process) with formation of a reddish-orange anion, which undergoes partial conversion into a dianion.

Alkylindenes react similarly to indene (in HMPT exchange between H and MgX begins at 35°C). The intensely coloured red anion is in a mesomeric form:



The anions formed from 1,4-dihydronaphthalene and especially from cyclohexa-1,4-diene exhibit a tendency to aromatisation:



(XV) (XVI)

The anion (XVI) can be formed when (XV) is treated with isopropylmagnesium chloride in HMPT at 90–95°C. The action of sodamide in HMPT produces considerable polymerisation.

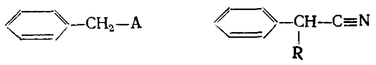
When isopropylmagnesium chloride interacts with 1,3-diphenylpropene in HMPT at room temperature, a red anion is formed:

$$Ph-CH=CH-CH_2Ph \rightarrow Ph-CH=CH-\overset{\ominus}{C}H-Ph$$

In this case, too, alkaline reagents cause considerable polymerisation.

4. Carbanions formed by Compounds containing Labile Hydrogen[79]

(*a*) **Derivatives of phenylacetic acid.** A hydrogen atom present in compounds containing phenyl and electron-acceptor groups is labile:

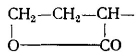


where A = COOH, CN. Phenylacetic acid reacts with isopropylmagnesium chloride or sodamide in HMPT in the cold to form a dianion; the disodium derivative is completely soluble in this solvent.

Benzyl cyanide on treatment with sodium hydride or sodamide in HMPT at 0°C forms a reddish-violet anion together with a certain amount of a dianion. α-Alkylbenzyl cyanides form singly charged anions at 0°C.

(*b*) **Derivatives of malonic acid.** The compounds

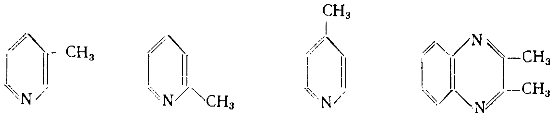
$CH_2(COOEt)_2$, $CH_2(CN)COOEt$, $CH_2(CN)_2$, $CH_2(COCH_3)COOEt$, $CH_2(COCH_3)_2$,



are metallated by sodium hydride or sodamide in HMPT at 0°C, the reaction mixture always containing a small quantity of dianions.

(*c*) **Aromatic compounds containing methyl groups.** Toluene and 2-methylfuran do not react with sodamide or sodium hydride in HMPT. 2-Methylthiophen reacts very slightly.

In the series of picolines

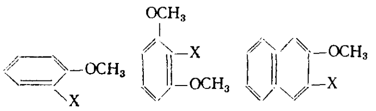


the methyl group exhibits acidic properties in positions 2 and 4, and in HMPT the 2-isomer reacts with isopropylmagnesium chloride to form a red anion. At 0°C the 2- and 4-isomers are able to react with sodamide to form sodium derivatives; with sodium hydride the reactions are very difficult. The 3-isomer is not known to react with sodamide in HMPT. 2,3-Dimethylquinoxaline is more acidic than 2-methylpyridine: it reacts with sodamide in HMPT at room temperature to form a greenish-violet dianion:

(*d*) **Various compounds containing labile hydrogen.** Alkaline reagents convert haloforms into CX_3^- anions, which in liquid ammonia readily add to the carbonyl group in ketones[80]. In HMPT this reaction goes with difficulty, but exchange with isopropylmagnesium chloride takes place readily. Novel organomagnesium compounds have been prepared by conducting the reaction in a 5 : 1 mixture of oxolan and HMPT at 80°C:[1,2,81,82]

$$X_3C-H + i\text{-}PrMgCl \rightleftarrows C_3H_8 + X_3C-MgCl$$
$$(X{=}Cl,\ Br).$$

Among methoxylated aromatic compounds



which are able to react to different positions, only the last forms a red carbanion on reaction with sodamide in HMPT.

In compounds containing an alkylthio-group, which is a better electron acceptor than the alkoxy-group, the anion can be stabilised by resonance:

$$\text{—CH}_2\text{—S—R} \rightarrow \text{—}\overset{\ominus}{\text{C}}\text{H—}\bar{\text{S}}\text{—R} \longleftrightarrow \text{—CH=}\overset{\ominus}{\underline{\text{S}}}\text{—R}$$

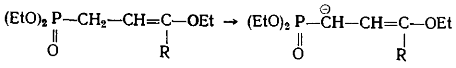
those which have been studied are[83]:

$HC(SEt)_3$, $H_2C(SEt)_2$, $PhCH(SEt)_2$, $PhCH(SPh)_2$

These compounds react with alkali-metal amides in liquid ammonia to form carbanions. The analogous reactions in HMPT yield different results: in di- and tri-ethylthiomethane the carbon–sulphur bond is cleaved; sodamide acts on 4-phenyl-3,5-dithiaheptane at 0°C to form a dark green carbanion; and the most acidic compound αα-diphenylthiotoluene is metallated by sodium hydride at 0°C.

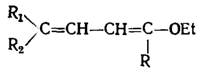
Acetophenone and acetonitrile react with sodium hydroxide in HMPT at 0°C with the loss of one or more protons.

Phosphonates[10] are readily converted into carbanions[84] by the action of sodium hydroxide:



$$(\text{EtO})_2\underset{\text{O}}{\overset{\|}{\text{P}}}\text{—CH}_2\text{—CH=}\underset{\text{R}}{\text{C}}\text{—OEt} \rightarrow (\text{EtO})_2\underset{\text{O}}{\text{P}}\text{—}\overset{\ominus}{\text{C}}\text{H—CH=}\underset{\text{R}}{\text{C}}\text{—OEt}$$

On condensation with carbonyl compounds they give ethoxydienes



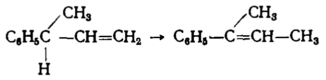
$$\text{R}_1\text{R}_2\text{C=CH—CH=}\underset{\text{R}}{\text{C}}\text{—OEt}$$

which are difficultly accessible by other methods[85].

These few examples indicate that carbanions are formed in HMPT quite easily, with the use of weaker bases and lower temperatures than are required for reaction in other solvents.

B. ISOMERISATION AND POLYMERISATION

Various isomerisations of prototropic type can occur in alkaline media, involving mesomeric carbanions. Such reactions occur considerably more rapidly in the presence of polar solvents. In dimethyl sulphoxide the allyl rearrangement is possible at 25°C, but in t-butyl alcohol only on heating[86]:



$$\text{C}_6\text{H}_5\underset{\text{H}}{\overset{\text{CH}_3}{\text{C}}}\text{—CH=CH}_2 \rightarrow \text{C}_6\text{H}_5\text{—}\overset{\text{CH}_3}{\text{C}}\text{=CH—CH}_3$$

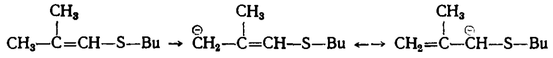
No systematic study of the various rearrangements in HMPT has yet been made, but certain results have already been obtained. The isomerisation of allylbenzene into propenylbenzene takes place in HMPT in the presence of sodium hydride in the cold[78]:

$PhCH_2—CH=CH_2 \rightarrow Ph—CH=CH—CH_3$ (yield 70%)

Under these conditions there is little formation of condensation products, but this becomes considerable if a stronger base (sodamide) is used, or a weak base (isopropylmagnesium chloride) at a high temperature[87]. In such cases anionic polymerisation takes place. Table 10 gives some examples of hydrocarbons which readily form anions under the influence of isopropylmagnesium chloride.

The rapid disappearance of colour on treatment with sodium hydride or sodamide is an indication of polymerisation, as in the case of allylbenzene, for example. Alkenes can be efficiently polymerised by means of organomagnesium compounds in solvents of low polarity, but under these conditions the reaction must be conducted under slight pressure in the presence of halides of metals of Groups IVb, Vb, and VIb.

The capacity for mesomerism of the allyl anion has been shown by the action of sodamide in HMPT at room temperature:



$$\text{CH}_3\text{—}\overset{\text{CH}_3}{\text{C}}\text{=CH—S—Bu} \rightarrow \overset{\ominus}{\text{C}}\text{H}_2\text{—}\overset{\text{CH}_3}{\text{C}}\text{=CH—S—Bu} \longleftrightarrow \text{CH}_2\text{=}\overset{\text{CH}_3}{\text{C}}\text{—}\overset{\ominus}{\text{C}}\text{H—S—Bu}$$

Table 10.

Hydrocarbon	Colour of anion
$PhCH_2—CH=CH—CH_3$	red
$Ph_2C=CH—CH_3$	red
$PhCH=CHCH_2CH=CH—CH_3$	pale pink
$PhCH=CHCH_2C≡C—C_5H_{11}$	dark blue
$PhC≡CCH_2CH=CH_2$	red
$PhCH_2C≡C—C_5H_{11}$	red

The resulting red anion is alkylated predominantly at the α-position relative to the sulphur atom[88].

The isomerisation

$$\underset{\text{(XVII)}}{\text{PhCH=CH—CH}_2\text{OR}} \rightleftarrows \underset{\text{(XVIII)}}{\text{Ph—CH}_2\text{—CH=CH—OR}}$$

(where R = C_2H_5, n-C_7H_{15}) takes place readily in HMPT under the influence of bases[89]. The ethers (XVIII) are characterised by an infrared absorption band at 1660 cm^{-1}. In acid media they form the 2,4-dinitrophenylhydrazone of the corresponding ketone, which is easily identified. The ethers (XVII) can be obtained by condensing cinnamyl bromides with sodium alkoxides in oxolan. If the same reaction is accomplished in HMPT, or the sodium derivatives of the cinnamyl alcohols (obtained in HMPT) are treated with alkyl halides RX, the ethers (XVIII) are the main products. The isomerisation of (XVII) into (XVIII) is effected by means of alkoxides in basic solvents. The ethers (XVII) dissolve in HMPT and form red anions under the action of sodamide, the colour subsequently becoming dark blue. Non-distillable products were isolated on hydrolysis. Isomerisation of (XVII) into (XVIII) is rapid in the presence of dry sodium t-butoxide in a 1 : 9 mixture of HMPT and benzene.

Thus the mesomerism of carbanions under the influence of bases in HMPT can be represented

$$\text{Ph—CH=CH—}\bar{\text{C}}\text{H—OR} \longleftrightarrow \text{Ph—}\bar{\text{C}}\text{H—CH=CH—OR}$$

However, it appears that dimethyl sulphoxide may be a better solvent for the isomerisation of alkenes. Thus in the presence of potassium t-butoxide but-1-ene isomerises into but-2-ene more readily in dimethyl sulphoxide than in HMPT and tetramethylurea[90].

C. USE OF ANIONS

Reactions involving the intermediate formation of anions occur more rapidly in dipolar aprotic solvents. Thus the rate of alkylation of derivatives of sodiomalonic ester in benzene is greatly increased by the addition of 10–20% of such a solvent[91], and the use of pure HMPT increases the reaction velocity with ethyl and butyl bromides by factors of 21 and 54 respectively. Dimethyl sulphoxide as solvent has a less marked effect on the rate of the corresponding reactions, which are accelerated by factors of 6.3 and 15 respectively.

Substitution Reactions

(*a*) Carbon–halogen bond

Halogen–halogen exchange

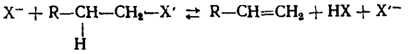
$$MX + RX' \rightleftarrows RX + MX'$$

involves nucleophilic substitution of X′ for X, but the result depends on the nature of the protic or aprotic solvent[3]. The specific solvation of the halogen in the alkyl halides by hydrogen bonding is significant in protic solvents. Solvation is stronger with small anions, so that the nucleophilic character of the halide anions is opposite to their basic strength:

$$I^- > Br^- > Cl^- > F^-$$

In dipolar aprotic solvents, on the other hand, nucleophilic character and basic strength of the anions coincide.

In HMPT exchange reactions often compete with those involving elimination



$$X^- + \underset{\displaystyle H}{R{-}\underset{|}{C}H{-}CH_2{-}X'} \rightleftarrows R{-}CH{=}CH_2 + HX + X'^-$$

Table 11 gives exchange results for the reaction n-$C_7H_{15}Br$ + MX.[92] The conversion RBr → RCl is effected by the action of lithium chloride, although such exchange is generally accomplished by the use of halides of metals in subgroups 1b and 2b. Potassium iodide brings about a 73% yield in the reaction RBr → RI.

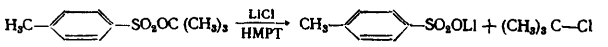
Table 11.

MX	Solvent	Temp., °C	Duration of reaction, h	min	Substitution, %	Elimination, %	Unchanged bromide, %
LiF	HMPT-oxolan	65	7	15	3	0	68
LiF	HMPT*	160—180	9	30	15.5	53.5	0
LiF	HMPT	100	36		1	32	46
LiF+Li_2CO_3	HMPT	100—110	36	30	0	51.5	5.5
LiCl	HMPT-oxolan	65	9	15	72	6.5	10
LiCl	HMPT*	160—240	5		0	25	0
LiCl	HMPT	90	48	30	34	49	17
LiCl+Li_2CO_3	HMPT	100	48		41.5	0	30
LiCl+$C_7H_{15}Cl$	HMPT	100	11	30		1	82
NaF	HMPT-oxolan	65	10		0.8	0	78
NaF	HMPT	90	10		0	9	87
NaF+Na_2CO_3	HMPT	100	10	20	0	62	6
NaCl	HMPT	90	9	20	7	0	84
KF	HMPT-oxolan	65	9		5	0	45
KF	HMPT	100	10	30	1	2	84
KI	HMPT-oxolan	65	9	45	41	0	3
KI	HMPT	110	10	20	73	0.5	8
Cu_2Cl_2	HMPT-oxolan	65	9	45	22	0	53
u_2Cl_2	HMPT	100	47	30	30	19	3

*Distilled off as produced.

In HMPT the fluoride and chloride ions are especially strong bases, and are able to eliminate hydrogen bromide from secondary bromides (Table 12).[92] The extent of elimination is increased by neutralising the hydrogen bromide evolved with lithium carbonate. This is a good method for the preparation of alkenes.

Toluene-p-sulphonates of tertiary alcohols do not form alkenes on reaction with lithium chloride in HMPT (exchange is very rapid even in the cold)[92]:



Which reaction occurs is greatly affected by the temperature: at ~ 60°C substitution is favoured; at 100–110°C elimination predominates.

Table 12.

MX	Solvent	Temp., °C	Duration, h	min	Substitution, %	Elimination, %	Unchanged, %
LiF	HMPT	90—100	8	50	0	74	11.5
LiCl	HMPT-oxolan	65	9	20	10	27	33
LiCl	HMPT	90	10	10	13	73.5	9
LiCl+Li_2CO_3	HMPT	90	10		7	79	4

(*b*) Carbon–oxygen bond

Table 13 gives results for alkylation with the formation of *O*-substituted products[70].

The basic character of the anions RO^- is exhibited in various elimination reactions—formation of an epoxide, formation of the alkenes, oct-1-ene and butadiene, by the action of sodium ethoxide and sodium butoxide on tetramethylene dibromide.

Table 13.

Compound	Sodium compound	Solvent	Reagent	Product	Yield, %
BuOH	NaH	HMPT	$PhCH_2Cl$	$BuOCH_2Ph$	89
BuOH	NaH	oxolan	$PhCH_2Cl$	$BuOCH_2Ph$	30
t-BuOH	NaH	oxolan-HMPT	$PhCH_2Cl$	t-$BuOCH_2Ph$	67
$CH_2{=}CH{-}CH_2OH$	NaH	ditto	$C_8H_{17}Br$	$C_8H_{17}OCH_2CH{=}CH_2$	54
$CH_2OH{-}CH_2OH$	NaH	"	$PhCH_2Cl$	$(PhCH_2OCH_2{-})_2$	71
$EtOCH_2{-}CH_2OH$	NaH	"	EtI	$EtOCH_2{-}CH_2OEt$	68
$HO(CH_2)_3OH$	NaH	"	EtBr	$EtO(CH_2)_3OEt$	61
$HO(CH_2)_3OH$	NaH	"	PhBr	$PrO(CH_2)_3OPr$	40
PhOH	NaH	"	$PhCH_2Cl$	$PhOCH_2Ph$	quant.
PhOH	NaH	"	BuCl	$PhOC_4H_9$	86
PhOH	NaH	"	$C_6H_{13}Br$	$PhOC_6H_{13}$	96
PhOH	NaH	"	$Br(CH_2)_3Br$	$PhO(CH_2)_3OPh$	quant.
PhOH	NaH	"	$Br(CH_2)_4Br$	$(PhOCH_2CH_2{-})_2$	quant.
$Me_2C(OH)CH_2Br$	$NaNH_2$	HMPT		$\underset{\diagdown O \diagup}{Me_2C - CH_2}$	57
EtCOOH	NaH	oxolan-HMPT	C_2H_5COCl	EtCOOCOEt	40
$C_5H_{11}COOH$	NaH	–	EtI	$C_5H_{11}COOEt$	76
$O{=}C\genfrac{}{}{0pt}{}{\diagup OK}{\diagdown OK}$	NaH	HMPT	$PhCH_2Cl$	$O{=}C\genfrac{}{}{0pt}{}{\diagup OCH_2Ph}{\diagdown OCH_2Ph}$	67

The yield of 40% resulting from acylation should be improved in a mixture of HMPT with a non-polar solvent.

(*c*) Carbon–nitrogen bond

Table 14 gives results for alkylation with the formation of *N*-substituted products[70].

Very rapid reaction occurs in HMPT between alkali-metal azides and primary bromides with the formation of organic azides:

$$RBr + N_3^- \rightarrow RN_3 + Br^-$$

With n-butyl bromide the reaction occurs more slowly in dimethylformamide and dimethyl sulphoxide than in HMPT.

The activation energy of this reaction is 15–17 and 13.5 kcal mole^{-1} in dipolar aprotic solvents and in HMPT respectively.

Table 14.

Compound	Sodium compound	Solvent	Reagent	Product	Yield, %
$PhNH_2$	$NaNH_2$	HMPT	EtI	$PhNHEt + PhN(Et)_2$	
$PhNH_2$	$NaNH_2$	HMPT	EtBr	$PhN(Et)_2$	87
$PhNH_2$	$NaNH_2$	HMPT	PhBr	Ph_3N	21
$PhNHCH_3$	$NaNH_2$	HMPT	BuI	$PhN(CH_3)(C_4H_9)$	70
Ph_2NH	$NaNH_2$	HMPT	Et_2SO_4	Ph_2NEt	85
Indole	$NaNH_2$	HMPT	$C_6H_5CH_2Cl$	1-benzylindole	81
Carbazole	NaH	oxolan	MeI	9-methylcarbazole	quant.
Phenothiazine	NaH	oxolan	MeI	10-methylphenothiazine	quant.
Phenothiazine	NaH	HMPT	MeI	10-methylphenothiazine	84
Phenothiazine	$NaNH_2$	HMPT	MeI	10-methylphenothiazine	quant.
Phenothiazine	$NaNH_2$	HMPT	Me_2SO_4	10-methylphenothiazine	quant.
CH_3CONH_2	$NaNH_2$	HMPT	$PhCH_2Cl$	$CH_3CONHCH_2Ph$	low
$EtOCNH_2$	$NaNH_2$	HMPT	BuBr	EtOCONHBu	low
$CH_3{-}CONHPh$	$NaNH_2$	HMPT	EtI	$CH_3CONPhEt$	quant.
Phthalimide	NaH	HMPT	$Br(CH_2)_4Br$	butane-1,4-diphthalimide	quant.
Phthalimide	K_2CO_3	HMPT	—	—	quant.
Phthalimide	K_2CO_3	HMPT	$BrCH_2COCH_3$	*N*-acetonylphthalimide	80
Phthalimide	$NaNH_2$	HMPT	$BrCH_2COPh$	*N*-phenacylphthalimide	77
Saccharin	NaH	oxolan	$PhCH_2Cl$	2-benzylsaccharin	50
Saccharin	NaH	HMPT	—		50

(*d*) Carbon–carbon bond

In HMPT alkylations take place with the formation of carbanions, the study of which is of great interest. In a mixture of HMPT and a non-polar solvent high yields are obtained when alkali-metal or magnesium salts were used. Thus the reaction

$$Et_3OC\,(CH_2)_5{-}Cl + NaCN \rightarrow EtO_2C{-}(CH_2)_5{-}CN$$

can give nitriles in 90% yield[93].

Various nitriles can be obtained also by the alkylation of other nitriles[94]

$PhCH_2CN$ and CH_3CN.

Table 15. RMgBr + R′–Br.

R—	R′—	R—R′	Yield, %, in	
			oxolan	HMPT
$n\text{-}C_4H_9{-}$	$n\text{-}C_7H_{15}{-}$	$n\text{-}C_{11}H_{24}$	8	42
$n\text{-}C_5H_{11}{-}$	$C_6H_5CH{=}CH{-}$	$C_6H_5CH{=}CH{-}C_5H_{11}$	30	29
$n\text{-}C_5H_{11}{-}$	$C_6H_5C{\equiv}C{-}$	$C_6H_5C{\equiv}C{-}C_5H_{11}$	10	55
$n\text{-}C_5H_{11}{-}$	$C_5H_{11}C{\equiv}C{-}$	$C_5H_{11}C{\equiv}CC_5H_{11}$		58
$CH_3{-}CH{=}CH{-}$	$n\text{-}C_7H_{15}{-}$	$CH_3CH{=}CH{-}C_7H_{15}$	71	43
$C_6H_5{-}$	$C_6H_5CH{=}CH{-}$	$C_6H_5CH{=}CH{-}C_6H_5$	20	20
$C_6H_5C{\equiv}C{-}$	$n\text{-}C_5H_{11}{-}$	$C_6H_5C{\equiv}C{-}C_5H_{11}$	0	43
$C_6H_6C{\equiv}C{-}$	$CH_2{=}CH{-}CH_2{-}$	$C_6H_5C{\equiv}C{-}CH_2CH{=}CH_2$	(60) (Ref.1 & 2)	66

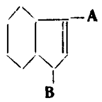
1. Condensation with Organomagnesium Compounds

In aliphatic ethers and even in oxolan aliphatic organomagnesium compounds do not react with halogenated compounds R′X in which X is not very labile, but these reactions can be conducted successfully in HMPT[95] (Table 15).

For organomagnesium derivatives of indene[96] and of fluorene[96] see Tables 16 and 17 respectively.

Reactions with organomagnesium derivatives of 2-alkylpyridines are indicated in Table 18.

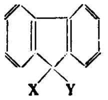
Table 16*. Organomagnesium derivatives of indene.



Organomagnesium compound	Hydrocarbon	Antagonist compound	Reaction product	Yield, %
i-PrMgCl	indene	C_2H_5I	$A{=}C_2H_5$ $B{=}H$	62
i-PrMgCl	ditto	Et_2SO_4	$A{=}C_2H_5$ $B{=}H$	92
i-PrMgCl	»	C_4H_9I	$A{=}C_4H_9$ $B{=}H$	82
i-PrMgCl	»	$CH_3C_6H_4SO_2OC_4H_9$	$A{=}C_4H_9$ $B{=}H$	64
Et_2NMgCl	»	C_4H_9I	$A{=}C_4H_9$ $B{=}H$	77
i-PrMgCl	»	$BrCH_2CH{=}CH_2$	$B{=}H$ $A{=}{-}CH_2CH{=}CH_2$	69
i-PrMgCl	»	$CH_3CH{-}CH_2$ (epoxide, –O–)	$A{=}{-}CH_2{-}CHOH{-}CH_3$ $B{=}H$	46
i-PrMgCl	»	$C_2H_5OCH_2Cl$	$B{=}H$ $A{=}{-}CH_2OC_2H_5$	40
i-PrMgCl	»	oxolan	$B{=}H$ $A{=}{-}(CH_2)_4OH$	51
i-PrMgCl	butylindene	C_4H_9I	$A{=}B{=}C_4H_9$	—
i-PrMgCl	ditto	CO_2 followed by esterification	$A{=}C_4H_9$ $B{=}COOC_2H_5$	—

*It has been shown[196] that RMgX metallises indene and fluorene derivatives in HMPT. Further reaction of the resulting organomagnesium compounds with electrophilic reagents may involve migration of the reaction centre in the case of indene (Editors).

Table 17. Fluorene derivatives.



Organomagnesium compound	Hydrocarbon	Antagonist compound	Reaction product	Yield, %
i-PrMgCl	fluorene	C_2H_5I	$X{=}H,\ Y{=}C_2H_5$	72
Et_2NMgCl	ditto	C_2H_5I	$X{=}H,\ Y{=}C_2H_5$	75
i-PrMgCl	»	$Br{-}CH_2{-}CH{=}CH_2$	$X{=}H$ $Y{=}CH_2{-}CH{=}CH_2$	57
i-PrMgCl	»	CO_2	$X{=}H,\ Y{=}CO_2H$	81
Et_2NMgCl	9-ethylfluorene	C_2H_5I	$X{=}Y{=}C_2H_5$	—
i-PrMgCl	ditto	C_4H_9I	$X{=}C_2H_5,\ Y{=}C_4H_9$	20
i-PrMgCl	»	CO_2	$Y{=}CO_2H,\ Y{=}Et$	low

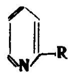
Under these conditions condensation can be accomplished with satisfactory yields between saturated organomagnesium compounds and alkyl halides, saturated organomagnesium compounds and alkynyl halides, and magnesium alkynyls and alkyl halides.

Organomagnesium compounds (other than aromatic Grignard reagents) react with vinyl bromide with the elimination of hydrogen bromide.

2. Condensation with Derivatives of Alkali Metals

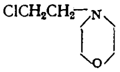
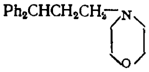
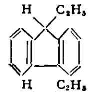
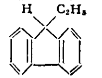
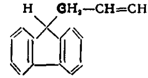
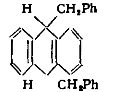
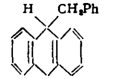
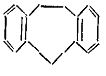
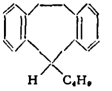
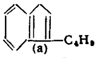
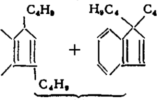
Table 19 lists some examples of condensations in which alkali-metal derivatives are used[77].

An alkyl bromide does not react with monosodium acetylide in oxolan, but such reaction is possible in dipolar aprotic solvents, in particular in dimethylformamide[97].

Table 18. Pyridine derivatives 

Solvent for Mg cpd.	Reactant	2-Substituent R	Yield, %
Oxolan	C_4H_9I	C_5H_{11}	66
Oxolan	$BrCH_2{-}CH{=}CH_2$	$CH_2CH_2CH{=}CH_2$	69
Ether-HMPT	$BrCH_2CH{=}CH_2$	$CH_2CH_2CH{=}CH_2$	40
Oxolan	$BrCH_2C\equiv CH$	$CH_2CH_2C\equiv CH$	30
Ether	PhCHO	CH₂CHOH—Ph	48
Ether-HMPT	PhCHO	CH₂CHOH—Ph	69
Oxolan	PhCHO	CH₂CHOH—Ph	71
Ether-HMPT	$CH_3COC_5H_{11}$	$CH_2{-}\underset{\mid\atop OH}{C}{-}(CH_3)C_5H_{11}$	36
Oxolan	$CH_3COC_5H_{11}$	$CH_2\underset{\mid\atop OH}{C}{-}(CH_3)C_5H_{11}$	50

Table 19.

Hydrocarbon	Metallating agent	Reagent	Reaction product	Yield, %
PhCH₂Ph	NaH	CO_2	$Ph_2CHCOOH$	33
PhCH₂Ph	$NaNH_2$	$Br(CH_2)_4Br$	$Ph_2CH(CH_2)_4CHPh_2$	87
PhCH₂Ph	$NaNH_2$			70
PhCH₂Ph	$NaCH_2Ph$	CO_2	$Ph_2CHCOOH$	50
PhCH₂Ph	$NaCH_2CH{=}CH_2$	CO_2	$Ph_2CHCOOH$	33
Fluorene	NaH	EtI		67
Ditto	NaH	EtI*		80
«	NaH	$BrCH_2CH{=}CH_2$*		55
9,10-Dihydro-anthracene	NaH	$PhCH_2Cl$		90
Ditto	$NaCH_2Ph$	$PhCH_2Cl$		50
	$NaNH_2$	BuI		68
Indene	NaH	BuI*		—
Ditto	NaH LiH	BuI	 (b) (a) + (b) (a)	61

*In oxolan.

In HMPT yields of 60–70% are obtained in such condensation (Table 20).[98]

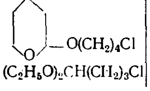
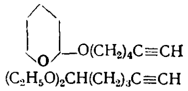
However, these reactions can be accomplished also in oxolan to which 10% of HMPT has been added, which tends to diminish the relative proportion of elimination reactions.

Table 20.

RX	Solvent	Reaction temp., °C	Further heating °C for h		Reaction product	Yield, %
n-$C_7H_{15}Br$	DMF + oxolan	40	50	4	$C_7H_{15}C\equiv CH$	52
n-$C_5H_{11}Br$	DMF + oxolan	20	100	4	$C_5H_{11}C\equiv CH$	47
n-$C_7H_{15}Br$	HMPT	5	40	1.5	$C_7H_{15}C\equiv CH$	65.6
n-$C_7H_{15}Br$	HMPT, 10 ml	20	40	3	$C_7H_{15}C\equiv CH$	72
n-$C_5H_{11}Br$	HMPT	20			$C_5H_{11}C\equiv CH$	57
$Br{-}(CH_2)_6{-}Br$	HMPT	20	40	3	$HC\equiv C(CH_2)_6C\equiv CH$	71
$C_6H_5CH{=}CHCH_2Cl$	HMPT	−50	0	2	$C_6H_5(CH{=}CH)_3C_6H_5$	8
C_4H_9OTos	HMPT	0	50	3	$C_4H_9C\equiv CH$	77
n-$C_7H_{15}Cl$	HMPT	20			$C_7H_{15}C\equiv CH$	60
n-$C_{12}H_{25}Br$	HMPT	10	70	3	$C_{12}H_{25}C\equiv CH$	72.6

The reaction goes especially well with primary halogen derivatives (bromides, chlorides) and toluene-*p*-sulphonates, and also when liquid ammonia is used as solvent, in which these reagents are less soluble. In HMPT the acetylide ion is a strong base, and causes considerable elimination in the cases of secondary and tertiary halides and toluene-*p*-sulphonates. Some of the acetylene derivatives obtained are listed in Table 21.[98]

Table 21.

RX	Solvent	Reaction temp., °C	Further heating °C for h		Reaction product	Yield, %
$C_4H_9OCH_2Cl$	HMPT	5	40	2	$C_4H_9OCH_2C\equiv CH$	32
$C_4H_9OCH_2Cl$	HMPT	−40	5	8	$C_4H_9OCH_2C\equiv CH$	12.5
$C_4H_9OCH_2Cl$	oxolan	20	75	1	$C_4H_9OCH_2C\equiv CH$	18
	HMPT	20	50	2.5		47
$(C_2H_5O)_2CH(CH_2)_3Cl$	HMPT	20	40-50	1	$(C_2H_5O)_2CH(CH_2)_3C\equiv CH$	47

Alkynes containing a trialkylgermyl group can similarly be obtained[99] in 60% yield:

$$Et_3Ge(CH_2)_4Br + NaC\equiv CH \rightarrow Et_3Ge(CH_2)_4C\equiv CH$$

The same method enables disubstituted derivatives of alkynes to be obtained under mild conditions[100] (Table 22). In procedure A sodium hydride in oxolan is used if the subsequent reaction is carboxylation or alkylation. In procedures B and C the active reagent is sodamide in HMPT in the cold:

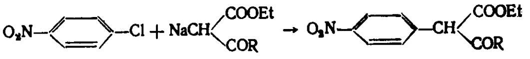
$$CH\equiv CH \xrightarrow[\text{oxolan}]{Na} CH\equiv C{-}Na \xrightarrow[\text{HMPT}]{RX} R{-}C\equiv C{-}H \rightarrow$$
$$\xrightarrow[\text{HMPT}]{NaNH_2} R{-}C\equiv C{-}Na \xrightarrow{R'X} R{-}C\equiv C{-}R'$$

Similarly, substituted alkynylamines can be obtained[84] by the use of RX or toluene-*p*-sulphonates:

$$(R)(R')N{-}C\equiv C{-}Li \xrightarrow{RX} (R)(R')N{-}C\equiv C{-}R$$

Tables 23 and 24 give data on the alkylation of various compounds[101].

Nucleophilic aromatic substitution is accelerated in dipolar aprotic solvents, but this applies only to the reactions of halogenated benzenes. Thus *o*- and *p*-chloronitrobenzenes and their derivatives arylate sodiomalonic and sodioacetoacetic esters in high yield[102]:

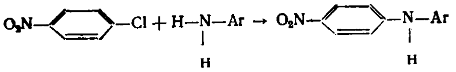


where R = OC_2H_5, CH_3. Reaction is most rapid in HMPT. The comparable solvents can be arranged in the sequence HMPT > dimethyl sulphoxide > dimethylformamide.

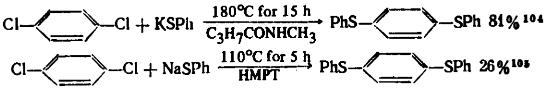
Table 22.

Alkyne	Procedure	Reagent	Product	Yield, %
Acetylene	C	BuBr	$BuC{\equiv}C{-}Bu$	50
Hexyne	B	BuBr	$BuC{\equiv}C{-}Bu$	74
Ditto	B	$C_5H_{11}Br$	$C_4H_9C{\equiv}C{-}C_5H_{11}$	77
»	B	$ClCH_2OEt$	$C_4H_9C{\equiv}C{-}CH_2OEt$	64
»	A	$Br(CH_2)_4Br$	$BuC{\equiv}C(CH_2)_4C{\equiv}CBu$	63
»	A	$Br(CH_2)_3Cl$	$BuC{\equiv}C(CH_2)_3Cl$	51
Heptyne	A(NaH)	BuI	$C_5H_{11}C{\equiv}C{-}C_4H_9$	47
Ditto	A	BuI	$C_5H_{11}C{\equiv}C{-}C_4H_9$	64
»	A	$C_7H_{15}Br$	$C_5H_{11}C{\equiv}C{-}C_7H_{15}$	79
»	A	$C_4H_9C{\equiv}C(CH_2)_3I$	$C_5H_{11}C{\equiv}C(CH_2)_3C{\equiv}CBu$	72

Partial replacement of chlorine by the dimethylamino-group does not occur in HMPT, unlike the reaction in dimethylformamide. The reaction velocity in HMPT is especially increased in the presence of copper[103]:



Reaction with *p*-dichlorobenzene occurs very slowly:



Some examples of arylation with bromobenzene and chlorobenzene under quite mild conditions have been reported in which the yields were satisfactory[70,106]. The reactions must occur by a mechanism of cleavage and addition, although the intermediate formation of dehydrobenzene has not been demonstrated.

Table 25 gives the results for several reactions[106].

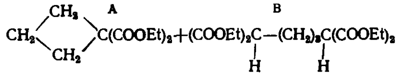
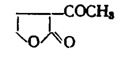
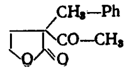
Table 23.

Metallated compound	Agent	Solvent	Reagent	Product	Yield, %
$PhCH_2COOH$	$NaNH_2$	oxolan + HMPT	$(CH_3)_2CHI$	$Ph{-}\underset{\displaystyle CH(Me)_2}{\underset{\mid}{CH}}{-}COOH$	60
$PhCH_2COOH$	$NaNH_2$	oxolan	$PhCH_2Cl$	$Ph{-}\underset{\displaystyle CH_2{-}Ph}{\underset{\mid}{CH}}{-}COOH$	70
$PhCH_2CN$	NaH	HMPT	$PhCH_2Cl$	$Ph{-}\underset{\displaystyle CH_2Ph}{\underset{\mid}{CH}}CN+\underset{\displaystyle CN}{\underset{\mid}{PhC}}(CH_2Ph)_2$	
$PhCH_2CN$	$NaNH_2$	ditto	$PhCH_2Cl$	$Ph{-}\underset{\displaystyle CH_2Ph}{\underset{\mid}{CH}}CN+\underset{\displaystyle CN}{\underset{\mid}{PhC}}(CH_2Ph)_2$	
$PhCH_2CN$	NaH	«	BuI	$Ph{-}\underset{\displaystyle Bu}{\underset{\mid}{CH}}{-}CN$	86
$\underset{\displaystyle Bu}{\underset{\mid}{PhCH}}CN$	NaH	«	BuI	$PhC(C_4H_9)_2CN$	95

3. Alkylation of Ambident Ions

Insufficient study has hitherto been made of the relative reactivities of the different nucleophilic centres in ambident ions. Different alkylation products are obtained

Table 24.

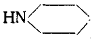
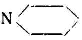
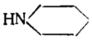
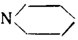
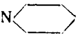
Metallated compound	Metallating agent	Reagent	Compound obtained
$H_2C(COOEt)_2$	NaH	$BrCH_2CH{=}CH_2$	$\underset{A}{CH_2{=}CHCH_2CH(COOEt)_2}+\underset{B}{(CH_2{=}CHCH_2)_2C(COOEt)_2}$
$H_2C(COOEt)_2$	NaH	$Br(CH_2)_3$	
$^{*}H_2C(COOEt)_2$	$NaNH_2$	$BrCH_2CH{=}CH_2$	A+B
$H_2C(COOEt)_2$	KOH	$BrCH_2CH{=}CH_2$	A
$H_2C\begin{smallmatrix}CN\\COOEt\end{smallmatrix}$	NaH	$BrCH_2CH{=}CH_2$	$CH_2{=}CHCH_2CH\begin{smallmatrix}CN\\COOEt\end{smallmatrix}+(CH_2{=}CHCH_2)_2C\begin{smallmatrix}CN\\COOEt\end{smallmatrix}$
$H_2C\begin{smallmatrix}CN\\CN\end{smallmatrix}$	KOH	$PhCH_2Cl$	$PhCH_2CH(CN)_2+(PhCH_2)_2C(CN)_2$
$H_2C\begin{smallmatrix}COOEt\\COCH_3\end{smallmatrix}$	NaH	$BrCH_2CH{=}CH_2$	$CH_2{=}CHCH_2CH\begin{smallmatrix}COOEt\\COCH_3\end{smallmatrix}+(CH_2{=}CHCH_2)_2C\begin{smallmatrix}COOEt\\COCH_3\end{smallmatrix}$
$H_2C\begin{smallmatrix}COCH_3\\COCH_3\end{smallmatrix}$	NaH	$BrCH_2CH{=}CH_2$	$CH_2{=}CHCH_2CH(COCH_3)_2+(CH_2{=}CHCH_2)_2C(COCH_3)_2$
	NaH	$PhCH_2Cl$	

*In oxolan.

depending on the nature of the cation, the alkylating agent, and the solvent. Little information is yet available on the part played by HMPT ¶.

In a study of the reaction of bromoethane with sodium phenoxide and 2-naphthoxide it was shown that the percentage of *O*-alkylated products increased with the basic character of the solvent[107]† (see Table 26).

Table 25.

Ph—X	Reagent	Product	Yield, %
PhBr	EtSH	Pt—S—Et	52
PhBr	*n*-BuSH	Ph—S—Bu	66
PhBr	PhSH	Ph—S—Ph	40
PhBr	Ph—CH$_2$—SH	Ph—S—CH$_2$—Ph	12
PhBr	Et$_2$NH	Ph—NEt$_2$	65
PhBr	HN 	PhN 	74
PhBr	Ph—NH—CH$_3$	Ph$_2$NCH$_3$	55
PhBr	Ph—C≡C—H	Ph—C≡C—Ph	45
PhBr	Ph$_3$CH	Ph$_4$C	57
PhCl	Et$_2$NH	PhNEt$_2$	30
PhCl	HN 	Ph—N 	84
PhCl	Ph—NH—CH$_3$	Ph$_2$NCH$_3$	55
PhCl	Ph—C≡C—H	PhC≡C—Ph	40
PhCl	Ph—CH$_2$—CN	Ph$_2$CHCN	60
PhF	HN 	PhN 	80
PhF	HNEt$_2$	Ph—NEt$_2$	65

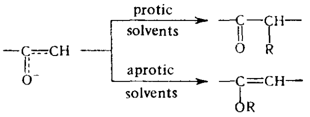
The mechanism of the reaction has been discussed[3]. Our results show that in HMPT alkylation occurs predominantly (86–100%) with the formation of *O*-substituted products[70].

When pyrrole is alkylated in a basic solvent, *N*-alkylated products are formed (at the more electronegative element)[108]. Benzyl chloride reacts with sodium indole in HMPT to give an 81% yield of *N*-benzylindole[70].

Table 26.

Solvent	Alkylation	
	C-derivative, %	*O*-derivative, %
CH$_3$OH	35	65
CF$_3$CH$_2$OH	93	7

In protic solvents (alcoholic alkalis) the enolates of ketones form mainly *C*-alkylated products[109]. It has recently been shown[110] that *O*-alkylated products—ethers of the enols—predominate in dipolar aprotic solvents:



The alkylating agent used was $(C_2H_5)_3OBF_4$ or an alkyl sulphate[110] (Table 27).

The effect of the solvent on the direction of alkylation of sodium ketones was first mentioned in a discussion of the reaction between bromoethane and the sodium derivative of diphenylacetophenone[111]:

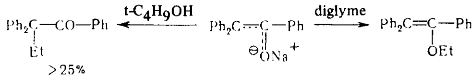
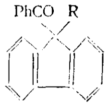


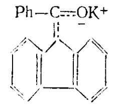
Table 27.

Ketone	Cyclohexanone		Acetophenone	Pentane-2,4-dione	Acetoacetic ester
Solvent*	DME	DMSO	DMSO	DMSO	DMSO
Unchanged material, %	32	11	16	13	0
Ether of enol, %	24	71	68.5	71	75
Other products**, %	44	18	15.5	16	25

*DME = 1,2-dimethoxyethane. HMPT was not used.
**C-Derivatives and poly-*O*- and -*C*-derivatives.

Alkylation of the potassium enolate (XX) in various solvents, including HMPT, gave *C*- and *O*-alkylated products (XIX and XXI)[112] (Table 28), isopropyl bromide being used as alkylating agent.


(XIX)


(XX)

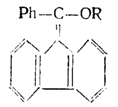

(XXI)

Table 28 shows that the yield of the enol ether is considerably increased in HMPT, which is capable of considerable solvation of alkali-metal cations.

Table 28.

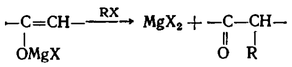
Solvent	Dielectric constant ε	Alkylation	
		C-derivatives, %	*O*-derivatives, %
Protic			
t-C$_4$H$_9$OH	10—11	96	4
C$_2$H$_5$OH	24—55	83	17
CH$_3$OH	32—33	82	18
Aprotic			
Diglyme	7—7.5	61	39
Oxolan	7—7.5	90	10
HMPT	29—30	44	56
DMSO	45—49	72	28

Weaker bases, such as organomagnesium compounds, react with enolisable ketones in the presence of HMPT to give yields of magnesium derivatives of the enolic form[113]. Table 29 gives data on the reaction between various organomagnesium compounds and di-isopropyl ketone[113]. The action of n-butylmagnesium bromide at 55°C produces considerable enolisation[113] in the ketones—butanone (75%), 2,4-dimethylpentan-3-one (95%), and cyclohexanone (90%).

¶For the influence of HMPT on the alkylation of the enolates of acetoacetic ester and pentane-2,4-dione see Refs. 196 and 197 (Editors).

†The changed ratios of *O*- and *C*-substituted products was explained[107] by selective solvation—by the formation of strong hydrogen bonds by the fluorinated alcohol (Editors).

In HMPT magnesium enolates are alkylated at a carbon atom by alkyl sulphates, toluene-*p*-sulphonates, and methyl iodide[114]:



$$\underset{\displaystyle\text{OMgX}}{-\text{C}}{=}\text{CH}- \xrightarrow{\text{RX}} \text{MgX}_2 + -\underset{\displaystyle\text{O}}{\overset{}{\text{C}}}-\underset{\displaystyle\text{R}}{\text{CH}}-$$

this being impossible in solvents of low polarity.

Table 29.

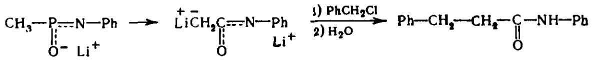
Organomagnesium compound	Enolisation	Reduction	Addition
CH_3MgBr	33	0	66
EtMgBr	100	trace	trace
Et_2Mg	40	trace	60
n-BuMgBr	100	0	trace
$(n\text{-Bu})_2Mg$	60	trace	40
i-PrMgBr	100	0	0
$(i\text{-Pr})_2Mg$	100	0	0

In the presence of strongly solvated cations (alkali-metal derivatives) *N*-alkylation takes place, with the formation of sodium iminoalkenylamines[115] (Table 30). With iodoethane high yields of *C*-alkylated derivatives are formed.

Table 30.

Solvent Base Imine	Diethylcellosolve Sodium hydride Acetophenone anil			HMPT, sodamide *N*-ethylcyclohexanimine			HMPT, sodamide *N*-ethylpentan-3-imine		
Alkylating agent	Et_3OBF_4	Et_2SO_4	EtI	Et_3OBF_4	Me_2SO_4	EtI	Et_3OBF_4	Me_2SO_4	EtI
Unchanged materials	8	9	5	29	11	15	26	17	20
Alkenylamine	88	49	5	53	75	17	29	57	0
C-Alkylated product	4	42	90	18	10	56	42	26	71
Polyalkylated product	—	—	—	—	4	12	3	0	9

Under the influence of a sufficiently strong base an ambident anion is able to form a dianion. Thus acetanilide has been quantitatively *N*-alkylated after the addition of sodamide in HMPT.[70] In liquid ammonia this reaction leads to the formation of a singly charged anion, but in excess of n-butyl-lithium in ether or oxolan a dianion is formed, with the formation of *C*-alkylated derivatives[116]:



$$CH_3-\underset{\displaystyle O^-\ Li^+}{P}{=}N-Ph \longrightarrow \overset{+\ -}{LiCH_2}\underset{\displaystyle O}{C}{=}N-Ph\ \ Li^+ \xrightarrow[2)\ H_2O]{1)\ PhCH_2Cl} Ph-CH_2-CH_2-\underset{\displaystyle O}{\overset{}{C}}-NH-Ph$$

Similar results can be obtained with methanesulphonamides[117].

4. Formation of Cyclopropane Compounds and Stereochemistry

Cyclopropane derivatives can be obtained by condensing unsaturated compounds (esters, nitriles, ketones) with carbanions formed from various α-halogen derivatives (esters, nitriles, ketones). The formation of these compounds is immensely influenced by the solvent: thus the following reaction yields the *cis*-isomer in benzene, and the *trans*-isomer in HMPT:

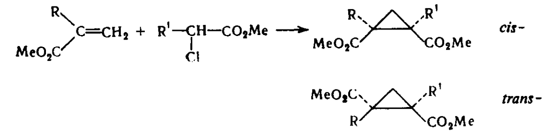


Table 31 gives some quantitative results on the formation of *cis*- and *trans*-isomers of various cyclopropane derivatives in benzene and in a mixture of benzene and HMPT[118,119].

Table 31.

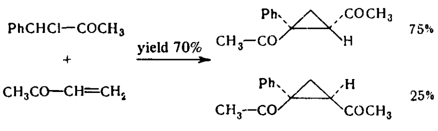
R and R′	Yield, %	Isomers, % *trans*	Isomers, % *cis*
C_6H_6			
R=R′=CH_3	71	7	93
R=H, R′=CH_3	70	17	83
R=R′=Et	55	0	100
R=H, R′=Ph	43	0	100
R=CH_3, R′=Ph	38	0	100
C_6H_6+HMPT (50:50)			
R=R′=CH_3	60	64	36
R=H, R′=CH_3	70	90	10
R=R′=Et	67	75	25
R=H, R′=Ph	65	56	21
R=CH_3, R′=Ph	46	43	25

A similar experiment has been made with α-chlorinated ketones. The highly reactive carbanion formed in HMPT enabled α-halogeno-ketones to be used, as the presence of a hydrogen atom in the α′-position made it possible for this reaction to compete with the Favorskii reaction; and also permitted the use of but-3-en-2-one, which under ordinary conditions polymerises before it can react. The reactions undergone by the butenone with various compounds and the yields are listed in Table 32.[120]

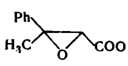
Table 32.

CH_3—CO—CH=CH_2	ROOC—CHCl—COOR	73
	Ph—CHCl—$COCH_3$	70
	Ph—CHCl—COOR	58
	CH_3—CHCl—$COCH_3$	40
	CH_3CHCl—COOR	10

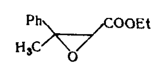
The investigations have refined the stereochemistry of the condensation



In HMPT the Darzens reaction between acetophenone and ethyl chloroacetate[121] leads to the formation predominantly of the isomer (XXII) (Table 33).

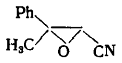


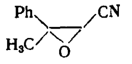
(XXII)



(XXIII)

The reaction between acetophenone and chloroacetonitrile results in the epoxides (XXIV) and (XXV)


(XXIV)

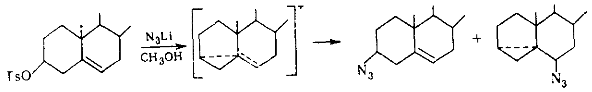

(XXV)

In HMPT a good yield is obtained, but approximately equal quantities of the isomers are formed [Table 34].

Table 33.

Solvent	Base	Duration of reaction, h	Yield, %	(XXII), %
Hexane	NaH	18	50	53
	NaH	8	25	50
Benzene	$NaNH_2$	8	40	50
Benzene		1.5	30	51
HMPT	$t\text{-}C_4H_9OK$	8	57	48
	NaH	1.5	70	59

Another example of the influence of the solvent on the mechanism and the stereochemistry of reactions occurs in steroid chemistry. The 5-en-3β-yl toluene-*p*-sulphonate (XXVI) [122] and the 20β-yl compound (XXX) [123] form different products, depending on the type of solvent (protic or aprotic), on reaction with alkali-metal azides. In methanol the compound (XXVI) yields, via an intermediate carbonium ion (XXVII), derivatives of an inactive steroid (XXIX) (S_N1 mechanism).

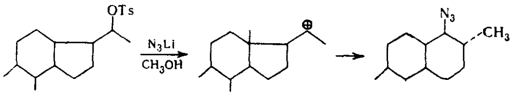


(XXVI) (XXVII) (XXVIII) (XXIX)

Table 34.

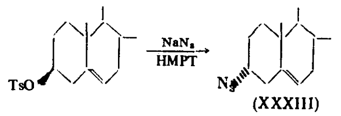
Solvent	Base	Duration of reaction, h	Yield, %	(XXIV), %
Benzene	$NaNH_2$	1.5	5	58
	$t\text{-}C_4H_9OK$	—	50	64
$t\text{-}C_4H_9OH$	$t\text{-}C_4H_9ONa$	—	60	63
$HMPT\text{-}t\text{-}C_4H_9OH$	$t\text{-}C_4H_9OK$	—	73	55
HMPT	NaH	—	62	45

The toluene-*p*-sulphonate (XXX) yields, on rearrangement of the intermediate carbonium ion (XXXI), the D-homo-derivatives (XXXII):



(XXX) (XXXI) (XXXII)

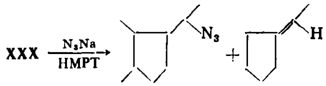
In aprotic dipolar solvents such reactions occur by an S_N2 mechanism with inversion of configuration:



(XXXIII)

The yield of the product (XXXIII) increases with the basic character of the solvent S (Table 35).

The toluene-*p*-sulphonate (XXX) forms mainly the 20α-azide (XXXIV) together with, owing to elimination, a small quantity of the derivative (XXXV):



(XXXIV) (XXXV)

Table 35.

Solvent	DMSO	*N*-Methylpyrrolidone	HMPT
(XXXIII), %	30	71	93

The yield of the product (XXXIV) also increases with the basic character of the solvent, as is evident from Table 36.

Reducing the azides with lithium tetrahydroaluminate gives good yields of the corresponding aminosteroids.

Table 36.

Solvent	DMSO	*N*-Methylpyrrolidone	HMPT
(XXXIV), %	46	53	65

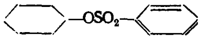
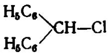
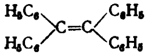
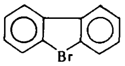
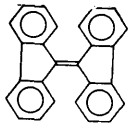
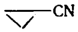
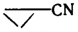
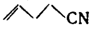
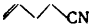
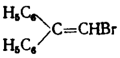
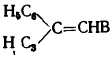
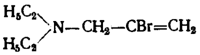
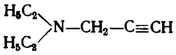
Table 37.

RMgX	Halogenated vinyl	Product	Yield, %	Ref.
$n\text{-}C_4H_9MgBr$	$n\text{-}C_5H_{11}CCl{=}CHCl$ (*cis*)	$C_5H_{11}C{\equiv}C{-}Cl$ $+C_5H_{11}C{\equiv}C{-}C_4H_9$	14 10	124
$n\text{-}C_7H_{15}MgBr$	$CHCl{=}CCl_2$	$C_7H_{15}C{\equiv}C{-}Cl$	48	125
$n\text{-}C_5H_{11}MgBr$	$PhCH{=}CHBr$	$PhC{\equiv}C{-}H$	27	126
PhMgBr	$PhCH{=}CHBr$	$PhC{\equiv}C{-}H$	20	126

Elimination Reactions

Reactions involving elimination may lead to the formation of carbenes, alkynes, or arynes. It has been noted earlier that the basic character of anions is most strongly developed in HMPT, so that elimination is often accompanied by nucleophilic substitution (S_N2). In HMPT elimination of hydrogen halides and of groups attached to sulphur is possible, but no systematic studies have yet been made of such processes. Halogenated vinyl compounds very readily undergo elimination under the influence of weak bases (organomagnesium compounds) in HMPT (Table 37).

Table 38.

Initial cpd.	Basic agent	Solvent	Principal product	Yield, %
	$NaNH_2$	HMPT		58 (dibrominated cpd.)
$C_6H_5CH_2Cl$	$NaNH_2$	HMPT	unchanged $C_6H_5CH_2Cl$ $(C_6H_5CH_2)_3N$ as hydrochloride *trans*-$C_6H_5CH{=}CHC_6H_5$	35—40 32* —
$C_6H_5CH_2Cl$	$NaNH_2$	HMPT oxolan	*trans*-$C_6H_5CH{=}CHC_6H_5$	50 (unpurified 67)
$C_6H_5CH_2Cl$	NaH	HMPT	unchanged $C_6H_5CH_2Cl$ $C_6H_5CH_3$, $C_6H_5CH_2CH_2C_6H_5$ $C_6H_5CH{=}CHC_6H_5$ + unidentifieds	65 —
$C_6H_5CH_2Br$	$NaNH_2$	HMPT benzene	$(C_6H_5CH_2)_3N$	79**
$C_6H_5CH_2Br$	NaH	HMPT	$C_6H_5CH_2{-}CH_2{-}C_6H_5$	62 (unpurified 72)
 $(H_5C_6)_2CH{-}Cl$	$NaNH_2$	HMPT	$C_6H_5CH_3$  $(H_5C_6)_2C{=}C(C_6H_5)_2$	16 87
	$NaNH_2$	HMPT benzene		60
$Cl{-}(CH_2)_3{-}CN$	$NaNH_2$	HMPT		54
$Cl{-}(CH_2)_3{-}CN$	NaH	HMPT		84
$CH_3CHCl{-}(CH_2)_2{-}CN$	NaH	HMPT		31
$Cl{-}(CH_2)_4{-}CN$	NaH	HMPT		40
 $(H_5C_6)_2C{=}CHBr$	$NaNH_2$	HMPT	$C_6H_5C{\equiv}C{-}C_6H_5$	80 (unpurified 89)
 $(H_5C_6)(H_3C)C{=}CHBr$	see Table II in Ref.128		$C_6H_5C{\equiv}C{-}CH_3$	20—40
$C_6H_5CH{=}CH{-}Br$	NaH	HMPT	$C_6H_5C{\equiv}C{-}H$	78
 $(H_5C_2)_2N{-}CH_2{-}CBr{=}CH_2$	$NaNH_2$	HMPT	 $(H_5C_2)_2N{-}CH_2{-}C{\equiv}CH$	73
$CH_3{-}(CH_2)_5{-}CBr{=}CH_2$	$NaNH_2$	HMPT	$CH_3{-}(CH_2)_5C{\equiv}CH$	70

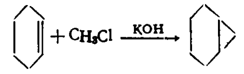
*Contains no unchanged benzyl chloride.
**Isolated as hydrochloride.

Elimination products can be obtained from various compounds by the action of H^-, NH_2^-,[127,128] and $CH{:}C^-$ [129] in HMPT. Table 38 shows that several of the reactions—the production of cyclopropyl cyanide, the production of acetylenic derivatives with and without rearrangement—give good yields. The action of such a strong nucleophile as NH_2^- on benzyl bromide in a mixture of HMPT and benzene yields tribenzylamine.

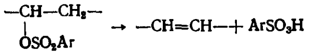
Compounds containing an α-halogen atom form stilbene or polyenes both in liquid ammonia and in HMPT. Analogous elimination is produced by the action of the acetylide ion on cinnamyl chloride, when 1,6-diphenylhexa-1,3,5-triene is obtained[129]:

$$PhCH{=}CH{-}CH_2Cl \rightarrow Ph{-}(CH{=}CH)_3Ph$$

It has been shown that these reactions do not involve the intermediate formation of carbenes, although in principle this seems possible: the reaction of chloroform and potassium hydroxide with cyclohexene in HMPT produces norcarane[130]:



Compounds containing sulphur can also undergo elimination. Thus alkenes are formed when arenesulphonates are heated in dipolar aprotic solvents[131] (Table 39):



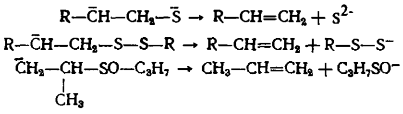
$$\underset{OSO_2Ar}{-CH}{-}CH_2{-} \rightarrow {-}CH{=}CH{-} + ArSO_3H$$

Table 39.

Sulphonate	Solvent	Temp., °C	Time, h	Alkene	Yield, %
Cyclohexyl toluene-p-	DMSO HMPT	90—95 100	5 6	cyclohexene cyclohexene	61 62
1-Methylheptyl benzene-	DMSO HMPT	100—107 100	0.75 3	octene octene	52 61.5

When cyclohexyl benzenesulphonate is heated in the presence of sodamide in HMPT to 40°C, cyclohexene is formed (58%).[128] In HMPT the acetylide anion converts ethoxyethyl methanesulphonate into ethoxyethylene $CH_2{:}CH.OC_2H_5$.[129]

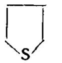
The autoxidation of thiols, disulphides, sulphones, and sulphoxides is often accompanied by undesirable β-elimination with the formation of alkenes[132]:



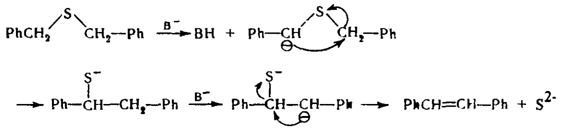
$$R-\bar{C}H-CH_2-\bar{S} \rightarrow R-CH=CH_2 + S^{2-}$$
$$R-\bar{C}H-CH_2-S-S-R \rightarrow R-CH=CH_2 + R-S-S^-$$
$$\bar{C}H_2-\underset{\substack{|\\ CH_3}}{CH}-SO-C_3H_7 \rightarrow CH_3-CH=CH_2 + C_3H_7SO^-$$

In protic solvents aliphatic sulphones are decomposed with difficulty to alkenes (the action of potassium hydroxide requires temperatures above 200°C), but the same compounds in HMPT undergo elimination at 80°C, although reaction is slow[133] (Table 40).

Table 40. Elimination (KOH–HMPT at 80°C).

Reactant	Product	Time, h	Yield, %
$(CH_3)_3C-S-S-C(CH_3)_3$	isobutene	20 141	36 63
$(CH_3)_3C-S-C(CH_3)_3$	isobutene	20 141	2 11
	butadiene	150	1
$i\text{-}C_3H_7-SO-C_3H_7$	propene	141	28
$n\text{-}C_4H_9\underset{\substack{\parallel\\ O}}{S}-C_4H_9$	isomeric butenes	141	10

In the presence of a base B⁻ [134] HMPT promotes the conversion of dibenzyl sulphide, through an intermediate carbanion, into stilbene:



It thus becomes clear why this sulphide can be obtained in high yield in oxolan:

$$PhCH_2SH \xrightarrow[2)\ PhCH_2Cl]{1)\ NaNH_2} S\,(CH_2-Ph)_2 \quad (83\%)$$

whereas in HMPT a considerable amount of stilbene is formed[135].

Autoxidation of Anions

Effective autoxidation of a large number of compounds which form anions is possible at room temperature[136]. The reactions occur especially efficiently in dimethylformamide or dimethyl sulphoxide in the presence of potassium t-butoxide as base. The following mechanism is possible[137] for the oxidation of toluene—formation of carbanion

$$PhCH_2-H + B^- \rightarrow BH + BHCH_2^- \tag{1}$$

formation of benzyl radical

$$PhCH_2^- + O_2 \rightarrow Ph-\dot{C}H_2 + O^{\cdot-} \tag{2}$$

formation of peroxy-radical

$$Ph\dot{C}H_2 + O_2 \rightarrow PhCH_2-O-O^{\cdot} \rightarrow \tag{3}$$

Autoxidation is more rapid the more rapidly is the carbanion formed.

The possibility of using HMPT as reaction medium in autoxidation was first noted by Wallace. It is to be preferred to other dipolar aprotic solvents for two main reasons.

1. It cannot give a carbanion, and therefore its oxidation is impossible. If isotopic exchange is carried out in the presence of a base between toluene, in which the methyl group is labelled with tritium, and various dipolar solvents, the times indicated in Table 41 are required for 10% exchange to occur[138].

Table 41.

Solvent	Time, min
Dimethyl sulphoxide	6
Dimethyl sulphone	12
1-Methylpyrrolid-2-one	48
Thiolan 1-monoxide	420
HMPT	14000

Table 41 shows almost complete absence of exchange with HMPT, the hydrogen atoms in which occupy the β-position with respect to the PO group. Dimethyl sulphoxide undergoes considerable autoxidation, which is possible also with diglyme and dioxan[139].

2. It is stable to the action of bases (even potassium hydroxide at 80°C), and is therefore more convenient than carboxyamides and lactams.

Table 42.

RSH (mole)	KOH/RSH	Solvent	RSH converted, %	Yield of RSO_2H, % (a)	Yield of R_2S_2, % (a)	Temp., °C	Time, h
C_6H_5SH (0.025)	4	HMPT	99	90	6.4	23.5	12
C_6H_5SH (0.025)	4	DMF	100	91	4.7	23.5	22
C_6H_5SH	4	HMPT	98	92.5	3.8	80	29
$o\text{-}CH_3C_6H_4SH$ (0.025)	4	HMPT	100	80	21	23.5	24
$o\text{-}CH_3C_6H_4SH$ (b) (0.025)	4	HMPT	99	95	4.5	80	24
$p\text{-}CH_3C_6H_4SH$ (0.025)	4	HMPT	100	94	6.4	80	24
$o\text{-}HOOC-C_6H_4SH$ (0.025)	4	HMPT	99	96	4.6	80	24
$(CH_3)_3CSH$ (0.024)	4	HMPT	99	71.6	25	23.5	12
$1\text{-}C_{16}H_{33}SH$ (0.025)	4	HMPT	91.6	38.4	55.6	23.5	24
$1\text{-}C_{16}H_{33}SH$ (0.025)	4	HMPT	97.5	96	0.5	80	21
$(C_6H_{11})_3CSH$	4	HMPT	100	62.5	37.4	80	42

(*a*) 100 x moles of product/theoretical moles.
(*b*) *o*-Sulphobenzoic acid is not formed.

Thiols and disulphides are oxidised to sulphonic acids in the highest yields (95–100%) in HMPT:[140]

$$RSH \rightarrow RSO_3H$$
$$R_2S_2 \rightarrow RSO_3H$$

Tables 42 and 43 [140] give data on the oxidation of thiols and disulphides by bases (only potassium hydroxide was used as base in Table 42).

The autoxidation of sulphides yields a mixture of carboxylic and sulphonic acids[141]. Tables 44 and 45 give data on the oxidation of sulphides.

The reaction of sulphoxides with potassium t-butoxide in HMPT at 80°C results in the formation of a mixture of carboxylic and sulphonic acids[142] (Table 46).

Ketones undergo autoxidation to acids, cyclic ketones forming dibasic acids (Tables 47 and 48). The reaction velocity is higher in HMPT than in the other two solvents: HMPT > $t\text{-}C_4H_9OH$ ≫ water. Of the three bases—potassium, sodium, and lithium hydroxides—the first two are the more effective (the reactions occur with surprisingly high yields). The character of the ketones is also of significance, those of them which easily form carbanions undergoing autoxidation more rapidly[143].

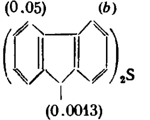
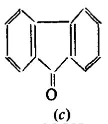
Table 43.

R_2S_2 (0.0125 M)	Solvent	Base (0.1 M)	Temp., °C	R_2S_2 converted, %	Yield of RSO_3H, %	Yield of RSH, %	Time, h
$n\text{-}Bu_2S_2$	HMPT	KOH	23.5	98	92.3	3	41
$n\text{-}Bu_2S_2$	HMPT	KOH	80	96	97	0	45
$n\text{-}Bu_2S_2$	DMF	KOH	23.5	87.7	88.1	0	45
$n\text{-}Bu_2S_2$	HMPT	NaOH	80	95	94.2	0.9	35
$(C_6H_5)_2S_2$	HMPT	KOH	23.5	97.7	88.1	—	22
$(C_6H_5)_2S_2$	HMPT	KOH	80	98	99	0	22.5
$(C_6H_5)_2S_2$	DMF	KOH	23.5	98.5	90	0.3	40
$(o\text{-}CH_3\text{—}C_6H_4)_2S_2$	HMPT	KOH	80	98	98	0	23

Under the influence of bases (t-butyl alcohol or potassium hydroxide) in HMPT, aromatic hydrocarbons are oxidised to the corresponding acids[138] (Table 49).

Methylthiophens are also converted into acids. The 2-isomers, which are able to form carbanions that are strongly stabilised by resonance, give high yields of the acids[144] (Table 50).

Table 44. Oxidation of benzyl sulphides [(*a*)].

Sulphide (M)	Products	Yield, %	Time, h	O_2/R_2S molar	Rate relative to toluene
$C_6H_5CH_2\text{—}S\text{—}C_6H_5$	C_6H_5COOH $C_6H_5SO_3H$ C_6H_5SH	62 44 32	23	0.145	6.30
$C_6H_5CH_2S\text{—}CH_3$ (0.05)	C_6H_5COOH CH_3SO_3H	77 73	67	0.083	3.61
$C_6H_5\underset{CH_3}{\underset{\mid}{CH}}\text{—}S\text{—}\underset{CH_3}{\underset{\mid}{CH}}\text{—}Ph$ (0.05) (*b*)	C_6H_5COOH	37	26	0.063	2.74
 (0.0013)		31	68	0.225	9.79
$C_6H_5CH_2\text{—}S\text{—}CH_2C_6H_5$	(*c*)	(*c*)	(*c*)	0.150	6.52
$C_6H_5CH_3$ (*d*) (0.05)	C_6H_5COOH	48	24	0.023	1.00

(*a*) In 2M $t\text{-}C_4H_9OK$–HMPT at 80°C.
(*b*) Polymeric substances containing a carbonyl chain.
(*c*) See Table 45.
(*d*) The oxidation of toluene under these conditions has been studied by Hofmann and his coworkers.

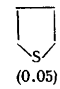
D. COMPARISON OF DIPOLAR APROTIC SOLVENTS

The preceding discussion has shown that S_N2 and S_E2 reactions are accelerated in dipolar aprotic solvents, the reaction velocity depending on the donor power of the solvents:

dimethylformamide < dimethyl sulphoxide < tetramethylurea < HMPT.

These solvents contain various polar groups: CO in dimethylformamide and tetramethylurea, SO in dimethyl sulphoxide, and PO in HMPT, with hydrogen atoms at different distances from these groups. The differences in structure among the solvents explain their varying stability and their different behaviour, which is sometimes undesirable in certain reactions.

Table 45. Oxidation of sulphides (*a*).

Sulphide (M)	Products (yield, %)	Time, h	O_2/R_2S molar	Rate relative to *toluene*
$C_6H_5S\text{—}CH_3$ (0.05)	$C_6H_5SO_3H$ (36.8) CO_2 (36.0)	46	0.0104	0.45
$(n\text{-}C_4H_9)_2S$ (0.05)	$n\text{-}C_4H_9SO_3H$ (8.5) $n\text{-}C_3H_7COOH$ (10.9)	45.5	0.0033	0.15
$(t\text{-}C_4H_9)_2S$ (0.05)	none	21	0	0
 (0.05)	$\begin{matrix}CH_2\text{—}COOH\\ \mid\\ CH_2\text{—}COOH\end{matrix}$ (5—10) (*b*)	70	0.0056	0.21
$(C_6H_5CH_2)_2S$ (0.05)	(*c*)	(*c*)	0.150	6.52
$(C_6H_5CH_2)_2S$ (0.05)	(*d*)	(*d*)	0.023	1.00

(*a*) In 2M $t\text{-}C_4H_9OK$ at 80 ± 0.5°C.
(*b*) Approximate representation of product of reaction.
(*c*) See Table I in Ref. 141.
(*d*) See Table 44.

Table 46.

Sulphoxide (mole)	Base (mole)	HMPT, ml	Duration of reaction, h	Products (mole, yield, %) (*a*)
$CH_3\underset{\underset{O}{\|}}{S}\text{—}CH_3$ (75 ml)	KOH (0.15)	—	68	CH_3SO_3H (*c*) (0.001) CO_2 (0.0028)
$CH_3\overset{\overset{O}{\|}}{S}\text{—}CH_3$ (*b*, *c*) (0.5)	$t\text{-}C_4H_9OK$ (0.15)	75	23	CH_3SO_3H (*d*, *f*) (0.011, 23) CO_2 (0.12, 24)
$C_6H_5\underset{\underset{O}{\|}}{S}\text{—}CH_3$ (*b*)	$t\text{-}C_4H_9OK$ (0.038)	25	69	$C_6H_5SO_3H$ (0.103, 86.4) CO_2 (0.00882, 67)
$C_6H_5CH_2\overset{\overset{O}{\|}}{S}\text{—}CH_2\text{—}Ph$ (*b*) (0.025)	$t\text{-}C_4H_9OK$ (0.15)	75	20	C_6H_5COOH (*e*) (0.22, 88) $C_6H_5CH{=}CHC_6H_5$ (*e*) (0.0061, 24)

(*a*) 100 x moles of product/mole of reactant.
(*b*) No reliable data from infrared spectra on formation of sulphone.
(*c*) Acetic acid (infrared and mass spectra) and formaldehyde (2,4-dinitrophenylhydrazone, m.p. 166°C) were isolated quantitatively.
(*d*) Verified by gas–liquid chromatography.
(*e*) Verified by gas–liquid chromatography.
(*f*) Russell and his coworkers found methanesulphonic acid and dimethyl sulphone on oxidation with a mixture of potassium t-butoxide and dimethyl sulphoxide[137].

1. Reactivity of Polar Group

A negative charge on oxygen gives the solvent a basic character. The atom adjacent to the oxygen (carbon, sulphur, or phosphorus) acquires a positive charge, which favours attack by nucleophilic agents B^-, either present initially or formed during the reaction. As a result, dimethylformamide and tetramethylurea may form amide ions able to compete with B^-:

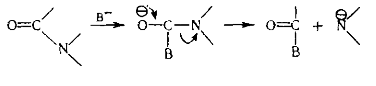


Table 47. Influence of solvent and base on the oxidation of acetophenone (*a*).

Base	Solvent	Temp., °C	Yield of benzoic acid, %	$10^2 O_2$ (*c*)/ketone molar	Time, h
t-C_4H_9OK	t-C_4H_9OH	23.5	66	1.60	45
t-C_4H_9OK	HMPT	23.5	88	4.88	44
KOH	HMPT	80	62	2.14	44
KOH	HMPT	23.5	35	0.42	44
NaOH	HMPT	80	60	2.00	21
NaOH	HMPT	23.5	46	0.43	21
LiOH	HMPT	80	14	0.009	24.5
LiOH	HMPT	25.0	—		24.5
LiOH	H_2O	80	—		42

(*a*) The concentrations used were 0.05 M acetophenone and 0.15 M base with an oxygen pressure of 1 atm.
(*b*) 100 x theoretically calculated moles of acid per mole of ketone. Except for the use of lithium hydroxide, the whole of the ketone is converted with a yield of 90–100%.
(*c*) Calculated from rate of consumption of oxygen.

Table 48. Oxidation of cyclic ketones (*a*).

Ketone	Temp., °C	Time, h	Base	Acid (yield, %)
Cyclohexanone	23.5	20	CH_3ONa	adipic (100)
Cyclohexanone	80	24	CH_3ONa	adipic (>90)
Cyclohexanone (*b*)	23.5	78	NaOH	adipic (94)
Cyclohexanone (*b*)	80	68	NaOH	adipic (82)
Cyclohexanone (*b*)	23.5	24	NaOH	adipic (81)
Cyclohexanone (*b*)	80	19	NaOH	adipic (88)
Cyclopentanone	23.5	23	CH_3ONa	glutaric (95)
Cyclopentanone	80	23	CH_3ONa	glutaric (100)
Cyclopentanone (*b*)	23.5	26	NaOH	glutaric (49)
Cyclopentanone (*b*)	80	24	NaOH	glutaric (76)
Cyclopentanone	23.5	19	CH_3ONa	pimelic (44)
Cyclopentanone	80	21	CH_3ONa	pimelic (41)
Cyclopentanone	80	21	CH_3ONa	dodecanoic (40)

(*a*) The concentrations used were 0.025 M ketone and 0.15 M base with 75 ml of HMPT.
(*b*) Results obtained mainly by the use of potassium hydroxide.

Such decomposition is improbable with HMPT, in which the phosphorus atom is sterically blocked, so that it is considerably more difficult for HMPT to form ions like the amide ions formed by dimethylformamide and tetramethylurea.

Strong bases (organic compounds of alkali metals) act effectively on dimethylformamide, dimethyl sulphoxide, and tetramethylurea, but do not act on HMPT under the conditions normally employed. Nor do organomagnesium compounds react with tetramethylurea and HMPT.[145,146]

Table 49.

ArH	ArCOOH	Yield, %
Toluene	benzoic acid	25—30
o-Xylene	phthalic acid	35—40
m-Xylene	isophthalic acid	50
p-Xylene	terephthalic acid	15
Tetralin	phthalic acid	46

Thus organometallic compounds (of the alkali metals and magnesium) can be obtained in HMPT. On the other hand, it is desirable to prepare them in a mixture of HMPT and a non-polar solvent (benzene, toluene). This precaution is unnecessary with unreactive organometallic compounds. Thus organocadmium, organozinc, organotin, etc. compounds can be obtained by direct reaction between the metal and the halogen derivatives in pure HMPT.

Table 50. Oxidation of alkylthiophens in HMPT.

Reactant (0.5 mole)	Base (0.15 M)	Temp., °C	Product	Yield, % (*a*)	Duration, h	Rate of consumption of oxygen	Rate of relative to toluene
2-Methylthiophen	t-C_4H_9OK	80	thiophen-2-carboxylic acid	75.8	70	0.0380 0.0320	1.50 (*b*)
2,5-Dimethylthiophen	t-C_4H_9OK KOH	23.5 80	thiophen-2-carboxilic acid	19.9 2.2	48 25	0.0075 0.0013	0.32 0.06
3-Methylthiophen	t-C_4H_9OK	80	thiophen-3-carboxylic acid	13.4 19.2	23 70	0.0334 0.0008 0.0007	1.40 0.03 (*c*)
Toluene	t-C_4H_9OK	80	benzoic acid	47.8	24	0.0230	1.00

(*a*) All yields based on theoretical.
(*b*) Rate of oxidation = moles of oxygen per mole of reactant per minute.
(*c*) Mean of two separate reactions.

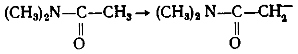
Sodium hydride can be used in various reactions with dimethylformamide, but it partly reacts with the latter even at room temperature[147]. Its use in reactions with dimethyl sulphoxide as solvent is not without danger, as the latter contains oxygen, and explosions are possible even at low temperatures[148].

Alkali-metal hydrides and amides do not interact with tetramethylurea or HMPT.

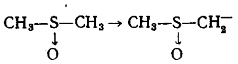
Alkali-metal hydroxides react readily with dimethylformamide, dimethyl sulphoxide, and tetramethylurea, but do not react with HMPT even at 80°C.

2. Electron-acceptor Effect of Polar Group

The electron-acceptor effect of the polar group makes an α-hydrogen atom labile; on loss of a proton the solvent is converted into a carbanion. Thus dimethylacetamide and dimethyl sulphoxide yield the corresponding carbanions:



$$(CH_3)_2N-\underset{\underset{O}{\|}}{C}-CH_3 \rightarrow (CH_3)_2N-\underset{\underset{O}{\|}}{C}-CH_2^-$$



$$CH_3-\underset{\underset{O}{\downarrow}}{S}-CH_3 \rightarrow CH_3-\underset{\underset{O}{\downarrow}}{S}-CH_2^-$$

Tetramethylurea and HMPT, in which the hydrogen atoms are in the β-position, are able to lose these atoms only in exceptional circumstances. The resulting carbanions are able to undergo the same reactions as those produced during substitution, addition, autoxidation, etc.

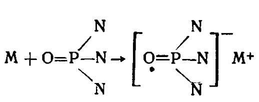
The ease with which the "dimsyl" anion is formed and its reactivity make it an excellent agent in syntheses[149]. On the other hand, dimethyl sulphoxide is not recommended as a solvent for reactions involving carbanions.

From the points of view of basic character and stability HMPT is regarded as the most suitable among dipolar aprotic solvents for the production and application of anions. At present most of these reactions are accomplished in liquid ammonia, but a great future belongs to HMPT, in view of the convenience of operation, absence of protolysis (e.g. preparation of $(C_6H_5)_3CM$), better solubility of various agents (e.g. higher aliphatic bromides).

V. USE OF HEXAMETHYLPHOSPHORIC TRIAMIDE AS ELECTRON-ACCEPTOR REACTION MEDIUM

A. FORMATION OF RADICAL-ANIONS

Normant and his coworkers were the first to observe that HMPT is able to dissolve alkali metals (lithium, sodium, potassium) with the formation of light blue solutions[150]. It was shown simultaneously that the solutions contained radical-anions and were paramagnetic[151–153]:



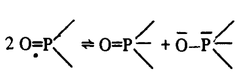
Electron spin resonance spectra were recorded for various concentrations

$$M + n\ \mathrm{HMPT} \leftrightarrows (M^+\ .\ .\ .e^-)_n\ \mathrm{HMPT}$$

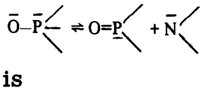
The stability of the radical-ions depends on the concentration and the nature of the cation. At concentrations near molar the blue colour disappears after 10–15 min with potassium, and after 5–6 h with sodium and lithium.

Other metals—magnesium[154] and the alkaline-earth metals (calcium, strontium, barium)[155]—also dissolve in HMPT. Freshly prepared solutions of these metals are light blue, having an absorption maximum at 770 nm. At the same concentration solutions of magnesium are more stable than those of sodium; solutions of the alkaline-earth metals have little stability, especially those of barium. In time the blue colour of the radical-anions passes into pale yellow (λ_{max} = 390 nm).

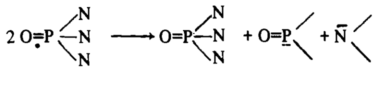
We have previously reported that this decomposition yields two anions and have suggested a mechanism[156]. The most probable scheme seems to be that the mesomeric radical-anion dismutates:



The resulting dianion is in turn converted into two anions:



The overall equation is



Polycyclic hydrocarbons are able to act as electron acceptors towards metals, and several radical-ions have recently been obtained in HMPT. The ease of formation of radical-ions depends on three main factors[157]—(*a*) the electron affinity of the hydrocarbon, which is always lower than that of a non-enolised ketone[158] (benzene < < phenanthrene < biphenyl < anthracene < *o*- and *p*-terphenyls < benzophenone < fluorene), (*b*) the reducing power of the metal (alkali metals > magnesium > alkaline-earth metals), and (*c*) the solvating power of the solvent (highest with HMPT, then dimethoxyethane and oxolan).

Biphenyl and naphthalene in oxolan form with lithium and sodium radical-ions which are used in various syntheses[159–161].

Radical-ions of naphthalene (1) and anthracene (2) are obtained also with sodium in HMPT.[162] Solutions of (2) are stable, but those of (1) decompose with time. This latter process has not yet been investigated; either the solvent may be decomposed by the radical-ion, or electron transfer may occur from naphthalene to HMPT. The acceptor powers of naphthalene and of HMPT cannot be compared by spectrophotometric methods, since unstable solutions of radicals are formed. Insufficient work has been done on determining the reduction potential of HMPT. Biphenyl and naphthalene do not form radical-ions with magnesium in oxolan, but their formation is possible in liquid ammonia[163]. The appearance of radical-ions in HMPT has also been observed by means of electron spin resonance[155].

Products of the interaction of naphthalene with magnesium in liquid ammonia are green after removal of most of the solvent; the magnesium–naphthalene–ammonia compound is decomposed by dimethyl sulphoxide and is insoluble in oxolan, but is dissolved by HMPT to form stable green solutions. Other radical ions of the type $ArH{\cdot}Mg^+$ can be obtained from these solutions[164]. In HMPT magnesium forms radical-ions with anthracene, pyrene, and 1,1-diphenylethylene[154]. Radical-ions of biphenyl can also be obtained in HMPT by the action of such metals as calcium, strontium, and barium.

Naphthalene, being a better electron acceptor than biphenyl, is able to accept an electron from the radical-ion of the latter to form the corresponding green radical-ions[155]:

$$\mathrm{Ph{-}Ph^{\cdot}} + \mathrm{Naph} \rightleftarrows \mathrm{Naph^{\cdot}} + \mathrm{Ph{-}Ph}$$

The electronic spectra of the various radical-ions obtained in HMPT do not depend significantly on the nature of the cation (Na^+ or Mg^{2+}), but their absorption maxima are slightly displaced to longer wavelengths in oxolan. HMPT is a good solvent for the preparation of ketyls[165].

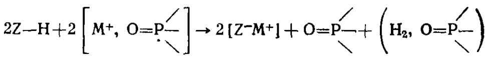
Radical-anions may be produced not only on the dissolution of metals but also during the electrolysis of alkali-metal salts in certain solvents (ammonia and the lower amines). Two laboratories have recently shown—simultaneously and independently—that HMPT may also be such a solvent[49,166]. When magnesium bromide is electrolysed with a calomel electrode in HMPT, an unstable light blue coloration appears around the cathode[49], and this is stabilised by the addition of lithium chloride[166]. In alcoholic medium (HMPT absent) evolution of hydrogen is observed. In HMPT containing a minute amount of alcohol a weak light blue coloration is evident in the catholyte, and electrolysis is not accompanied by hydrogen evolution. These facts indicate that HMPT accepts an electron with formation of a radical-ion.

B. APPLICATION OF RADICAL-ANIONS

The solutions of radical-ions formed when alkali metals are dissolved in HMPT can be used for those reactions—metallation, reduction, isomerisation, polymerisation, etc.—which occur in solutions of these metals in liquid ammonia[151].

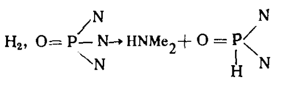
1. Formation of Anions and Metallation

Solutions of radical-anions are nucleophilic reagents, able to replace labile hydrogen in compounds containing it:



$$2Z{-}H + 2\left[M^+,\ O{=}\dot{P}\Big\langle\right] \rightarrow 2\,[Z^-M^+] + O{=}P\Big\langle + \left(H_2,\ O{=}P\Big\langle\right)$$

the anion Z^- or a metallated product being obtained. Hydrogen is not evolved in these reactions, but is bound by the HMPT into a complex, which decomposes according to the equation



$$H_2,\ O{=}P(N)_2{-}N \rightarrow HNMe_2 + O{=}P(H)(N)_2$$

The reactions occur more effectively with potassium and lithium than with sodium. For these reactions the HMPT can be mixed with other solvents (ether, oxolan, benzene). The radical-ions tend to decompose, and the stoichiometric quantity of ZH is introduced into the reaction mixture at the very start in order to avoid such decomposition.

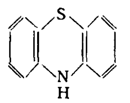
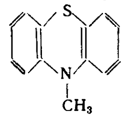
Table 51 gives results for the production of several heteroanions[167]. Information on the metallation of certain "acidic" hydrocarbons is given in Table 52.[168]

The aprotic solvent HMPT enables very weak acids (e.g. toluene) to be metallated by alkali metals. The action of lithium or potassium produces the deep red colour characteristic of the benzyl radical. Carboxylation yields phenylacetic acid, but always in low yield (the red solutions are decolorised). 1,3-Diphenylpropane and ethylbenzene have also been detected among the decomposition products.

Metallation by alkali metals in HMPT should be applicable to macromolecules containing labile hydrogen atoms—polyvinyldiphenylmethane, polyvinylfluorenone.

Alkynes, which are stronger acids than the above hydrocarbons, are not metallated by alkali metals when the solvent is HMPT alone. When a mixture of hexyne and HMPT is shaken with potassium and heated at 55°C, 37% of hexyne is recovered: the radical-ion decomposes. Even phenylacetylene, a relatively acidic compound, is not metallated. The phosphorodiamidite anion, which appears on decomposition of the radical-ion, is bound to both ends of the triple bond.

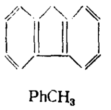
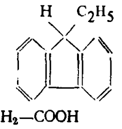
Table 51.

Metallated compound	Metal	Reactant	Product	Yield, %
n-C_4H_9OH	Na	$PhCH_2Cl$	$C_4H_9OCH_2Ph$	77
$Ph{-}NH{-}C_2H_5$	K	C_2H_5I	$Ph{-}N(C_2H_5)_2$	77
	Na	CH_3I		85
CH_3CONH_2	K	$PhCH_2Cl$	$CH_3CO{-}NH{-}CH_2Ph$	negligible*

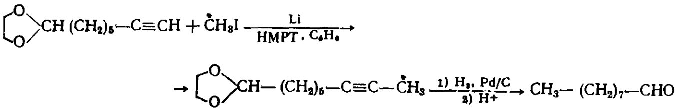
*Negligible yield also when sodamide employed.

This great difference in the behaviour of alkali metals is HMPT and in liquid ammonia can be explained by the formation of complexes between alkynes and HMPT. However, metallation is possible in a mixture of HMPT and a non-polar solvent (benzene, toluene, etc.), where the complexes will be decomposed. Table 53 gives results obtained by the use of a mixed solvent[169].

Table 52.

Hydrocarbon	Metal	Reactant	Product	Yield, %
Ph_3CH	Na	CO_2	$Ph_3C{-}COOH$	50
—	K	$PhCH_2Cl$	$Ph_3C{-}CH_2{-}Ph$	90
—	K	$PhCOCl$	$Ch_3C{-}CO{-}Ph$	70
——	K	$Br(CH_2)_4Br$	$Ph_3C(CH_2)_4CPh_3$	60
Ph_2CH_2	Na	CO_2	$Ph_2CH{-}COOH$	30
—	K	n-C_4H_9I	$Ph_2CH{-}C_4H_9$	64
—	K	$PhCH_2Cl$	$Ph_2CH{-}CH_2{-}Ph$	66
—	K	$Br(CH_2)_4Br$	$Ph_2CH(CH_2)_4CHPh_2$	87
—	Li	—	—	90
—	Li	—	—	65
	Na	C_2H_5I		73
$PhCH_3$	Li	CO_2	$PhCH_2{-}COOH$	negligible
Ph_3GeH	K	n-C_4H_9Br	$Ph_3Ge{-}C_4H_9$	62

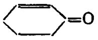
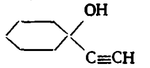
The same conditions have been effectively applied to the preparation of nonanal[170], which is formed as an intermediate in the synthesis of labelled oleic acid:



The yield of the labelled compound is 95% based on the iodomethane.

Formation of carbanions is successful if the functional group of the compound is attached to an active CH_2 or CH_3 group[154] (Table 54). In some cases (acetophenone, acetonitrile) it is necessary to use a mixture of HMPT with an inert solvent to avoid the formation of condensation products. A mixture of solvents is also in carbonylation and acylation.

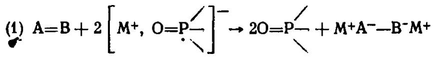
Table 53.

Alkyne	Reactant	Product	Yield, %
$Et_2NCH{-}C{\equiv}CH$	$Br(CH_2)_4Br$	$C{\equiv}C{-}CH_2NEt_2$ $(CH_2)_4$ $C{\equiv}C{-}CH_2NEt_2$	50
$PhC{\equiv}CH$	CO_2	$PhC{\equiv}C{-}COOH$	70
$HC{\equiv}CH$	n-$C_6H_{13}Br$*	$CH_3(CH_2)_5{-}C{\equiv}CH$	14
$HC{\equiv}CH$			50

*HC ⁝ C, a stronger base in HMPT, causes the elimination of hydrogen bromide.

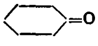
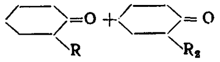
2. Reduction of Unsaturated Compounds

The transfer of electrons from a radical-ion to an unsaturated system A=B results in the formation of a dianion:


$$(1)\quad A{=}B + 2\left[M^+,\ O{=}\dot{P}{\lessgtr}\right]^- \rightarrow 2O{=}P{\lessgtr} + M^+A^-{-}B^-M^+$$

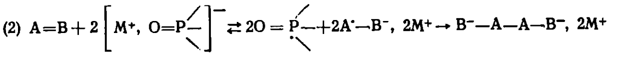
HMPT is again regenerated, and may in principle act in catalytic quantities.

Table 54.

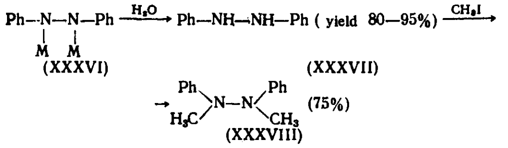
Metallated compound	Metal	Reactant	Products
$PhCH_2COOH$	Na	CO_3	$PhCH(COOH)_2$
$Ph{-}CH_2{-}CN$	K	$PhCH_2Cl$	$PhCH(CN){-}CH_2{-}Ph + PhC(CN){-}(CH_2Ph)_2$
$CH_2(COOEt)_2$	K	$CH_2{=}CHCH_2Br$	$RCH(COOEt)_2$*
$CH_2(CN)(COOEt)$	K	$CH_2{=}CHCH_2Br$	$R{-}CH(COOEt)(CN) + R_2C(COOEt)(CN)$
	K	$CH_2{=}CHCH_2Br$	
$PhCOCH_3$	K	$CH_2{=}CHCH_2Br$	$PhCOCH_2{-}R + PhCOCH_2R + PhCOCR_3$
CH_3CN	K	$C_7H_{15}Br$	$C_7H_{15}CH_2CN + (C_7H_{15})_2CH{-}CN$

*R = CH₂ : CHCH₃.

Another possible path for this reaction is the formation of a dimeric dianion alone:


$$(2)\quad A{=}B + 2\left[M^+,\ O{=}P{\lessgtr}\right]^- \rightleftarrows 2O{=}\dot{P}{\lessgtr} + 2A^{\cdot}{-}B^-,\ 2M^+ \rightarrow B^-{-}A{-}A{-}B^-,\ 2M^+$$

Let us examine reaction (1) in greater detail. In HMPT—an aprotic solvent—the monomeric dianion is produced in the free form, and can then be used in various reactions (reduction, alkylation, etc.), in contrast to liquid ammonia and primary amines, in which the monomeric dianion is present in protonated form. On treating a solution of azobenzene in HMPT with an alkali metal, we obtain the compound (XXXVI), which is hydrolysed to 1,2-diphenylhydrazine (XXXVII) and alkylated by iodomethane to (XXXVIII):[171]



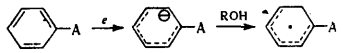
(XXXVI) (XXXVII) (XXXVIII)

Table 55.

Unsaturated compound (0.1 M)	Metal (0.2 g-atom)	Product	Yield, %
$PhCH{=}N{-}Bu$	K	$Ph{-}CH_2{-}NH{-}Bu$	70
$PhCH{=}N{-}Bu$	Li	$Ph{-}CH_2{-}NH{-}Bu$	65
$C_6H_{11}N{=}CH{-}CH(CH_3)_2$	Li	$C_6H_{11}NH{-}CH_2{-}CH(CH_3)_2$	50
		$Ph_2C{=}NH$	33
$Ph_2C{=}N{-}NH{-}Ph$	Li	$+Ph{-}NH_2$	33
$(H_{13}C_6)(H_3C)C{=}N{-}Ph$	Li	$(H_{13}C_6)(H_3C)CH{-}NH{-}NH{-}Ph$	60
	Li		
$Ph_2C{=}N{-}OH$		$+PhNH_2$	8
		$Ph_2C{=}NH+$	50
		$PhCH{=}N{-}Ph$	10
$(C_5H_{10})C{=}NOH$	Li	$(C_5H_{10})CH{-}NH_2$	25

Compounds containing the grouping CH : N (imines, oximes, hydrazones) may undergo reduction. Thus benzophenone phenylhydrazone (Table 55) is reduced in a protic medium (oxolan and t-butyl alcohol); the yield of benzophenone oxime is determined using thin-layer chromatography by hydrolysis and conversion to the 2,4-dinitrophenylhydrazone. Rearrangements of this type have been found only with aldoximes[172,173].

In the case of ethers of phenols and arylamines subject to the action of alkali metals the benzene ring may undergo either reduction or cleavage. In protic medium elimination is insignificant, since the resulting radical-ion adds a proton and is converted into a radical:



where A = OR, NR₂. The latter, in its turn, is reduced, and then protonated. Hydrolysis of the final product yields cyclohexenone (data on the Birch reduction):

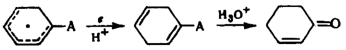
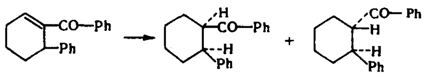


Table 56 gives results for the reduction of certain aromatic compounds in a mixture of HMPT and t-butyl alcohol[171,174].

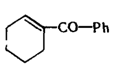
The chemical reduction of α-ethylenic ketones by alkali metals in liquid ammonia and primary amines results in the formation of saturated ketones. This reaction can be effected also in HMPT using lithium and potassium (yield 80%) and the same ratio of isomers for the ketone (XXXIX):[175]

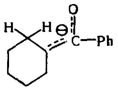


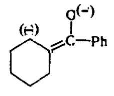
(XXXIX) *cis* (80%) *trans* (20%)

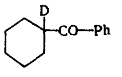
Data on the reduction of several ketones are given in Table 57.[174]

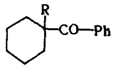
Electrolytic reduction involves electron transfer from the radical-ion to the substance which is reduced. The ketone (XL) is converted into a high yield (around 80%) of the saturated ketone when an ethereal solution of magnesium bromide or calcium iodide is used as electrolyte.


(XL)


(XLI)


(XLII)


(XLIII)


(R = CH_3, $—CH_2—CH=CH_2$)

(XLIV)

Table 56.

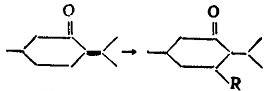
Aromatic compound	Product	Yield, %
Anisole	cyclohex-2-enone	50
Phenetole	cyclohex-2-enone	25
NN-Dialkylanilines (CH_3, C_2H_5)	cyclohex-2-enone	20
2-Ethoxynaphthalene	tetralone	60
1-Methoxynaphthalene	1-methoxynaphthalene	15
	1,2-dihydronaphthalene	15
	1,4-dihydronaphthalene	30

The mechanism of this reduction in an aprotic solvent has not yet been finally established. Some results indicate that the enolate ion (XLI) is formed more rapidly than the dianion (XLII). In fact treatment of the ketone (XLI) with a solution of lithium in HMPT followed by the action of deuterium oxide yields the α-deuterated ketone (XLIII). The same lithium derivative yields α-alkylated ketones (XLIV).[176]

Table 57.

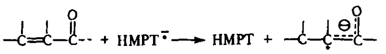
Unsaturated ketone	Yield of saturated ketone, %	Unsaturated ketone	Yield of saturated ketone, %
$CH_3—CO—CH=C(CH_3)_2$	60	$CH_3COC(CH_3)=CH—CH(CH_3)_2$	55
$CH_3COCH=CH—Ph$	30	Isophorone	60
$CH_3COCH=CH—Et$	30	Carvone	40
$CH_3COCH=CH—CH(CH_3)_2$	40	Pulegone	65
$CH_3COCH=CH\text{-}n\text{-}C_5H_{11}$	45		

Formation of an α-substituted ketone (XLVI) is possible from pulegone (XLV):

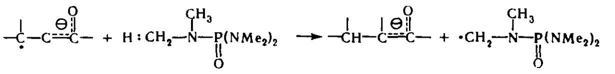

(XLV) (XLVI)

where R = CH_3 (60%), allyl (63%).

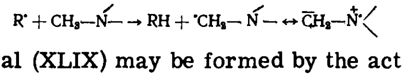
Formation of the enolate ion (XLI) has been clearly established when liquid ammonia is used as solvent. With HMPT as solvent a radical mechanism also seems possible, in which (*a*) the ketone is reduced to a radical-ion:


(XLVII)

(*b*) The radical-ion (XLVII) forms the enolate ion (XLVIII) with a methyl hydrogen of the HMPT, which gives the radical (XLIX):


(XLVIII) (XLIX)

It is known that tertiary amines can act as hydrogen donors towards radicals[177,178]:



The radical (XLIX) may be formed by the action of alkali metals on HMPT in the presence of various aliphatic-aromatic hydrocarbons. The action of potassium on toluene enables various derivatives—in particular ethylbenzene and 1,3-diphenylpropane—to be isolated without protonation. The same operations with ethylbenzene yield cumene[179]. Under similar conditions tetralin gives mono- and di-methyltetralins (undoubtedly dimers).[179] The same results have been achieved by the electrolytic reduction of tetralin in HMPT in the absence of contamination by a protic solvent[166].

Under the same reduction conditions α-ethylenic acids are converted into saturated acids[174]:

$$PhCH=CH—COOH \rightarrow Ph—CH_2—CH_2—COOH\ (60\%)$$
$$(CH_3)_2CH—CH=CH—COOH \rightarrow (CH_3)_2CH—CH_2—CH_2—COOH\ (65\%)$$

In a mixture of HMPT with ether or oxolan lithium does not reduce oct-3-yne or hex-3-yne, but causes them to isomerise into alk-1-ynes[174]:

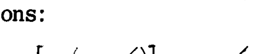
$$CH_3C \equiv C—CHOHCH(CH_3)_2 \rightarrow CH \equiv C—CH_2—CH_2—CHOH—CH(CH_3)_2\ ‡$$

In a 1 : 5 mixture of HMPT and benzene, on the other hand, only *trans*-alkenes are formed after reduction:

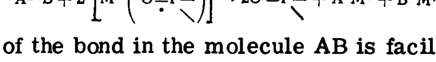
$$C_6H_{13}C\equiv C—CH_3 \rightarrow C_6H_{13}CH=CH—CH_3\ (60\%)$$
$$C_4H_9C\equiv C—C_5H_{11} \rightarrow C_4H_9CH=CH—C_5H_{11}\ (55\%)$$

3. Reduction with Elimination

The transfer of electrons from a radical-ion to a molecule A–B may result in the formation of (*a*) an anion and another radical:



or (*b*) two anions:



Rupture of the bond in the molecule AB is facilitated when the anions A^- and B^- are stabilised by conjugation. Table 58 gives several examples[180].

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‡Since these results are unpublished[174], it is not possible to amend the formulae and the text (Ed. of Translation).

Hexa-alkyldigermanium compounds have recently been cleaved by means of potassium in HMPT to give a quantitative yield of the potassium derivatives, which are stable in HMPT and condense with halides of metals in the same group to give mixed compounds[181] $R_3Ge-MR'_3$, where M = Ge, Si, Sn.

Table 58.

Initial cpd.	Metal	Reagent	Product	Yield, %
$PhCH_2Cl$	K	H_2O	$PhCH_2—CH_2—Ph$	75
$PhOCH_3$	K	H_2O	$Ph—OH$	80
$PhO—CHPh_2$	K	H_2O	$Ph—OH+Ph_2CH_2+Ph_3COH$	*
Ph_3P	K	C_2H_5I	$Ph_2P—C_2H_5$	58
$CH_3S—S—CH_3$	K	$PhCH_2Cl$	$CH_3S—CH_2—Ph$	81
$CH_3S—S—CH_3$	K	$ClCH_2CH_2OH$	$CH_3S—CH_2—CH_2OH$	56
$CH_3—NH—NH—Ph$	Li	H_2O	$PhNH_2$	14
$Ph_3C—CH_2Ph$	K	CH_3I	$Ph_3C—CH_3$	72
$Ph_3Ge—GePh_3$	K	$PhCH_2Cl$	$Ph_3Ge—CH_2—Ph$	56

* PhOH 47%; CH_2Ph_2 52%; Ph_3COH 46%.

The cleavage of ethers by alkali metals in HMPT has been studied in part in Ref. 89. Reduction is possible when the ether contains a weakly acceptor group. Aliphatic ethers cannot be cleaved. Diaryl ethers give phenols. Data on the cleavage of alkyl aryl ethers are given in Table 59, and data on aryl benzyl ethers in Table 60.

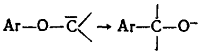
Table 59.

Ether	Products (yield, %)
$C_6H_5O-CH_3$	C_6H_5OH (76-80)
$C_6H_5O-C_2H_5$	C_6H_5OH (20) + C_6H_5OH.HMPT complex (65)
2-$C_{10}H_7$-OCH_3	$C_{10}H_8$ (48) + 2-naphthol.HMPT complex (38)
2-$C_{10}H_7OC_2H_5$	2-naphthol.HMPT complex (51)

Reduction does not always proceed smoothly: the carbanion may cause elimination with the formation of 1,2-diphenylethane, as has already been observed in liquid ammonia[182]:

$$PhCH_2^- + Ph—CH_2—OCH_2—Ph \rightarrow Ph—CH_2—CH_2—Ph + PhCH_2O^-$$

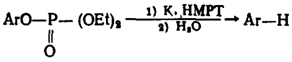
Ethers may undergo the Wittig rearrangement[183], which results in the formation of alcohols:



$$Ar—O—\overline{C}\langle \rightarrow Ar—\overset{|}{\underset{|}{C}}—O^-$$

Table 61 shows the reduction of some β-unsaturated ethers.

The reduction of aryl toluene-*p*-sulphonates by potassium in HMPT yields mainly phenols, but when aryl phosphates are reduced, hydrocarbons are formed[89]:



$$ArO—\underset{\underset{O}{\|}}{P}—(OEt)_2 \xrightarrow[2)\ H_2O]{1)\ K,\ HMPT} Ar—H$$

Table 60.

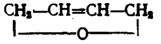
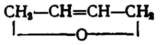
Ether	Cleavage product (yield, %)
$C_6H_5CH_2OC_6H_5$	$C_6H_5CH_3$ (21) + C_6H_5OH (55) + C_6H_5OH.HMPT complex (16)
$C_6H_5CH_2OC_6H_5$	C_6H_5OH (29) + C_6H_5OH·HMPT complex (31)
$C_6H_5CH_2OC_7H_{15}$	$C_6H_5CH_3$ (60) + $C_7H_{15}OH$ (70)
$(C_6H_5CH_2)_2O(K)$	$C_6H_5CH_3$ (60) + $C_6H_5CH_2OH$ (44) + $C_6H_5CHOHCH_2Ph$ (15)
$(C_5H_5CH_2)_2O(Li)$	$C_6H_5CH_3$ (20) + $C_6H_5CH_2OH$ (33) + $C_6H_5CHOHCH_2Ph$ (27)+ + $C_6H_5CH_2CH_2Ph$ (2)
$(C_6H_5)_2CHOC_6H_5$	$(C_6H_5)_2CH_2$ (50) + C_6H_5OH (44) + C_6H_5OH.HMPT complex (12) + $(C_6H_5)_3COH$ (44)
$(C_6H_5)_2CHOC_7H_{15}(K)$	$(C_6H_5)_2CH_2$ (53) + $C_7H_{15}OH$ (64) + $Ph_2CHC_7H_{15}$
$(C_6H_5)_2CHOC_7H_{15}(Li)$	$(C_6H_5)_2CH_2$ (42) + $C_6H_5CHOHC_6H_5$ (4) + $C_7H_{15}OH$ (64) + + $(C_6H_5)_2CHC_7H_{15}$
$(C_6H_5)_3COC_7H_{15}$	$(C_6H_5)_3CH$ (73) + $C_7H_{15}OH$ (66)

Such reduction can be effected also in liquid ammonia[184]. Non-aliphatic mixed ethers containing a heteroatom Z can be converted under the same conditions into two anions:

$$Ar—O—Z \rightarrow Ar—O^- + Z^-$$

where Z = B, Si, Ge, Sn. On protonation ZH is obtained (indirect reduction of ZX to ZH), and on alkylation the derivatives Z–R[185] (see Table 62).

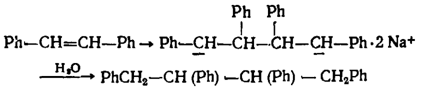
Table 61.

Ether	Products (yield, %)
$CH_2=CHCH_2OC_6H_5$	C_6H_5OH (26) + C_6H_5OH.HMPT complex (33)
$CH_2=CHCH_2OC_7H_{15}$	$C_7H_{15}OH$ (73)
$C_6H_5CH=CHCH_2OC_6H_5$	C_6H_5OH (44) + C_6H_5OH.HMPT complex (46)
$C_6H_5CH=CHCH_2OC_7H_{15}$	$C_7H_{15}OH$ (67)
	$CH_3—CH=CH—CH_2OH$ (29)
	$CH_3—CH=CH—CH_2OC_4H_9$ (43)

4. Condensation and Polymerisation

Since HMPT is widely used as a Lewis base in many processes, including those involving organometallic compounds, it may find application also in anionic polymerisation[186]. This type of polymerisation is observed in radical-ionic solutions of alkali metals with various activated vinyl compounds[157,158,187]. The species M^+, $HMPT^•$ and M^+, $ArH^•$, which are formed in HMPT, may serve as radical-ions.

In the presence of sodium in HMPT *trans*-stilbene gives a dianion, protonation of which yields "*meso*"-1,2,3,4-tetraphenylbutane[150]:

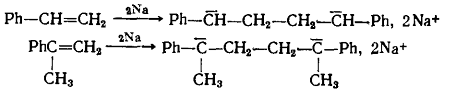


$$Ph{-}CH{=}CH{-}Ph \rightarrow Ph{-}\underline{C}H{-}\overset{Ph}{\overset{|}{C}H}{-}\overset{Ph}{\overset{|}{C}H}{-}\underline{C}H{-}Ph\cdot 2\,Na^+$$
$$\xrightarrow{H_2O} PhCH_2{-}CH\,(Ph){-}CH\,(Ph){-}CH_2Ph$$

Table 62.

Compound A.OR	Reagent	Products (yield, %)
$B(OC_6H_5)_3$	n-C_4H_9Br	$C_6H_5O{-}n{-}C_4H_9$ (93)
$(CH_3)_3SiOC_6H_5$	H_2O	C_6H_5OH (17) + C_6H_5OH.HMPT complex (53)
$(CH_3)_3SiOC_6H_5$	n-C_4H_9Br	$C_6H_5O{-}n{-}C_4H_9$ (83)
$(C_6H_5)_3SiOC_6H_5$	C_3H_5Br	$C_6H_5OC_2H_5$ (67) + $(C_6H_5)_3SiOSiPh_3$ (12)
$\begin{matrix}H_3C\\H_5C_6\end{matrix}\!>Si(OC_6H_5)_2$	C_2H_5Br	$C_6H_5OC_2H_5$ (65) + C_6H_5OH.HMPT (22)
$HSi(OC_6H_5)_3$	$ClSi(C_6H_5)_3$	$C_6H_5OSi(C_6H_5)_3$ (34)
$(C_2H_5)_3GeOC_6H_5$	$ClCH_2C_6H_5$	$C_6H_5OCH_2C_6H_5$ (92)
$(C_4H_9)_3SnOC_6H_5$	C_4H_9Br	$C_6H_5OC_4H_9$ (79), $Sn(C_3H_9)_4$ (77)

Styrene and α-methylstyrene have been dimerised in oxolan solution in the presence of sodium, which is used as electron donor with respect to the carbon atom adjacent to the phenyl group[188]:



$$Ph{-}CH{=}CH_2 \xrightarrow{2Na} Ph{-}\bar{C}H{-}CH_2{-}CH_2{-}\bar{C}H{-}Ph,\ 2Na^+$$
$$\underset{\underset{CH_3}{|}}{PhC}{=}CH_2 \xrightarrow{2Na} Ph{-}\underset{\underset{CH_3}{|}}{\bar{C}}{-}CH_2{-}CH_2{-}\underset{\underset{CH_3}{|}}{\bar{C}}{-}Ph,\ 2Na^+$$

This condensation goes still further with potassium in oxolan at between −40° and −30°C and in the presence of small quantities of HMPT as electron donor. After hydrolysis the reaction mixture contains a certain amount of dimers; all the polymers obtained are of low molecular weight. Solutions of diphenylmagnesium in HMPT are used as initiator for the anionic polymerisation of styrene, α-methylstyrene, and 2-vinylpyridine. The stability of the active centres has been determined spectrophotometrically. Polymerisation is quantitative[189]. Naphthalene–magnesium–HMPT solutions also bring about the polymerisation of styrene[164].

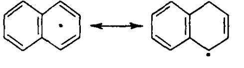
From the results obtained and some unpublished data[190] it can be concluded that HMPT–alkali-metal systems, even when present in small quantities, considerably increase the rate of polymerisation. They enable lower temperatures to be used and various difficult copolymerisations to be brought about more completely. The polymerisation promoters used are active in the presence of HMPT.

C. COMPARISON OF ELECTRON ACCEPTORS

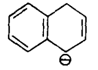
When electron acceptors are used, they are generally completely regenerated (in the case of reduction) or 50% reduced (in the production of anions and metallation). Compounds containing one or more multiple bonds—aromatic ketones and polycyclic hydrocarbons—are acceptors. In the presence of metals aromatic ketones form radical-ions (ketyls) (L), which are converted into alcohols (LI) on protonation followed by reduction:

$$Ar_2C{=}\dot{O} \leftrightarrow Ar_2\dot{C}{-}O^- \quad Ar_2CHOH$$
(L) (LI)

Polycyclic hydrocarbons react with active metals to yield radical-ions and dianions. Thus naphthalene is able to form the radical-ion (LII) or the dianion (LIII):



(LII)



(LIII)

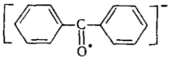
The latter (LIII) is protonated and converted into dihydronaphthalene by a compound Z–H capable of forming Z^- or a metal derivative Z–M.

The system (L) acceptor–alkali metal is most effective in oxolan in various reactions involving metallation followed by carbonylation, especially when the products are to undergo chemical separation[159–171]. But the presence of the acceptor and its reduction product in the reaction medium is very often an undesirable condition for studying the reaction and isolating the products. This difficulty disappears when the system HMPT—alkali metal is used, since the acceptor and its reduction product are then soluble in water, and can easily be separated.

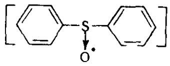
D. COMPARISON OF DIPOLAR APROTIC SOLVENTS

The solvents—dimethylformamide, tetramethylurea, and dimethyl sulphoxide—have been compared above from the viewpoint of their donor power. These same solvents can be acceptors of electrons, because of the presence of a polar group, and are able to form radical-ions, though these are unstable.

Aromatic ketones, in virtue of their carbonyl group, also form radical-ions (LIV), in which delocalisation of the negative charge promotes stabilisation:

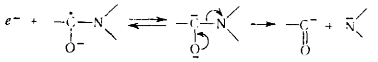


(LIV)



(LV)

Amides, which are not stabilised, decompose rapidly into two anions[191–193]:

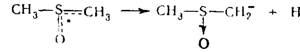


In tetramethylurea alkali metals form fairly unstable light blue solutions, the colour of which is preserved for several seconds at ordinary temperatures and for 1 min at −40°C.[191,192] Only triphenylmethane is metallised in this solution by a potassium–sodium alloy.

Similar phenomena are observed when HMPT is used as solvent, but the radical-ions formed are more stable. At ordinary temperatures the mean lifetime of such a radical-ion varies from 10–15 min with potassium to several hours with lithium and sodium.

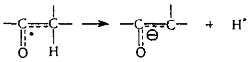
Aromatic sulphoxides approach diaryl ketones, since their polar group SO is conjugated with phenyl groups. The radical-ion (LV), however, is less stable.

In the presence of potassium, solutions of diphenyl sulphone in 1,2-dimethoxyethane yield a light blue coloration, which is unstable even at −70°C and gives an electron spin resonance signal[194]. With dimethyl sulphoxide under the same conditions, alkali metals form the "dimsyl" anion (LVII):[195]



(LVI) (LVII)

The radical-ion (LVI) would be unstable, but would play the same part as amides containing hydrogen in the α-position relative to the carbonyl group (dimethylacetamide, *N*-methylpyrrolidone) and enolisable ketones, which yield enolate anions with alkali metals:



The stability of the radical-ions formed by different solvents can be placed in the sequence—HMPT˙ < < $((CH_3)_2N)_2CO^{\cdot}$ > $(CH_3)_2CO^{\cdot}$—in which HMPT is the only dipolar aprotic solvent that enables active solutions of metals to be used in syntheses.

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Laboratoire de Synthèse organique,
La Sorbonne,
Paris

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Hydrophobic Regions on the Active Surface of Choline-esterases

M.I.Kabachnik, A.A.Abduvakhabov, I.I.Agabekova, A.P.Brestkin, R.I.Volkova,
N.N.Godovikov, E.I.Godyna, S.S.Mikhailov, M.Ya.Mikhel'son, V.I.Rozengart,
E.V.Rozengart, and R.V.Sitkevich

The methods of synthesis of *S*-alkyl(aryl) derivatives of methylphsophonothioic acid and methods for the investigation of their anticholine-esterase activity have been briefly described. Data confirming the anticholine-esterase activity of the compounds synthesised are presented.

It has been shown that, in the inhibition of choline-esterases by organophosphorus compounds, the hydrophobic sorption of these substances on the active surface of the enzymes plays an important and sometimes a decisive role.

It is suggested that the presence of hydrophobic regions on the active surface of choline-esterases tends to increase the probability of the sorption of acetylcholine (a choline esterase substrate) on this surface.

The bibliography includes 68 references.

CONTENTS

I. INTRODUCTION

Choline-esterases (CE) are important enzymes for vital processes whose purpose is to hydrolyse acetylcholine (AC), one of the mediators in nerve excitation. According to modern concepts[1-5], the catalytic centres in these enzymes consist of two distinct regions which are separated in space: anionic and esterase regions. The anionic region is probably formed by the carboxylate anion of a dibasic aminoacid included in the polypeptide chain of the enzyme. This may be an aspartic or glutamic acid residue. The role of the anionic region consists in the specific sorption of the trimethylammonium group of acetylcholine, which helps to ensure a favourable orientation of the substrate molecule on the active surface of the enzyme.

The esterase component, where the hydrolysis of acetylcholine takes place, is located at a distance of 4–5 Å from the anionic component. It has a complex structure in which the hydroxyl of serine, an aminoacid also included in the polypeptide chain of the enzyme, plays a central role. Proton-donating and proton-accepting groups are present in the immediate vicinity of the serine hydroxyl. These may be respectively the tyrosine hydroxyl and the imidazole group of histidine.

It is still unknown how the functional groups comprising each of these active components are located in the overall structure of the enzyme, i.e. whether they belong to the same polypeptide chain or to different chains, but it may be supposed that the mutual approach of these groups, leading to the formation of the active centre, takes place at the instant of interaction with the substrate and involves its direct participation[5,6].

The information available on the structure of the active surface of choline-esterase is largely due to large-scale and intense studies on the properties and activity of organophosphorus inhibitors (OPI), carried out at an increasing rate for more than 25 years[7-10].

The following mechanism of the hydrolysis of acetylcholine by choline-esterases has been generally accepted. Initially the substrate is sorbed on the active surface of the enzyme with formation of a Michaelis complex and subsequent acetylation of the serine hydroxyl. The last stage involves the deacetylation of the enzyme by water and the restoration of its initial structure. There is every reason to suppose that this is not spontaneous water hydrolysis but a more complex process.

It is known that the inhibition of choline-esterase by OPI consists in the phosphorylation of the serine hydroxyl in the esterase component of the enzyme. In contrast to the deacetylation of choline-esterases, which occurs in the enzymic hydrolysis of acetylcholine and other substrates, dephosphorylation takes place extremely slowly and therefore the inhibition is almost irreversible. It is significant that the hydrolysis of the phosphorylated enzyme requires the dissociation not of an *O*-acyl but of an *O*-alkyl bond, which is not characteristic of choline-esterases.

The activity of the inhibitor depends primarily on its phosphorylating capacity, i.e. on the effective positive charge of the phosphorus atom. However, the anticholine-esterase activity of OPI is not determined solely by their phosphorylating capacity[7,10-13]. Ionic and ion-dipole interactions also plays an important role. They are shown most clearly on introduction of a cationic group into the eliminated component† of the OPI molecule. OPI is then fixed on the anionic region of the enzyme as a result of which the probability of the reaction between the inhibitor and the esterase component is enhanced. First examples of such cationic OPI were investigated in 1955–1958—they contained ammonium[14-17] or sulphonium[18-26] groups.

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† We refer to the group of atoms linked directly to the phosphorus atom and split off on phosphorylation of choline-esterase as the eliminated component of the OPI molecule.

In the study of the first ammonium OPI it was impossible to demonstrate sufficiently clearly the role of the 'onium group, since the tertiary analogues of thiophosphonylcholine are so highly protonated owing to the high basicity of the amino-nitrogen at biological pH values that conversion to a quaternary base enhances the anticholine-esterase activity only by a factor of 3–4.

The role of the positive charge was revealed much more clearly in studies on certain OPI containing sulphides and sulphonium groups[20–26]. In sulphide OPI the sulphur atom is incapable of being protonated under the usual conditions and therefore the appearance of a charge on conversion into sulphonium compounds increases the anticholine-esterase activity by a factor of 2000–3000.[26] Later a similar striking increase of activity was achieved also with nitrogen-containing OPI derived from aromatic amines of low basicity. Such amines are protonated to only a slight extent at pH 7–8 and therefore the appearance of a charge on their conversion into quaternary bases also increases the activity of such OPI by a factor of several thousand[27].

The position of the 'onium atom in the OPI molecule is very important. The greatest effect is achieved when the atom carrying the positive charge is located in the eliminated component of the OPI molecule at the same distance from the phosphorus atom as that between the quaternary nitrogen atom and the carbonyl carbon in acetylcholine.[8,24,25]

It should be noted that, on introduction of a cationic group into the OPI molecule, there is not only a possibility of ionic interaction but, by virtue of the inductive effect, there is a significant increase also in electrophilic phosphorylating capacity. These two effects are difficult to separate experimentally[24,26,28].

The electrophilic reactivity of OPI and their capacity to interact with the anionic component of the enzyme are the two properties of the inhibitor which have been widely discussed in numerous publications dealing with the relation between the structure of OPI and their activity.

However, as will be shown below, these two factors do not exhaust the possibilities of the interaction between OPI and the active surface of choline-esterase. It may be supposed that Coulombic attraction is not the only important factor in the interaction between the cationic "head" of acetylcholine and the anionic group of choline-esterases. The three methyl groups linked to the nitrogen atom also play a significant role in this interaction[29,30]. It has been found that uncharged 3,3-dimethylbutyl acetate, the t-butyl group of which imitates sterically the trimethylammonium group of acetylcholine, is hydrolysed by choline-esterase only a little more slowly than acetylcholine itself[31,32]. Hence it may be supposed that the introduction of the t-butyl group in the required position into the molecule of the choline-esterase inhibitor can also intensify its interaction with the enzyme. There is also some other evidence in support of this hypothesis, for example the high anticholine-esterase activity of the pinacolyl esters of alkylphosphonic acids[8,12].

The first results of studies on this problem[33,34] led to the hypothesis that, around the active centre of choline-esterases, there are several hydrophobic regions which can interact with the alkyl groups of both substrates and inhibitors[5].

The hypothesis of the "hydrophobic interaction" is nowadays widely used in enzymology. It has been shown for various enzymes, such as pepsin, chymotrypsin, trypsin, carboxypeptidase, and others, that the rate of the enzymic hydrolysis of substrates depends significantly on the size of their constituent hydrocarbon groups capable of being sorbed on the hydrophobic regions of the catalytic centre of the enzyme[35–39].

The mechanism of the inhibition of choline-esterases was not examined previously from this standpoint. This review presents the results of systematic studies on the "topography" of the hydrophobic regions located on the active surface of horse serum choline-esterase and the acetylcholine-esterase from bull erythrocytes.

II. MATERIALS FOR INVESTIGATION

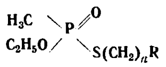
Enzymes. We employed a preparation of choline-esterase from horse blood serum (BuCE, EC, 3.1.1.8), manufactured at the Mechnikov Institute, which had a purification factor of 60 and a specific activity of 1.2–1.6 μmole of AC per minute per milligramme of protein at 25°C, pH 7.5, and a substrate concentration of 0.02 M.

The stroma of bull erythrocytes carefully washed free of haemoglobin and then lyophilised, serves as a source of acetylcholine-esterase (ACE, EC, 3.1.1.7).[40,41]

OPI preparations. These consisted of *S*-alkyl(aryl) derivatives of methylphosphonothioic acid some of the physicochemical constants of which are listed in Table 1.

Table 1. Designation and constants of the organophosphorus inhibitor (OPI)

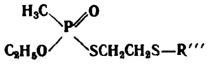
Series I



$H_3C(C_2H_5O)P(O)S(CH_2)_nR$

No.	R	n	B.p., °C/mmHg	n_D^{20}	d_4^{20}
1	2	3	4	5	6
1	CH_3	1	62—64/1	1.4760	1.0969
2	CH_3	2	85—86/2.5	1.4820	1.0712
3	CH_3	3	100—102/2	1.4810	1.0530
4	CH_3	4	108—110/3	1.4678	1,0306
5	CH_3	5	105—106/1	1,4712	1.0178
6	CH_3	6	124—126/2.5	1.4650	1.0040
7	CH_3	7	155—156/5	1.4690	0.9957
8	CH_3	8	142—144/2	1.4702	0.9841
9	CH_3	9	152—153/2	1.4705	0.9725
10	$(CH_3)_3C$	1	78—80/2	1.4640	1.0262
11	$(CH_3)_3C$	2	76—77/1	1.4746	1.0120
12	$(CH_3)_3C$	3	84—85/1	1.4710	1.0015
13	$(CH_3)_3C$	4	124—126/2	1.4700	0.9896
14	$(CH_3)_3C$	5	126—128/1.5	1.4670	0.9811
15	$(CH_3)_3C$	6	134—136/2	1.4700	0.9723
16	$(CH_3)_2CH$	1	120—121/2.5	1.4770	1.0610
17	$(CH_3)_2CH$	2	73—74/1	1.4710	1.0394
18	$(CH_3)_2CH$	3	84—85/1	1.4768	1.0270
19	$(CH_3)_2CH$	4	126—127/1	1.4698	1.0010
20	$(CH_3)_2CH$	6	132—134/1	1.4705	0.9862
21	C_6H_5	1	135—136/1.5	1.5462	1.1521
22	C_6H_5	2	136/2	1.5398	1.1369
23	C_6H_5	3	150—151/2	1.5346	1.0808
24	C_6H_5	4	137—139/1	1.5300	1.1068

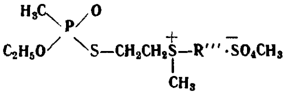
Series II



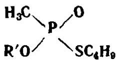
$H_3C(C_2H_5O)P(O)SCH_2CH_2S{-}R'''$

1	2	3	4	5
25	CH_3	110—112/1.5	1.5211	1.1665
26	C_2H_5	98—99/1	1.5181	1.1429
27	n-C_4H_9	132—133/1	1.5082	1.0963
28	n-C_6H_{13}	137—138/1	1.5037	1.0650
29	n-C_8H_{17}	170—171/1	1.4998	1.0341
30	n-$C_{10}H_{21}$	192—195/1	1.4880	1.0097

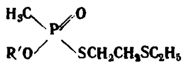
Table 1 Cont'd.

Series III


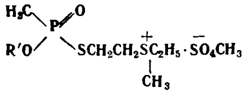
1	2	3	4	5
31	CH_3	—	1.5255	—
32	C_2H_5	—	1.5210	—
33	n-C_4H_9	—	1.5212	—
34	n-C_6H_{13}	—	1.4944	—
35	n-C_8H_{17}	—	1.4898	—
36	n-$C_{10}H_{21}$	—	1.5002	—

Series IV


1	2	3	4	5
37	CH_3	64—65/1	1.4772	1.0825
38	n-C_3H_7	85—86/1	1.4692	1.0280
39	n-C_4H_9	92—93/1.5	1.4675	1.0125
40	n-C_5H_{11}	87/1.5	1.4700	0.9983
41	n-C_6H_{13}	116/2	1.4706	0.9930
42	n-C_7H_{15}	$70/2 \cdot 10^{-2}$	1.4693	0.9783
43	n-C_8H_{17}	$95/3 \cdot 10^{-2}$	1.4697	0.9656
44	n-C_9H_{19}	$110/2 \cdot 10^{-2}$	1.4690	0.9680
45	n-$C_{10}H_{21}$	$120/2 \cdot 10^{-2}$	1.4710	0.9643
46	$(CH_3)_2CH$	79/1.5	1.4703	1.0166
47	$(CH_3)_2CHCH_2$	80/1.5	1.4693	1.0053
48	$(CH_3)_2CH(CH_2)_2$	108/2	1.4693	0.9965
49	$(CH_3)_2CH(CH_2)_3$	$73/3 \cdot 10^{-2}$	1.4725	0.9929
50	$(CH_3)_2CH(CH_2)_4$	$76/3 \cdot 10^{-2}$	1.4693	0.9835
51	$(CH_3)_2CH(CH_2)_5$	$92—94/3 \cdot 10^{-2}$	1.4730	0.9818
52	$(CH_3)_3CCH_2$	82—83/2	1.4636	0.9891

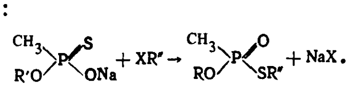
Series V


1	2	3	4	5
53	CH_3	100/1.5	1.5252	1.1728
54	n-C_3H_7	105/2	1.5101	1.1089
55	n-C_4H_9	$95—96/3 \cdot 10^{-2}$	1.5082	1.0960
56	n-C_5H_{11}	$104—105/2 \cdot 10^{-2}$	1.5040	1.0706
57	n-C_6H_{13}	$103—104/10^{-2}$	1.4984	1.0493
58	n-C_7H_{15}	$120—121/2 \cdot 10^{-2}$	1.4994	1.0430
59	n-C_8H_{17}	$117/10^{-3}$	1.4974	1.0365

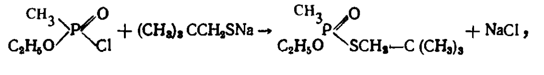
Series VI


1	2	3	4	5
60	CH_3	—	1.5201	—
61	n-C_3H_7	—	1.5010	—
62	n-C_4H_9	—	1.5092	—
63	n-C_5H_{11}	—	1.5045	—
64	n-C_6H_{13}	—	1.5044	—
65	n-C_7H_{15}	—	1.4982	—
66	n-C_8H_{17}	—	1.5000	—

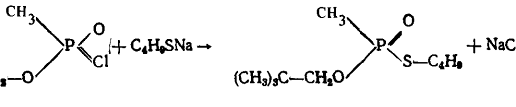
The general method for the preparation of S-alkyl O-ethyl methylphosphonothiolates and O-ethyl S-(ω-phenylalkyl)-methylphosphonothiolates (series I) and also O-alkyl S-n-butyl methylphosphonothiolates (series IV) consisted in the alkylation of sodium O-alkyl methylphosphonothioate with the corresponding alkyl halides or ω-halogenophenylalkanes[33,34,42-44]:



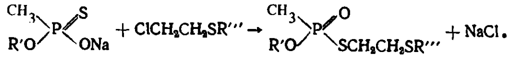
Exceptions were O-ethyl S-(2,2-dimethylpropyl) methylphosphonothiolate (Table 1, compound 1.10), which was synthesised by the reaction of O-ethyl methylphosphonochloridate with sodium 2,2-dimethylpropanethiolate[34]:



and S-n-butyl O-2,2-dimethylpropyl methylphosphonothiolate (Table 1, compound IV, 5.2), which was obtained by the interaction of O-2,2-dimethylpropyl methylphosphonochloridate with sodium butanethiolate:



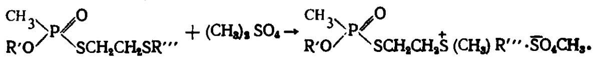
All the S-(β-alkylthioethyl) O-ethyl methylphosphonothiolates (series II) and O-alkyl S-(β-ethylthioethyl) methylphosphonothiolates (series V) were obtained by the reaction of sodium O-alkyl methylphosphonothioate with β-chloroethylalkyl sulphide[45,46]:



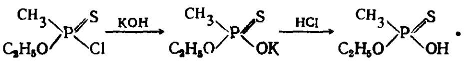
Next compounds of series II and V were converted by dimethyl sulphate into the corresponding S-methyl methosulphates:

$$C_2H_5O\,(CH_3)\,P\,(O)\,S\,(CH_2)_2\overset{+}{S}(CH_3)\,R'''\cdot\overset{-}{S}O_4CH_3 \text{ (series III)}$$

$$\text{and } R'O\,(CH_3)\,P\,(O)\,S\,(CH_2)_2\overset{+}{S}\,(CH_3)\,C_2H_5\cdot\overset{-}{S}O_4CH_3 \text{ (series IV):}$$



O-Alkyl methylphosphonothioates were obtained by the hydrolysis of O-alkyl methylthiophosphonochloridates[47]:



Some of the physical constants and the pK_a values of these substances are listed in Table 2.

III. RESEARCH METHODS

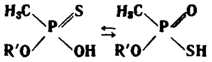
1. Estimation of Anticholine-esterase Activity

The anticholine-esterase activity of the OPI was estimated from the rate constant k_{II} for their interaction with the enzyme[4,48,49].

The enzyme (E) and the inhibitor (I) were incubated in the presence of 0.007 M phosphate buffer for a definite period (t, minutes) and then acetylcholine was added to the reaction mixture. The reaction between the OPI and the enzyme tended to cease completely in a dilute reaction mixture containing acetylcholine at a concentration corresponding to complete saturation of the enzyme by the substrate. The acetic acid formed in the hydrolysis of acetylcholine under the action of the residual concentration of the enzyme was determined by potentiometric titration with 0.1–0.12 N sodium hydroxide solution. The rate of reaction A_t corresponding to t minutes of incubation of E with

I was determined from the slope of the experimental linear plots of the volume of the solution of alkali against time. In some of the experiments A_t was found from the change in the concentration of acetylcholine in the reaction mixture, which was determined by Hestrin's method[50].

Table 2. Constants for *O*-alkyl methylphosphonothiolates:



R′	B.p., °C/mmHg	n_D^{20}	d_4^{20}	p*K*a		
				60% alcohol	80% alcohol thionic form	thiolic form
CH_3	98—99/3	1.5062	1.2527	3.27	3,78	3.48
C_2H_5	71—72/1	1.4927	1.1762	3.35	3.92	3.66
n-C_3H_7	92—93/1	1.4874	1.1285	3.42	3.96	3.59
n-C_4H_9	102—103/1	1.4830	1.0991	3.41	3.99	3.43
n-C_5H_{11}	106/2	1.4823	1.0686	3.46	3.99	—
n-C_6H_{13}	110/2	1.4814	1.0498	3.47	4.00	—
n-C_7H_{15}	$74/2\cdot10^{-2}$	1.4794	1.0315	3.46	3.97	—
n-C_8H_{17}	$84/2\cdot10^{-2}$	1.4790	1.0196	3.46	4.01	—
n-C_9H_{19}	$97/2\cdot40^{-2}$	1.4786	1.0087	3.49	4.00	—
n-$C_{10}H_{21}$	$115/2\cdot10^{-2}$	1.4780	0.9983	3.44	4.01	—

Since the reaction was carried out under standard conditions, the measured rates A_t were directly proportional to the corresponding concentrations of the active centres of the enzyme $[E]_t$. Accordingly the values of $[E]_t$ were calculated from the formula

$$[E_t] = [E]_0\, A_t/A_0, \qquad (1)$$

where A_0 is the rate of the enzyme reaction in the absence of the inhibitor with all other conditions kept constant and $[E]_0$ the initial concentration of the active centres of the enzyme in the reaction mixture. $[E]_0$ for the given initial enzyme solution was determined in a preliminary experiment by Berry's method[15,52] involving partial phosphorylation of the active centres of the enzyme (between 20 and 80%) with a highly active organophosphorus inhibitor—Gd-42 (Tables 1 and 6, compound III. 32)—at a known concentration, the inhibitor being completely consumed in the reaction. The end of the reaction was inferred from the constancy of A_t as a function of the duration of incubation of E with I. The data obtained were used to calculate k_{II} by the equation

$$k_{II} = \frac{2.303}{t\,([I]_0 - [E]_0)} \lg \frac{[E]_0\,([I]_0 - x)}{[I]_0\,([E]_0 - x)}\,, \qquad (2)$$

where $[I]_0$ is the initial concentration of the OPI in the reaction mixture and x the decrease of the concentration of the enzyme and the OPI calculated from the difference $[E]_0 - [E]_t$. This formula is readily transformed into another more convenient for practical use[53]:

$$k_{II} = \frac{2.303}{t\,([I]_0 - [E]_0)} \lg \left[\frac{A_0}{A_t}\left(1 - \frac{[E]_0}{[I]_0}\right) + \frac{[E]_0}{[I]_0}\right]. \qquad (3)$$

The concentration in the reaction mixture of the inhibitor of low activity was always many times higher than that of the enzyme, i.e. $[I]_0 \gg [E]_0$. In this case Eqns. (2) and (3) become

$$k_{II} = \frac{2.303}{t\,[I]} \lg \frac{A_0}{A_t}\,. \qquad (4)$$

However, for the majority of the OPI, the constant k_{II} falls significantly with increase in time t.[54,55]

Kinetic studies have shown[55-57] that this type of relation between k_{II} and t follows from the generally accepted two-phase mechanism of the interaction between E and I:

$$E + I \underset{k_{-2}}{\overset{k_2}{\rightleftarrows}} EI \xrightarrow{k_3} EI' + P_t, \qquad (5)$$

where EI is the enzyme–inhibitor complex, analogous to the Michaelis complex, EI′ the phosphorylated enzyme, and P*t* the corresponding mercaptan split off from the OPI on phosphorylation of the enzyme. Therefore we found the value of k_{II} corresponding to the beginning of the reaction between E and I.

For certain OPI, the constant k_{II} was determined at different temperatures, which made it possible to find the activation energy E_{act} for the inhibition of choline-esterases and to calculate the pre-exponential factors *PZ* in the Arrhenius equation.

2. Determination of the Rate Constants for Alkaline Hydrolysis

To estimate the electrophilic reactivity of the OPI, we determined the rate constants for their alkaline hydrolysis. An aqueous or aqueous alcoholic solution of the OPI was incubated at 25°C with a 2.5-fold excess of sodium hydroxide. The concentration of the OPI in the reaction mixture $[I]_0$ was usually 0.01 M and that of alkali $[B]_0$ was 0.025 M. The pH at the beginning of the reaction was 10.5–10.8. Samples were removed at definite time intervals and their sodium hydroxide concentration was determined by potentiometric titration. The pH at the beginning of the experiment fell by not more than 0.3. The hydrolysis rate constant k_{OH} was calculated from the formula

$$k_{OH} = \frac{2.303}{t\,([B]_0 - [I]_0)} \lg \frac{[I]_0\,([B]_0 - x)}{[B]_0\,([I]_0 - x)}\,,$$

where x is the decrease of the concentration of NaOH and the OPI during the experiment, determined from the difference between the amounts of alkali consumed in the titration of a control reaction mixture ($t = 0$) and in the experiment after a period of incubation t.

The OPI containing a cationic group in the molecule are hydrolysed rapidly and their k_{OH} were found by direct titration of the reaction mixture at pH 10.5.[58] Since the concentration of OH^- ions in these experiments was constant, k_{OH} was calculated from the equation

$$k_{OH} = \frac{2.303}{t\,[OH]} \lg \frac{[I]_0}{([I]_0 - x)}\,,$$

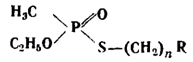
where x is the decrease of the inhibitor concentration determined from the amount of alkali consumed in the titration.

Determination of pK_a. To estimate the electrophilic reactivity of certain OPI, we also employed the ionisation constants (pK_a) of the corresponding *O*-alkyl methylphosphonothioates.

All the pK_a determinations were made by measuring the pH (using a silver, silver chloride electrode at 20°C) of partly neutralised (degree of neutralisation 30, 50 and 80%) 3.5×10^{-3}–50.1×10^{-3} M acid solutions. Since the ionic strength of the solution did not exceed 0.01, a correction for activity coefficients was not introduced. The calculation was based on the formula

$$K_a = [H^+]\frac{[Na^+] + [H^+] - \frac{K_W}{[H^+]}}{M - \left\{[Na^+] + [H^+] - \frac{K_W}{[H^+]}\right\}}.$$

Table 3. Inhibiting activity of series I compounds. *S*-Alkyl *O*-ethyl methylphosphonothiolates and *O*-ethyl *S*-(ω-phenylalkyl) methylphosphonothiolates with the general formula

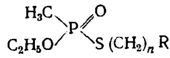


Series & no.	R	*n*	BuCE			ACE			k_{OH}, litre mole^{-1} min^{-1}
			k_{II}, litre mole^{-1} min^{-1}	E_{act}, kcal mole^{-1}	$10^{-10}pz$, litre mole^{-1} min^{-1}	k_{II}, litre mole^{-1} min^{-1}	E_{act}, kcal mole^{-1}	$10^{-10}pz$, litre mole^{-1} min^{-1}	
I.1	CH_3	1	$6.4 \cdot 10^1$	12.0	4	$2.2 \cdot 10^2$	11.0	3	0.15
I.2	CH_3	2	$1.4 \cdot 10^2$	12.0	12	$5.2 \cdot 10^2$	—	—	0.13
I.3	CH_3	3	$8.2 \cdot 10^2$	12.5	90	$1.2 \cdot 10^3$	—	—	0.15
I.4	CH_3	4	$2.6 \cdot 10^3$	12.0	170	$2.6 \cdot 10^3$	—	—	0.13
I.5	CH_3	5	$3.8 \cdot 10^4$	12.5	4100	$1.6 \cdot 10^4$	10.8	130	0.12
I.6	CH_3	6	$3.3 \cdot 10^4$	—	—	$2.1 \cdot 10^4$	—	—	0.13
I.7	CH_3	7	$4.1 \cdot 10^4$	—	—	$3.6 \cdot 10^4$	10.7	260	0.13
I.8	CH_3	8	$3.4 \cdot 10^4$	—	—	$3.1 \cdot 10^4$	—	—	0.13
I.9	CH_3	9	$3.8 \cdot 10^4$	—	—	$1.6 \cdot 10^4$	—	—	0.13
I.10	$C(CH_3)_3$	1	$2.1 \cdot 10^4$	12.5	3170	$2.0 \cdot 10^4$	11.0	120	0.10
I.11	$C(CH_3)_3$	2	$4.7 \cdot 10^3$	12.5	510	$1.6 \cdot 10^3$	11.0	16	0.16
I.12	$C(CH_3)_3$	3	$1.8 \cdot 10^4$	12.2	1660	$2.2 \cdot 10^3$	—	—	0.13
I.13	$C(CH_3)_3$	4	$9.1 \cdot 10^4$	12.0	5870	$7.2 \cdot 10^3$	—	—	0.15
I.14	$C(CH_3)_3$	5	$9.0 \cdot 10^4$	—	—	$1.1 \cdot 10^4$	—	—	0.12
I.15	$C(CH_3)_3$	6	$9.9 \cdot 10^4$	—	—	$1.9 \cdot 10^4$	—	—	0.15
I.16	$CH(CH_3)_2$	1	$6.7 \cdot 10^2$	—	—	$1.6 \cdot 10^3$	—	—	0.14
I.17	$CH(CH_3)_2$	2	$2.3 \cdot 10^3$	12.0	150	$1.3 \cdot 10^3$	—	—	0.16
I.18	$CH(CH_3)_2$	3	$2.5 \cdot 10^3$	—	—	$8.3 \cdot 10^2$	—	—	0.13
I.19	$CH(CH_3)_2$	4	$5.9 \cdot 10^4$	—	—	$9.0 \cdot 10^3$	—	—	0.16
I.20	$CH(CH_3)_2$	6	$9.3 \cdot 10^4$	—	—	$2.2 \cdot 10^4$	—	—	0.13
I.21	C_6H_5	1	$1.2 \cdot 10^5$	—	—	—	—	—	0.11
I.22	C_6H_5	2	$1.4 \cdot 10^4$	—	—	$1.2 \cdot 10^4$	—	—	0.14
I.23	C_6H_5	3	$8.5 \cdot 10^4$	—	—	$1.8 \cdot 10^4$	—	—	0.11
I.24	C_6H_5	4	$1.1 \cdot 10^5$	—	—	$3.4 \cdot 10^4$	—	—	0.12

Since O-alkyl methylphosphonothioates can exist in two tautomeric forms (Table 2), the pK_a values for both forms were calculated by the method described previously[59]. These values characterise the effective positive charge at the phosphorus atom in the acids and consequently to some extent also the phosphorylating capacity of the corresponding esters. Since the pK_a values of the acids vary relatively little when the size of R increases from CH_3 to $C_{10}H_{21}$ (Table 2), one may assume that the phosphorylating capacities of the corresponding OPI are also virtually identical. For other series of OPI, a similar conclusion follows from the constancy of the alkaline hydrolysis rate constant within each series (Tables 3, 5, and 6). Thus the OPI in each series react with the esterase component of choline-esterases as phosphorylating agents of virtually equal effectiveness.

A. Effect of the Structure of the Hydrocarbon Group in the Eliminated Components of OPI on their Anticholine-esterase Activity

The first series of OPI used to investigate the effect of hydrophobic sorption on the rate of phosphorylation of the enzyme have the general formula



where R = H, $C(CH_3)_3$, $CH(CH_3)_2$, or C_6H_5.

The results of these investigations are presented in Table 3 and show that the rate constants for alkaline hydrolysis (k_{OH}) and also the activation energies E_{act} for the compounds investigated in reactions with choline-esterases are almost constant, while the inhibition rate constants k_{II} differ sharply.

In the subseries of straight-chain alkane derivatives (compounds I.1–I.9) the constants k_{II} increase with the length of the chain of the alkyl group up to the hexyl derivative (I.5) for BuCE and up to the octyl derivative (I.7) for ACE. Further increase in the length of the alkyl chain in the case of BuCE does not cause significant changes in k_{II} and in the case of ACE actually leads to an appreciable decrease of the constant[33,34] (Fig. 1). Thus a simple increase in the length of the hydrocarbon group leads to a sharp increase of the rate of inhibition—by a factor of 170 for ACE and 600 for BuCE.

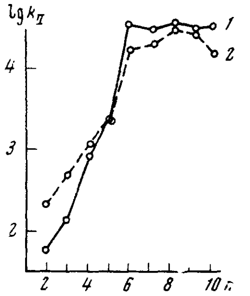


Figure 1. Variation of the rate constants k_{II} for the inhibition of BuCE (curve *1*) and ACE (curve *2*) by compounds of the type $C_2H_5O(CH_3)P(O)SC_nH_{2n+1}$ with the length *n* of the straight alkyl chain.

The second subseries of compounds, in which the alkylthio-substituent contained a t-butyl group at different distances from the phosphorus atom (compounds I.10–I.15), proved to be extremely interesting. The $C(CH_3)_3$ group is a complete steric analogue of the $N(CH_3)_3$ group in the acetylcholine molecule. The first member of this subseries (I.10) exhibits a fairly high anticholine-esterase activity. Then [compound (I.11)] k_{II} decreases. In experiments with BuCE subsequent members of the subseries (I.12–I.13) showed an increase of k_{II} with increase in the number of methylene groups *n*, but the change in k_{II} on going to compounds I.14 (*n* = 5) and I.15 (*n* = 6) is already small (Fig. 2). In experiments with ACE there was a continuous increase of k_{II} with *n*.

Next it was found that in this subseries of OPI all three methyl residues at the quaternary carbon atoms are important. The replacement of one methyl residue by a hydrogen atom, i.e. the replacement of the t-butyl group by an isopropyl group, results in a significant decrease of k_{II}, particularly for OPI with a small n (compounds I.16–I.18). A feature of the compounds of the third subseries which distinguishes them from those of the second is the absence of a decrease of k_{II} on going from the first member (I.16, $n = 1$) to the second (I.17, $n = 2$). The variation of k_{II} with n in this subseries has much in common with that for compounds of the first subseries.

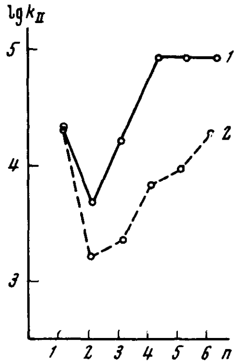


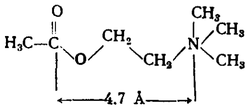
Figure 2. Variation of the rate constants k_{II} for the inhibition of BuCE (curve *1*) and ACE (curve *2*) by compounds of the type $C_2H_5O(CH_3)P(O)S(CH_2)C(CH_3)_3$ with the number of methylene groups n.

In the fourth subseries of the first series of OPI (I.21–I.24) under consideration an ω-phenylalkyl group is attached to sulphur. The high anticholine-esterase activity of the first member of the subseries (I.21, $n = 1$) is striking here. On going to the second member (I.22, $n = 2$), k_{II} decreases sharply. Further increase of n leads to an increase of k_{II}, up to $n = 4$.[44]

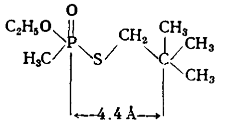
The very high anticholine-esterase activity of individual members of this series of OPI is particularly noteworthy. Thus the rate of inhibition of BuCE by compounds I.13, I.14, I.15, I.20, I.21, I.23, and I.24 is not inferior to that by an inhibitor as powerful as armin ($k_{II} = 2 \times 10^{-5}$).[49]

The data obtained will make it possible to elucidate the effect on k_{II} of the gradual conversion of the terminal methyl group into a t-butyl group. This effect is seen from an examination of Table 4, which lists the relative values of k_{II} for the OPI. k_{II} for the first compound in each of the five groups ($n = 1$, $n = 2$, $n = 3$, $n = 4$, and $n = 6$) was assumed to be unity.

Table 4 shows clearly that the gradual "conversion" of the methyl into a t-butyl group is accompanied in all cases, except for the inhibition of ACE by compounds with $n = 4$ and 6, by an increase of k_{II}. To what extent this increase is specific, i.e. whether it is associated with the presence of the tetrahedral t-butyl group as such or whether it is due to a simple increase in the "bulk" of the alkyl substituent, can be seen by comparing the constant k_{II} for compounds containing a t-butyl group with those for the corresponding compounds with an n-butyl group. The greatest effect of the t-butyl group for BuCE and ACE was observed with the compound in which $n = 1$. Here the distance between the quaternary carbon atom and the phosphorus atom is almost equal to the distance between the quaternary nitrogen atom and the carbonyl carbon atom in the AC molecule:



Acetylcholine



Compound I.10

Table 4. Variation of the inhibiting activity of compounds of the type $C_2H_5O(CH_3)P(O)S(CH_2)_nR$ as the group R is varied from methyl to t-butyl for different n (based on the results in Table 1).

Compound	n	R	k_{II} (relative values)	
			BuCE	ACE
I.1	1	CH_3	1	1
I.2	1	CH_2CH_3	2	2
I.16	1	$CH(CH_3)_2$	10	7
I.10	1	$C(CH_3)_3$	330	90
I.4	1	C_4H_9	40	12
I.2	2	CH_3	1	1
I.3	2	CH_2CH_3	6	2
I.17	2	$CH(CH_3)_2$	17	2
I.11	2	$C(CH_3)_3$	34	3
I.5	2	C_4H_9	275	30
I.3	3	CH_3	1	1
I.4	3	CH_2CH_3	3	2
I.18	3	$CH(CH_3)_2$	3	1
I.12	3	$C(CH_3)_3$	22	2
I.6	3	C_4H_9	40	18
I.4	4	CH_3	1	1
I.5	4	CH_2CH_3	15	6
I.19	4	$CH(CH_3)_2$	23	3
I.13	4	$C(CH_3)_3$	35	3
I.7	4	C_4H_9	16	14
I.6	6	CH_3	1	1
I.7	6	CH_2CH_3	1	1.5
I.20	6	$CH(CH_3)_2$	3	2
I.15	6	$C(CH_3)_3$	3	1
I.9	6	C_4H_9	1	0.7

It is striking that here k_{II} for compound I.10 is approximately eight times higher than k_{II} for its isomer I.4. A similar effect of the complete conversion of the methyl into a t-butyl group is observed for compound I.3 ($n = 4$) and I.6 ($n = 4$) in relation to BuCE. In all other cases the isomers with a straight alkyl chain have a higher value of k_{II} than the compounds with a t-butyl group.

Table 3 shows that the observed increase of k_{II} as the hydrocarbon group of the OPI becomes longer and more branched is caused solely by a change in the probability factor—the pre-exponential factor PZ in the Arrhenius equation. The activation energy E_{act} is almost constant: it amounts to 12.0–12.5 kcal mole^{-1} for the interaction of the OPI investigated with BuCE and between 10.7 and 11.0 kcal mole^{-1} for the interaction with ACE. The rate constants for the non-enzymatic alkaline hydrolysis of these compounds proved to be invariant to an equal extent: they vary from 0.13 to 0.15 litre mole^{-1} min^{-1} at pH 10.5.[33,34] As stated above, these findings indicate that the electrophilic phosphorylating capacity of this series of OPI is identical. The differences between them are determined by the different rates of their sorption on the membrane and consequently the different concentrations at any instant of the sorbed and appropriately oriented OPI molecules on the surface of the enzyme. This is equivalent to differences in the rate of formation of an enzyme–inhibitor EI complex, which has in fact been confirmed by careful kinetic analysis[56,57].

Since the reaction takes place in water, the increase in the extent of sorption of the OPI molecules with increase in the size of the *S*-alkyl substituent may be associated solely with the presence on the surface of the enzyme of hydrophobic regions: the hydrophilic medium (water) displaces the hydrocarbon groups of the OPI to these hydrophobic regions of the enzyme and thereby ensures their more complete sorption. Regions of this kind in the polypeptide chain of the enzyme may be formed by leucine, isoleucine, valine, and phenylalanine residues.

Evidently one of such hydrophobic regions, adapted for the sorption of the trimethylammonium group of acetylcholine, surrounds the anionic component of the active centre of the enzyme. One cannot exclude the possibility that the t-butyl group of compound I.10, in which the distance between the group and the phosphorus atom is close to that between the esterase and anionic sites of the enzyme, is sorbed precisely on this region. In this connection we must note yet again the higher value of k_{II} for compound I.10 compared with that for its isomer I.4.

Table 5. Inhibiting activity of series III compounds: *S*-methyl methosulphates of *S*-(*β*-alkylthioethyl) *O*-ethyl methylphosphonothiolates with the formula

Series & no.	R'''	k_{II}, litre mole^{-1} min^{-1}		k_{II}(ACE) / k_{II}(BuCE)	k_{OH} litre mole^{-1} min^{-1}
		BuCE	ACE		
III.31	CH_3	$1.0 \cdot 10^6$	$5.5 \cdot 10^7$	55.0	17.0
III.31	C_2H_5	$3.7 \cdot 10^6$	$2.5 \cdot 10^8$	67.5	17.0
III.33	n-C_4H_9	$1.1 \cdot 10^7$	$2.2 \cdot 10^8$	20.0	20.0
III.34	n-C_6H_{13}	$8.9 \cdot 10^7$	$1.1 \cdot 10^9$	12.4	21.4
III.35	n-C_8H_{17}	$1.0 \cdot 10^8$	$4.6 \cdot 10^8$	4.6	25.0
III.36	n-$C_{10}H_{21}$	$1.8 \cdot 10^8$	$4.0 \cdot 10^8$	2.2	19.0

The nearest homologue of substance I.10, i.e. substance I.11 (R = t-C_4H_9, $n = 2$), has a constant k_{II} smaller by a factor of 3.5. The distance between the phosphorus atom and the tertiary carbon atom in this compound (5.3 Å) is somewhat greater than the optimum value (4.7 Å) and the methyl groups sorbed on the hydrophobic surround of the anionic component prevent the exact orientation of the electrophilic phosphorus atom in relation to the hydroxy-group of the esterase site of the enzyme. Hence follows a sharp decrease of the probability factor *PZ* (by a factor of 6 for BuCE and 8 for ACE).

However, on further increase of n in this subseries an increase of k_{II} is again observed (up to $n = 4$ for BuCE and up to $n = 6$ for ACE). The rate of formation of the enzyme–inhibitor complex increases. Apparently on the surface of the enzyme there is yet another hydrophobic region of a similar type separated from the first by hydrophilic units. In BuCE it is undoubtedly complementary to the t-butyl group, as can be seen from the data in Table 4 (groups with $n = 4$ and $n = 6$). In ACE this is not so and, with the exception of the first compound ($n = 1$), the isomeric compounds with straight-chain alkyl substituents are in all cases more active than the compounds with the t-butyl group and the activity of the OPI with $n = 6$ altogether depends little on the structure of the terminal group. The isopropyl derivatives (Table 3) behave similarly to the straight-chain subseries but with the difference that these compounds reach the second hydrophobic region of the enzyme starting with $n = 4$ (compound I.19). This corresponds to the chain length with $n = 6$ in the subseries of the straight-chain alkyl derivatives.

The phenylalkyl derivatives containing the bulky phenyl group at the end of the chain show the same type of variation of k_{II} as in the subseries with the t-butyl group.

Although in relation to ACE this behaviour is shown less markedly, nevertheless the increase of k_{II} with increasing length of the hydrocarbon group in the compounds of the first and second subseries (Table 3) suggests that in ACE in the vicinity of the anionic site there is also a hydrophobic region, although its role is less pronounced than that of the hydrophobic region surrounding the anionic site.

It is noteworthy that a similar relation between the rate of inhibition of ACE and the structure of the hydrocarbon group in derivatives of di-O-ethyl phosphorothioate was found by O'Brien and Bracha[60]. Their investigations confirmed the above conclusions concerning the existence of hydrophobic regions in the vicinity of the anionic site of the enzyme.

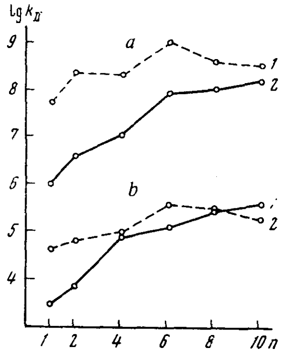
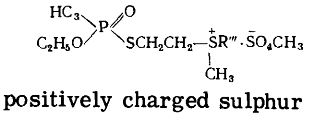


Figure 3. Variation of the rate constants k_{II} for the inhibition of BuCE (curves *1*) and ACE (curves *2*) by compounds of the type $C_2H_5O(CH_3)P(O)SC_2H_4\overset{+}{S}(CH_3)C_nH_{2n+1}$ (*a*) and $C_2H_5O(CH_3)P(O)SC_2H_4SC_nH_{2n+1}$ (*b*) with the length *n* of the straight alkyl chain.

In order to show that the second hydrophobic region in both BuCE and ACE is in fact located beyond the anionic site, compounds of series of II and III were investigated. Compounds of series III are of particular interest:



$$\begin{matrix} HC_3 \\ C_2H_5O \end{matrix} \!\!>\! P \!\!<\!\! \begin{matrix} O \\ SCH_2CH_2\text{—}\overset{+}{S}R''' \cdot \overset{-}{S}O_4CH_3 \\ \qquad\qquad\qquad | \\ \qquad\qquad\qquad CH_3 \end{matrix}$$

They contain a positively charged sulphur atom which should be fixed precisely at the anionic site of the enzyme. If the hypothesis of the existence and particular location of the above hydrophobic region is correct, an increase in the size of the hydrocarbon group R''' should entail an increase in the inhibiting activity of these compounds.

The data in Table 5 and Fig. 3 show that k_{II} does indeed increase with increase in the size of R''', particularly in reactions with BuCE. Compound III.36 is more active than III.31 by a factor of 180 in relation to BuCE and by a factor of 7.3 in relation to ACE. The increase of R''' is accompanied by an appreciable equalisation of the k_{II} for the two enzymes. While the first two compounds (III.31 and III.32) inhibit ACE 60–70 times faster than BuCE, the inhibition by the last compound III.36 is only 2.2 times faster[46,61] (Table 6).

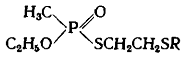
Table 6. Inhibiting activity of series II compounds. *S*-(β-alkylthioethyl) *O*-ethyl methylphosphonothiolates:

$C_2H_5O(CH_3)P(O)SC_2H_4SR'''$

Series and no.	R'''	k_{II}, litre mole^{-1} min^{-1}		$k_{II}(ACE)$ / $k_{II}(BuCE)$	k_{OH} litre mole^{-1} min^{-1}
		BuCE	ACE		
II.25	CH_3	$3.2\cdot10^3$	$4.0\cdot10^4$	12.5	0.29
II.26	C_2H_5	$6.8\cdot10^3$	$6.0\cdot10^4$	8.8	0.28
II.27	*n*-C_4H_9	$7.8\cdot10^4$	$9.0\cdot10^4$	1.2	0.31
II.28	*n*-C_6H_{13}	$1.3\cdot10^5$	$4.0\cdot10^5$	3.1	0.28
II.29	*n*-C_8H_{17}	$3.0\cdot10^5$	$3.3\cdot10^5$	1.1	0.29
II.30	*n*-$C_{10}H_{21}$	$4.0\cdot10^5$	$2.0\cdot10^5$	0.5	0.27

It is significant that, apart from these findings, in this series of compounds the rate constants for non-enzymatic alkaline hydrolysis also vary within very narrow limits (16.0–22.0 litre mole^{-1} min^{-1}) and therefore here too one may speak of the constancy of the electrophilic reactivity of the OPI.

A similar relation between k_{II} and R obtains also for compounds with an uncharged sulphur atom (series II, Table 6 and Fig. 3):



Compound II.30 inhibits BuCE approximately 130 times faster and ACE only five times faster than compound II.25. In this series an increase in the size of R leads not only to an equalisation but actually to a reversal of the relative values of k_{II} for the enzymes investigated: substance II.25 inhibits ACE 12.5 times faster than BuCE, while the inhibition of ACE by compound II.30 is slower by a factor of 2 than that of BuCE (Fig. 3). Here too the rate of alkaline hydrolysis is virtually the same for all the substances.

Thus the data obtained leave no doubt about the existence of a hydrophobic region beyond the anionic site. This region is fairly extensive: in BuCE at a distance equivalent to 3–5 methylene groups from the anionic site there is a region which greatly increases the sorption of the t-butyl group.

In ACE this region is less distinctive and evidently this is why the hydrophobic properties of OPI do not play such an important role in the inhibition of ACE as in the inhibition of BuCE.

In the determination of the inhibiting effect of compounds of series II and III additional data were obtained on the different roles of the anionic sites in BuCE and ACE in the sorption of charged OPI. The ratio of the constants k_{II} for corresponding pairs of charged and uncharged OPI varies from 140 to 680 for BuCE and from 1400 to 4200 for ACE (Table 7).

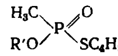
Thus in the sorption of OPI by enzymes the anionic region plays a more important role in ACE than in BuCE, while the hydrophobic environment of the anionic site is more important in BuCE.

Table 7. Comparative estimates of the inhibiting activities of *S*-(β-alkylthioethyl) *O*-ethyl methylphosphonothiolates $C_2H_5O(CH_3)P(O)SC_2H_4SR'''$ and their *S*-methyl methosulphates $C_2H_5O(CH_3)P(O)SC_2H_4\overset{+}{S}(CH_3)R'''.SO_4CH_3$ (according to data in Tables 5 and 6)

R		CH_3	C_2H_5	C_4H_9	C_6H_{13}	C_8H_{17}	$C_{10}H_{21}$
Ratio of k_{II} values for charged and uncharged OPI	BuCE	320	550	140	680	330	450
	ACE	1370	4200	2440	2750	1400	2000

B. Effect of the Structure of the Hydrocarbon Group in the Non-eliminated Components of the OPI on their Anticholine-esterase Activity

The next three series of compounds (IV, V, and VI) were synthesised in order to elucidate the hydrophobic region surrounding the esterase component of the enzyme. The reactivity of a series of *O*-n-alkyl *S*-n-butyl methylphosphonothiolates was investigated first:



(series IV, Table 8), where R' represents n-alkyl groups with a chain length comprising between 1 and 10 carbon atoms[47,62,63]. As mentioned above, the phosphorylating capacity of these compounds is virtually the same.

Table 8. Inhibiting activity of series IV compounds. *O*-n-alkyl *S*-n-butyl methylphosphonothiolates:

$R'O(CH_3)P(O)SC_4H_9$

Series and no.	R'	k_{II}, litre mole^{-1} min^{-1}		Series and no.	R'	k_{II}, litre mole^{-1} min^{-1}	
		BuCE	ACE			BuCE	ACE
IV.37	CH_3	$5.8\cdot10^1$	$2.6\cdot10^2$	IV.41	C_6H_{13}	$5.0\cdot10^4$	$4.2\cdot10^3$
I.3	C_2H_5	$5.2\cdot10^2$	$1.2\cdot10^3$	IV.42	C_7H_{15}	$1.1\cdot10^6$	$4.5\cdot\ 0^3$
IV.38	C_3H_7	$4.5\cdot10^3$	$5.6\cdot10^3$	IV.43	C_8H_{17}	$3.6\cdot10^5$	$4.1\cdot10^3$
IV.39	C_4H_9	$1.2\cdot10^4$	$1.4\cdot10^4$	IV.44	C_9H_{19}	$7.0\cdot10^5$	$6.2\cdot10^3$
IV.40	C_5H_{11}	$1.6\cdot10^4$	$6.8\cdot10^3$	IV.45	$C_{10}H_{21}$	$6.2\cdot10^4$	$2.9\cdot10^3$

Table 8 shows that the anticholine-esterase activity of the compounds investigated depends significantly on the length of the *O*-alkyl group. In experiments with BuCE a gradual increase in the length of the group up to heptyl leads to an increase of the inhibition rate constant. The heptyl derivative proved to be a very powerful inhibitor of BuCE, its anticholine-esterase activity exceeding that of the methyl derivative by a factor of 18 000. A further increase in the length of the substituent entails some decrease of k_{II}.

A different type of relation with the structure is observed in the interaction of the OPI of this series with ACE. The anticholine-esterase activity increases with hydrocarbon chain length only as far as butyl (the butyl derivative is 50 times more effective than the methyl derivative). The anticholine-esterase activity of the OPI with longer alkyl groups (between pentyl and decyl) is somewhat lower and varies within narrow limits. The variation of the anticholine-esterase activity in this series is determined, as in the previous series, mainly by the variation of the capacity of the OPI for the formation of an enzyme–inhibitor complex as a result of the sorption of the hydrocarbon components of the alkoxy-groups on the hydrophobic regions of the active surface of the enzyme.

The relations found in these experiments resemble those described above for studies on the series of *S*-n-alkyl *O*-ethyl methylphosphonothiolates (Table 3), but differ from them in important details.

Comparison of the effects of both series of OPI on BuCE showed that, with increase in the length of the alkoxy-group, the maximum effect is observed for the heptyl derivative, whereas variation of the length of the alkylthio-group shows the maximum effect with the hexyl derivative. Bearing in mind that in the first case the hydrocarbon group is linked to the phosphorus atom via an oxygen atom and in the second via a sulphur atom, one may assume that the maximum anticholine-esterase activity of these two series of compounds corresponds to the same length of the alkoxy- or alkylthio-substituents.

Table 9. Inhibiting activity of series V and VI compounds in relation to BuCE. *O*-n-alkyl *S*-(β-ethylthioethyl) methylphosphonothiolates and their *S*-methyl methosulphates:

$$R'O(CH_3)P(O)SC_2H_4SC_2H_5 \quad (V)$$

$$R'O(CH_3)P(O)SC_2H_4\overset{+}{S}(CH_3)C_2H_5\cdot\overset{-}{S}O_4CH_3 \quad (VI)$$

Series and no.	R′	k_{II}, litre mole^{-1} min^{-1}	Series and no.	R′	k_{II}, litre mole^{-1} min^{-1}
V.53	CH_3	$9.6\cdot10^2$	VI.60	CH_3	$7.7\cdot10^5$
II.26	C_2H_5	$4.4\cdot10^3$	III.32	C_2H_5	$3.8\cdot10^6$
V.54	C_3H_7	$5.8\cdot10^4$	VI.61	C_3H_7	$3.8\cdot10^7$
V.55	C_4H_9	$1.6\cdot10^5$	VI.62	C_4H_9	$4.8\cdot10^7$
V.56	C_5H_{11}	$1.7\cdot10^5$	VI.63	C_5H_{11}	$7.5\cdot10^7$
V.57	C_6H_{13}	$3.7\cdot10^5$	VI.64	C_6H_{13}	$1.8\cdot10^8$
V.58	C_7H_{15}	$2.8\cdot10^6$	VI.65	C_7H_{15}	$2.5\cdot10^8$
V.59	C_8H_{17}	$1.1\cdot10^6$	VI.66	C_8H_{17}	$2.8\cdot10^8$

This finding can have two explanations. The first involves the assumption that the hydrophobic regions located beyond the anionic and esterase components of the active centre of the enzyme are equidistant from these sites. The second involves the recognition that the sorption of the alkoxy- and alkylthio-groups takes place on the same region of the enzyme surface.

The second assumption must be immediately rejected in relation to ACE. In the series of *S*-n-alkyl *O*-ethyl methylphosphonothiolates the maximum activity on ACE (as well as on BuCE) is attained with the hexyl derivative (Table 3), whereas in the *O*-alkyl *S*-n-butyl methylphosphonothiolate series the butyl derivative is the most active (Table 8).

In order to obtain additional information about the localisation of the hydrophobic regions of choline-esterase with which alkoxy-groups may interact and in particular in order to find whether these groups are sorbed in the region of the anionic component of the enzyme, special experiments were carried out, consisting in the investigation of the anticholine-esterase activity of two series of OPI[62]—*O*-n-alkyl *S*-(β-ethylthioethyl) methylphosphonothiolates (series V) and the corresponding *S*-methyl methosulphates (series VI). The choice of these OPI was based on the fact that the reaction of choline-esterase with OPI of type VI, containing the sulphonium group, should necessarily involve the interaction of the 'onium group with the anionic site. Under these conditions, the alkoxy-group is incapable of being sorbed on the hydrophobic regions in the vicinity of the anionic centre. The results of the investigation of these two series of OPI in relation to BuCE are presented in Table 9.

Table 9 shows that, with increase in the length of the hydrocarbon component in the alkoxy-group in the OPI series of type V, there is an appreciable increase of k_{II}. The maximum value of k_{II} was noted for the heptyl derivative (higher by a factor of 2900 than for the methyl derivative). The constant k_{II} for the octyl derivative is somewhat lower. In the series of OPI of type VI the anticholine-esterase effect also increases with the length of the hydrocarbon component of the alkoxy-group. Comparison of these two series of inhibitors shows that all the *S*-methyl methosulphates have k_{II} values higher by 2–3 powers of 10 than their uncharged analogues.

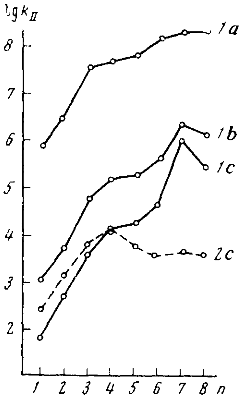


Figure 4. Variation of the rate constants k_{II} for the inhibition of BuCE (curves *1*) and ACE (curve *2*) by compounds of the type $C_nH_{2n+1}O(CH_3)P(O)SR$ with the length *n* of the straight alkyl chain: *a*) $R = C_2H_4S(CH_3)C_2H_5$; *b*) $R = C_2H_4SC_2H_5$; *c*) $R = n\text{-}C_4H_9$.

One may assume with certainty that the higher anticholine-esterase activity of the *S*-methyl methosulphates observed in all cases depends on the interaction between the charged sulphonium group and the anionic site of BuCE and in particular on the associated orienting effect. Therefore one may assume that the increase of the anticholine-esterase activity with increasing length of the hydrocarbon component of the alkoxy-group is also a consequence of the orienting effect, due to its sorption on a suitable hydrophobic region of BuCE.

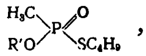
Since the anionic centre of BuCE in the interaction with series VI OPI is occupied by a group containing sulphonium sulphur, one may conclude that the hydrophobic region of the active surface of BuCE on which the alkoxy-group is sorbed is located outside the anionic site of the enzyme.

In all probability the alkoxy-group of uncharged OPI is also sorbed on the same hydrophobic region of choline-esterase. This conclusion follows from an examination of Fig. 4, where the variation of lg k_{II} with the number of carbon atoms in the alkoxy-group is plotted for the OPI of series IV, V, and VI.

Fig. 4 shows that the curves representing the effect on BuCE by the inhibitors of all three series vary in exactly the same sense and actually coincide in detail (the sharp rise on increasing n from 1 to 3, the inflection in the region with $n = 3-5$, and another sharper rise as n is increased to 7). This agreement can only be explained by the fact that the hydrocarbon components of the alkoxy-groups of the OPI of all three series interact with the same hydrophobic region of BuCE. The overall extent and location of this region probably correspond sterically to the heptyl group. However, the stepped form of the curve may be an indication that in fact we are dealing here with two hydrophobic regions separated by a hydrophilic group.

Fig. 4 also shows that the effects of the same series of OPI on BuCE and ACE (curves *1* and *2*) differ significantly. Whereas up to $n = 4$ the inhibition of both enzymes is almost the same, further increase in the length of the hydrocarbon group, which results in an appreciable increase of effectiveness in relation to BuCE, has completely no effect on the capacity of the OPI to inhibit ACE. We are inclined to explain this difference by the fact that in the region of the esterase centre ACE has not two but only one hydrophobic region, corresponding sterically to the butyl group.

To characterise more fully the steric configuration of the hydrophobic regions located in the vicinity of the esterase centre of the choline-esterases, a study was made of the effect on the choline-esterases of compounds containing a branched substituent in the alkoxy-group[64] (compounds IV.46–IV.51):


$$(H_3C)(R'O)P(=O)SC_4H_9 \, ,$$

where $R' = (CH_3)_2CH(CH_2)_n$.

Table 10. Inhibiting activity of series IV compounds. *S*-Butyl *O*-isoalkyl methylphosphonothiolates:

$R'O(CH_3)P(O)SC_4H_9$

Series & no.	$R' = (CH_3)_2CH(CH_2)_n$	k_{II}, litre mole^{-1} min^{-1}	
	n	BuCE	ACE
IV.46	0	$4.5\cdot10^2$	$3.2\cdot10^3$
IV.47	1	$4.4\cdot10^3$	$1.5\cdot10^4$
IV.48	2	$3.4\cdot10^4$	$6.1\cdot10^4$
IV.49	3	$3.9\cdot10^4$	$4.3\cdot10^5$
IV.50	4	$6.5\cdot10^4$	$9.3\cdot10^3$
IV.51	5	$3.1\cdot10^4$	$8.6\cdot10^3$

Table 10 shows that, with increase in the length of the hydrocarbon group, the anticholine-esterase activity of the compounds in relation to BuCE increases up to the isoheptyl derivative, while that in relation to ACE increases up to the isohexyl derivative. Further increase in the length of the group results in a decrease of k_{II}, the decrease for BuCE being slight (approximately by a factor of 2). On the other hand, in the case of ACE k_{II} for the isoheptyl derivative is smaller by a factor of 46 than for the isohexyl derivative. Moreover, it is seen that the first members of this series of compounds, up to the isohexyl derivative, are more active in relation to ACE than BuCE.

Above it was shown that an increase in the length of the alkoxy-group in the series of *O*-n-alkyl *S*-butyl methylphosphonothiolates does not result in a significant change of the electrophilic activity of the phosphorus atom in these compounds. It may be supposed that also in the series of *O*-isoalkyl derivatives the length of the hydrocarbon substituent will not have a significant influence on the magnitude of the effective positive charge of the phosphorus atom. This means that in this series too the factor determining the anticholine-esterase activity should be the hydrophobic interaction between the isoalkyl group and the hydrophobic regions on the surface of choline-esterase.

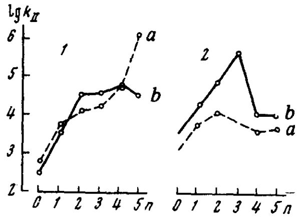


Figure 5. Variation of the rate constants k_{II} for the inhibition of BuCE (diagram *1*) ACE (diagram *2*) by compounds of the type $C_2H_5(CH_2)_nO(CH_3)P(O)SC_4H_9$ (*a*) and $(CH_3)_2CH(CH_2)_nO(CH_3)P(O)SC_4H_9$ (*b*) with the number of methylene groups n.

Since there is every reason to suppose that the hydrocarbon components of the isoalkyl and n-alkyl derivatives interact with the same parts of the enzyme, it is of interest to compare the effects of both series of compounds. Such a comparison is made in Fig. 5, where the isoalkyl derivatives are represented by compounds with an isopropyl substituent located at different distances from the phosphorus atom (curve *b*) while the series of OPI with straight-chain alkoxy-groups consists of compounds containing the ethyl group at the same distances (curve *a*). Thus compounds with the same length of a straight hydrocarbon chain are compared at each point. In the case of BuCE (Fig. 5) it is seen that initially (for $n = 0$ and 1) the branching of the substituent has no effect. For $n = 2-3$, i.e. in the region of the inflection in the curve, the branched-chain compounds are somewhat more effective, but on further increase in the length of the substituent the branched-chain group not only does not increase the anticholine-esterase activity but becomes a serious obstacle in the interaction between the OPI and the enzyme: k_{II} for the branched-chain compound with $n = 5$ is lower by a factor of 34 than for the corresponding straight-chain alkyl derivative.

In the interaction with ACE (Fig. 5), the branching of the substituent initially enhances appreciably the anticholine-esterase effect. The contribution of the branched-chain group is particularly pronounced for $n = 3$: k_{II} for this compound is higher by a factor of 63 than the constant for the corresponding OPI with a straight-chain substituent. Further separation of the isopropyl group from the phosphorus atom prevents the interaction of the OPI with ACE:

k_{II} diminishes by a factor of 46 and approaches the values of the rate constants for the straight-chain OPI. A still greater increase in the length of the substituent does not alter the anticholine-esterase activity of either series of OPI.

The above data confirm and complement the above considerations concerning the characteristics of the hydrophobic regions in the vicinity of the esterase component of the active centre of the choline-esterases. Probably in BuCE this region actually consists of two hydrophobic components. In general they are both complementary to hydrocarbon substituents with a straight-chain structure but the first, located closer to the esterase site, is not quite so rigorously specific and therefore the branching of the hydrocarbon substituent of the OPI does not prevent its sorption. The structure of the second (more remote) hydrophobic region is adapted solely for the sorption of a straight-chain substituent.

In ACE there is only one hydrophobic region. Its structure differs significantly from that of the first hydrophobic region of BuCE and is rigorously complementary to the isohexyl group (the maximum in curve *2b* in Fig. 4).

Yet another comparison is of interest for the characterisation of the configurational features of the hydrophobic region in the vicinity of the esterase component of the choline-esterases. Above, in the discussion of the anticholine-esterase properties of the OPI containing a branched-chain component in the alkylthio-group, it was noted that the introduction of a t-butyl substituent into this group significantly increases the capacity of the OPI to inhibit choline-esterase (Table 3).

An organophosphorus inhibitor containing the t-butyl group in the alkoxy-part of the molecule was synthesised[64]. Comparison of its activity with a series of other OPI described above shows how the gradual introduction of such a group affects the anticholine-esterase properties (Table 11).

Table 11. Anticholine-esterase effectiveness and the rate of alkaline hydrolysis (40°C) of OPI of the type $RCH_2O(CH_3)P(O)SC_4H_9$.

Series and no.	R	BuCE		ACE		k_{OH}, litre mole^{-1} min^{-1}
		k_{II}, litre mole^{-1} min^{-1}	relative value	k_{II}, litre mole^{-1} min^{-1}	relative value	
I.3	CH_3	$5.2\cdot10^2$	1	$1.1\cdot10^3$	1	0.145
IV.38	CH_3CH_2	$4.5\cdot10^3$	9	$5.8\cdot10^3$	5	0.160
IV.47	$(CH_3)_2CH$	$4.4\cdot10^3$	8	$1.5\cdot10^4$	13	0.146
IV.52	$(CH_3)_3C$	$9.5\cdot10^2$	2	$5.9\cdot10^3$	5	0.200
IV.39	$n\text{-}C_4H_9$	$1.6\cdot10^4$	30	$6.8\cdot10^3$	6	—

For comparison, the table also lists the anticholine-esterase activities of substances with R = $n\text{-}C_4H_9$, which is isomeric with the t-butyl group.

Table 11 shows that the degree of branching of the group R has little effect on the mobility of the P–S bond, which we estimated from the rate constant for alkaline hydrolysis. Consequently, the anticholine-esterase activities found must also be attributed to the different capacities of the hydrocarbon groups for sorption on the active surface of the enzyme.

Examination of the data for BuCE shows clearly yet again that the hydrophobic part of this enzyme has a structure complementing an unbranched hydrocarbon group. Indeed the replacement of one H atom by a CH_3 group on going from I.3 to IV.38 (increase in the length of the straight chain) increases the activity by a factor of 9, while the replacement of a second hydrogen atom by a methyl group (compound IV.47) has no effect despite the increase in the size of the group, and the introduction of a third methyl group (compound IV.52) causes a distinct decrease of activity. At the same time compound IV.39 is 15 times more active than the isomeric t-butyl derivative.

Compound IV.47 is the most effective in relation to ACE, the introduction of a third methyl group reducing the activity by a factor of 2.5. The straight-chain compound with R = $n\text{-}C_4H_9$ has no advantages compared with the t-butyl derivative.

Thus the hydrophobic region in ACE, in contrast to BuCE, complements best the isobutyl group. The above comparison leads to the conclusion that the fit of the hydrophobic regions in the vicinity of the esterase centre in both choline-esterases to the tetrahedral structure of the t-butyl group is poor. Therefore in the series of compounds investigated the introduction of such a group into the alkoxy-substituent results in a distinct hindrance of the sorption of the inhibitor on the active surface.

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Analysis of the results of the investigations leads to a general hypothesis concerning the location of the hydrophobic regions in the vicinity of the active centres of BuCE and ACE and certain characteristics of these regions[65].

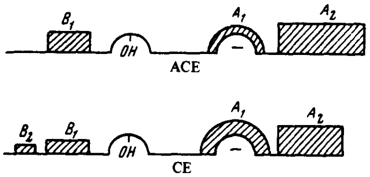

Figure 6. Topography of the hydrophobic regions on the active surface of ACE and BuCE.

The structure of the hydrophobic regions on the active surface of choline-esterase is shown schematically in Fig. 6. In the vicinity of the anionic centre there are two hydrophobic regions: A_1 surrounding directly the anionic centre and A_2 located at some distance beyond it. There is reason to believe that in BuCE region A_1 plays a relatively greater role than in ACE. Thus, according to Augustinsson[66], van der Waals forces play a major role together with Coulombic forces in the interaction of substrates and inhibitors with the anionic site in BuCE, while in ACE purely Coulombic forces predominate. The region A_2 is also different in the two choline-esterases: in BuCE its extent corresponds to a chain of six carbon atoms and in ACE to a chain of eight carbon atoms. The steric configuration of this region in both enzymes is such that it complements best groups containing the highly branched t-butyl substituent.

Near the esterase site of BuCE there are two hydrophobic regions separated by a hydrophilic group. The overall extent of these hydrophobic regions corresponds to a chain of seven carbon atoms. They are both in general complementary to straight-chain groups, but the first (B_1) is not quite so rigorously specific and branched-chain groups can also be sorbed on it.

In ACE there is only one hydrophobic region, the structure of which differs significantly from that of the B_1 region in BuCE: it is rigorously complementary to the isohexyl group.

An important characteristic of the steric configuration of the B_1 regions in both enzymes is that they are completely unadapted for the sorption of groups containing the t-butyl substituent. Thus differences in the structures and extents of the hydrophobic regions located on the active surface of BuCE and ACE have been established. It is quite likely that these differences are to a large extent responsible for the different properties of the two choline-esterases.

The problem naturally arises of the biological value of this type of structure of the active surface of the choline-esterases. What is the purpose of the extensive hydrophobic regions surrounding the catalytic centre of the enzyme? It is hardly likely that the hydrophobic regions were formed in the evolutionary process solely as essential constructional details. The following hypothesis may be put forward: acetylcholine consists of highly hydrophilic molecules capable of being sorbed not only at the active site of choline-esterases but also at any other site on the polypeptide chains of the enzyme. Such sorption would lead to retardation of the hydrolysis of acetylcholine. The hydrophobic regions prevent the "parasitic" sorption of acetylcholine and thereby increase the likelihood of its sorption at the active centre of choline-esterase. They play the role of a kind of energy "hill" from which the acetylcholine molecule "rolls down" on to the active site of the enzyme. In this way the effective cross-section of the active site of the enzyme in the hydrolysis of acetylcholine is increased.

In this connection it is essential to consider also the problem of the structure of the active site of the choline receptor (CR). There is very significant evidence suggesting the hypothesis that there are hydrophobic regions also around the CR active site[5] and that there must be at least three of them: one fits the methyl groups of acetylcholine, another serves as the anionic site of the choline receptor, and the third is a site with affinity for the ester group. This hypothesis is supported by the enormous amount of factual data on the relation between the structure and the effect of substances blocking the choline receptor which have now accumulated. The empirical rule according to which acetylcholine must be made more "bulky" in order to prepare blocking substances was formulated long ago. Indeed, the introduction into the acetyl component of the acetylcholine molecule of phenyl, cyclohexyl, and large alkyl groups converts acetylcholine from an exciting to a blocking agent. An increase in the "bulk" of the cationic head has the same effect. It is striking that, as acetylcholine becomes more "bulky" at either end, its cholinomimetic, exciting effect is gradually weakened, then the blocking effect appears, and its intensity increases. This is easily understood. Not only rapid sorption but also easy desorption of the substance from the receptor is important for the exciting effect[67,68]. Retardation of desorption leads to the blocking effect. Naturally, the introduction of bulky hydrophobic groups into the acetylcholine molecule increases the interaction with the hydrophobic regions in the vicinity of the active site of the choline receptor and hinders desorption.

It is reasonable to suppose that, for the interaction of acetylcholine itself with choline-esterases, the biological purpose of the hydrophobic regions consists in a reduction of the "parasitic" sorption and an increase in the probability of the collision of the acetylcholine molecule with the active site of the choline receptor.

Returning now to the problem of choline-esterases we must finally conclude that the inhibiting capacity of the organophosphorus inhibitors depends, at any rate for the series of compounds which we investigated and possibly others as well, not only on the intrinsic phosphorylating capacity of the compound (electrophilic reactivity) but mainly on the rate of sorption, i.e. the rate of formation of the enzyme–inhibitor complex.

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Institute of Organic Derivatives of the
Elements, USSR Academy of Sciences,
Moscow

Pavlov First Leningrad Medical Institute

Sechenov Institute of Evolutionary
Physiology and Biochemistry, USSR
Academy of Sciences, Leningrad

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The Juvenile Hormone of Insects and Its Analogues

Yu.S.Tsizin and A.A.Drabkina

The review deals with the chemistry of the juvenile hormone of insects and its analogues. The literature data on the isolation, determination of the structure, and synthesis of the juvenile hormone and natural compounds imitating its activity are quoted. Synthetic substances exhibiting the activity of the hormone are described and the problem of the relation between their structure and physiological activity is discussed.
The bibliography includes 134 references.

CONTENTS

I. INTRODUCTION

In recent years there has been a considerable increase of interest in insect hormones. While the chemical nature of the hormones of vertebrates has been successfully investigated for more than 50 years, the information about the structure of the most important insect hormones was obtained only as late as the 1960's. Nevertheless, apart from their great theoretical importance, studied on the endocrinology of insects may lead to the creation of fundamentally new means for combating pests.

A distinctive feature of insects is a clear-cut development in discontinuous stages during the growth process according to the scheme egg → larva (several stages) → pupa → adult insect (imago). The development and growth of the larva is accompanied by moulting. In some families the chrysalis stage is absent. The larval development and metamorphosis (the transformation into the adult insect) are under hormonal control.

The endocrine system of insects consists of the following components: groups of neurosecretory cells of the brain and the abdominal nerve chain, corpora cardiaca, corpora allata, and prothoracic glands or their analogues. The polypeptide hormone of the neurosecretory cells has been called the activating hormone, since one of its main functions is to stimulate the activity of the prothoracic glands, which produce the moulting hormone (acdysone), and the corpora allata, which secrete the juvenile hormone (JH). The development of insects is controlled by the activating hormone, ecdysone, and the juvenile hormone[1-3]. Moulting takes place in the presence of an enhanced secretion of ecdysone, and the juvenile hormone prevents metamorphosis, preserving the larval nature of the moulting; it is non-specific even within different insect orders. The amount of juvenile hormone varies in different stages of insect development: it is absent in the embryonic period, appears in the moulting stage, and in pupal moulting its concentration falls. Moulting of the imago is possible only in the absence of the juvenile hormone. The removal of the corpora allata from larvae leads to the formation of dwarf imagos[4]. The introduction into the insect organism of the juvenile hormone in the pre-imago period, when the hormone should be absent, leads to additional moulting and the appearance of giant forms. It is noteworthy that the giant individuals are non-viable and as a rule soon die[5,6]. In adult insects the juvenile hormone again begins to be produced and fulfils a number of functions the principal of which is gonadotropic. It has been shown that the juvenile hormone is identical with the gonadotropic hormone[7-10] and that the necessary condition for the regulation of ovogenic processes by the juvenile hormone is the absence of ecdysone[6]. Finally, the juvenile hormone has a prothoracotropic activity, stimulating the function of the prothoracic glands, which produce ecdysone[11,12].

Even before the determination of the structure of the juvenile hormone, a number of natural and synthetic compounds with juvenile-hormonal activity were found. Such activity is shown by extracts of plant, bacterial, and animal origin[13,14]. The juvenile hormone and its analogues influence insects both following injection and local application. In this connection it has often been suggested that the juvenile hormone and substances imitating its activity might be applied to combat harmful insects[15-19]. Hormonal insecticides should have a number of advantages over "traditional" insecticides. It is believed that they ought to be non-toxic to warm-blooded animals, should be effective in trace amounts, and that insects would be unable to develop resistance to them.

Since a large number of compounds with juvenile-hormonal activity are now known, it has become necessary to estimate quantitatively their effectiveness. The most suitable object for this purpose proved to be the pupae of the flour beetle *Tenebrio molitor* and the wax moth *Galleria mellonell*. The activity is expressed in "tenebrio" and "galleria" units. One "tenebrio" unit[20] and one "galleria" unit[21] are defined as the minimum amount of the substance in microgrammes which has a positive effect in 40 and 50% respectively of the test insects. Hence the specific activity of substances may be expressed as the number of "tenebrio" or "galleria" units per microgramme. Frequently the amount of test substance in microgrammes per insect is recorded and the effect is determined from the extent of preservation of the larval or pupal characteristics and is estimated on an n-point scale established arbitrarily for the insect species tested[22,23].

In order to unify the methods for the estimation of juvenile-hormonal activity, Wigglesworth[24] suggested that the minimal amounts of the test substance, expressed in microgrammes per gramme of insect weight, which give rise to a positive effect should be compared.

There are a number of reviews in the Soviet[3,25] and non-Soviet[1,2,26–29] literature on insect hormones. In most of them the biological aspects are considered. The latest review by Röller and Dahm deals mainly with the work of the authors themselves[28]. Nevertheless the problem of the synthesis of the juvenile hormone has attracted the attention of chemists in various countries: in the last two years nine versions of the synthesis of the juvenile hormone have been published. The problem of the relation between the structure and biological activity of juvenile hormone analogues is also extremely important. Therefore it is of interest to review the information on the chemistry of the juvenile hormone and substances imitating its activity.

II. ISOLATION AND DETERMINATION OF THE STRUCTURE OF THE JUVENILE HORMONE

Work on the isolation and determination of the structure of the juvenile hormone is associated with the name of the great American entomologist Williams. It is extremely difficult to isolate the juvenile hormone from the corpora allata because the glands contain a negligible amount of the hormone. Williams observed that the abdomens of the males of the large butterflies *Hyalophora cecropia* and *Samia cinthia* contain an unusually large amount of the juvenile hormone[30–33]. By extracting with ether the abdomens of the males of *Hyalophora cecropia*, he obtained a neutral oil with a considerable juvenile-hormonal activity. This extract, called "cecropia oil", served as a source for the isolation of the juvenile hormone. The preparation of purified extracts has been frequently reported[20,27,34]. Karlson[20] used for this purpose double chromatography on alumina and achieved purification by a factor of 8.

By 1965 three groups of American investigators carried out intensive research on the isolation of the juvenile hormone from "cecropia oil". It is interesting to compare their results. Williams and Law[35], who employed extraction with methanol, chromatography on silicic acid, and gas–liquid chromatography, obtained a fraction which was more active than the initial "cecropia oil" by a factor of 50 000. They showed by mass-spectrometry that the active component in an epoxy-derivative of the ethyl ether of a C_{16} aliphatic acid with a molecular weight of 284. However, tests on synthetic specimens of methyl (±)-9,10-*cis*- and (±)-9,10-*trans*-epoxyhexadecanoates showed that they are completely inactive although their mass spectra did not differ from that of the active fraction isolated from "cecropia oil". The isomeric synthetic epoxides and the natural juvenile hormone were not separated on the gas-liquid chromatograph employed by Williams and Law. The investigators were at the threshold of discovery and only the inadequate resolving power of their instruments prevented them from determining the exact structure of the juvenile hormone[28].

Meyer[36] reported a degree of purification by a factor of 3×10^5 using a five-stage process including gas-liquid chromatography. Two active fractions were obtained. Repeated chromatography did not lead to the isolation of the individual substances. According to Röller[28], the active fractions contained an admixture of the pyrolysis products of the juvenile hormone, which is unstable in chromatography above 210°C.

Finally in the same year a group of investigators at Wisconsin University led by Röller[37,38] isolated the juvenile hormone from "cecropia oil" in a pure form having obtained a degree of purification by a factor of 1.05×10^5. At all stages biological control was based on *Tenebrio molitor* larvae. The initial unpurified "cecropia oil" had an activity of 25 "tenebrio" units, while the pure juvenile hormone had an activity of 2.6×10^6 "tenebrio" units per microlitre. Later Röller improved the method of isolation of the juvenile hormone by replacing one thin-layer chromatographic stage by molecular distillation (Scheme 1)[39].

Scheme 1

Isolation of the juvenile hormone from the butterflies *Hyalophora cecropi a*

Process		Activity "tenebrio" units per μg	Overall activity, %
I. Extraction with ether	875 abdomens (380 g) ↓ 180 g of crude oil	0.04	100
II. Precipitation at −80°C	↓ 47 g of purified oil ↓	0.13	85
III. Molecular distillation (60–90°C, 2×10^{-5} mmHg)	5.4 g of distillate ↓	1.1	83
IV. Thin-layer chromatography, silica gel *G*, chloroform : ethyl acetate = 2:1, zone with $R_f = 0.6–0.9$	440 mg ↓	13	80
V. Thin-layer chromatography, silica gel *G*, chloroform : pentane = 2:1, zone with $R_f = 0.05–0.3$	5.4 mg ↓ 810 μg of JH	100	75
VI. Gas–liquid chromatography		5000	56

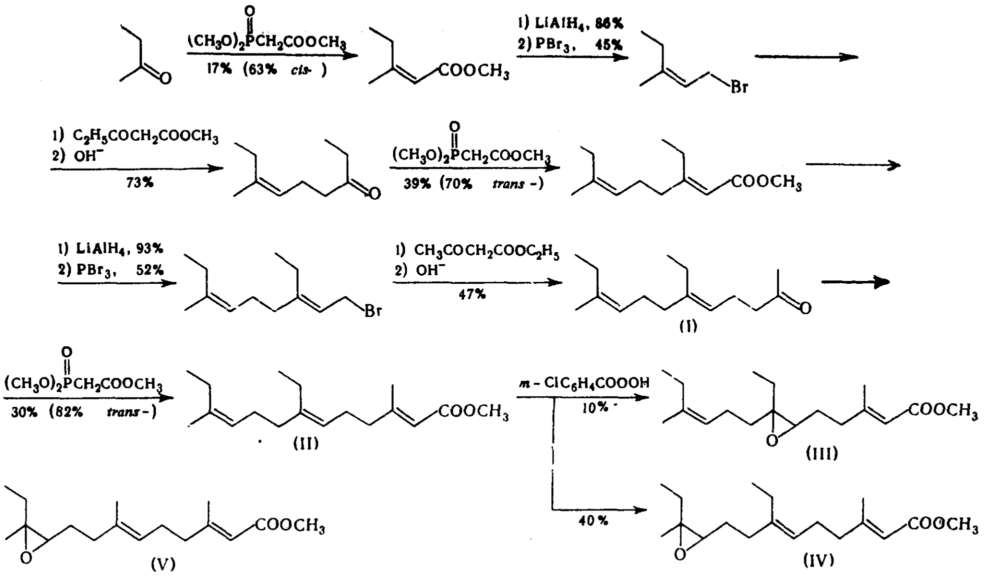
Although Röller and coworkers had at their disposal not more than 0.2–0.3 mg of the pure substance, the structure of the juvenile hormone was established in less than two years. The study of the juvenile hormone and the product of its reduction by hydrogen over palladium (20–30 μ g) on a combined gas chromatograph and mass-spectrometer[40] led to the determination of the overall formula ($C_{18}H_{30}O_3$), the molecular weight (294), the presence of a methoxycarbonyl group, branching, and three double bonds or rings[41]. The cleavage of 15 μg of the juvenile hormone with osmium tetroxide and periodate and investigation of the PMR spectrum (200 μg) in combination with mass-spectrometric data led to the identification of the juvenile hormone as methyl 10,11-epoxy-7-ethyl-3,11-dimethyltrideca-2,6-dienoate (IV) with the *trans*-configuration of the substituents at the 2,3-double bond.

The configuration of the substituents at the 6,7-double bond in the oxiran ring was not elucidated. A few months later Röller and coworkers[42] reported the first synthesis of racemic juvenile hormone. The synthesis was carried out by a gradual increase in chain length (Scheme 2).

The introduction of the double bonds by three applications of the phosphonate modification of the Wittig reaction was accompanied by the separation of the *cis*- and *trans*-isomers. In the first case the isomers were separated by fractionation on a 60 cm Teflon column and in the second and third cases by adsorption chromatography on silica gel. The last stage, the conversion of (II) into the epoxy-derivative with *m*-chloroperbenzoic acid, led to a mixture of epoxides (III) and (IV), which were separated by thin-layer chromatography on silica gel. Conversion of the triene ester (II) into the epoxy-derivative by the van Tamelen method[44] gives (IV) without an admixture of the isomer in a yield of 60%. At the same time Röller and Dahm[45] obtained by a similar mechanism a further four geometrical isomers of the juvenile hormone and later they synthesised all eight isomers of the hormone[28].

Comparison of the biological activities of the natural juvenile hormone and the synthetic specimens showed that

Scheme 2



synthetic methyl (±)-*trans*,trans,*cis*-10,11-epoxy-7-ethyl-3,11-dimethyltrideca-2,6-dienoate (IV) has the same activity as the natural hormone. The remaining isomers are less active (Table 1). All eight isomers of the juvenile hormone have also been obtained by the Hoffman La Roche Company, but their synthesis has not been published. The results of tests of these isomers on the bug *Rhodnius prolixus* are quoted by Wigglesworth[24] (Table 1).

Table 1. Physiological activity of the juvenile hormone and its isomers.

Compound	Configuration			Activity	
	C 2—3	C 6—7	C 10—11	"Tenebrio" units per μg (Ref.28)	g/g of insect wt. (Ref.24)
Natural hormone	—	—	—	5000	
Synthetic (±)-isomer 1	*trans-*	*trans-*	*cis-*	5000	0.18
Ditto 2	*trans-*	*trans-*	*trans-*	2000	0.6
» 3	*trans-*	*cis-*	*cis-*	200	1.8
» 4	*trans-*	*cis-*	*trans-*	150	13.5
» 5	*cis-*	*trans-*	*cis-*	10	9.0
» 6	*cis-*	*trans-*	*trans-*	10	16.0
» 7	*cis-*	*cis-*	*cis-*	10	63.0
» 8	*cis-*	*cis-*	*trans-*	10	45.0
Synthetic 6,7-epoxy-derivative of (±)- isomer	*trans-*	*trans-*	*trans-*	200	18.0
Synthetic ethyl ester 1 of (±)-isomer	*trans-*	*trans-*	*cis-*	40000	0.18

It has still not been shown whether the juvenile hormone derived from "cecropia oil" is optically active. Biological tests of the (±)-*trans*,*trans*,*cis*-isomer on *Tenebrio molitor* showed that either the enantiomers have the same biological activity, or, what is more likely, the natural juvenile hormone is also a mixture of the (+)- and (−)-forms[28]. This problem will have to be solved in the future.

In 1968 Meyer isolated from "cecropia oil" a second juvenile hormone (V), which is produced by the corpora allata in smaller amounts. It differs from (IV) by the presence of a methyl instead of an ethyl group at C_7. The isolation was based on the application of gas–liquid chromatography in the last stage. It was shown[46] that the ratio of the hormones varies, depending on the stage of development of the insect, between 4 : 1 and 7 : 1. It is suggested[16] that the second hormone is a precursor in the biosynthesis of (IV) and is responsible for 13–20% of the endocrine activity. Röller[28] did not detect the second active substance in "cecropia oil".

The biosynthetic pathways for the juvenile hormone are unknown. It has been established that insects synthesise the acyclic sesquiterpenes farnesal and farnesol from mevalonate[47,48]. However, so far it has not been shown whether the isoprene units are methylated at some stage in the biosynthesis or whether insects employ other precursors.

The mechanism of the action of the juvenile hormone is also unknown. The latest electrophysiological studies[49] appear to confirm the earlier hypothesis that the juvenile hormone affects the permeability of cell membranes[50].

All the hormones known until recent years belong to two classes of natural substances. They are either peptides and aminoacids or steroids. Ecdysone is not an exception in this sense, since it contains the hydrocarbon skeleton of cholesterol. The determination of the structure of the juvenile hormone of insects, which is a terpenoid, significantly extends out concepts concerning hormones. In this connection it should be noted that recently substances with a powerful hormonal activity—prostaglandins—were discovered in the secretions of vertebrates; like the juvenile hormone, they do not belong to any of the classes indicated above[51].

III. SYNTHESIS OF THE JUVENILE HORMONE

Less than two years have elapsed since the first synthesis of the juvenile hormone achieved by Röller and Dahm. During this period, eight versions of the synthesis of this biologically active compound have been reported. Synthetic studies are being carried on in the laboratories of the largest universities and commercial companies in the USA and Western Europe. Few natural substances are being investigated so intensively, which is evidence of a considerable interest in the juvenile hormone. In the synthesis of the juvenile hormone molecule the greatest difficulties are encountered in the formation of three centres which can give rise to geometrical isomers. Two approaches to the problem of the synthesis of the juvenile hormone can be clearly distinguished. The first is based on the use of highly stereospecific reactions which lead to the formation of the required isomers and the second involves reactions which yield a mixture of the *cis*- and *trans*-isomers with their subsequent separation by means of effective fractionating columns, and column, thin-layer, or gas–liquid chromatography.

It is at present difficult to assess fully the advantages and disadvantages of all the known syntheses of the juvenile hormone. Many of these have been described very schematically. So far as is known, no attempt has been made so far to separate the synthetic juvenile hormone into enantiomers.

The stereospecific syntheses consist of a large number of stages and use certain new reactions, methods, and reagents. Below they are described in greater detail.

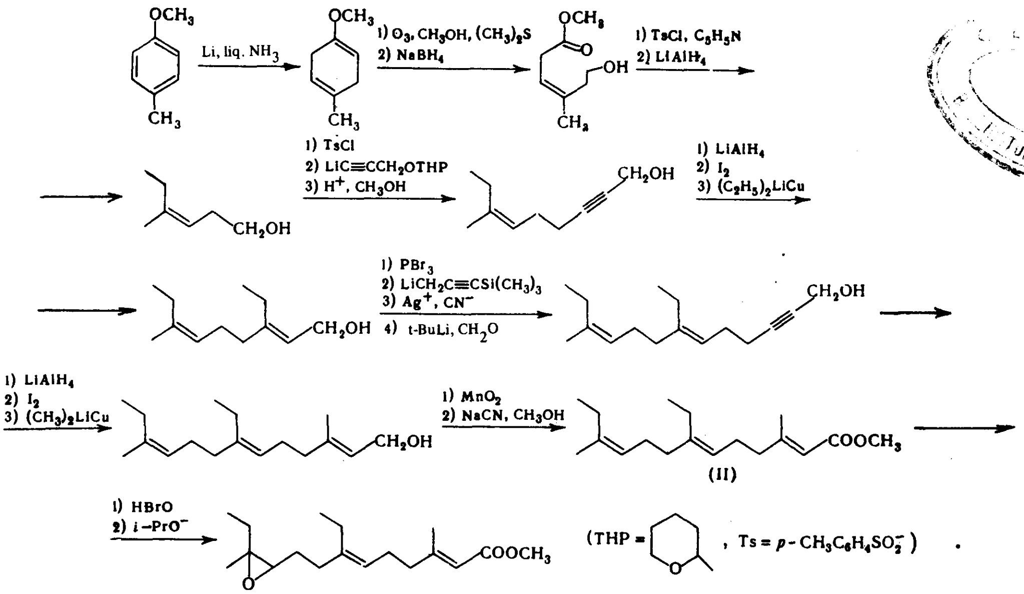
The stereospecific synthesis of the juvenile hormone was achieved in 1968 by Corey and coworkers[52] at Harvard University. Corey's scheme is based on a starting material which ensures the formation of the *cis*-configuration in the oxiran ring and certain new methods developed by the author were employed (Scheme 3).

The product of the Birch reduction of *p*-methoxytoluene was ozonised, converted into an aldehyde-ester, and reduced with sodium borohydride. The reduction of the *p*-toluenesulphonate of the resulting hydroxyester with lithium aluminium hydride led to the formation of the *cis*-isomer of a C_7 unsaturated alcohol. The reaction of the *p*-toluenesulphonate of the unsaturated C_7 alcohol with the lithium derivative of propargyl tetrahydropyranyl ether in hexamethylphosphoramide and subsequent treatment with acid methanol gave an acetylenic C_{10} alcohol. To convert the latter into *trans*, cis-3-ethyl-7-methylnona-2,6-dienol, Corey employed the stereoselective *C*-alkylation with alkylcopper reagents which he discovered recently[53–55]. Next the diene alcohol was converted into the bromide, which was alkylated with the lithium derivative of 1-trimethylsilylpropyne[56]. After the removal of the trimethylsilyl protecting group, an unsaturated hydrocarbon was obtained, which was converted by the action of t-butyllithium and paraformaldehyde into a C_{16} acetylenic alcohol. The repeated application of the stereoselective alkylation reaction in the synthesis led to the preparation of a C_{17} *trans,trans,cis*-triene alcohol. Treatment of the C_{17} alcohol with an excess of manganese dioxide in hexane at 0°C and subsequently with sodium cyanide and methanol gave the methyl ester of a trienoic acid (II). This new method for the conversion of aldehydes into carboxylic acid esters was also developed by Corey[57] and is of general value (yields in excess of 95%). The ester (II) was converted into the epoxy-derivative by treatment with hypobromite and subsequent elimination of hydrogen bromide.

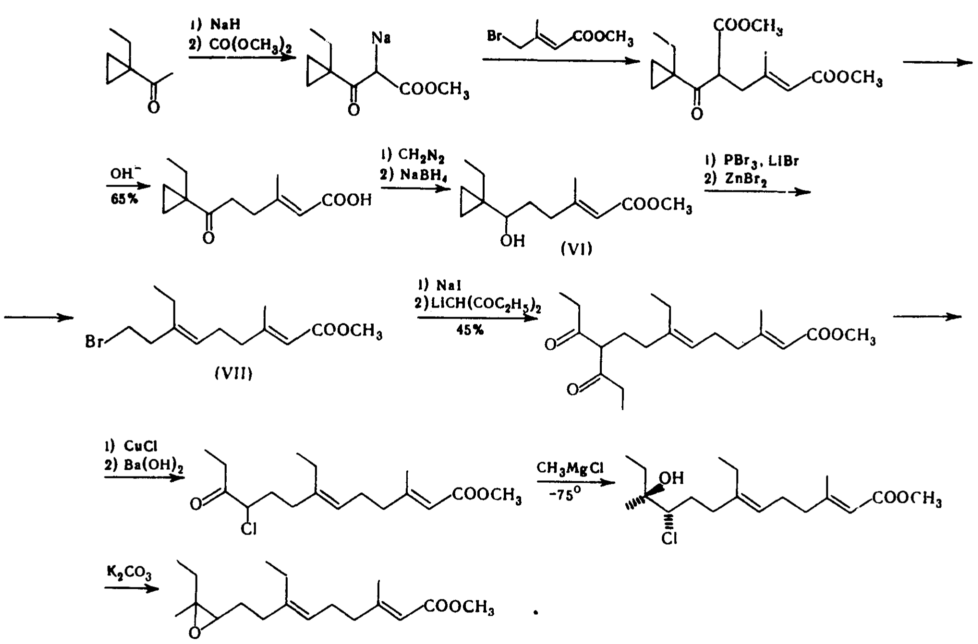
Johnson's twelve stage synthesis yields the racemic juvenile hormone containing admixtures of less than 8% of the *trans,trans,trans*-isomer and 0–5% of the *trans,cis,cis*-isomer. It is based on the application of Julia's method[59,60] for the synthesis of trisubstituted olefinic bonds, which includes the rearrangement of cyclopropylmethanols into homoallylic bromides. In all stages except two the products were obtained in yields greater than 90% (Scheme 4).

The sodio-derivative of the product of the Claisen condensation of 1-acetyl-1-ethylcyclopropane with carbonic ester was converted by reaction with methyl *trans*-γ-bromo-ββ-dimethylacrylate[61] into a ketodiester. The latter was converted in three stages into the hydroxyester (VI) and then into the homoallylic bromide (VII) by a modification of Julia's method developed by the author[62]; (VII) contained less than 5% of the *trans,cis*-isomer. The bromide (VII) was converted into the corresponding iodide and condensed with the lithio-derivative of hepta-3,5-dione. After substitution with chlorine of the mobile hydrogen atom in the β-diketone formed and alkaline

Scheme 3



Scheme 4

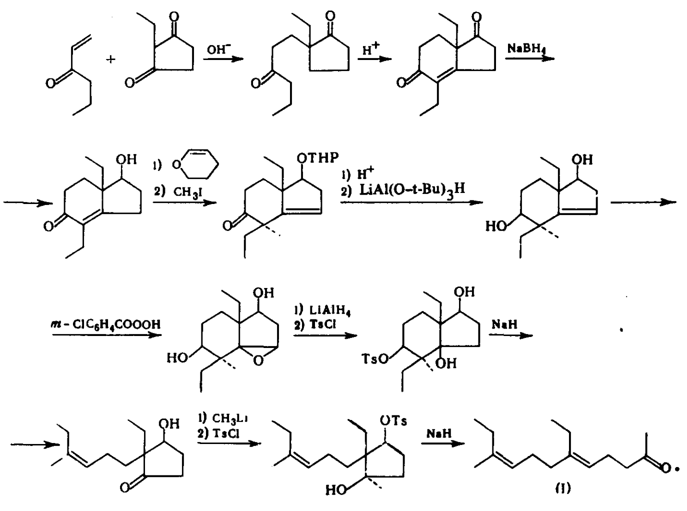


hydrolysis, the reaction product was purified by preparative gas–liquid chromatography and then treated at –75°C with an excess of methylmagnesium chloride, hydrogen chloride being eliminated with potassium carbonate in methanol, which ensures the *cis*-configuration of the substituents in the oxiran ring (< 8% of the *trans*-isomer). The stereospecific synthesis of an important intermediate for the preparation of the juvenile hormone, *trans,cis*-6-ethyl-10-methyldodeca-5,9-dien-2-one, was achieved at the Institute of Steroid Chemistry of the Syntex Corporation in California [compound (I) in Scheme 5][63].

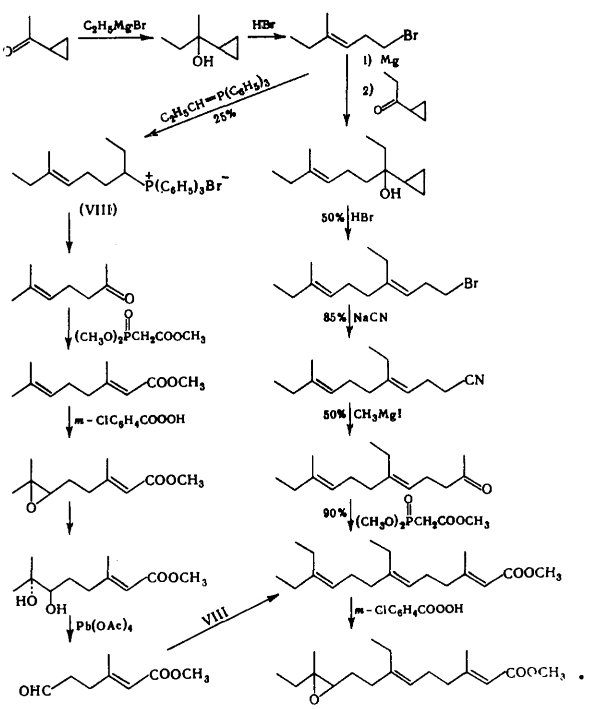
Brown et al.[64] developed two methods for the synthesis of a mixture of isomers of the juvenile hormone (Scheme 6). The authors state that the preparation exhibits 0.3 of the activity of the natural hormone and is used for entomological studies. Double bonds are formed both by the Julia method and by the Wittig reaction.

At the beginning of 1969 a further two papers on the synthesis of the juvenile hormone were published almost simultaneously. The synthesis achieved by Schulz[65]

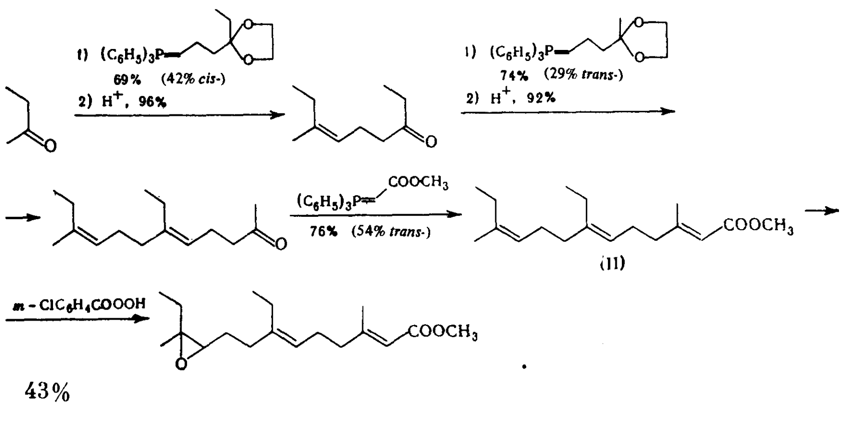
Scheme 5



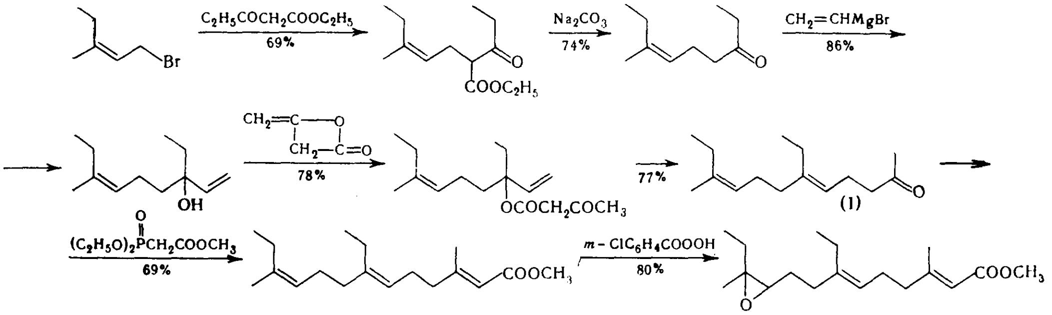
Scheme 6



Scheme 7



Scheme 8

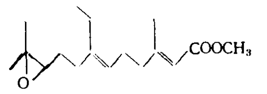


includes only three stages for the formation of the C_{17} skeleton: $C_4 + C_6 + C_5 + C_2$. The synthesis consists in a gradual increase in chain length using the Wittig reaction (Scheme 7).

The isomers of the C_{10} and C_{15} ketals and of the triene ester (II) were separated by fractionation on a Teflon column (l = 100 cm). The ketones obtained after hydrolysis were additionally purified by chromatography on silica gel. The authors state that they can obtain by this method all the geometrical isomers of the juvenile hormone and its homologues with different substituents at C_3, C_7, and C_{11}. However, it should be noted that the syntheses of the phosphoranes derived from the initial ketals and the separation of the isomers are fairly laborious processes.

Mori et al.[66] achieved a non-stereospecific synthesis of the juvenile hormone [compounds (IV) and (V)] and yet another homologue, which differs from the juvenile hormone by the presence of a methyl instead of an ethyl group at C_{11} [compound(IX)]. The final product consisted of a mixture of isomers. The synthesis is based on the application of the Normant[67] and the Carrol–Caymel[68] reactions and the phosphonate modification of the Wittig reaction[43]. The ratio of the *cis*- and *trans*-isomers in the intermediate and final product was determined by gas-liquid chromatography (Scheme 8).

The intermediate C_{10} and C_{15} ketones were obtained as individual isomers by the fractionation of the dioxolan derived from the C_{10} ketone[69] and repeated recrystallisation of the semicarbazone of the C_{15} ketone.



(IX)

IV. NATURAL AND SYNTHETIC ANALOGUES OF THE JUVENILE HORMONE

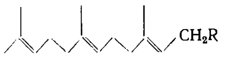
1. Farnesol Derivatives

At the beginning of the 1960's natural and synthetic compounds exhibiting the juvenile-hormonal activity in insects were discovered[20,27,70–75]. It was already clear that the structure of the juvenile hormone resembles that of terpenes. Farnesal and farnesol, acyclic sesquiterpenes widely distributed in nature, attracted particular attention. They were detected in the organisms of beetles[70], butterflies[47,76], bumble bees[77], and other insects. The hypothesis that farnesol functions as the juvenile hormone[70,72] was not confirmed[27,37,75]. Biological tests on a number of natural and synthetic terpenoids showed that none of them has a sufficiently high activity to be identified with the juvenile hormone[20,27,76,78].

Nevertheless these studies helped elucidate the structural elements responsible for the physiological activity, elucidate the relation between the shape and dimensions of the molecules and their juvenile-hormonal activity, and solve the problem of the mechanism of the action of the juvenile hormone at a molecular level. To obtain compounds more readily available than the juvenile hormone in order to combat harmful insects, the search for substances imitating its activity has been begun.

It is noteworthy that experiments designed to determine the juvenile-hormonal activity have been performed on different objects and by different methods (injection and surface application) and therefore it is frequently impossible to compare the results obtained by different investigators. Insects of different species show different sensitivity in relation to the juvenile hormone and its analogues. Hence there is a potential possibility of creating selective hormonal insecticides. The most active substances are described below and data on the relation between their structure and biological activity are given.

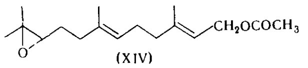
Tests of farnesol isomers on the pupae of the flour beetle *Tenebrio molitor* showed that *trans,trans*-farnesol (X) has the maximum activity[79]. This finding holds also for other sesquiterpenes: the *trans*-isomers are the most active[24,28]:



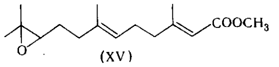
(X) R=OH, (XI) R=OCH_3, (XII) R=$N(C_2H_5)_2$, (XIII) R=$OCOCH_3$

Farnesyl methyl ether (XI) and farnesyldiethylamine (XII) are more effective by a factor of 10 and 17 respectively than farnesol (X) in tests on the pupae of the wax moth *Galleria mellonella*[80,81]. The length of the terpene alcohol molecule and the position of the hydroxy-group are important for juvenile-hormonal activity. Thus geraniol, linalo-ol and bisabolol are inactive. The effect of the length of the molecule on juvenile-hormonal activity is clearly shown by alkyl methyl ethers. Dodecyl methyl ether is the most active[80,82]. A change in chain length by three carbon atoms leads to total loss of activity. The presence of groups with a definite polarity is also essential for activity. Farnesene and dihydrofarnesene on the one hand and the highly polar farnesylic acid, dodecyl alcohol, and dodecylamine on the other are completely inactive or show a weak activity. Moreover, Schneiderman[80] noted the importance of molecular properties such as the capacity to form complexes with proteins and lipoproteins and to penetrate cell membranes.

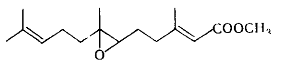
After the detection of the epoxy-group in the juvenile hormone, a number of sesquiterpene epoxides were obtained. 10,11-Epoxy-*trans,trans*-farnesyl acetate (XIV) shows a higher activity than farnesyl acetate (XIII).[44,83] The conversion of the methyl ester of *trans,trans*-farnesylic acid into an epoxy-derivative with *m*-chloroperbenzoic acid in dichloromethane gives a mixture of epoxides [80% of (XV) and 20% of (XVI)], which were separated by thin-layer chromatography:



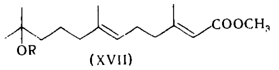
(XIV)



(XV)



(XVI)



(XVII)

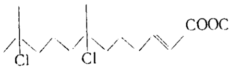
(R=CH_3, C_2H_5)

Tests with surface application on *Tenebrio molitor* showed that (XV) is 1600 times more active than farnesol (X), while (XVI) is inactive[83]. It is interesting that (XV) is less active than farnesol when injected[28].

Compounds with *O*-alkyl substituents at C_{11} [compound (XVII)] also exhibit juvenile-hormonal activity[84].

Law and Williams[85] obtained the most active synthetic product by passing hydrogen chloride through an alcoholic solution of farnesylic acid. It consists of at least 22 components, five of which are active[39] and is known as "Law's mixture"[86] or "synthetic juvenile hormone"[87]. When "Law's mixture" is obtained in various alcohols, the juvenile-hormonal activity varies as follows: ethanol > methanol > propanol > pentanol. When the reaction is carried out in ethanol, a highly active product, effective in insects of various species, is obtained[24,85,88-90].

Sorm and coworkers[91] isolated the principal component of "Law's mixture" obtained in methanol. It is the dihydrochloride of the methyl ester of farnesylic acid (XVIII):



(XVIII)

Compound (XVIII) showed a high juvenile-hormonal activity in relation to the bugs *Pyrrhocoris apterus*[91-95], *Rhodnius prolixus*[24], and others.

Farnesol[96] and a number of similar compounds[97,98] have been patented as insecticides and agents preventing the metamorphosis of insects.

At the beginning of 1969 a very interesting paper was published by Wigglesworth[24] in which he quotes the results of tests of 42 compounds on *Rhodnius prolixus*. All eight isomers of the juvenile hormone (Table 1) and the most active synthetic and natural substances were tested for the first time under identical conditions. Most of the specimens tested by Wigglesworth were obtained from the Hofman-La Roche Company. Many specimens have not been described in the literature. Table 2 lists the most interesting compounds. Using earlier data[79-81] and the results of his own investigations, Wigglesworth[24] formulated the following postulates.

1. A definite length and shape of the molecule is necessary for juvenile-hormonal activity. Substituents at the 2,3- and 6,7-double bonds must have the *trans*-configuration.

2. The balance between the lipophilic and hydrophilic groups in the molecule is significantly reflected in its juvenile-hormonal activity. Marked hydrophilic properties due to the presence of groups such as hydroxyls and carboxyls or, conversely, unduly lipophilic properties of the molecule lead to a decrease or disappearance of activity. The small differences in the structure of membranes in different insect species account for the significant difference in their sensitivity to juvenile hormone preparations.

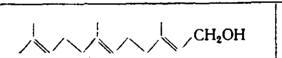
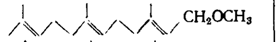
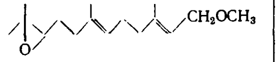
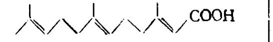
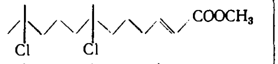
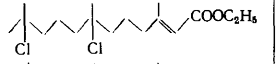
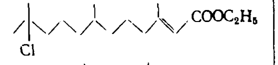
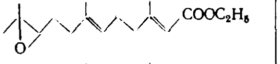
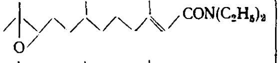
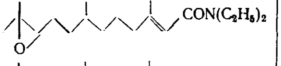
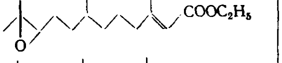
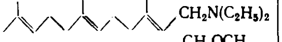
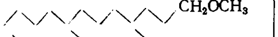
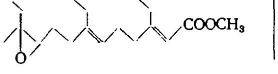
3. Substances which are most active on local application are also active when injected. There are, however, exceptions. The physical properties of the cuticle (the external skeleton of insects) and the amount of lipids in the haemolymph influence the penetration of the hormone and are responsible for the specific differences in sensitivity.

4. The differences in geometrical form and possibly in physical properties (for example, the proportions of the polar and non-polar groups in the molecule) appear to be more important for juvenile-hormonal activity than the presence of specific chemical groups.

5. In an early paper Schmialek[47] pointed out that an important factor influencing juvenile-hormonal activity is

the ease with which a given hormonal preparation breaks down in the insect organism. This, for example, explains the higher activity of farnesyl methyl ether compared with farnesol.

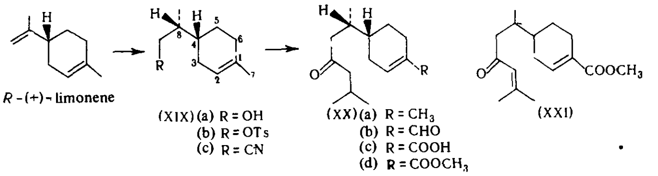
Table 2. Juvenile-hormonal activities of farnesol derivatives.

Compound	Structural formula	Activity, μg/g of insect wt.
Farnesol		45.0
Farnesyl methyl ether		0.6
10,11-Epoxyfarnesyl methyl ether		0.9
Farnesylic acid		90.0
Law's mixture		2.7
Dihydrochloride of methyl ester of farnesylic acid		2.2
Dihydrochloride of ethyl ester of farnesylic acid		0.5
Ethyl 11-chloro-3,7,11-trimethyldodeca-2-enoate		1.8
Ethyl ester of 10,11-epoxyfarnesylic acid		2.2
10,11-Epoxy-3,7,11-trimethyldodec-2-enoic amide		90.0
10,11-Epoxy-3,7,11-trimethyldodec-2-enoic *NN*-diethylamide		9.0
Ethyl 10,11-epoxy-3,7,11-trimethyldodec-2-enoate		0.5
Farnesyldiethylamine		1.8
Dodecyl methyl ether		250.0
Synthetic juvenile hormone		0.18

2. Juvabione and Its Analogues

In 1965 Sláma and Williams[99] accidently observed that the larvae of the bug *Pyrrhocoris apterus* undergo additional moulting on coming into contact with paper of American origin. Since such changes are caused only by the juvenile hormone[100], experiments were performed to isolate the active substance called the "paper factor"[99,101,102]. Bowers showed that the "paper factor" is present in the wood of the balsam fir *Abies balsamea*, which is used as the principal new material for the manufacture of paper pulp in Canada and the Northern USA. Further studies led to the determination in the structure of the "paper factor"[103]. It proved to be the methyl ester of the known todomatuic acid isolated by Japanese chemists from sulphite liquors, and was given the trivial name juvabione (XXd). Another active monocyclic sesquiterpene—dehydrojuvabione (XXI)—was isolated by Sorm and coworkers[104] from a fir native to Czechoslovakia.

Juvabione and dehydrojuvabione act selectively on bugs of the family *Pyrrhocoridae* and are inactive in tests on other insects[24,99,101,104]. Recently the absolute configuration of juvabione was established. Earlier Japanese investigators believed that both asymmetric centres of the (+)-todomatuic acid have the *R*-configuration[105]. The conversion of *R*-(+)-limonene into (+)-todomatuic acid (XXc) and (+)-juvabione (XXd), identical with the natural compounds, was achieved in 1968.[106]

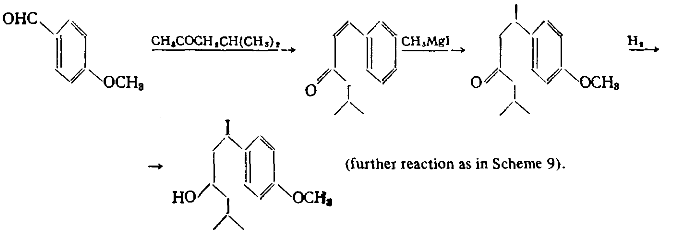


The unsaturated alcohol (XIXa) was obtained by the hydroboration and oxidation of natural limonene with subsequent separation of the 3,5-dinitrobenzoates of the epimeric alcohols. Initially the configuration of compound (XIXa) was established incorrectly. Subsequently X-ray diffraction analysis of the *p*-iodobenzoate of the alcohol (XIXa) showed that the (+)-todomatuic acid and (+)-juvabione obtained by the authors have the 4(*R*),8(*S*)-configuration of the asymmetric centres[107].

The first synthesis of (±)-juvabione was achieved by a 15-stage procedure starting with *p*-methoxyacetophenone (Scheme 9). All the stages take place with high yields; the overall yield of the mixture of the diastereoisomers of todomatuic acid was 6.8%. The diastereoisomers were separated by the crystallisation of the semicarbazones[108,109].

Tests of the biological activities of the compounds obtained on *Pyrrhocoris apterus* showed that the synthetic (±)-juvabione is less active by a factor of approximately 2 than the natural (±)-juvabione (XXd). The methyl ester of (±)-epitodomatuic acid is even less active.

A mixture of (±)-juvabione diastereoisomers was obtained by Indian investigators by a similar procedure, differing only in the first stages[110]:



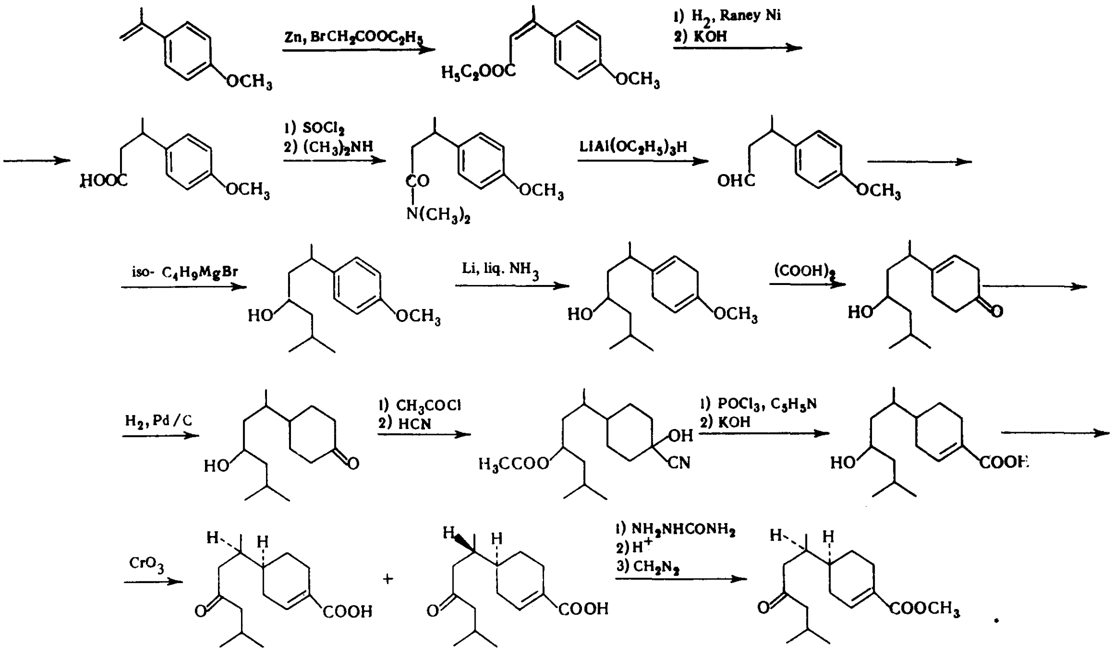
(further reaction as in Scheme 9).

The diastereoisomers could not be separated by thin-layer or gas–liquid chromatography, as had been noted also by Japanese chemists[109].

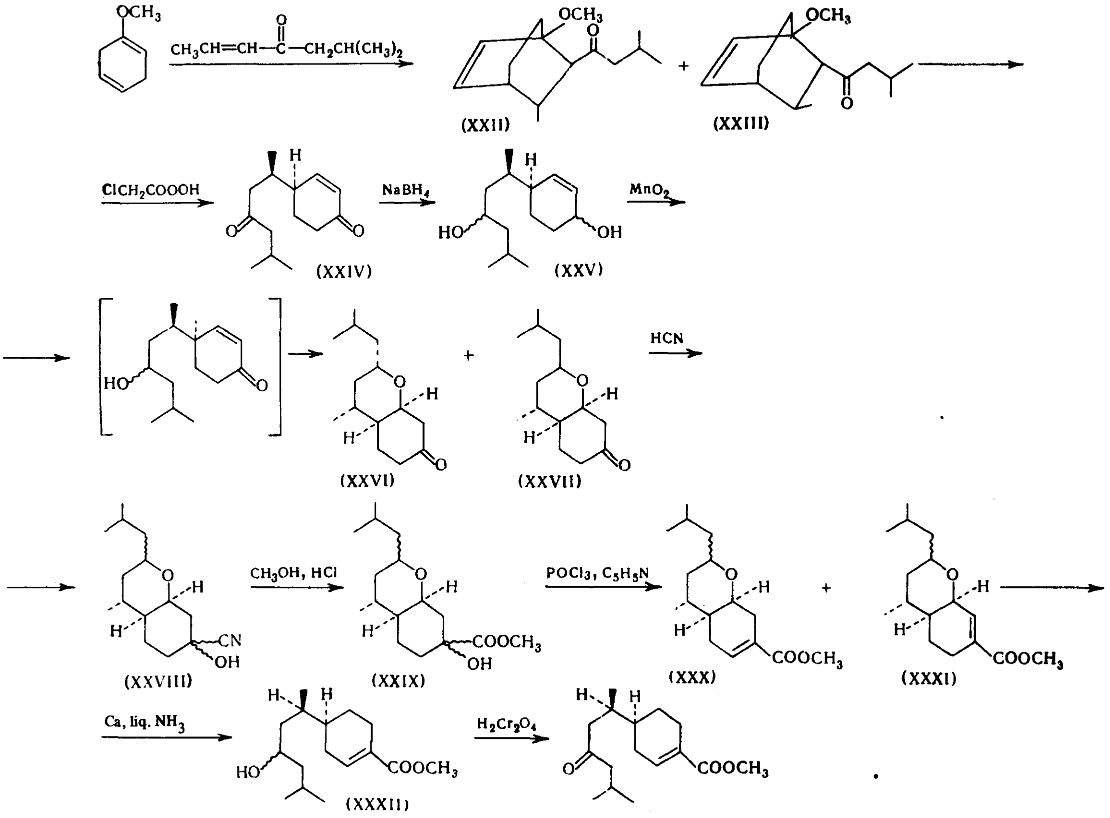
Birch et al.[111] developed a novel stereospecific synthesis (±)-juvabione (Scheme 10). Diels–Alder condensation of 1-methoxycyclohexa-1,4-diene with *trans*-6-methylhept-2-en-4-one gave a 75–80% yield of the adducts (XXII) and (XXIII) in proportions of 1 : 1. The rigid cyclic system and the different positions of the carbonyl group and the double bond ensure sufficient differences in the properties of the isomers to allow their separation on a fractionating column. Oxidation of the isomer (XXII) with chloroperacetic acid gave the diketone (XXIV), which was reduced with sodium borohydride to a mixture of stereoisomeric diols.

Oxidation of (XXV) with manganese dioxide gives a 5 : 1 mixture of the ketoesters (XXVI) and (XXVII), which were separated by chromatography on silica gel. The PMR spectra of both isomers indicate a *cis*-fusion of the rings,

Scheme 9

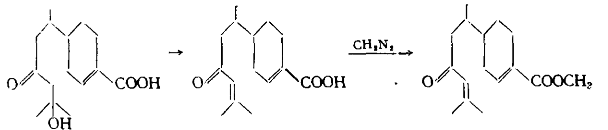


Scheme 10



i.e., they differ in the configuration of the side chain. Although both isomers can be converted into juvabione, only the isomer present in a larger amount was used in the preparation of the cyanohydrin (XXVIII). (XXVIII) was converted in the usual way into the hydroxyether (XXIX), the dehydration of which with phosphorus oxychloride in pyridine led to the formation of a 2 : 1 mixture of the unsaturated esters (XXX) and (XXXI), which were separated by chromatography on silica gel. Cleavage with calcium in liquid ammonia leads to the hydroxyester (XXXII), which is oxidised by chromic acid to (±)-juvabione.

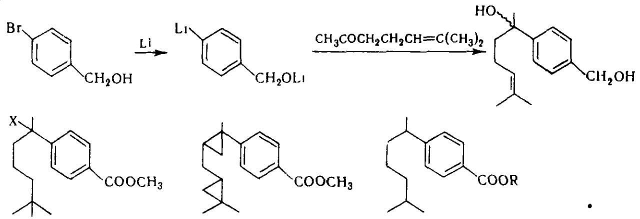
A non-stereospecific synthesis may be achieved by reduction of the double bond in (XXIV) followed by a selective reaction of the diketone with HCN and subsequent conversion of the cyanohydrin into an $\alpha\beta$-unsaturated ester. The authors of the first synthesis of (±)-juvabione obtained also dehydrojuvabione as a mixture of (±)-dihydrojuvabione and its stereoisomer. The method of synthesis resembles in many ways that of juvabione. The double bond conjugated with the carbonyl group was formed in the last stages by dehydration of the unsaturated hydroxy-acid[112]:



(XXI) .

Juvabione and dehydrojuvabione, which act selectively on different insect species, are active only when employed in microgramme amounts, while the juvenile hormone and some of its synthetic analogues suppress metamorphosis in amounts of 0.001–0.0001 μg. In search for more effective selective hormonal insecticides, Czechoslovak investigators[18] synthesised a series of aromatic analogues of juvabione. The specific effect of these compounds on bugs of the family *Pyrrhocoridae* is maintained[19,95].

The compounds obtained were patented, since some of them are 100 times more active than juvabione[113]. Moreover, they are comparatively readily available. The key stage in the synthesis is the condensation of the lithium derivative of benzyl alcohol with 6-methylhept-5-en-2-one. The subsequent reactions yielded a number of analogues of juvabione which were tested on two species of the family *Pyrrhocoridae*:

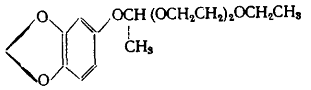


(X = Cl, Br) (R = CH₃, C₂H₅ etc.) .

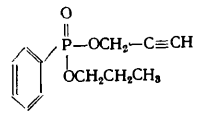
The observed differences in sensitivity show that the preparations may be specific even within a single family.

3. Synergists

Synergists for insecticides such as pyrethrines or carbamates have found wide application in practice. In his attempt to employ the JH-active 10,11-epoxyfarnesyl methyl ether together with synergists, Bowers[114] observed that some of them exhibit a distinctive juvenile-hormonal activity. The experiments were performed on pupae of the flour beetle *Tenebrio amolitor* and larvae of the bug *Oncopeltus fasciatus*. The synthetic synergists sesoxane (XXXIII) (in doses up to 0.5 μg) and Niagara 16 388 (XXXIV) show the highest activity. The remaining synthetic and natural synergistic agents (sesamin and sesamolin) are inactive or weakly active:



(XXXIII)



(XXXIV)

Bowers showed that sesoxane acts similarly to other substances with juvenile-hormonal activity and not by activating the corpora allata.

At present the juvenile hormone and its analogues are being very intensively investigated. There is no doubt about the theoretical value of such studies. Certain important problems, in particular the determination of the mechanism of the action and of the biosynthesis of the juvenile hormone will probably be elucidated in the near future. Possibly a more rigorous correlation will be established between the structure and physiological activity of the compounds. The prospects for practical application of compounds with juvenile-hormonal activity as a "third generation" of chemical pesticides are very good and therefore further development of studies in this field is to be expected.

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During the preparation of the review for the press, a number of studies on the synthesis of the juvenile hormone[115–118] and substances with juvenile-hormonal activity were published[119–123]. The work of Czechoslovak investigators on tests of compounds of the farnesyl series on *Galleria mellonella* is noteworthy[124].

Studies on the mechanism of action[125,126] and the effect of JH-active substances on the metamorphosis[127,128], ovogenesis[129], and metabolism[130] of insects are being continued.

Bowers' report on the preparation of methylenedioxyphenyl ethers, some of which showed an activity higher than that of the juvenile hormone when tested on the beetle *Tenebrio molitor* and the bug *Oncopeltus fasciatus*, is extremely interesting[131]. The sterilising effect of JH-active substances on introduction into insect males is noteworthy[92,132].

The publication of two reviews on insect hormones[133,134] should be noted.

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Parasitology and Tropical
Medicine, Moscow

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The Application of Nuclear Magnetic Resonance in the Study of the Conformational Equilibria of Cyclic Compounds

T.M.Ivanova and G.P.Kugatova-Shemyakina

The NMR spectroscopic methods used to investigate mobile conformational equilibria and to determine the rate constants are discussed. A critical comparison has been made of the accuracy of the results obtained by high-resolution and spin-echo NMR methods. A systematic account of the thermodynamic parameters of the ring inversion of cyclic compounds obtained by NMR methods has been given. The possibility of employing NMR spectra for the determination of conformational equilibrium constants is discussed.
The bibliography includes 224 references.

CONTENTS

I. INTRODUCTION

In recent years there has been an intense development of the field of structural chemical studies which has come to be called conformational analysis. The development of Barton's ideas[1] concerning the relation between the physical and chemical properties of molecules, in particular between reactivity and the steric position of atoms and groups of atoms, proved to be extremely fruitful in a wide variety of chemical fields. Particularly important advances have been made in the conformational analysis of cyclic compounds for which a comparatively small number of conformations (in many cases not more than two) is possible owing to the limitations imposed on structural isomers. The interest in conformational studies has been largely reflected by the simultaneous publication of two extensive monographs[2,3].

Both chemical methods, based on definite reactions of model compounds, and many physical methods, with the aid of which it is possible to establish either the complete structure of the molecule (X-ray analysis, electron diffraction, microwave spectra) or certain details of this structure (dipole moments, vibrational spectra, NMR spectra, optical rotatory dispersion) are used at present to investigate conformations. Among the latter group of methods, NMR spectra occupy a special place. By virtue of their specificity, NMR spectra permit in many cases a rapid and reliable determination of the steric orientation of groups containing magnetically active nuclei and the relative amount of such groups in the molecule. They are more selective, than, for example, dipole moments and vibrational spectra; in the latter the vibrations of individual bonds and groups are frequently not entirely characteristic, which may lead to conclusions with little justification. Moreover, NMR spectra permit the investigation of processes involving the attainment of conformational equilibrium and the determination of the lifetime of the molecule in each form, while with the aid of other methods only indirect conclusions concerning such problems may be made. Although the method began to be developed comparatively recently, extensive data have now accumulated on fixed conformations and also on the inversion of cyclic systems. Without exaggeration, one may say that conformational analysis has to a large extent stimulated the development of the NMR method for the study of mobile equilibria. A number of techniques have been developed permitting the determination of the thermodynamic parameters of the ring inversion of cyclic systems. The most extensive studies of this kind have been made for cyclohexane derivatives, but there are also data on the inversion of other cyclic compounds, in particular medium-ring and heterocyclic compounds. Extensive data on the NMR spectra of rigid polycyclic systems, mainly steroids, are given in the book of Bhacca and Williams[4].

This review deals with the application of NMR spectra in the study of mobile conformational equilibria, mainly of monocyclic systems. Initially, methods which have now been developed for the investigation of ring inversion will be considered and their comparative accuracy will be estimated. The second part of the review gives a systematic account of the data on the thermodynamic parameters of the inversion of cyclic compounds obtained with the aid of NMR methods. The scope of the use of NMR spectra for the determination of conformational energies in six-membered rings is also briefly discussed. The majority of published results concern proton magnetic resonance spectra, but in recent years interesting data have been obtained with the aid of the fluorine resonance, also discussed in the review.

II. METHODS FOR THE INVESTIGATION OF RING INVERSION

The conformational hypotheses concerning the structure of cyclohexane and many other derivatives are based on the concept of the rapid conversion of one chair form of the molecule into another with the boat forms as intermediates. In this process the axial bonds of one chair conformation become the equatorial bonds in the other and conversely. Since it was shown in early studies that the axial and equatorial protons of six-membered rings are magnetically non-equivalent, the study of the inversion of cyclic systems is a special case of the study of the exchange of protons (or other magnetically active nuclei) between non-equivalent positions; hindered rotation and intermolecular exchange in chemical reactions belongs to the same class of problems.

In recent years the "kinetic" field of NMR spectroscopy has been developing very vigorously. A number of methods and theoretical procedures have been developed, whereby one can use all the parameters of NMR spectra which vary with the rate of exchange of the nuclei: the multiplicity of the spectrum, intensity ratios, chemical shifts, and component widths.

The existing methods belong mainly to two categories: high-resolution and spin-echo spectroscopy. Their fundamental principles and practical applications in the study of ring inversion will be discussed below. The applicability of the method is undoubtedly not limited to the inversion of cyclic compounds; all the relations between the parameters of the spectrum and the rates of exchange may be applied to hindered rotation and, after appropriate modification, to the study of chemical reaction kinetics. In the investigation of mobile conformational equilibria, one usually employs the methods of high-resolution spectroscopy, which have been developed in detail. Detailed descriptions of these procedures are given in a number of monographs[5,6] and in this review only their principal postulates will be briefly described. The double-resonance and spin-echo methods, recently proposed for the investigation of ring inversion, will be considered in greater detail.

1. High-resolution NMR Spectroscopic Methods

The theoretical basis of these methods is the semiclassical treatment of Gutowsky et al.[7], who examined the Bloch equations for two protons with resonance frequencies ω_A and ω_B undergoing exchange between equilibrium positions A and B (it is assumed that the lifetime $\tau_A = \tau_B = \tau$). The expression for the total magnetisation averaged with respect to proton exchange is[7]:

$$G = \overline{G}_A + \overline{G}_B = \frac{-2\omega M_0\tau\{2+(1/T_2 - i\Delta\omega)2\tau\}}{(1+2\alpha_A\tau)(1+2\alpha_B\tau)-1}, \qquad (1)$$

where, as usual, $\alpha_A = 1/T_2 - i(\Delta\omega + \delta\omega/2)$, $\alpha_B = 1/T_2 - i(\Delta\omega - \delta\omega_2)$, M_0 is the equilibrium value of nuclear magnetisation, $\Delta\omega$ the difference between the applied radiofrequency ω and the frequency of the midpoint between two resonance components, and T_2 is the transverse relaxation time. Eqn. (1) was obtained on the basis of simple considerations by McConnell[8], who included directly in the Bloch equations terms taking into account the exchange: G_A/τ and G_B/τ. For non-identical probabilities $p_A \neq p_B$ of the presence of the proton in A and B (p_A and p_B may be regarded as the "molar concentrations" of A and B),

$$p_A + p_B = 1 \quad \tau_A/p_A = \tau_B/p_B, \qquad (2)$$

analytical expressions defining the total magnetisation were obtained by Gutowsky and Saika[9] and subsequently by other investigators[10,11].

It follows from Eqn. (1) that the form of the NMR spectrum is determined by $\delta\omega$, T_2, and the rate of proton exchange $1/\tau$. At high rates of exchange ($\tau\delta \ll 1$) one signal with a frequency ω_0 is observed; with increase of τ, the signal gradually widens, and for $\tau > \sqrt{2}/2\pi\delta\omega$ two broad signals are observed. The value of τ corresponding to the merging of the signals may be called the coalescence point. On further growth of τ, the width of the signals diminishes and the distance between them increases to $\delta\omega$ (Fig. 1).

Eqn. (1) contains an implicit relation between all the parameters of the NMR spectrum and the rate of exchange, but for the solution of practical problems it is convenient to obtain analytical relations between $1/\tau$ and quantities measured directly from the spectrum. Such relations have been obtained for three readily measurable parameters: (a) the distance between the lines (for $\tau\delta \ll 1$);[13] (b) the intensity ratios I_{max}/I_{min} for incomplete resolution of the doublet[14-16]; (c) the line widths in the limiting cases of rapid and slow exchange[17,18].

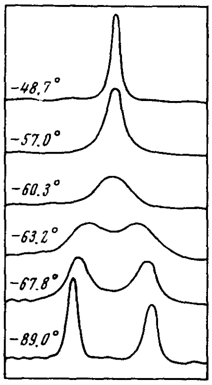

Figure 1. Spectra of $C_6D_{11}H$ at different temperatures[12].

a. Change in the distance between the components of the spectrum. An explicit expression relating the distance between the signals to the rate of exchange was obtained by Gutowsky and Holm[13]. Starting with Eqn. (1), they obtained an equation of the fifth degree in $\Delta\omega$, which becomes very simple when the width of the lines $1/T_2$ is small compared with the distance $\delta\omega$ between them:

$$\delta\omega_e = (1-2/\tau^2\delta\omega^2)^{1/2}\,\delta\omega; \quad \tau\delta\omega > \sqrt{2}. \qquad (3)$$

Thus, when measuring the distance $\delta\omega_e$ between the components under various conditions (usually the lifetime is varied by altering the temperature), it is possible to determine τ by Eqn. (3) provided that the distance $\delta\omega_\infty$ is known for $\tau \to \infty$. In practice, however, failure to take into account the widths of the components may introduce a significant distortion into the results already when $1/T_2\delta\omega > 1/3$.[13] Gutowsky and Holm showed that this is equivalent to applying a correction to $\delta\omega_\infty$. The true distance $\delta\omega$ may be obtained from a plot of $\delta\omega/\delta\omega_\infty$ against $2/T_2\delta\omega_\infty$.[13] In practice T_2 may be determined from the line width when $\tau \to 0$; $\delta\omega_\infty$ is measured at $\tau \to \infty$.

b. Intensity ratio in the spectrum. Starting with postulates analogous to those discussed above, it is possible to express the average lifetime τ of the protons undergoing exchange in terms of the ratio r of the intensity at the maximum of the signal to the intensity in the centre of the spectrum, between the signals, when the symmetrical doublet (or other symmetrical multiplet signal) is completely resolved[14-16]. The expression is of the form

$$\tau\delta\omega = \sqrt{2}\,[r + (r^2 - r)^{1/2}]^{1/2}; \quad \tau\delta\omega > \sqrt{2}. \qquad (4)$$

The determination of the rate of exchange reduces in this case to the measurement of the intensity at the maximum and the minimum intensity in the "hollow" between the signals for different degrees of incomplete resolution. It is also necessary to know the distance $\delta\omega$ between the components at $\tau \rightarrow \infty$. Expressions of this kind, relating τ to the peak intensity of the signal for rapid[10] and slow[11] exchange, have been obtained in a number of studies.

c. Change in signal width. The applicability of the methods described above is restricted to the range of comparatively low rates of exchange. In order to obtain the necessary parameters, all the measurements must be made over a narrow temperature range below the point of coalescence. Moreover, it is also necessary to know the chemical shift $\delta\omega$ at $\tau \rightarrow \infty$, which sometimes gives rise to additional difficulties. Meiboom and coworkers[15,17] and Piett and Anderson[18] suggested that the variation of the transverse relaxation time with τ be used for the estimation of the rates in the extreme cases of rapid and slow exchange. Employing the approach of Gutowsky and Saika[9], Piett and Anderson[18] showed that, for low rates of exchange, the observed line width is

$$1/T_2' = 1/T_2 + 1/\tau, \qquad (5)$$

where T_2 is the transverse relaxation time in the absence of exchange and T_2^1 is the "new" transverse relaxation time. When the rate of exchange diminishes, the width of each component will tend to an effective natural value. For rapid exchange, the following expression was obtained:

$$1/T_2' = 1/T_2 + p_A p_B (\delta\omega)^2 \tau. \qquad (6)$$

The line width can be determined either directly from the high-resolution spectrum or by the usual methods based on measurements of signal decay. It is significant that the temperature variation of line widths may be slower and may be observed over a wider range than, for example, the temperature variation of the distance between the components described by Eqn. (3). Therefore the above methods greatly extend the range of measurable rates of exchange.

2. Methods Based on Complete Calculation of the Spectrum

In recent years a new approach to the determination of the rates of exchange from NMR spectra became possible as a result of the availability of high-speed computers. It reduces to the complete analysis of the outline of an AB or more complex systems as a function of the lifetime τ. A general quantum-mechanical theory of the effect of exchange on the parameters of the NMR spectrum, based on the time variation of the components of the density matrices, was developed by Kaplan[19] and Alexander[20]. The corresponding expressions for the system AB were obtained by Heidberg et al.[21]. The method involving the complete calculation of the spectrum requires the derivation of the equations and their numerical solution for each specific problem. The value of τ, which gives the best description of the spectrum when the other parameters are specified is determined by an iterative procedure. As a rule, the calculated and observed spectra are compared visually. However, recently Jonáš et al.[22] developed a convenient program for the comparison of the observed and calculated outlines by means of a computer.

3. Double Resonance

Recently a double-resonance technique was proposed for the investigation of the rates of exchange. The method was developed by Forsen and Hoffman[23,24] and applied in the study of the rate of inversion of cyclohexane by Anet and Burn[25]. The idea of the method is as follows. Suppose that there is exchange between two non-equivalent positions A and B, and the following two obligatory conditions are fulfilled: (1) the lifetimes τ_A and τ_B must be sufficiently long for a satisfactory resolution of the signals A and B; (2) the lifetime τ_A must be comparable to the spin-lattice relaxation time T_{1A}. If the signal B is saturated instantaneously, the signal A will decay exponentially with the time constant τ_{1A}:

$$M_z^A = M_0^A\,[\tau_{1A}/\tau_A \exp(-t/\tau_{1A}) + (\tau_{1A}/T_{1A})], \qquad (7)$$

where M_0^A is the initial magnetisation of A. The new "generalised" relaxation time τ_{1A} is defined thus:

$$1/\tau_{1A} = 1/\tau_A + 1/T_{1A} \qquad (8)$$

and the new equilibrium magnetisation is given by

$$M_z^A(t \rightarrow \infty) = M_0^A(\tau_{1A}/T_{1A}). \qquad (9)$$

Thus the ratio of the initial and final magnetisations M_0^A/M_Z^A, which can be readily obtained experimentally, yields τ_{1A}/T_{1A}; by plotting $\lg[M_Z^A(t) - M_Z^A(t \rightarrow \infty)]$ against t, we obtain a straight line with slope τ_{1A}. It is then easy to determine τ_A and T_{1A} from Eqn. (9).

When the saturating field at B is removed, the A signal returns to its initial value M_Z^A, but the corresponding relation is not exponential; in the general case it cannot be described with the aid of a single time constant[23,24]. Forsen and Hoffman examined also two other possibilities: the return of the magnetisation of the signal to the initial value after saturation of the same signal and after the simultaneous saturation of the A and B signals[23]. Subsequently the same workers[24] applied the method to the study of exchange between several non-equivalent positions. As already stated, the double-resonance method can be applied only over a very restricted range of rates of exchange, since the lifetime must be comparable to the spin–lattice relaxation time. The latter may be varied somewhat by the addition of paramagnetic substances. The lower limit to the measured rates is imposed by the requirement that the signals do not overlap, i.e. the lifetime must be greater than the reciprocal of the distance between the corresponding lines.

The advantages of the method are due primarily to the fact that the lifetimes measured with its aid cannot be determined by other high-resolution procedures. Moreover, it is noteworthy that the experiment in which two parameters (rate of exchange and spin–lattice relaxation times) are measured simultaneously is relatively simple and the amount of calculation in the interpretation of the data is also small. The method does not require a very high resolution and an accurate determination of the chemical shifts. However, a high sensitivity of the detecting system is essential.

4. The Spin-echo Method

Recently Gutowsky, Allerhand and coworkers[26-31] developed a fundamentally new approach to the determination of the rate of proton exchange from NMR spectra. It is based on the observation of spin-echo signals† when a chain of high-frequency pulses in the Carr–Purcell sequence[32] is applied to the spin system investigated: at time $t = 0$ a 90° pulse is applied and then at times $(2n - 1)t_{av}$ a sequence of 180° pulses is observed. These pulses generate a spin echo at times $2nt_p$ (here t_p is the period between the 90° pulse and the first 180° pulse). In the general case the amplitudes of the observed echo signals are functions of the shift $\delta\omega$, the spin–spin coupling constant J, the transverse relaxation time T_2^0 in the absence of exchange‡, the distance between the 180° pulses, t_{av}, the population of the p_A and p_B levels, and the rate of exchange $1/2\tau$. It is important that the duration of the pulses is short compared to T_2 (and to the spin–lattice relaxation time T_1) and also to the intervals between the pulses, so that the relaxation and exchange effects during the application of the pulse may be neglected.

The simplest relations between these quantities are obtained for the AB system when $J = 0$. For this case, Allerhand and Gutowsky[26,27] employed a semiclassical approximation taking into account the exchange terms[7,8,13]. Earlier Luz and Meiboom[33] obtained an approximate analytical expression for the decay of the spin-echo signals under conditions where (1) the distance between the 180° pulses is small ($t_{av} \ll T_2$) and (2) the exchange is fairly rapid ($1/2\tau \gg \delta\omega$):

$$1/T_2 = 1/T_2^0 + p_A p_B (\delta\omega)^2 \tau \,[(1 - 2\tau/t_{av}) \tanh t_{av}/(2\tau)]. \qquad (10)$$

Gutowsky and Allerhand showed[26,27] that, although Eqn. (10) may be applied over a fairly wide range of values of the independent variables, for high values of t_{av} and for slow exchange its application leads to significant errors. Their general examination of the problem led to the conclusion that the expression for the variation of the magnetisation component may be represented by two terms, one of which varies exponentially with time and the other is pseudoexponential. However, the latter is small in most practical cases, so that only the contribution of the exponential term need be considered.

The following expression was obtained for identical populations $p_A = p_B = 0.5$:[27]

$$1/T_2 = 1/T_2^0 + 1/2\tau + 1/t_{av} \sinh^{-1} F ,$$

where

$$F = (1/\tau\sigma) \sinh (t_{av}\sigma/2); \quad \sigma = [(1/\tau)^2 - (\delta\omega)^2]^{1/2} . \qquad (11)$$

In the limiting cases Eqn. (11) leads to the following relations. (1) Slow exchange ($1/\tau < \delta\omega$):

$$1/T_2 = 1/T_2^0 + 1/2\tau . \qquad (12)$$

(2) Rapid exchange ($1/\tau \geqslant \delta\omega$):

$$1/T_2 = 1/T_2^0 + 1/2\tau - {}^1/_2 [(1/\tau)^2 - (\delta\omega)^2]^{1/2} . \qquad (13)$$

For very rapid exchange ($1/\tau \gg \delta\omega$), Eqn. (13) yields the result obtained on the basis of another approximation by Piett and Anderson[18]:

$$1/T_2 = 1/T_2^0 + {}^1/_4 (\delta\omega)^2 \tau . \qquad (14)$$

Eqn. (13) can also be used to determine the rates of exchange from the line widths in high-resolution NMR spectra; it can be applied in the case of much lower rates of exchange than Eqn. (14).

When the distance between the pulses diminishes ($t_{av} \rightarrow 0$), $1/T_2$ approaches asymptotically the effective natural line width (independent of the rate of exchange). This gives rise to the possibility of determining T_2^0 from spin-echo experiments with very rapid repetition of pulses.

Thus the rate of exchange $1/\tau$ may be determined by measuring the spin-echo signal decay as a function of the distance between the 180° pulses. Since Eqn. (11) includes, apart from τ and t_{av}, also the two independent variables T_2^0 and $\delta\omega$, it is usually solved by iterative methods[26,27]. Allerhand and Gutowsky developed programs whereby it is possible to obtain "true" values of the parameters after, as a rule, not more than ten iterations. The initial values of $1/\tau$ and $\delta\omega$ may be chosen with the aid of the Luz–Meiboom equation [Eqn. (10)].

The spin-echo method has the advantage that in this case there is no need for a direct determination of the parameters $\delta\omega$ and T_2^0; they are obtained additionally in the iterative process from the functional relation between $1/T_2$ and $1/t_{av}$. We may note that, in order to calculate the amplitude of the echo signals, it is by no means obligatory to express the variation of T_2 in an analytical form: it is possible to solve directly modified Bloch equations in a numerical form by means of appropriate programs. Although such calculations do require a considerable machine time, accurate values are then obtained over the entire range of variation of the parameters. However, for the majority of practical problems, the relation between T_2 and $1/t_{av}$ is satisfactorily described by Eqn. (11).

The semiclassical approach described above can be applied only to a system AB. If the coupling constant J_{AB} is comparable to the chemical shift, $\delta\omega$, significant changes may be introduced into the results of the spin-echo experiments. Allerhand and Gutowsky[31] examined, using a quantum-mechanical approach, the time variation of the components of the density matrix[20,21] for the system AB under conditions corresponding to the application of a Carr–Purcell sequence of pulses. In the general case eight recurrent equations were obtained, the coefficients of which are complex functions of the experimental quantities. However, as in the case examined above, a significant success may be achieved here by the numerical solution of the equations. By varying the independent variables τ, $\delta\omega$, J, and t_{av} over a wide range, Allerhand and Gutowsky showed that the results obtained[26,27,30] for an AB system with $J = 0$ are not applicable to interacting nuclei for low rates of exchange. When $1/2\tau$ (s^{-1}) is small compared with the geminal coupling constant J, modulation of the echo signal amplitudes should be observed. The modulation frequency depends on the distance between the pulses t_{av}, the constant J, and also $\delta\omega$, particularly if $J/\delta\omega \simeq 1$. In the limiting case where $J = 0$, the same results are obtained as in the semiclassical theory. The modulation greatly depends also on the rate of exchange. When $1/2\tau$ increases, the modulation frequency falls and the time variation of the echo signal amplitude approaches the exponential form. When $1/2\tau \gtrsim 20J$, the relation is rigorously exponential and can be described by a single decay constant. Thus in spin-echo experiments geminal coupling may be neglected only at high rates of exchange. In particular, for cyclohexane, which is an A_6B_6 system, $J_{HH} = 12.6$ Hz,[34] and therefore the semiclassical approach may be employed here at rates of inversion $k > 1/200$ s^{-1}. All these results have been qualitatively confirmed in spin-echo experiments with 1,1-difluorocyclohexane[31].

Gutowsky et al.[29] also developed a general theory of the effect of rates of exchange on the spin-echo signal amplitudes based on the formal matrix approach of Anderson and Weiss[35-37]. Among the series of interesting consequences

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† For transient processes, see Ref. 6, p. 61.

‡ It is assumed that the transverse relaxation times for positions A and B are equal.

of this treatment, the authors demonstrated an analogy between the exchange effects and the quadrupole spin–lattice relaxation effects and showed that in principle quadrupole relaxation times may be measured by spin-echo methods§.

5. Accuracy of the Determination of the Rate Constant by Different NMR Methods

When a particular method is employed, it is necessary to bear in mind the resulting accuracy in the determination of the rate constant and then in the thermodynamic parameters of the system. Frequently, as experimental data accumulated, it became clear that many NMR methods probably involve serious systematic errors. The determination of the barrier to the hindered rotation of NN-dimethylformamide constitutes a striking example; its estimates vary from 7 to 24 kcal $mole^{-1}$,[23] while the experimental error quoted in each case does not exceed 1 kcal $mole^{-1}$.

Apart from the purely experimental errors (instability of the field, incorrect calibration, inaccuracies in temperature measurement), systematic errors can arise as a result of an incorrect choice of the model for the description of the real system. The simple semiclassical model for an AB system with $J = 0$ [7,9,13] becomes inapplicable in more complex cases where it is necessary to estimate the rate from equations for a system with $J \neq 0$.[19,20,39] However, even if the application of the semiclassical model is justified, usually further simplifications are made in order to obtain analytical relations and to employ readily available parameters: differences between the chemical shifts, intensity ratios, and line widths.

High-resolution NMR methods permit the measurement of the rate constant within very narrow ranges. The least accurate is the widely used method for the determination of the rate constants based on the merging of the signals at the coalescence temperature. In the first place the coalescence temperature cannot be determined with sufficient accuracy. This method yields no information about the process kinetics unless one assumes that Eyring's pre-exponential factor may be used and a transmission coefficient of unity is adopted.

The methods for the determination of τ from the change in the chemical shift and the intensity ratio are suitable only for low rates of exchange at temperatures below the coalescence point. Usually $\delta\omega_e$ is small and varies within a narrow temperature range; for example, for cyclohexane appreciable changes in $\delta\omega_e$ are observed between 64° and 72°C, i.e. over a range of only 6 deg. In order to increase $\delta\omega$, it is necessary to employ spectrometers with a higher field strength. $\delta\omega_\infty$ must be measured fairly accurately; a 10% error in the measurement of $\delta\omega_\infty$ leads to a much greater error in the thermodynamic parameters. A high accuracy in the measurements of $\delta\omega_e$ is also necessary, particularly when $\delta\omega_e$ approaches $\delta\omega_\infty$, i.e. in the region where $\delta\omega$ is already relatively insensitive to changes in temperature. Moreover, there is a possibility of a temperature variation of $\delta\omega_\infty$,[26,40] and failure to take this into account must lead to an additional systematic error in the determination of the rate of inversion. For very low rates of exchange, Eqn. (3) leads to large errors in the determination of τ and may not be used[16].

Allerhand, Gutowsky, and coworkers[41] analysed Eqns. (3) and (5) and showed that they yield high values of the rates, the error depending on the ratios of three parameters: $\delta\omega$, $1/\tau$, and the transverse relaxation time T_2^0. In particular, when Eqn. (3) is used, the error for a chosen pair of values of $\delta\omega$ and $1/\tau$ increases as T_2^0 falls.

Since both methods yield rate constants over a limited range of temperatures, small systematic errors in the measurement of τ may lead to considerably greater errors in the activation parameters. To extend the range of measured rates, the relation between line width and τ is employed in high-resolution methods at temperatures above the coalescence point. Here the inaccuracies may be attributed to the employment of temperatures close to the coalescence point of approximation (6), which is suitable only for very high rates of exchange[41]. However, it is precisely in the range of temperatures close to T_C that the contribution of the "exchange term" is most significant. In this case one may employ a more general expression for line width[10,40]. With increase in the rate, the contribution of the exchange term becomes extremely small and approaches the experimental error in the determination of line widths. In practice such a limiting value of the broadening due to exchange amounts to 0.05 Hz. Evidently, for systems which are not very complex, the most reliable values of τ may be obtained by complete calculation of the outline of the spectrum for various values of τ and subsequent comparison with the experimental spectra[21,22].

The spin-echo method developed by Gutowsky, Allerhand, and coworkers has a fundamental advantage: it permits the determination of the rates of exchange over a much wider range than high-resolution NMR methods. In particular, this applies to the region of high rates, where (for specified values of $\delta\omega$ and T_2^0) the maximum measurable rate depends on the accuracy with which it is possible to determine T_2^0/T_2 when this quantity tends to unity. In this case the limit of the possible errors in τ measured by the spin-echo method is

$$^1/_2\tau \leqslant p_A p_B T_2^0 (\delta\omega)^2 \, . \tag{15}$$

Such rates of exchange are not measurable by high-resolution NMR methods. The most favourable situation for measurement by the spin-echo method obtains in the case where the transverse relaxation time of the test substance is high, as, for example, in $C_6D_{11}H$ ($T_2^0 = 10$ s at $-100°$ and 85 s at 25°C). The spin-echo method permits the investigation of the ring inversion of deuterocyclohexane in the range where the rate varies by five powers of ten[30]: from 0.5 s^{-1} to 4×10^4 s^{-1}, extending thereby the range of attainable τ by a factor of more than 50. These data were obtained by Allerhand, Chen, and Gutowsky on a 24 MHz spectrometer. Evidently, by employing spectrometers with a higher field strength, the range of rate constants may be extended further by a factor of several units. The accuracy of the determination of τ by spin-echo methods does not exceed the accuracy of the high-resolution NMR method (10–20%), but, since τ is measured over a much wider range, the thermodynamic parameters obtained should be more reliable.

Spin-echo measurements have yet another advantage: they permit the determination at the same time of $\delta\omega$ and T_2^0, and $\delta\omega$ may be obtained at high rates of exchange for which high-resolution NMR spectroscopy is inapplicable.

Despite its undoubted advantages, the spin-echo method is comparatively rarely used to determine the rates of exchange. To a large extent, this is because the method has been developed quite recently. It requires additional

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§ Powles and Strange[38] examined approximately the determination of the rate of intermolecular exchange for an AB system from spin-echo experiments.

apparatus, which has only now begun to be produced commercially outside the USSR and is more time-consuming than high-resolution NMR methods. The interpretation of the results is laborious and requires special programs and considerable machine time. Probably spin-echo measurements also include some phenomenological errors the source of which is as yet obscure. The point is that these measurements tend to yield high values for $\delta\omega$. Thus low-temperature NMR spectra yield $\delta\omega = 0.48$ p.p.m. for $C_6D_{11}H$[12,42,43] and $C_6D_8H_3$,[44] while the value obtained from spin-echo results for the same temperatures is higher by approximately 30%. In the study of 1,1-difluorocyclohexane[31] by the spin-echo method it was necessary to adopt $\delta\omega = 18.5$ p.p.m.; the value $\delta\omega = 15.6$ p.p.m., determined from low-temperature NMR spectra[22], gave a poor agreement between the results. The possible reasons for these discrepancies have been discussed[29]. The inconsistency is probably associated with the fact that the approximation in which the decay of the echo signal amplitudes is described by a single constant T_2 becomes inapplicable and it is necessary to take into account the pseudoexponential terms.

III. ENERGY PARAMETERS OF THE INVERSION OF CYCLIC COMPOUNDS

1. Cyclohexane

The classical model for the investigation of ring inversion by NMR spectroscopy is cyclohexane. The interest in this molecule is due, on the one hand, to the fact that it occupies a central place in the theory of conformational analysis. On the other hand, the rates of inversion of cyclohexane are in a favourable range and therefore it is frequently used to test a particular method.

Cyclohexane and its derivatives have been investigated by all the NMR spectroscopic methods developed hitherto (Table 1). At the coalescence temperature and below the

Table 1. Thermodynamic parameters of ring inversion in cyclic compounds.

No.	Compound	$\Delta H^{\neq}$ (E_a), kcal mole^{-1}	$\Delta F^{\neq}$ (°C) kcal mole^{-1}	ΔS e.u.	Solvent	Method	Refs.
1	Cyclohexane	11.5±0.2[1]	10.1±0.1 (−67)	—	CS_2	*b*	45
2	Cyclohexane	9.0±0.2	10.6 (−67)	−7.9[2]	CS_2	*d*, *e*[3]	46
3	Cyclohexane	11.5	10.7 (−67)	+4.0[4]	CS_2		47
4	Cyclohexane (C_6HD_{11})	10.9±0.6 (11.3)	10.3 (−67)	+2.9±2.3	CS_2	*b*, *e*	42
5	Cyclohexane (C_6HD_{11})	10.5±0.5	10.2 (−67)	+1.4±1.0	CS_2	*c*, *e*	12,43
6	Cyclohexane	9.1±0.5 (9.5)	10.3 (−68)	−5.8±2.4	CS_2	*f*	30
7	Cyclohexane (C_6HD_{11})	9.1±0.1 (9.5)	10.3 (−68)	−5.8±0.4	CS_2	*f*	30
8	Cyclohexane	10.8	10.2	+2.8[4]	CS_2	*d*, *g*, *i*	25
9	Fluorocyclohexane	9.6±0.4	9.7 (−57)	−0.8±0.5	$CFCl_3$	*d*, *e*	48
10	Chlorocyclohexane	—	10.5	—	CS_2	*a*	49
11	Chlorocyclohexane	—	11.7 (−65)	—	CS_2	*a*	50
12	Bromocyclohexane	—	10.8	—	CS_2	*a*	49
13	Bromocyclohexane	—	11.7 (−65)	—	CS_2	*a*	50
14	Iodocyclohexane	—	11.7 (−65)	—	CS_2	*a*	50
15	Cyclohexanol	—	11.7	—	CS_2	*a*	50
16	3,3,5,5-Tetradeutero-1,1-dimethylcyclohexane	—	10.4 (−60)	—	CS_2	*a*	51
17	*trans*-1,2-Dichlorocyclohexane	—	11.9 (−45)	—	CS_2	*a*	52
18	*trans*-1,2-Dibromocyclohexane	—	11.8 (−45)	—	CS_2	*a*	52
19	*trans*-1,3-dichlorocyclohexane	—	9.8 (−79)	—	CS_2	*a*	53
20	*trans*-1,3-Dibromocyclohexane	—	9.9 (−79)	—	CS_2	*a*	53
21	1,1-Difluorocyclohexane	10.4 (10.9)	9.7[5]	+3.0±2	propene	*g*[6]	54
22	1,1-Difluorocyclohexane	9.04 (9.5)	9.8 (−46)	−3.3	CS_2	*g*[7]	22
23	Ditto	8.6 (9.1)	9.8 (−46)	−5.0	$CFCl_3$	*g*[7]	22
24	"	9.4 (9.8)	9.5	−0.6	CS_2	*f*	31
25	1,1,4,4-Tetramethylcyclohexane	—	11.6 (−53)	—	CS_2	*a*	51
26	Ditto	13.3 (13.7)	11.4	+9.1	CS_2	*c*, *d*	55
27	6,6-Dimethoxy-1,1-dimethylcyclohexane	—	11.0 (−70)	—	CS_2	*a*	51
28	1,1,4,4-Tetramethylcyclohexane	8.6±1.2	10.5±0.4[4]	−9.5±6[4]	toluene	*g*	56
29	1,1-Difluoro-4,4-dimethylcyclohexane	8.9[5] (9.4)	10.2[5]	−5.4±2	propene	*g*[6]	54
30	1,1-Difluoro-4-ethyl-4-methylcyclohexane	7.92[5] 8.4	9.84[5]	−8.3±2	propene	*g*[6]	54
31	1,1,2,2-Tetrafluorocyclohexane	7.51[5] (8.0)	10.87[5]	−13.6±2	propene	*g*[6]	54
32	4-chloro-1,1-difluorocyclohexane	10.79[5]	10.21[5]	+2.5±1	propene	*g*[6]	54
33	Perfluorocyclohexane	7.5±0.3	9.9 (−66.5)	—	CCl_3F	*d*, *e*	57
			10.9 (+25)	−10.7	$C_6H_5CF_3$	*d*, *e*	57
34	Ditto	9.9±0.2 (10.5)	11.2	−4.4	liquid, isopentane	*f*	58
35	Isomers of fully acetylated inositol						
	cis-	6.6	15.4 (+18)	−30.1	$CHCl_3$	*b*	59
36	*allo*-	5.5	12.6 (−34)	−29.6	$CHCl_3$	*b*	
37	*muco*-	4.7	10.5 (−77)	−29.2	$CHCl_3$	*b*	59
38	Cyclohexene	5.3	5.3 (−164)	0[8] 1.3[9]	CF_3Br	*a*	60
39	4-Bromocyclohexene	6.1	5.9±0.1 (−148)	+1.4	$CD_2{=}CDCl$	*b*	61
40	1,1-Difluoro-4,4-dimethylcycloheptane	(6)	—	—		*f*	62
41	Cyclo-octane	—	7.8 (−64)	+0.3	CS_2	*f*	47
			7.8 (−110)	−5.7	CF_2Cl_2	*f*	47
42	Cyclo-octane	7.7±0.3	8.1 (−115)	−4.4	$CCl_2{=}CHCl$	*b*, *e*	63
43	Cyclo-octatetraene	13.7	13.7 (−10)	0	CS_2	*a*	64
44	Fluoro-cyclo-octatetraene	—	12.0 (−33)	—	CS_2	*a*	65
45	2,3,4,5,6,7-Hexadeutero-cyclo-octatetraenyldimethylmethanol	15.4	17.4 (+41)	−6.3	CCl_4	*b*	66
46	2,3,4,5,6,7-Hexadeuteroethylcyclooctatetraene carboxylate	12.8	15.3 (+40)	−8.0	CCl_4	*b*	66
47	*cis*-1,2-Dibromocyclooctatriene	—	13.0 (−16)	—	$CDCl_3$	*a*	67
48	3,5,7-cyclooctatrienone	11.9	—	—	CS_2	*g*	68
49	*cis*-Hydrindane	—	6.4 (−133)	—	CS_2	*a*	69
50	2,2-Difluoro-*cis*-decalin	15.0±0.9	12.3	8±5	acetone	*g*	70
51	1,1,3,3-Tetradeutero-2,2-difluoro-*cis*-decalin	13.4±0.8	12.4	2±3	propene	*g*	70
52	2,2-Difluoro-9-methyl-*cis*-decalin	9.1±0.6	12.1	−13±3	propene	*g*	70
53	2,2-Difluoro-10-methyl-*cis*-decalin	10.6±0.6	12.8	−10±3	acetone	*g*	70

Table 1 (contd.).

No.	Compound	$\Delta H^{\neq}$ (E_a), kcal mole^{-1}	$\Delta F^{\neq}$ (°C), kcal mole^{-1}	ΔS e.u.	Solvent	Method	Refs.
54	9-Ethyl-2,2-difluoro-*cis*-decalin	9.5±0.5	11.8	−11±4	acetone	*g*	70
55	Pentamethylene sulphoxide	—	14.2 (−70)	—	CH_2Cl_2	*a*	71
56	Pentamethylene sulphone	—	14.9 (−63)	—	CH_2Cl_2	*a*	71
57	Tetrahydrothiopyran	—	11.6 (−93)	—	CH_2Cl_2	*a*	71
58	Tetrahydropyran	—	10.7 (−80)	—	CD_3OD	*a*	71
59	Piperidine	—	14.5 (−63)	—	CD_3OD	*a*	71
60	3,3,5,5-Tetradeuteropiperidine	(14.5)	—	—	CH_3OH	*g*	72
61	Tetradeutero-*N*-methylpiperidine	(14.4)	—	—	CH_2OH	*g*	72
62	Tetradeutero-*N*-t-butylpiperidine	(14.0)	—	—	CH_3OH	*g*	72
63	Perfluoropiperidine	5.7±1.5	8.9 (−67)	−15.5	$CFCl_3$		73
64	4,4,5,5-Tetradeutero-1,2-dithiane	11.5	11.7	0	CS_2		71
65	Ditto	—	11.6 (−43)	—	CS_2	*a*	74 75
66	3,3,6,6-Tetramethyl-1,2-dithiane	15.6 (16.1)	13.8 (−2)	+6.7	CS_2	*b*	75
67	4,5-*cis*-Di-acetoxy-1,2-dithiane	12.0	13.9 (−8)	−7.2	CS_2		71
68	1,3-Dithiane	—	9.4 (−80)	—	CS_2	*a*	76
69	5,5-Dimethyl-1,3-dithiane	—	10.3 (−70)	—	CS_2	*a*	76
70	2,2-Dimethyl-1,3-dithiane	11.2	9.8 (−80)	—	CS_2	*a*	76
71	1,3-Dioxane	—	9.7 (−82)	—	acetone	*a*	76
72	1,3-Dioxane	10.2±1.0	9.0 (−73)	+6±5	acetone	*d*	77
73	2,2-Dimethyl-1,3-dioxane	6.3	7.8 (−73)	−7	CCl_2F_2	*d*	77
74	5,5-Dimethyl-1,3-dioxane	12.4±0.8	10.5 (−73)	+9±4	acetone	*d*	77
75	2,2,5,5-Tetramethyl-1,3-dioxane	9.1±0.9	8.2 (−73)	+4±5	acetone	*d*	77
76	5,6-Dimethyl-1,3-dioxane	12.8±2	11.2 (−50)	+7.3	acetone	*a*	76
77	2,2-Dimethyl-1,3-dioxane	—	<8.0	—	acetone	*a*	76
78	3,3,6,6-Tetramethyl-1,2-dioxane	17.9 (18.5)	14.6 (+12)	+14.4	CS_2	*a*, *b*	75
79	3,3,6,6-Tetramethyl-1,2-dioxane	(11.7)	—	—	CH_2Cl_2		78
80	*N*-Methylmorpholine	—	11.5 (−31)	—	CH_2Cl_2	*a*	79
81	*NN*-Dimethylpiperazine	—	12.6 (−8.5)	—	CH_2Cl_2	*a*	79
82	*NN*-Dimethylpiperazine	—	13.0	—	CH_2Cl_2	*d*, *e*	80
83	*NNN′N′*-Tetramethylpiperazine dichloride	9.3±1.2	12.9[4] (0)	−13.5±5.6	CS_2	*g*	56
84	Tetramethyl-*s*-tetrathiane	—	16.1±1 (+50)	—		*a*	81
85	Acetone diperoxide	11.7	15.4 (+29)	−12.1	CS_2	*c*, *d*	55
86	Acetone diperoxide	12.3	15.4 (+29)	−12.1	$CDCl_3$	*b*	82
87	2,3-Diazabicyclo[2,2,1]hept-5-ene	16.9±0.6 16.2±0.8	14.5±0.2 (−9) 13.9±0.2 (−5)	+8.3±2.1 +7.6±2.6	$CDCl_3$ pentane	*b*, *d* *b*, *d*	83 83
88	2,3-Diazabicyclo[2,2,1]-heptane	14.8±0.5 15.7±1.0	13.0±0.2 (−9) 12.6±0.4 (−5)	+6.0±2.0 +11.5±4	$CDCl_3$ pentane	*b*, *d* *b*, *d*	83
89	2,3-Diazabicyclo[2,2,2]-octane	14.9±0.8 12.4±0.6	12.2±0.2 (−9) 11.8±0.3 (−5)	+10.0±3 +2.8±2.5	$CDCl_3$ pentane	*b*, *d* *b*, *d*	83 83
90	Dimethyl 3,6-diphenyltetrahydropyridazine-1,2-dicarboxylate	16.4±1	18.5 (97)	−7±3		*d*	84
91	Diethyl ester of above acid	—	18.5 (95)	—	pentane	*a*	84
92	Dimethyl 4,5-dimethyltetrahydropyridazine-1,2-dicarboxylate	—	19.7 (123)	—	pentane	*a*	84
93	Diethyl ester of above acid	—	20.3 (133,5)	—		*a*	84
94	Dimethyl 3,6-diphenylpiperidazinedicarboxylate	15.6±1	16.7±0.3 (55)	[illegible]±3		*d*	84
95	Dimethyl 4,5-dimethylpiperidazinedicarboxylate	—	19.4±0.4 (74)	—		*a*	84
96	*N*-Methylhexahydro-1,3,5-triazine	14.2±1.5	12.6±0.1 (0)	2.2±5.5	pentane	*g*	85
97	*N*-Ethylhexahydro-1,3,5-triazine	12.1±0.8	11.9±0.1 (0)	−3.4±2.9	pentane	*g*	85
98	*N*-Isopropylhexahydro-1,3,5-triazine	11.3±1.1	10.8±0.1 (0)	−2.6±4.0	pentane	*g*	85
99	*N*-t-Butylhexahydro-1,3,5-triazine	10.8±0.7	10.2±0.1 (0)	−1.8±2.6	pentane	*g*	85
100	1,3,5-Trimethylhexahydro-1,3,5-triazine	15.2±0.2 (15.7)	13.2±0.2 (−6)	7.5	$CHFCl_2$ $CDCl_3$	*g* *g*	86
101	1-Methylaziridine	(19)	—	—	liquid	*b*	87
102	1-Methyl-2,2-dimethyaziridine	(6.8±0.7) (7.8±0.8) (10.0±1.0)	— — —	— — —	CH_3OH CCl_4 liquid	*e* *e* *e*	88 88 88
103	1-Methyl-2-methylene-aziridine	(6.4±0.6)	—	—	liquid	*e*	88
104	1-Phenylaziridine	—	12.8 (−40)	—	CS_2	*a*	89
105	1-Methanesulphonylaziridine	—	14.0 (−25)	—	$CDCl_3$	*a*	89
106	*NN*-Dimethylcarbamoylaziridine	—	10.8 (−86)		$CH_2{=}CHCl$	*a*	89
107	1-Methoxycarbonylaziridine	—	7.6 (−138)	—	$CH_2{=}CHCl$	*a*	89
108	1-Phenylsulphonylaziridine	10.9±2	10.0±0.1	3.6±6	$CDCl_3$	*d*	90

Remarks. Designation of methods: (*a*) from coalescence temperature; (*b*) from temperature variation; (*c*) from intensity ratio *r*; (*d*) from signal width in high-resolution spectra; (*e*) from signal width in rapid sweep method; (*f*) spin-echo method; (*g*) total calculation of spectrum; (*i*) double-resonance method; +—approximate estimate.

[1] Erroneous value; according to Jensen et al.[45], the value should be $\Delta H = 5.9$ kcal mole^{-1}.

[2] For chair–chair ring inversion. [3] At 40 MHz. [4] Chair–boat. [5] Value averaged with respect to the temperature range investigated. [6] Calculation by Alexander's method[20]. [7] Calculation for case AB.[20] [8] For half-chair–half-chair inversion. [9] For half-chair–boat inversion.

cyclohexane (C_6H_{12}) spectrum consists of a twelve-spin system, is extremely complex, and cannot be approximated by a simple doublet[45] or quartet[46]. However, these difficulties are eliminated when deuterated derivatives are employed[12,25,30,42]. At low temperatures the $C_6D_{11}H$ spectrum consists of two broad lines of equal intensity; the signal width may be greatly reduced with the aid of H–D double resonance[25,42,43]. With increase of temperature, the signals become broader and merge at the coalescence temperature (−61.4°C), above which a single narrow line is observed (Fig. 1).

If the rate constant is determined for a number of temperatures, the thermodynamic parameters of the inversion process may be obtained from the usual relations:

$$k = \frac{kT}{h}\exp(\Delta S^{\neq}/R)\exp(-\Delta H^{\neq}RT)\,, \qquad (16)$$

$$\Delta H^{\neq} = -R(\partial \ln k/\partial T^{-1})_p - RT\,, \qquad (17)$$

$$\Delta S'^{\neq} = (\Delta H^{\neq} - \Delta F^{\neq})/T\,, \qquad (18)$$

$$k = {}^1/_2\tau = A\exp(-E_a/RT)\,. \qquad (19)$$

The data in Table 1 show that the Gibbs free energies of activation for the inversion of cyclohexane agree to within 0.2 kcal mole^{-1} in six cases out of seven[¶], while the values of $\Delta H^{\neq}$ and $\Delta S^{\neq}$ differ significantly. Only the parameters obtained by high-resolution methods agree satisfactorily[25,42,43]. The ring inversion of cyclohexane has been investigated over the widest temperature range by the spin-echo method[30], which should apparently have yielded the most accurate values of the energy parameters. However, the results of Allerhand, Chen, and Gutowsky do not agree with the results from high-resolution spectra[†], the differences being illustrated in Fig. 2.

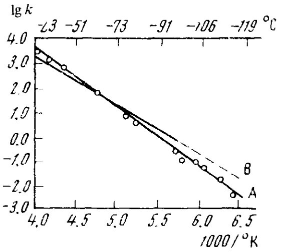

Figure 2. Temperature variation of the rate constant for ring inversion in cyclohexane determined by high-resolution (B) and spin-echo (A) methods[46].

The discrepancies are evidently associated with large systematic errors in the determination of the temperature variation of the rate constant. There are particularly large differences in the entropies found by different workers: they vary from +4.9 to −6.5 e.u. These results show that the experimental values of $\Delta S^{\neq}$ must be treated with caution in a discussion of the mechanism of ring inversion and the structure of the molecule in the transition state. In a number of studies attempts were made to estimate the entropy on the basis of the possible symmetry of the intermediate form[12,46,98]. If the rotational and vibrational contributions are neglected, such estimates may be made either by taking into account the symmetry numbers σ and the statistical weight w,[12,46] or by calculating directly the number of possible ways in which one form can be converted into another[25,98]. If the half-chair form is adopted for the intermediate state, the number of such ways is six and $S = R \ln n = 3.6$ e.u. Calculation from the expression $\Delta S = R \ln(w^{\neq}/w)\,(\sigma/\sigma^{\neq})$ also yields a positive entropy[98]. Harris[‡] pointed out that the entropies can be negative only when the intermediate state has a planar shape in the ring inversion process. However, according to calculations[99], the energy of this state should be of the order of 30 kcal mole^{-1}. The agreement between the ΔS values predicted on the basis of symmetry and the experimental data from high-resolution spectra[25,42,43] may be evidence of a high reliability of the latter.

Recently computational methods have been widely used for the investigation of the conformations of cyclic compounds[99-104]. They are based on the calculation of the energy of the molecule by classical methods for specified potential functions, taking into account mainly the extension of the bonds, the deformation of valence angles, the torsional strain, and the interaction of atoms not linked by valence bonds. Cyclohexane was investigated in greatest detail by Hendrickson[99,104]. Fig. 3, taken from Hendrickson's paper[104], shows the geometry of the intermediate states in the chair–boat inversion of the symmetrical forms. The boat–skew boat conversion is achieved by a pseudorotation the potential barriers for which are low, in contrast to the barriers in symmetrical transitions. Hendrickson obtained the following values for the barriers in the transitions: chair–chair 11.0 kcal mole^{-1}, chair–boat 6.4 kcal mole^{-1}, and chair–twist-boat 5.6 kcal mole^{-1}. Evidently all the calculated values agree very well with experiment.

It is noteworthy that in all the conformational calculations for cycloalkanes a considerable improvement is achieved when the valence angles corresponding to minimum strain are assumed to be not tetrahedral but 112°,[102-104] which agrees with the latest electron diffraction data for cyclohexane[105] and certain cycloalkanes[106].

2. Cyclohexene

Compared with cyclohexane, the ring inversion of cyclohexene and its conformations have been investigated in much less detail. Nevertheless the conformational studies on these molecules are just as important, since the cyclohexene ring is included in a large number of natural compounds and determines their structure to a great extent.

The geometry of the cyclohexene ring is determined to a considerable degree by the presence of a double bond: four carbon atoms must be located in one plane. As a result, cyclohexene can adopt the form either of a half-chair or a boat (Fig. 4). Thermodynamic calculations showed that[107] the boat form is less stable to the extent of 2.7 kcal mole^{-1} than the half-chair. However, the valence angles of the trigonal and tetrahedral carbon atoms in both conformations must be distorted. Corey and Sneen[108] determined by vector analysis the cyclohexane (half-chair) model for which the simultaneous distortion of all the valence angles is a minimum. A similar determination was made by Boucourt and Hainaut[109], who suggested that 112° be adopted for all the tetrahedral angles in cyclohexene.

Many experimental data now show that cyclohexene and some of its derivatives exist in the half-chair conformation[110-114]. The frequencies of the skeletal vibrations and the CH vibrations in the infrared and Raman spectra of gaseous, liquid and solid cyclohexene also agree better with the half-chair form[115].

[¶] It is interesting to compare the parameters of the ring inversion of cyclohexane obtained from NMR spectra with data derived by other methods. The first estimates of the height of the barrier in cyclohexane varied from 10 to 14 kcal mole^{-1}.[91,92] Later direct measurements of the decay of ultrasound yielded 8.3 kcal mole^{-1} [93] and 10.8 kcal mole^{-1}.[94] The following values have been obtained for the energy of the labile intermediate form, which cannot be estimated directly from NMR spectra: 5.9 kcal mole^{-1},[95] 5.5 kcal mole^{-1},[96] and 4.8 kcal mole^{-1}.[97]

[†] The spin-echo results agree with those of Harris and Sheppard[46], who also determined the rate constants over a fairly wide temperature range. However, subsequently Harris and Sheppard[98] reinterpreted their measurements in a different way and obtained $H = 10.3$ kcal mole^{-1}, in agreement with the enthalpies found by Anet and coworkers[25,42].

[‡] Ref. 40 in the paper of Bovey et al.[48]

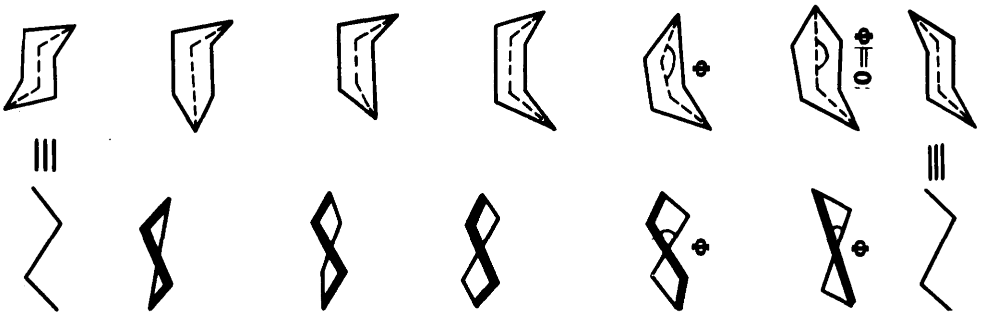

Figure 3. Intermediate states in the symmetrical ring inversion of cyclohexane[104].

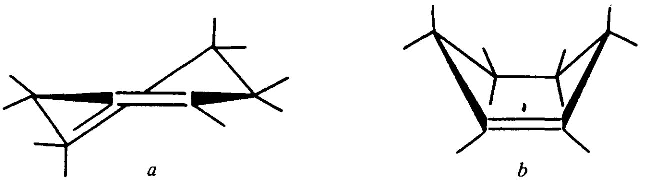

Figure 4. Cyclohexene conformations: *a*) half-chair; *b*) boat.

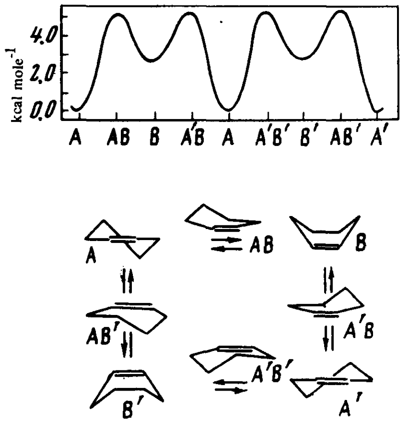

Figure 5. Intermediate forms and the energy barrier in the ring inversion of cyclohexene[60].

As for cyclohexane, one conformer of cyclohexene may be converted into another. Until recently, the rate of conversion and the potential barrier separating the conformers were unknown. It might have been supposed that, in view of the characteristics of the structure of cyclohexene, the half-chair—half-chair conversion would be much faster than the chair—chair conversion. Recently Anet and Hag[60] showed that the rate of inversion of cyclohexene approaches the upper limit accessible to NMR methods. At room temperature the NMR spectrum of cyclohexene shows the signal due to the olefin protons (5.59δ) and the complex multiplets of the allylic (1.96δ) and homoallylic (1.65δ) protons[116]. Anet and Hag[60] investigated *cis*-3,3,4,5,6,6-hexadeuterocyclohexene. At −150°C the band due to the homoallylic protons is significantly split and becomes a doublet at −164°C. Since at −170°C δ_{a-e} does not yet reach a constant value, it may be supposed that δ_{a-e} for cyclohexene is actually 24 Hz§.[60] The rate constant determined from the coalescence temperature of the signals is $k = 53$ s^{-1}, whence the free energy of activation $\Delta F^{\neq} = 5.3$ kcal mole^{-1}. Thus in cyclohexene the height of the barrier in the ring inversion process is smaller by a factor of approximately two than in cyclohexane. Since the energy of the boat form is higher than that of the half-chair form[107], it may be supposed that the boat form is intermediate in the inversion process. The possible pathways in the inversion process and the corresponding forms of the barrier proposed by Anet and Hag[60] are presented in Fig. 5. The authors adopted a structure with five carbon atoms in one plane (AB, AB′, A′B′) as the transition state, since the distortion of the valence angles and the interaction between methylene groups would be too high for the completely planar form. The enthalpy and entropy of activation for the inversion process cannot be determined directly from the NMR spectroscopic data[60]. The values quoted in Table 1 were obtained by taking into account the symmetry of the possible transition states and the statistical factors. The average lifetime of the cyclohexene molecule before inversion at 25°C may be calculated from $\Delta H^{\neq}$ and $\Delta S^{\neq}$. It proved to be about 10^{-9} s, i.e. smaller by five powers of ten than the lifetime of the cyclohexane molecule (4×10^{-4}).

Apart from unsubstituted cyclohexene, the inversion of 4-bromocyclohexene was also investigated[61]. At −159°C Jensen and Buchweller[61] observed a complete separation of the signals due to the tertiary proton corresponding to the axial and equatorial orientations with $\delta_{a-e} = 27.3$ Hz. The rate constant ($k = 47.7$ s at −124°C) and the height of the barrier ($\Delta F^{\neq} = 5.93 \pm 0.1$ kcal mole^{-1}) obtained by these investigators are very close to the corresponding values for unsubstituted cyclohexene. Jensen and Buchweller also determined the conformational energy of bromine in the cyclohexene ring (about 0.1 kcal mole^{-1}), which proved to be smaller almost by a factor of four than the energy of the substituent in cyclohexane. This result is in qualitative agreement with Sakashita's data obtained

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§ The assignment of the signal in the weak field to an equatorial proton and that in the strong field to an axial proton was made by analogy with cyclohexane. It has been confirmed by the study of the ring inversion of 4-bromocyclohexene[61].

from vibrational spectra[117]. In practice, however, the values determined both from the vibrational spectra and NMR spectra are smaller than the experimental errors and therefore one may suppose that in 4-bromocyclohexene the axial form has no advantage over the equatorial form on energy grounds. However, the axial form of 3-halogenocyclohexenes is probably more favourable[118].

In a number of studies attempts were made to determine the preferred conformations of cyclohexene derivatives from the widths of the NMR signals[119-121]. Some information about the geometrical structure of the cyclohexene ring can be derived also from the vicinal coupling constants. The values of J_{HH} were determined for three cyclohexene derivatives[122-124]. The dihedral angles for the half-chair forms of conduritols[124] were calculated from the Karplus equation and compared with the values determined from Barton's models[123,125] and calculated by Corey and Sneen[108]. All three methods give similar valence angles, but these are only approximate.

The long-range coupling constants for allylic ($J_{He'}$ = −0.5 Hz, $J_{Ha'}$ = −2.1 Hz) and homoallylic (J = 1−3 Hz) protons have been determined[122-124] and interaction via four saturated bonds (about 0.5−2 Hz) has been observed.

3. Cyclobutane

In the crystalline phase certain cyclobutane derivatives (tetraphenylcyclobutane[126] and *trans*-1,3-cyclobutanedicarboxylic acid[127]) have a planar ring structure but, according to electron diffraction, cyclobutane itself is non-planar[128]. NMR spectroscopic studies have shown[129] that the cyclobutane molecule undergoes interconversion between two equivalent forms (Fig. 6), in which the orientation of the substituent may be referred to as axial or equatorial by analogy with the nomenclature for six-membered rings; the structure with a pseudoaxial substituent is more planar. According to the estimates of Meiboom and Snyder[129], the dihedral angle θ is 18°.

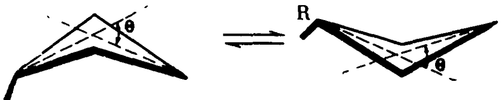

Figure 6. Ring inversion in cyclobutane.

The barrier in the ring inversion of cyclobutane is probably low, but has not been estimated experimentally at present¶. However, the chemical shift and the coupling constants of the signals due to geminal fluorine-19 nuclei[130] in the NMR spectra of certain fluorinated cyclobutane derivatives, used to calculate the free energy differences between the two conformers, were found to vary with temperature. For R = C_6H_5, this difference is about 1 kcal mole^{-1}, which is consistent, as regards order of magnitude, with the value calculated by Allinger et al.[102] Allinger's calculations also showed that the buckled form is more favourable than the planar form to the extent of about 1 kcal mole^{-1} and yields the angle θ = 20°.

The NMR spectra of 3-isopropylcyclobutanols and 3-isopropylcyclobutylamines[131] are also consistent with the non-planar structure of the cyclobutane ring.

4. Cycloheptane

The cycloheptane molecule does not have a highly symmetrical form analogous to the chair form of cyclohexane. The four conformations of cycloheptane with the minimum energy, the geometry of which was calculated by Hendrickson[104], are shown in Fig. 7. The most stable is the twist-chair form. As in the boat form of cyclohexane, which can be converted into a series of twist-boat forms by pseudorotation, in cycloheptanes pseudorotation can take place for the chair−twist-chair and boat−twist-boat conformations. The boat and chair conformations can be interconverted by symmetrical inversion. The barrier to pseudorotation is represented by a simple sinusoidal curve, the symmetrical forms corresponding to its maxima and minima. The energy differences in pseudorotation are small and cannot be estimated from the NMR spectra.

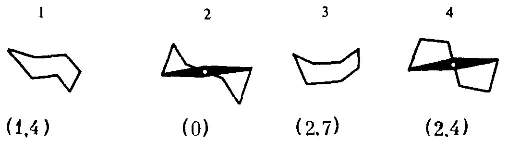

Figure 7. Stable conformations of cycloheptane: 1) chair; 2) twist-chair; 3) boat; 4) twist-boat; the relative energies are indicated in brackets[104].

The ring inversions in a number of substituted cycloheptanes were investigated by Roberts using the resonance of the fluorine-19 nuclei[62]. The fact that the spectra of 1,1-difluorocycloheptane and 1,1,3,3-tetrafluorocycloheptane do not show a temperature variation up to −180°C agrees best with the existence of cycloheptane in the twist-chair form, which undergoes rapid pseudorotation. At the same time the spectrum of 1,1-difluoro-4,4-dimethylcycloheptane does alter significantly as the temperature is reduced. On the basis of these changes, one may conclude that fluorine atoms are present in positions resembling equatorial and axial positions. The barrier to the interconversion of the two forms (or two sets of equivalent forms) is low and amounts to 6 kcal mole^{-1} according to preliminary estimates[62].

5. Cyclo-octane

The ring inversion of cyclo-octane was investigated by Meiboom[47], Harris and Sheppard[46], and Anet and coworkers[68,133]. On lowering the temperature, the proton signal in the $C_8D_{15}H$ spectrum broadens and at −111 °C two

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¶ In oxetan, where as a result of the replacement of a methylene group by a heteroatom in the four-membered ring several 1,2- and 1,3-interactions are eliminated, the barrier in the ring inversion process is only 35 cm^{-1} according to the estimate of Chan et al.[132]

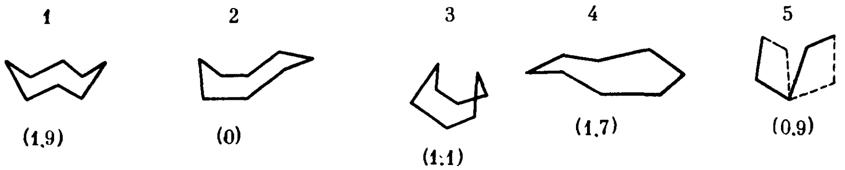

Figure 8. Cyclo-octane conformations with minimum energies: 1) chair–chair; 2) boat–chair; 3) boat–boat; 4) twist-chair–chair; 5) S_4; the relative energies are indicated in brackets[104].

sharp lines separated by about 19 Hz are observed[133]. The activation parameters for the inversion process were calculated from the temperature variation of the band outline (Table 1, Nos. 41 and 42). However, it is impossible to arrive at unambiguous conclusions concerning the nature of the conformations undergoing interconversion. From the conformational standpoint, cyclo-octane is probably the most complex cyclic molecule. Theoretical analysis shows[100,104] that there exist a large number of conformations of cyclo-octane with approximately the same energy. The boat-chair form (C_s symmetry) is probably the most favourable on energy grounds[100,104]. However, the energies of five other symmetrical forms are in the range of 2 kcal mole^{-1}: chair–chair (extended crown), boat–boat (saddle, symmetry D_{2d}), twist-chair–chair (D_2), twist-chair–boat, and the form with symmetry S_4 (Fig. 8). The regular crown form of cyclo-octane, in contrast to the "crown" of cyclohexane (chair), does not correspond to an energy minimum; according to Hendrickson's calculations[104], its energy is higher by 2.8 kcal mole^{-1} than the energy of the boat–chair form. The transitions between the cyclo-octane conformations can take place, apart from the interconversion of symmetrical forms, via a pseudorotation, the barriers to which are not high. Thus the signals in the NMR spectrum at a low temperature may correspond to a whole set of conformations, provided that pseudorotation is sufficiently rapid. By studying the temperature variation of the NMR spectra of three deutero-derivatives of cyclo-octane ($C_8D_{14}H_2$) and alkyl-substituted cyclo-octanes, Anet and St. Jacques[133] concluded that they agree best with the boat–chair form. X-Ray diffraction studies showed that many cyclo-octane derivatives have the same conformation[134]. However, in order to interpret the NMR spectra of fluorinated cyclo-octanes, Roberts[62] chose the S_4 form (twist-boat). Since the energy of the S_4 form differs only by 1 kcal mole^{-1} from that of the boat–chair form[104], the replacement of a hydrogen atom by a fluorine atom can shift the conformational equilibrium towards the S_4 form.

The cyclo-octane conformations were examined theoretically also by Bixon and Lifson[103] and Allinger et al.[102] In all these studies the energy minimum was obtained for the boat–chair form.

Recently ring inversion in eight-membered unsaturated systems was investigated by NMR spectroscopy: cyclo-octatetraene[64,66], fluorocyclo-octatetraene[65], cyclo-octatrienone[68], and substituted cyclo-octatriene[67].

In cyclo-octatetraene derivatives[64-66] bond displacement may occur as well as the interconversion of two boat forms (*t* and *b*, symmetry D_{2d}) (Fig. 9). The transition state for both processes is probably a planar form. Calculation of the barrier to the inversion of cyclo-octraene, taking into account the σ-strain of the system[69], yielded results in good agreement with experiment.

6. Decalin

An interesting example of complex systems undergoing ring inversion is provided by *cis*-decalin derivatives. While the NMR spectrum of *trans*-decalin, which has a fixed conformation, consists of a complex multiplet, in the *cis*-decalin spectrum there is a comparatively narrow singlet even at −120°C.[135,136] On this basis, it was initially suggested that the barrier to the ring inversion of *cis*-decalin is low, not exceeding 6 kcal mole^{-1}; however, recently it was suggested[137] that the low width of the signal may be due not to rapid ring inversion but to the similarity of the chemical shifts of the axial and equatorial protons.

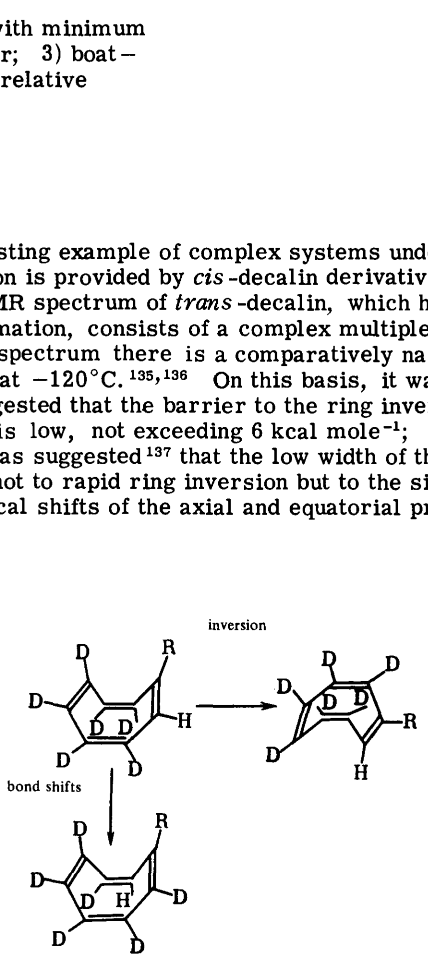

Figure 9. Ring inversion and bond shifts in cyclo-octatetraene[66].

The ring inversion of *cis*-decalin derivatives was investigated by Roberts[62,70] using fluorine-19 resonance. In the spectrum of 2,2-difluoro-*cis*-decalin two AB quartets, corresponding to the axial and equatorial positions of fluorine atoms, appear in place of the average signal when the temperature is reduced. The activation energy for the ring inversion proved to be somewhat higher than for cyclohexane (Table 1, No. 50). Since the bulk of the fluorine atoms is small, it may be supposed that in unsubstituted *cis*-decalin the inversion barrier is approximately the same. The introduction of a methyl group in the 9- or 10-position of 2,2-difluoro-*cis*-decalin results in a lowering of the barrier. This is apparently due to the fact that for both forms undergoing interconversion there is a *syn*-axial interaction of the methyl group with the fluorine atom.

The NMR spectra of 1-methyl-, 3-methyl-, 6-methyl-, and 6,9-dimethyl-*cis*-decalin do not show a temperature variation, in agreement with the existence of a single energetically favourable conformation.

Theoretical calculations have been made for the conformations of decalin[101,102] and show that, in contrast to the earlier hypothesis[138], the double chair conformation is the most favourable for both *cis*-decalin and *trans*-decalin.

7. Heterocycles

Compared with hydrocarbons, in heterocyclic systems there are a number of additional factors which may influence the ring-inversion parameters. Apart from different bond lengths and valence angles, as a result of which the ring geometry and the intensities of interactions between atoms not linked by valence bonds are different from those in the hydrocarbon analogues, electronic effects due to the presence of unshared electron pairs, vacant *d* orbitals, and conjugation may play a major role in heterocycles.

Although the amount of data obtained up to the present time on the ring inversion of heterocyclic compounds is small, it is evident that they cannot be interpreted by simple analogy with the hydrocarbons. In some cases the corresponding parameters are in fact similar but the agreement may be the result of the opposed effects of several factors.

The barriers for pyran (10.7 kcal mole^{-1}) and thiopyran (11.6 kcal mole^{-1})[71] are close to the corresponding value for cyclohexane, but in piperidine the barrier is probably higher[71,72]. On the other hand, about 6 kcal mole^{-1} was obtained for perfluoropiperidine[73]. The barrier in *NN*-dimethylpiperazine, the geometry of which is close to that of the cyclohexane ring[79] according to electron diffraction data[105], is almost the same as in cyclohexane. The barriers in hexahydro-1,3,5-triazines[85], the skeleton of which consists exclusively of C–N bonds, are also close to this value. However, the data obtained for triazines and the mechanisms proposed for ring inversion differ somewhat[85,86]. A decrease of the barrier with increasing dimensions of the substituent of the nitrogen was also noted for 1,3,5-triazines[85]; this can probably be accounted for by a tendency of the pyramidal nitrogen atom to assume a more planar structure with increase of the size of the substituent.

The orientation of unshared electron pairs plays a major role in ring inversion processes in heterocyclic systems incorporating nitrogen, oxygen, and sulphur. For alkyl-substituted piperidines, it has been established with the aid of NMR spectra[72,139] and dipole moment studies[140] that the alkyl group is equatorial. However, there exist at present two opposed views concerning the orientation of the unshared pair in piperidine itself. According to the first view, the dimensions of the unshared pair exceed those of the hydrogen atom[72,139] and accordingly piperidine must be predominantly in the conformation with an axial hydrogen atom; according to the second view, the unshared pair is smaller[141,142]. The recent calculation by Allinger and coworkers[143] for piperidine conformations showed that hydrogen in the axial orientation has a small advantage on energy grounds (0.6 kcal mole^{-1}). Since the difference between the energies is small, evidently in real systems the presence of substituents or small deformations of the ring can displace the equilibrium in the opposite direction.

The available data on the ring inversion of substituted 1,3-dioxanes[77], containing two heteroatoms, show that the decisive factor in these compounds is probably the interaction of atoms not linked by valence bonds. The barrier in unsubstituted 1,3-dioxane is almost identical with that in cyclohexane[77]. As a result of intensive 1,3-*syn*-axial interactions, the energy of the ground state of 2,2-dimethyl-1,3-dioxane is increased, which leads to a decrease of the barrier†. At the same time in 5,5-dimethyl-1,3-dioxane, where such interactions do not occur, the barrier is 10.5 kcal mole^{-1} (Table 1, No. 74). It should also be noted that the conformational energies of the 5-alkyl substituents in 1,3-dioxanes are very much lower than the corresponding values for cyclohexane[145].

Among six-membered rings containing a large number of heteroatoms, acetone diperoxide[55,82], and tetramethyl-*s*-tetrathiane[81] were investigated. The barriers in these compounds are significantly higher than in tetramethylcyclohexane. Here non-valence interactions probably do not play a dominant role and other factors are more important; in particular, ring inversion can involve other intermediate forms than in cyclohexane. It has been suggested that the twist-boat form and not the chair form is the most stable for tetramethyl-*s*-tetrathiane[81,146]. The high barrier in this compound made it possible to isolate a stable conformer at −80°C,[146] as had been done for chlorocyclohexane[147].

The ring inversion of tetramethyl derivatives of 1,2-dithiane and 1,2-dioxane[75] has also been investigated. The difference between the barriers in these compounds has been explained by the absence of intermediate forms in ring inversion; the existence of a symmetrical boat form of tetramethyldioxane is impossible because of the interaction between the methyl groups; at the same time in tetramethyldithiane this form can be realised owing to the greater length of the C–S bonds.

The barriers to the inversion of tetra- and hexa-hydropyridazines are much higher[83] than in the corresponding hydrocarbons. While the barriers in cyclohexane and cyclohexane differ sharply, those in the above compounds are similar (Table 1, Nos. 90–95).

In heterocyclic systems containing nitrogen there is a possibility of yet another conformational transition—inversion at the nitrogen atom. In six-membered rings (piperazines[79] and triazines[85,86]) the rate of this process is still too high to investigate by NMR methods; however, in aziridine (ethyleneimine) derivatives, where the nitrogen atom is incorporated in a strained three-membered ring, the inversion is slower. A number of substituted aziridines have now been investigated[87–90,148–151] and attempts have been made to estimate the role of the various factors influencing the heights of the barriers in these compounds. Thus bulky substituents at the nitrogen atom apparently increase the rate of inversion[148], since they increase the steric strains in the ground state; these strains are removed in the transition state, which has a planar structure. The conjugation effect, which leads to a "flattening" of the pyramidal structure of the nitrogen atom, acts in the same direction: the rates of ring inversion in acetylaziridines[89] are much higher than in alkylaziridines. An "extreme" example in this case is formamide, which has

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† Since the C–O bond is much shorter (1.43 Å) than the C–C bond (1.53 Å), the conformational energy of 2-alkyl substituents in 1,3-dioxane reaches 3 kcal mole^{-1} [99] (compared with 1.6 kcal mole^{-1} in cyclohexane). Eliel and Knoeler[144] showed that in the *trans–cis* isomerisation of 2-alkyl-5-t-butyl-1,3-dioxane the t-butyl group passes to the axial position. This is apparently the first example of the axial orientation of the t-butyl group in a six-membered ring. In the analogous situation cyclohexane goes over to the boat form[95].

an almost planar structure: here the barrier to the nitrogen inversion is only 1 kcal mole^{-1}.[152] Solvents have a considerable influence on the barriers to ring inversion in aziridines: in hydroxylated solvents the rate of inversion is significantly lower[87,148]. Probably in this case the solvent forms a weak bond of the hydrogen type with the unshared electron pair of the nitrogen atom.

Simultaneous inversion at the nitrogen atoms has also been observed in a series of diazabicycloheptanes and diazabicyclo-octanes[84].

IV. CONFORMATIONAL ENERGIES OF SUBSTITUENTS

It is by no means possible to obtain the absolute values of the thermodynamic parameters of ring inversion in all cyclic systems. However, it is possible to determine by a relatively simple procedure quantities which are sometimes of no less interest. These are the so called conformational energies of substituents, i.e. the differences between the free energies of the conformers with R in the axial and equatorial positions. The equilibrium constant K for this process is defined by the expression:

$$K = N_a/N_e\,, \qquad (20)$$

where N_a and N_e are the mole fractions of the axial and equatorial forms in the equilibrium mixture. The values of K may be determined with the aid of kinetic methods, for example, from the different reactivities of substituted cyclohexanes as a function of the orientation of the substituent. This approach has been developed independently and successfully employed for the determination of conformational energies by Eliel and coworkers[153] and Winstein[154]. Subsequently a number of physical methods were developed for the determination of the content of the conformers in the mixture, among which those based on vibrational and NMR spectra became most widely used. At present the conformational energies of a large number of substituted cyclohexanes have been determined. In this section the scope of the determination of conformational energies of substituents by NMR methods will be briefly discussed. Attention will be concentrated on a comparative estimate of the accuracy of the methods. The effects of various factors on the conformational energies have been discussed in reviews[155,156].

N_a and N_e may be determined most directly by measuring the areas of the signals corresponding to the two conformers in the low-temperature NMR spectra where these signals are completely or partly separated. The conformational energies of chloro- and bromocyclohexane[49,157], iodocyclohexane[157], and fluorocyclohexane[48,157] were determined in this way. In all these studies measurements were made of the intensities of signals due to the tertiary proton, which can be identified without error. However, in principle, one can employ for this purpose other signals, for example those of the hydroxyl and methyl protons[76,158,159].

However, this method for the measurement of conformational energies is not always feasible owing to experimental difficulties. Moreover, in this case one obtains the free energies for temperatures between −60° and −100°C. The use of these values at other temperatures is not always justified, since ΔG may vary with temperature.

In order to determine K from NMR spectra, it is possible to use parameters which differ for conformers with axial and equatorial orientations of the substituents and which become averaged out in the inversion process: chemical shifts, coupling constants, and signal widths. If the corresponding parameters are known for fixed conformations, it is possible to determine the relative concentrations of both forms in the equilibrium mixture and hence the equilibrium constant by Eqn. (20).

1. Determination of Conformational Energy from the Chemical Shift

If ring inversion takes place in a substituted cyclohexane, a chemical shift of the signal (usually of the tertiary proton) is observed in the NMR spectrum:

$$\delta = N_e\delta_e + N_a\delta_a\,, \qquad (21)$$

where δ_a and δ_e are the chemical shifts of the axial and equatorial forms, and N_a and N_e are their mole fractions. The method was proposed by Elial who used it to investigate the equilibrium in bromocyclohexane[160]. The shifts δ_a and δ_e may be determined from the low-temperature NMR spectra with "frozen" inversion. The compositions of the equilibrium mixtures of a number of halogeno-substituted cyclohexanes[49,50,52] and cyclohexyl ethers[161] were determined by this procedure. For substituents with high electronegativities, the difference δ_{a-e} between the chemical shifts of the signals due to the tertiary proton may become considerable (0.7–0.8 p.p.m.).[50]

However, methods in which model compounds with known conformations are used have become most widespread. Usually *cis*- and *trans*-4-t-butyl derivatives of cyclohexane are used as the "fixed" forms. Since the t-butyl group in the cyclohexane rings always occupies an equatorial position[154,162], the *cis*-isomer yields in this case δ_a and the *trans*-isomer δ_e‡. In some studies other 4-alkyl derivatives of cyclohexane[163] or 3-alkyl derivatives[164] were employed as model compounds. The method has been used to determine the conformational energy of the amino-group[163,164] and the nitro-group[165] and also in the investigation of the conformational equilibria in a number of other cyclohexane[166], cyclohexanol[167], and cyclohexanone[168] derivatives. The dependence of the conformational energy on the presence of hydrogen bonds has been established by this method for the amino-group: the relative constants of the conformers differ significantly in neutral, protonated, and proton-donating solvents (Table 2). In most studies the chemical shift of the tertiary proton was determined; however, the chemical shifts of the hydroxyl proton, for which the difference between the axial and equatorial positions amounts to about 30 Hz, were also employed for this purpose.

Evidently fixed models may be used only when the alkyl groups do not have a significant influence on the chemical shifts of the tertiary proton, do not distort the cyclohexane ring, and merely stabilise the conformation. The effect of the diamagnetic anisotropy of alkyl substituents in cyclohexane was studied in a number of investigations[175,180–184]. It has been shown experimentally that the effect of a 4-alkyl substituent is small[175]. However, an axial alkyl group in the 3-position displaces significantly the signal of an axial H_1 proton[175,183,184] and therefore the conformational energies obtained with 3-alkyl substituted model compounds are

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‡ δ_a refers to the conformer in which the substituent occupies an axial position. This applies also to the coupling constant and signal widths discussed below. Since the chemical shifts of tertiary protons are usually investigated, this nomenclature is not altogether convenient.

probably unreliable. This has been demonstrated experimentally by Eliel and Martin[169] for halogeno-substituted cyclohexanes. Recently Jensen and Beck[171] compared the low-temperature NMR spectra of a number of cyclohexane derivatives with those of model compounds having a 4-t-butyl group. In all the compounds, the chemical shifts of the axial and equatorial α-protons differed at low temperatures from the chemical shifts of the corresponding 4-t-butyl derivatives. In all cases the conformational energies determined by Eliel's method proved to be lower than the result obtained by measuring the areas and by "freezing" the ring inversion with subsequent determination of δ_a and δ_e. Thus the fixed model method probably yields only semiquantitative results.

In addition the chemical shift method involves also a number of factors which may lead to significant errors in the determination of the conformational equilibrium position. Since the tertiary proton signal constitutes the X part of the ABX or A_2B_2X system and is greatly complicated as a result of spin–spin coupling, the chemical shifts cannot be determined with adequate precision. To eliminate this difficulty, the protons in the relevant positions are usually replaced by deuterium[154,173,185]. The accuracy of the determination of the equilibrium constant diminishes if the difference δ_{a-e} between the chemical shifts due to the fixed conformers is small (as in nitrocyclohexane[177,186]) or if the conformational equilibrium is strongly displaced towards one of the forms, in particular when $\delta - \delta_e$ is small[163,166]. The chemical shifts δ_a and δ_e have an "intrinsic" temperature variation and therefore in the extrapolation of the results obtained at low temperatures to other conditions it is necessary to apply corrections[171].

Table 2. Conformational energies of monosubstituted cyclohexanes obtained by NMR methods.

Substituent	$-\Delta G$	t, °C	Solvent	Method	Refs.
1	2	3	4	5	6
F	0.24	−56	$CFCl_3$	*a*	48
	0.15	25	$CFCl_3$	*b*	48
	0.25	−93	CS_2	*a*	157
	0.24	room	CS_2	*b*	157
	0.15	25	+	*c*	169
Cl	0.44	25	+	*c*	169
	0.51	−81	CS_2	*a*	157
	0.49	25	CS_2	*b*	157
	0.41	−93	CS_2	*a*	49
	0.38	36	CCl_4	*c*	170
	0.43	36	*o*-dichlorobenzene	*c*	170
	0.49	−83	CS_2	*a*	171
	0.55		CS_2	*b*	171
Br	0.37	25	+	*c*	169
	0.53	−83	CS_2	*a*	171
	0.57		CS_2	*b*	171
	0.51	−81	CS_2	*a*	49
	0.48	−81	CS_2	*a*	157
	0.44	room	CS_2	*b*	157
	0.2	25	CCl_4	*c*	166
	0.24	25	liquid	*c*	162
	0.7	20	CCl_4	*d*	172
	0.37	35	CCl_4	*c*	170
	0.42	36	*o*-dichlorobenzene	*c*	170
I	0.43	−81	CS_2	*a*	157
	0.41	20	CS_2	*b*	157
OH	0.6	20	CCl_4	*c*	166
	0.73	30	CCl_4	*c*	167
	0.75	40		*c*	159
	0.43	20	CCl_4	*d*	172
	1.0	28	CCl_4	*d*	173
	0.82	36	CCl_4	*c*	174
	1.05	36	t-BuOH	*c*	174
	0.88	30	2D2PrOH	*c*	161
	1.07	20	CCl_4	*c*	175
OCH_3	0.6	20	CCl_4	*c*	166
OCD_3	0.56	−96	CD_2CDCl	*a*	147
OCHO	0.27	25	CS_2	*b*	161
$OCOCF_3$	0.68	25	CS_2	*b*	161
	0.54	−84	CS_2	*a*	171
	0.55		CS_2	*b*	171
$OCOCH_3$	0.68	25	CS_2	*b*	161
	0.66	28	CS_2	*e*	173
	0.7	25	CCl_4	*c*	166
	0.72	−83	CS_2	*a*	171
	0.64		CS_2	*b*	171
OT_s	0.6	25	CCl_4	*c*	166
ONO_2	0.59	25	CS_2	*b*	161
SH	0.9	25	CCl_4	*c*	174
SCH_3	0.7	25	CCl_4	*c*	174
SC_6H_5	0.8	25	CCl_4	*c*	166
NH_2	1.26	20	C_6H_6	*d*	172
	110	20	C_6H_6	*d*	172
	1.30	20	$CHCl_3$	*f*, *c*	164
	1.15	20	CCl_4, C_6H_{12}, CH_3CN	*c*	163
	1.45	20	$CDCl_3$, EtOH, t-BuOH	*c*	163
NH^+_3	1.7	20	CF_3COOH, HOAc	*c*	163
$NHCH_3$	1.1–0.9	25	$CHCl_3$	*c*	164
NO_2	0.78	37	liquid, $CDCl_3$	*d*	188
	1.02	25	$CDCl_3$	*f*	165
	1.3	25	$CDCl_3$	*f*	177
	1.1	25	$CDCl_3$	*d*	177
CH_3	1.78**	30	$CDCl_3$	*b*	178
	1.68	30	CCl_4	*c*	167
	1.70	32	CCl_4	*c*	170
C_2H_5	1.68	30	CCl_4	*c*	167
$CH(CH_3)_2$	2.22	30	CCl_4	*c*	167
	2.20	25	$CHCl_3$	*c*, *f*	164
C_6H_{11}	2.15	32	CCl_4	*c*	170
C_6H_5	3.0	25	$CDCl_3$	*f*	179
$CO_2C_2H_5$	1.1	25	CCl_4	*c*	166
C≡CH	0.18	41	CCl_4	*c*	158

Remarks: *a*) from measurements of signal areas at a low temperature; *b*) from chemical shifts (δ_a and δ_e obtained at a low temperature); *c*) from chemical shifts (δ_a and δ_e obtained from the spectra of *t*-butyl derivatives); *d*) from coupling constants (J_{HH} obtained from spectra of model compounds); *e*) from coupling constants (J_{HH} determined at a low temperature; *f*) from band width; +—value averaged for a number of solvents; **determined from the spectra of diazirines.

2. Determination of Conformational Energies from Spin–Spin Coupling Constants

The method is based on the difference between the vicinal coupling constant J_{HH} as a function of the axial or equatorial positions of the protons relative to the cyclohexane ring. Numerous experimental data show that J_{aa} varies in the range from 9 to 12.5 Hz and J_{ae} from 3.5 to 6 Hz.[187] The number of available measurements of J_{ee} is smaller; it probably does not exceed 2–3 Hz. The approach to the determination of equilibrium constants based on J_{HH} values was developed for ethane derivatives[6] and was then employed in studies on ring inversion in substituted cyclohexanes[172,173]. If the equilibrium mixture contains x moles of one conformer and $1 - x$ of another, then, as a result of inversion, averaged constants will be obtained:

$$\begin{aligned} J_{12}^{av} &= J_{14}^{av} = xJ_{ae} + (1-x)J_{ea} \simeq J_{ae} \, , \\ J_{13}^{av} &= J_{15}^{av} = xJ_{aa} + (1-x)J_{ee} \simeq J^{*} \, . \end{aligned} \qquad (22)$$

Thus, when the first-order condition $\delta_{12} \gg J_{12}$ holds, (which is usually the case for electronegative substituents), the α-proton signal will be a 1 : 2 : 1 triplet with spacings J^{*}; each component of the triplet will in turn be another triplet with spacings J_{ae}. In practice, however, the signal is rarely fully resolved. In some cases, as a result of the superposition of individual components, a symmetrical quintet[177] or septet is observed, as happens for nitrocyclohexane[176,188]. Usually the signal has an unresolved contour. Nevertheless in many cases it is possible to determine averaged constants either directly or from measurements of signal widths at a specified height[172]. J_{aa}, J_{ae}, and J_{ee} are frequently obtained from the spectra of *cis*- and *trans*-4-t-butylcyclohexyl-R.[173,188]

The method for the determination of the equilibrium positions from the averaged coupling constants becomes extremely approximate for small values of x ($x < 1/5$). Moreover it has a number of additional limitations. In particular, it has been shown that in cyclic systems $J_{ae} \neq J_{ea}$.[189-191] In the analysis of the spectra of the compounds investigated no account was taken also of long-range interaction constants which may reach 2 Hz for equatorial H_1 and H_3 protons[192].

3. Determination of Equilibrium Constants from Signal Widths

When the tertiary proton multiplet is unresolved, the conformational energies may be determined from the signal width. This parameter has been used in the very early studies to determine the configurations and fixed conformations of cyclohexane derivatives[193].

The equilibrium constant for a mixture of conformers is

$$K = \frac{w_a - w}{w_e - w} \, , \qquad (23)$$

where w is the observed signal width, w_e the signal width for the conformer with a fixed equatorial position of the substituent, and w_a the signal width for a fixed axial position of the substituent. As in methods (a) and (b), the signal widths for *trans*- and *cis*-4-t-butylcyclohexyl-R are frequently adopted as w_a and w_e. This method is the most approximate, but in a number of cases it yields conformational energies in satisfactory agreement with the values obtained by other methods[165,177,194-197].

Table 2 lists the conformational energies of substituents in the cyclohexane ring and it is indicated which of the methods discussed above was used to obtain the value. The methods discussed can be arranged in the following sequence in terms of decreasing accuracy: chemical shifts > coupling constants > widths. However, frequently even approximate measurements of band widths yield satisfactory conformational energies and under favourable conditions the determination of K from NMR spectra is not inferior in accuracy to the most precise kinetic and thermodynamic methods.

V. APPLICATION OF FLUORINE-19 RESONANCE

In recent years ^{19}F NMR spectra have been used to investigate the mobile and fixed conformations of cyclic systems[62,198]. Perfluorocyclohexane[57], fluorocyclohexane[48], *gem*-difluorocyclohexane[22,62], substituted *gem*-difluorodecalins[70], cyclobutane derivatives[130], and large-ring systems have been investigated by this method[62,65].

The use of the chemical shifts of fluorine has a number of advantages, since they are more sensitive to the molecular environment and exceed by a factor of several tens the proton chemical shifts. In fluorine-substituted cyclohexanes the difference δ_{a-e} between the signals of the axial and equatorial fluorine atoms is 20 p.p.m., i.e. it exceeds by a factor of almost 50 the corresponding value for protons. The spin–spin coupling constants J_{FF} are of the order of 250–280 Hz and the constants J_{FaHa}§ also exceed the J_{aa} values for protons. The high values of δ_{a-c} permit the investigation of ring inversion in fluoro-substituted cyclic compounds over a wide range of temperatures by high-resolution NMR methods. Moreover, fluoro-substituted cyclohexanes are very convenient for the investigation of ring inversion by spin-echo methods for two reasons: (1) at the resonance frequencies employed in the spin-echo experiments $2\pi J_{FF} \lesssim \delta\omega$ and therefore it is possible to make measurements over a wide range of exchange rates; (2) the vicinal coupling constant J_{HF} is almost independent of the rate of exchange at very high and very low rates and does not affect the echo-signal amplitude, so that it can be disregarded in the determination of the rate[31].

The rates of inversion of fluorinated cyclohexane derivatives were determined by both high-resolution NMR methods[22,48,54] and by the spin-echo method[31,58]. The temperature variation of the chemical shift of fluorine was used to estimate the percentage contents of the conformers of 2,2-difluoro-*cis*-decalin[70] and alkyl derivatives of 1,1-difluorocyclohexane[54,62]. It has been shown[48] that the equatorial position is preferred for the fluorine atom to a much lesser extent than for chlorine and bromine atoms. The conformational energy of fluorine determined from the signal areas and from chemical shifts was found to be 0.153 and 0.242 kcal mole^{-1} respectively, in good agreement with the data derived by other methods[202,203].

For a correlation between the parameters of the fluorine-19 spectra and the structure of substituted cycloalkanes, further accumulation of experimental data is necessary. However, it is already evident that this method may be effective in studies on the conformations of cyclic compounds.

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After the manuscript had been sent to the editorial board, a large number of new data on the ring inversion of cyclic compounds were published. Those which are of greatest interest may now be indicated briefly.

With reference to p. 517: Allinger and coworkers calculated theoretically the conformations and energies of a large number of cycloalkanes and cyclic ketones[204]. The predicted barrier to ring inversion in cyclohexanone is 4.8 kcal mole^{-1}, which agrees well with recent experimental data by Gerig[205] and Jensen and Beck[206], who showed that

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§ The vicinal coupling constants J_{FH} obtained in a number of investigations[130,199-201] show that the same relation applies to them as in the case of J_{HH}: J_{aa} is the maximum, J_{ee} is a minimum, and J_{ae} is intermediate.

the replacement in the cyclohexanone ring of one sp^3-hybridised atom by an sp^2-hybridised atom leads to an appreciable decrease of the barrier. A similar result was obtained for *cis*-decalones[207].

With reference to p. 519: Roberts and coworkers[208] investigated by the resonance of fluorine-19 nuclei the ring inversion in a number of cyclo-octane derivatives. They succeeded in detecting both types of conformational transitions: ring inversion and pseudorotation. For the majority of the compounds investigated, the boat-chair form is the most stable at low temperatures. Its stability has been confirmed recently by X-ray diffraction studies on *trans*-1,2-dichlorocyclo-octane[209]. It is interesting to note that the dihedral angles obtained in this investigation are in excellent agreement with the values predicted by Hendrickson[104].

The bond shift in cyclo-octatetraene was investigated by Anet and Bock[210]; Lack and Roberts[211] determined the barriers for *cis*-hydrindane derivatives.

With reference to p. 521: The conformational transitions in heterocyclic compounds were investigated: in difluoropiperidine[212], 1,3-dithiane derivatives[213], six-membered rings with silicon atoms[214,215], bicyclic diazo-compounds[216,217], and aziridines[218] and at tervalent oxygen[219] and arsenic[220] atoms. Jensen and Bushweller[221] continued their studies on the isolation of "pure" conformers of cyclohexane derivatives.

With reference to p. 524: Recently Jensen, Bushweller, and Beck determined the conformational energies of 22 functional groups in the cyclohexane ring; probably these are the most reliable data obtained hitherto. The conformational energies of ester groups[223] and amino-groups[224] have also been investigated.

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Institute of the Chemistry of
Natural Compounds,
USSR Academy of Sciences,
Moscow

U. D. C. 535.371

Chemiluminescence Excitation Mechanisms

R.F.Vasil'ev

A systematic review of modern views on the factors which favour the formation of chemical reaction products with greater equilibrium excitation is presented. The excitation can be electronic (for reactions in solution) or electronic and vibrational (for gas-phase reactions). In the latter case, fine details can be revealed, and particular features of the excitation process can be related to the electronic structure of the reactants (atoms or simple molecules). With complex molecules (typical of liquid-phase reactions) only a qualitative or semi-quantitative interpretation is possible. Examples are chosen from among those reactions whose chemiluminescence is adequately understood. Although the excitation mechanism is specific for a particular reaction type, excitation is favoured in general by the participation of ions, radical-ions, and charge-transfer states; these species also favour the retention of the reaction energy as internal energy of the products. 119 references.

CONTENTS

I. INTRODUCTION

The number of papers published on chemiluminescence has been steadily rising during the past few years: new chemiluminescent reactions have been discovered, and new methods of utilising chemiluminescence have been proposed. The rate of publication in the field of chemiluminescence has doubled in 5–6 years, which is higher by a factor of 2–3 than the corresponding figure for scientific information as a whole (doubling every 10–15 years[1,2]).

Papers on chemiluminescence can be divided into several categories, depending on the detail in which the given chemiluminescent system is discussed: 1) initial observations and rough description of the system; 2) identification of the emitter of chemiluminescence and of the chemical steps leading to excitation; 3) quantitative study of the excitation and emission steps.

The present review is devoted to the elementary mechanisms by which chemical energy is converted into light, and will deal mainly with papers in the third category.

II. GENERAL PROBLEMS IN CHEMILUMINESCENCE

A. Definition of Chemiluminescence

The term chemiluminescence usually denotes the emission (in excess of equilibrium) of radiation by particles which have gained excitation in a chemical reaction. If the reaction is split into two stages—the formation of excited particles, and the emission (or quenching) of radiation—it is possible to write a simple relationship between the absolute intensity of chemiluminescence I (in quanta per unit volume and per unit time) and the absolute rate of formation of excited particles $w_{\mathrm{P}*}$ (per unit volume and per unit time):

$$I = \eta_{\mathrm{P}} w_{\mathrm{P}}. \tag{1}$$

where η_{P} is the relative probability or quantum yield of light emission by the excited product $\mathrm{P}*$.

The above definition is too general, and the formula is oversimplified: not surprisingly, therefore, its application in real cases gives rise to difficulties and confusion. We shall consider these difficulties in detail.

1. In keeping with the terminology currently accepted in luminescence, the prefix "chemi" relates to the mode of supply of the excitation energy (cf. photoluminescence, radioluminescence, cathodoluminescence, etc.). Strictly speaking, the name chemiluminescence should be reserved for the emission of light which is observed on mixing reactive materials. However, mixtures of reactants are sometimes chemically inert, and an additional agency is needed to activate them (heat, electrical discharge or electrolysis, illumination). Nevertheless, it is not correct in these cases to talk of thermoluminescence[†], electroluminescence, or photoluminescence: the phenomenon should be called chemiluminescence, because the elementary act which gives rise to an excited particle is the chemical reaction between the reactants. In particular, some agencies can give rise to electronically excited particles which react to give an electronically excited product (for example, the reactions of electronically excited $\mathrm{O}(^1D)$ and $\mathrm{N}(^2D)$ atoms produced by an electrical discharge in the gas): in this case the emission from the product should be classified as chemiluminescence, but the emission from the primary particles is (evidently) not chemiluminescence. In the most recent terminology, the mode of activation or of generation of the reactive particles is also stated (e.g., thermochemiluminescence, electrochemiluminescence, photochemiluminescence).

2. Opinions differ as to the nature (chemical, or physical) of processes such as the transfer of an electron from one particle to another. If the process gives rise to excitation, followed by light emission, we shall term it chemiluminescence only if we take the view that the process itself is chemical. A physical process is sometimes defined as one in which the coordinates of the nuclei

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[†] The term "thermoluminescence" is particularly unfortunate. Literally, it denotes luminescence induced by heating, and some authors actually define it in this way. But this definition is meaningless, since thermal energy by itself cannot give rise to luminescence (i.e. to emission in excess of equilibrium). Thermoluminescence (or thermal de-excitation) is the correct name of an entirely different phenomenon: the emission of light observed on heating solids which have been previously exposed to ionising radiation.

remain unchanged: in this sense, the electron-transfer process is undoubtedly physical. However, the transfer of an electron gives rise to particles with entirely different chemical properties (ions and neutral molecules, or atoms), and there are grounds for treating the process as chemical. In this review, the luminescence arising from processes such as the transfer of an electron from a radical-anion to a radical-cation will be treated as chemiluminescence.

3. In some systems the light is emitted not by the product but by a third particle, excited by energy transferred to it from the excited product. In this case the elementary excitation act is purely physical, but the primary excited particle is formed by a chemical process, and many of the properties of the emission (intensity, time dependence, and spectral composition) are intimately bound up with a chemical mechanism. Hence this type of emission must be classified as chemiluminescence.

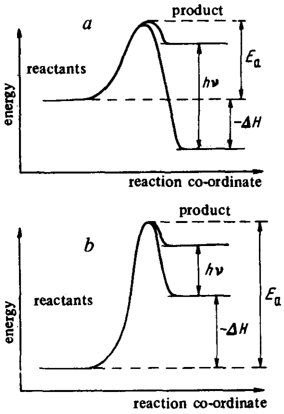

Figure 1. Model of the origin of chemiluminescence in (*a*) exothermic and (*b*) endothermic reactions.

4. Chemiluminescence is not necessarily confined to exothermic reactions. An amount of energy equal to (or not greater than) the sum of the activation energy E_a and the heat of reaction $-\Delta H$ can be converted into excitation energy (Fig. 1). The newly formed reaction products, when chemically activated, contain energy in excess of equilibrium even in the case of endothermic processes. If this excess of energy is lost by radiation, the process is no different from chemiluminescence. Of course, in endothermic reactions rotational and vibrational levels are more likely to be excited than electronic levels, and the radiation will lie in the long-wave (infrared) region of the spectrum.

5. The emission yield η_P is the ratio of the rate of emission (radiative deactivation) from P* to the sum of the rates of all the processes removing P*. The value of η_P for chemical excitation is the same as the emission yield for any other mode of excitation (e.g., photon absorption) under the same conditions (composition, temperature, and other parameters affecting the emission yield). Hence, this quantity is sometimes known from photoluminescence data for the compound P even before the chemiluminescence is measured. However, it is important to remember that the emission yield η_P is equal to the photoluminescence quantum yield only when the same excited state of the particle P is obtained both by chemical excitation and by the absorption of a photon. The situation is illustrated in Fig. 2 for a hypothetical organic molecule. The singlet state S_1 is populated as a result of photoexcitation. If the chemiluminescence is associated with a transition from the singlet state, its emission yield is equal to the photofluorescence quantum yield.

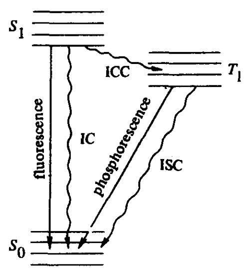

Figure 2. Excited states of a typical organic molecule and optical transitions between states: internal conversion (IC) and intersystem crossing (ISC). *S* and *T* are singlet and triplet states respectively.

However, if a triplet state becomes populated during the chemiluminescent reaction and the emission originates from this state the emission yield becomes equal to the photophosphorescence quantum yield (i.e. the number of quanta of phosphorescence per quantum of light absorbed) divided by the intersystem conversion yield of the triplet state T_1 from the singlet state S_1 (i.e. the ratio of the rate of transitions from S_1 to T_1 to the overall rate of all deactivation paths available to S_1.

In the light of the above, chemiluminescence can be defined as follows: the emission of radiation is termed chemiluminescence if the elementary act by which the emitter is formed consists in a chemical reaction or in the transfer of energy from a chemically excited product formed either spontaneously or as a result of a special energetic interaction.

Chemiluminescence is observed in a particular spectral region if the following conditions apply:

1. The energy of the photon is not less than the sum of the activation energy and the heat of reaction:

$$h\nu \leqslant E_a - \Delta H$$

or

$$\lambda \geqslant 28.6/(E_a - \Delta H)$$

if the wavelength is expressed in μm and the energy in kcal mole^{-1}. (Exceptions to this rule are discussed in section III. A. 5 below.)

2. The lifetime of the excited state of the emitter (with respect to radiation) is small compared to the characteristic relaxation time of the scattering processes for excess energy, or in other words the rate of emission is large compared to the rate of the radiationless deactivation processes, or the emission yield η_P is relatively high.

The overall schemes of chemiluminescence are summarised in Table 1, where the symbol w denotes the total rate of formation of the product P, η_P^{exc} is the excitation efficiency or yield, i.e. the ratio of the number of excited particles to the total number of particles of the same kind produced by the reaction, η_{PA} is the energy transfer efficiency, i.e. the relative contribution of the rate of energy transfer to the overall rate of deactivation of the excited product P*, η_A is the emission yield of the acceptor A, I_P and I_A are the quantum intensities of the emission for the product and the acceptor respectively.

Table 1. Summary of chemiluminescence.

Stage	Particles involved	Rate
Energy interaction	Unreactive components	
	→ Reactive components	
Chemical reactions	→ Non-excited product P	$(1-\eta_P^{exc})w$
	→ Excited product P*	$\eta_P^{exc}\, w$
Physical processes:		
Radiationless deactivation	→ Non-excited product P	
Emission (chemiluminescence)	→ Non-excited product and photon $P + h\nu_P$	$\eta_P\, \eta_P^{exc}\, w = I_P$
Transfer of excitation energy	→ Non-excited product and excited acceptor $P + A^*$	$\eta_{PA}\eta_P^{exc}\, w$
Emission in the acceptor molecule	→ Non-excited acceptor and photon $A + h\nu_A$	$\eta_A\eta_{PA}\eta_P^{exc}\, w = I_P$
Deactivation of the acceptor, energy transfer from A* to another acceptor, etc.	→ Non-excited acceptor and other products	

The proposed scheme leads to the following expression for the total quantum intensity of chemiluminescence I:

$$I = I_P + I_A = (\eta_P\eta_P^{exc} + \eta_A\eta_{PA}\eta_P^{exc})\, w\,. \qquad (2)$$

If energy transfer is negligible, the scheme is simplified and Eqn. (2) reduces to Eqn. (1). However, it may be necessary to consider additional processes, for example parallel reactions giving rise to excited products other than P*, chemical reactions of the excited states leading to new emitters of chemiluminescence, secondary energy transfer from an acceptor A* to another acceptor capable of luminescence, etc. The formula for the intensity then retains the form of Eqn. (2) but becomes more complicated.

B. Chemiluminescence Yield

The most important quantitative parameter of chemiluminescence is the chemiluminescence yield η_{cl}, i.e. the ratio of the absolute chemiluminescence intensity to the rate of the reaction leading to the formation of the excited product‡:

$$\eta_{cl} = I/w\,. \qquad (3)$$

In the light of the above considerations, the chemiluminescence yield is given by the expression in brackets in Eqn. (2):

$$\eta_{cl} = (\eta_P + \eta_A\eta_{PA})\,\eta_P^{exc}\,. \qquad (4)$$

If the scheme is complicated by the presence of additional processes, a more complex expression for the yield is obtained, but in every case it is possible to identify two factors one of which is the excitation yield. These factors have entirely different physical significance, since they stem from different stages in the chemiluminescent process (the chemical excitation stage and the physical energy transfer and emission stage).

We shall not be particularly concerned with the emission stage in the following sections, because light emission from atoms and molecules has been adequately treated in recent monographs[3,4,5], mainly as a result of research on photoluminescence, and also because it tells us very little about the specific features of the chemical excitation mechanism. The excitation stage, on the other hand, will be fully discussed because of the need for quantitative information on the elementary chemical act. This type of information has only just begun to appear in the literature.

In any form of luminescence, the yield reflects the efficiency with which the energy supplied to the system is converted into light. Often the concept of yield is itself far from straightforward, and needs to be discussed specially[6]; this is particularly true of types of luminescence which have not yet been extensively studied (such as chemiluminescence).

It would appear that formula (3) offers a method of determining the yield η_{cl}, but this requires a measurement of the absolute intensity and of the absolute reaction rate. The experimental determination of the intensity involves only practical difficulties (which can, however, be very serious). Much more fundamental difficulties arise in the determination of the reaction rate—we need to know the rate of the particular step which gives rise to excitation. These difficulties become more intractable, the more complicated the reaction. In general, the reaction mechanism must be known, otherwise the problem of measuring the rate of one particular step becomes meaningless. Often, and particularly with complex and with "new" chemiluminescent reactions, the mechanism is not known, and different definitions of the chemiluminescence yield are used in these systems in order to achieve some measure of quantitative description of the phenomenon. For example, the intensity of luminescence is referred to the rate of consumption of one of the reactants, or alternatively the total light emission is referred to the initial concentration. Difficulties in the experimental determination of the yields and in their theoretical interpretation usually arise on going from gas reactions to reactions in a condensed phase, from light particles to polyatomic molecules, and from vibrational to electronic excitation.

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‡This quantity is sometimes called the chemiluminescence quantum yield, a term derived from photochemistry and luminescence, where it is used to denote the yield of reaction product or of light per quantum absorbed. In chemiluminescence the relevant concept is the yield of quanta per reacting molecule. Hence it is better to avoid the term "chemiluminescence quantum yield".

III. CHEMICAL EXCITATION MECHANISMS

A. Simple Gas Reactions

In the gas phase the medium has no effect on the various elementary acts, and therefore more reliable and unambiguous information on the chemical reaction mechanism can be obtained. Nevertheless, the theoretical treatment of the excitation act meets with serious difficulties even in the simplest systems.

It is difficult to calculate the reaction rate, and it is even harder to determine to what extent and in what form the energy is concentrated in the products.

1. *Reaction rate*

Consider a simple exchange reaction (Fig. 3)

$$\mathrm{A + BC \rightarrow AB + C} \qquad \text{(I)}$$

where A, B, and C are atoms. The molecule BC is taken to be immobile in Fig. 3, and is treated as a target for the impinging A atom.

A simple expression for the reaction rate w can be written by making two assumptions:

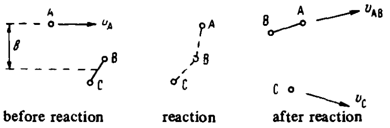
a) the molecule BC approximates to a sphere of radius b_0; the reaction proceeds with probability $p = 1$ if the atom A (treated as a point) collides with the sphere or approaches it tangentially; if the atom does not touch the sphere, $p = 0$.

b) the velocity of all A atoms is the same.

With these assumptions we can write

$$w = \frac{d[\mathrm{AB}]}{dt} = \pi b_0^2 v_\mathrm{A}[\mathrm{A}][\mathrm{BC}] = k[A][\mathrm{BC}] \qquad (5)$$

where $k = \pi b_0^2 v_\mathrm{A}$ is the rate constant for the reaction, and v_A is the velocity of the A atom.



before reaction   reaction   after reaction

Figure 3. Exchange reaction A + BC →AB + C.

In reality, however, the interaction between the particles BC and A is a function of the distance b, and the reaction probability p (per single collision between A and BC) depends on b, on v_A, and on the internal energy state of the reactants and of the products. Therefore, the cross-section πb_0^2 should be replaced by a cross-section for the reaction from the state n_i for the reactants to the state n_j for the products:

$$\int_0^\infty p(v_\mathrm{A}, b, n_i, n_j)\, 2\pi b\, db = \sigma_{ij}(v_\mathrm{A}, n_i, n_j) \qquad (6)$$

where n_i denotes the quantum numbers corresponding to internal energy states (electronic, vibrational, and rotational) of the initial reactants, and n_j those of the products.

Furthermore, since neither v_A (the relative approach velocity of A and BC) nor the state of internal motion of the reactants is constant, a distribution function for the particles among these parameters must be introduced: $F(v_\mathrm{A}, n_\mathrm{i})$. The resulting expression for the rate of production of the product in the quantum state n_j, which is particularly important in chemiluminescence, takes the form

$$\frac{d[AB(n_j)]}{dt} = \sum_{n_i}\int_0^\infty \sigma_{ij} v_\mathrm{A} F(v_\mathrm{A}, n_i)\, dv_\mathrm{A} = w_j\ . \qquad (7)$$

The distribution function F contains the concentrations of the reactants as factors, but (strictly speaking) only in the equilibrium system, and in this case we can write

$$F(v_\mathrm{A}, n_i) = f(v_\mathrm{A}, n_i)[\mathrm{A}][\mathrm{BC}]\ . \qquad (8)$$

Equilibrium implies a lack of reaction, and we can dismiss this case as trivial. However, the assumption is often made that the reaction can proceed with very small departures from equilibrium. In this case, inserting Eqn. (8) into Eqn. (7), we obtain the customary rate law for a bimolecular reaction:

$$w_j = k_j[\mathrm{A}][\mathrm{BC}] \qquad (9)$$

where

$$k_j = \sum_{n_i}\int_0^\infty \sigma_{ij} v_\mathrm{A} f(v_\mathrm{A}, n_i)\, dv_\mathrm{A}\ . \qquad (10)$$

It follows that the rate constant—whose evaluation is the aim of most of the quantitative work in chemical kinetics—is merely an averaged parameter only indirectly related to the real interaction probabilities of the particles and to the mechanism of the reaction.

To a first approximation§, the excitation yield defined above is equal to the ratio

$$\Sigma_2 k_j / \Sigma_1 k_j = \eta_\mathrm{P}^\mathrm{exc} \qquad (11)$$

where the summation 1 is taken over all the states of AB and the summation 2 is taken only over the states which give rise to the experimentally observed chemiluminescent emission.

The exact calculation of the probability p (formula 6) is a quantum-mechanical problem: the result of the interaction between A and BC depends on the properties of the surface (or, more accurately, the hypersurface in multidimensional space) which describes the potential energy for the reaction. The form of the surface must be obtained by a quantum-mechanical calculation. Satisfactory calculations so far have been made[7] only for the simplest of all reactions: $\mathrm{H + H_2 = H_2 + H}$.

Evidently, a complete solution of the problem is not likely to be achieved in the near future, even for relatively simple cases and with the approximation discussed above. Nevertheless, we already have interesting examples of partial solutions, which assist in the qualitative interpretation of experimental results for the more complex systems.

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§We ignore the rates at which the given state of the product is populated by internal conversion from other states. Strictly speaking, the right-hand side of Eqn. (9) should then include additional terms of the form

$$\sum_l k_{lj}[\mathrm{AB}(n_l)] - \sum_l k_{jl}[\mathrm{AB}(n_j)]\ .$$

2. *Vibrational excitation in exchange reactions*

Vibrational excitation in exchange reactions has been studied in detail. Reactions of the type

$$H + X_2 \xrightarrow{k_v} HX + X \qquad \text{(II)}$$

where X = Cl, Br, or I have been investigated by infrared chemiluminescence[8-13], and reactions of the type

$$M + X_2 \xrightarrow{k_v} MX_v + X \qquad \text{(III)}$$

where M = Na, K, Rb, Cs, in crossed molecular beams[14-17]. In these reactions the energy is insufficient to excite the electronic levels of the product. The rate constants k_V describe the population of the rotational states of the v-th vibrational level.

From recent experimental results, and their theoretical treatment, it has been possible to draw various important conclusions regarding the forces between the reactants which eventually lead to the reaction.

It has been shown that in reaction (II) the probability of forming HX in high vibrational states is low. For example, in the case of HCl the following relative rate constants have been obtained for the population of the vibrational states: $k_6 = 0.004$, $k_5 = 0.04$, $k_4 = 0.3$, $k_3 \simeq k_2 \simeq k_1 = 1$. In other words, only a small fraction of the total energy of the reaction (2 eV) is converted into internal energy, whilst the major part is converted into translational energy.

In reaction (III), on the other hand, the greater part of the energy (also ~ 2 eV) is converted into vibration, and the constant k_V is a maximum for the highest possible quantum number v. Furthermore, the cross-section¶ of reaction (III) is significantly higher than the corresponding value for gas-kinetic reactions, and the molecule MX after the reaction tends to move in the same direction as the atom M before the collision.

These features have been successfully correlated with the properties of the potential energy hypersurface. Polanyi and coworkers[10], without attempting to calculate the equation of the hypersurface, took some "ready-made" surfaces, and integrated the classical equations of motion of the atoms A, B, and C for a representative choice of trajectories, allowing for energy and momentum conservation (Monte Carlo method). The form of the surface was found to determine the point at which most of the energy is evolved: whilst the distance between A and B decreases (i.e. during the approach stage—attractive case), whilst the distance between B and C increases (i.e. during the separation stage—repulsive case), or during the transitional phase.

These workers showed that when A is a light atom and B and C are heavy atoms (as in the case of reaction (II)) the proportion of the energy converted into vibrations decreases as the amount evolved during the approach stage decreases, i.e. as the "repulsive" character of the interaction potential increases.

Attraction between the reactants is more characteristic of reaction (III): an electron can be transferred from M to X_2 even at large separations, and the strong coulombic attraction between M^+ and X^-X favours the evolution of reaction energy during the early stages of the reaction, and hence its conversion into vibrational energy. This "harpoon" mechanism is consistent with the ionic character of the M–X bond and with the large cross-section of the reaction. For a particular set of parameters of the reaction system, the theoretical angular distribution of the receding products agrees with that obtained experimentally.

Undoubtedly, the molecular beam method gives a great deal of valuable information about the elementary chemical act, and also in particular on reactions of interest from the standpoint of their chemiluminescence. Unfortunately, the probability of emission during purely vibrational transitions is very low, and existing infrared detectors are too insensitive to reveal the chemiluminescence of the products of reactions (II) and (III) in a molecular beam.

Even in infrared chemiluminescence experiments involving much larger numbers of excited molecules than the molecular beam experiments it is necessary to use large reaction vessels and multiple passes.

The examples considered above are not exhaustive. Vibrational chemiluminescence in exchange reactions has been observed also in the systems H + O_3, H + O_2, H + NOCl, H + NO, etc. In the reaction

$$H + O_3 \rightarrow O_2 + OH; \quad (-\Delta H = 77 \text{ kcal mole}^{-1})$$

(believed to be responsible for the hydroxyl bands in the luminescence of the night sky[17]) the higher vibrational levels of OH (up to $v = 9$) are populated with a higher probability than the lower levels. This is evidence that attraction is predominant in the interaction potential of the reactants[18]. On the other hand, repulsion is predominant in the reaction between N and NO_2 to give N_2O and O.[19]

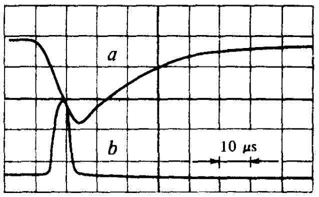


Figure 4. Photolytic pulse (a) and laser pulse (b) in an F_2O + H_2 chemical laser.

As a result of reaction, some of the sublevels can be more densely populated than sublevels situated at lower energies: in other words, a population inversion is established, and this phenomenon can lead to laser action. Thus, Kasper and Pimentel[20] were able to demonstrate chemical laser action with a mixture of Cl_2 + H_2, using flash photolysis to initiate the chain reaction by decomposing the chlorine molecule into atoms. The spectrum of the laser flash consisted of several narrow lines from vibrational-rotational transitions in the HCl molecule (in the region 3.6–3.8 μm), which appeared sequentially with an interval of the order of microseconds. Other examples of chemical lasers are known: the emission from HF (2.7–3.9 μm), produced by secondary reactions in the flash photolysis of UF_6 with H_2 and hydrocarbons[21,22], and of F_2O

¶The main attraction of the molecular beam method is that the cross sections and the angular distribution of the products (rather than the rate constants) are determined directly. Reactions are therefore characterised in greater details than is possible by conventional gas-kinetic methods.

with hydrogen[23]. The following series of reactions takes place in the UF_6 system:

$$UF_6 + h\nu \rightarrow UF_5 + F,$$
$$F + H_2 \rightarrow H + HF, \quad -\Delta H = 32 \text{ kcal mole}^{-1}$$
$$H + UF_6 \rightarrow UF_5 + HF; \quad -\Delta H = 46 \text{ kcal mole}^{-1}$$

The F_2O system has the advantage that a chain reaction takes place and therefore a single photolytic photon can produce many vibrationally excited molecules of hydrogen fluoride:

$$F_2O + h\nu \rightarrow OF + F,$$
$$F + H_2 \rightarrow HF + H,$$
$$OF + H_2 \rightarrow HOF + H,$$
$$H + F_2O \rightarrow HF + OF.$$

The second and last of the above reactions can excite up to the third and the sixth vibrational level respectively. Laser action is observed as a pulse of radiation (Fig. 4) which is much shorter than the flash of photolytic light.

3. *Electronic excitation of atoms in exchange reactions*

As a rule, excitation in exchange reactions is concentrated on the particle in which a new bond is formed as a result of the reaction. Polanyi and coworkers[12,14] have recently pointed out an exception to this rule: the formation of an electronically excited halogen atom X in reactions of type II:

$$H + X_2 \rightarrow HX + X^* ({}^2P_{1/2})$$

(X = Br, I), and also, with even higher probability, in the reaction

$$H + HX \rightarrow H_2 + X^* ({}^2P_{1/2}).$$

The X^* atoms are detected by their emission by the forbidden transition ${}^2P_{1/2} \rightarrow {}^2P_{3/2}$ (10.5 kcal mole^{-1}, 2.7 μm spectral region for the bromine atom).

These processes are much harder to treat theoretically than the processes involving vibrational–rotational excitation. The interpretation involves two potential energy hypersurfaces, one for the electronically excited and one for the non-excited products; at large distances between the reactants these merge into a single surface. The probability of motion of the system over both these surfaces has to be evaluated.

Moulton and Herschbach[25] examined formally analogous reactions (involving also vibrationally excited molecules) in molecular beams. The classical work of Polanyi in the early 1930's had shown (see Ref. 26) that in the chemiluminescent reactions of alkali atoms with halogen molecules the metal atoms are excited by the elementary step (interaction of the metal with the vibrationally excited molecule):

$$M + MX_v \rightarrow MX + M^*.$$

The large cross-sections for this reaction suggest that the interaction is more likely to be chemical ("reactive energy transfer") than a simple vibrational–electronic transfer of energy from MX to M. Moulton and Herschbach gave a direct experimental demonstration of this effect using the "three-beam" method. They observed chemiluminescence from potassium whose electronic levels had been excited by the reactive energy transfer process (V) from the vibrationally excited product of the exchange reaction (IV):

$$\underset{\text{beam 1}}{K} + \underset{\text{beam 2}}{Br_2} \rightarrow KBr_v + Br \qquad (IV)$$
$$\underset{\text{product beam}}{KBr_v} + \underset{\text{beam 3}}{Na} \rightarrow K^* ({}^2P) + NaBr. \qquad (V)$$

The product beam was crossed with a beam of sodium atoms above the photocathode of a photomultiplier with a filter for the 766.5/769.9 nm lines of the radiative transition ${}^2P \rightarrow {}^2S$ in the potassium atom. The heat of reaction (IV) is 45 kcal mole^{-1}. About one-half of the KBr molecules had an energy in excess of the 41 kcal mole^{-1} needed to excite the K atom in reaction (V) (the energy of the potassium ${}^2P$ level plus the difference between the K–Br and Na–Br bond energies). About 40% of these actually followed reaction (V). Because of the high emission probability, the K^* atoms were observed within the reaction zone. Thus, one photon was detected for every 5 KBr molecules entering the reaction zone. (The Na atoms were taken in 10^7-fold excess.) From these results Moulton and Herschbach extimate a cross-section of ~ 150 Å^2 for reaction (V)—at least, well in excess of 10 Å^2—i.e. much larger than the gas-kinetic cross-section. This cross-section is larger by an order of magnitude than the cross-section for "non-reactional" transfer, e.g.

$$NaBr_v + K \rightarrow NaBr + K^*$$

which was also investigated by the same authors[25]. These large cross-sections are consistent with the "harpoon" mechanism envisaged for the process.

4. *Electronic excitation of molecules*

Many instances of visible and u.v. chemiluminescence from molecules have been reported in flames, cold flames, and in pre-ignition reactions (see review articles 26–29).

The mechanism of some of these reactions has been studied in fair detail: the rate constants (but not the cross-sections) of the individual steps have been obtained, as well as their temperature coefficients, and a great deal is known about the electronic states of reactants and products, their nature (multiplicity, symmetry type), vibrational–rotational structure, the form of the potential surfaces (or, more accurately, their cross-sections), and the intersections of the different surfaces. It is relatively easy to obtain, experimentally, well resolved chemiluminescence spectra giving valuable information on these reactions.

The adiabatic correlation rules (see Ref. 5, p. 130, and Ref. 26, p. 185) are of the utmost importance in the formation of electronically excited molecules. These rules set stringent limits to the number and the type of electronic states in the products which can be obtained from the states of the initial reactants and which correlate with these states. The formation of excited products often involves a transition to a "forbidden" potential surface at the point where it intersects an "allowed" surface: such a non-adiabatic transition has a low probability.

a. Exchange reactions. Vibrational–rotational excitation is commonest in exchange reactions. However, if the sum of the activation energy and the heat of reaction is greater than the electronic excitation energy of the product, the latter can be produced in an electronically excited state. Of course, this outcome is most likely when the reactants are chemically very active.

Figs. 5 and 6 show the reaction paths for the two bimolecular reactions $NO + O_3 = NO_2 + O_2$ and $SO + O_3 = SO_3 + O_2$: the pre-exponential factors and activation energies are indicated[28]. In spite of their formal similarity, these reactions show some interesting differences. The pre-exponential factors describing the population of the ground

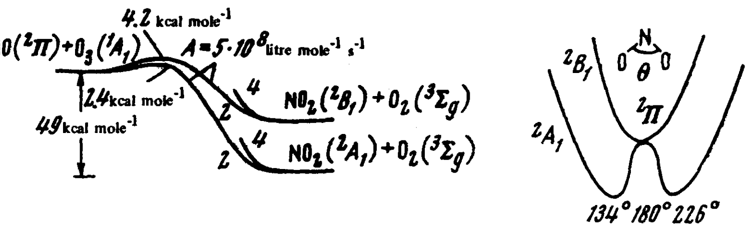


Figure 5. Potential energy diagram for the reaction $NO + O_3 \rightarrow NO_2 + O_2$. The initial state correlates with the doublet but not with the quartet final state.

$^2A_1$ state and the excited $^2B_1$ state of the NO_2 molecule in the reaction $NO + O_3$ have the same value (5×10^8 litre mole^{-1} s^{-1}). On the other hand, in the reaction $SO + O_3$ the ground $^1A_1$ state of the SO_2 molecule is populated with a pre-exponential of 1.5×10^9 litre mole^{-1} s^{-1}, whereas the corresponding values for the excited $^3B_1$ and $^1B_1$ states are 4×10^7 and 1×10^8 respectively. Thrush[28] explains these differences in terms of the adiabatic correlation rules and of the nature of the potential energy surfaces of reactants and products. For $SO + O_3$, one triplet surface for the reactants changes *smoothly* into a triplet surface for the non-excited products of the same symmetry, but it *intersects* two surfaces for the excited products of different symmetry. The probability of reaction to give the excited state is lower, because the probability of the required intersection is low. For the reaction $NO + O_3$, orbital degeneracy (π state) produces two doublet surfaces for the reactants which change *smoothly* into two doublet surfaces for the products.

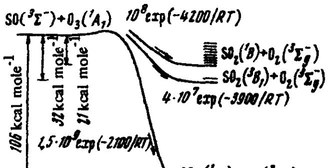


Figure 6. Potential energy diagram for the reaction $SO + O_3 \rightarrow SO_2 + O_2$.

There have been no reports so far of the population of the $^1\Delta g$ (22 kcal mole^{-1}) and the $^1\Sigma g$ (38 kcal mole^{-1}) electronic states of the oxygen molecule in these reactions, although deviations from Wigner's rule can be expected only for reaction paths leading to SO_2 in the $^1A_1$ and $^1B_1$ states. The general rule that excitation is concentrated in the products which contain the newly formed bond may apply also to these reactions.

It is interesting to note that the excited states are populated with high efficiency: although only 70–80% of the reaction energy is converted into electronic excitation, the rate constants are lower than the rate constants for the formation of non-excited molecules by only one to three orders of magnitude. (The excitation energy of NO_2 $^2B_1$ is not accurately known, but it is close to 40 kcal mole^{-1}.)

Like purely vibrational excitation, electronic excitation in exchange reactions gives rise to a non-Boltzmann distribution of the product molecules among the vibrational levels of the upper electronic state. This has been observed, for example, in diffuse flames associated with the reaction of alkali metal vapours with halogenomethanes[30–32]. The emitter of chemiluminescence in these reactions, C_2 in the $A^3\pi_g$ state (55.4 kcal mole^{-1} above the $^3\pi_u$ ground state), is excited during the elementary act

$$C + CX \rightarrow C_2 + X.$$

Table 2. Vibrational levels v' whose population $N(v')$ is a maximum, and relative population $N(v')/N(0)$ of the vibrational levels of the electronically excited $A^3\Pi$ state of the C_2 radical (produced in the reaction between potassium vapour and halogenated methanes).

Halogenated methanes	$CHCl_3$	CCl_4	CBr_4	CI_4
Energy of the C–X* bond, kcal mole^{-1}	77	77	66	50
v'	2	6	1	3
$N(v')/N(0)$	2	55	2	17

*Estimated by Miller and Palmer[31] with an accuracy of 4 kcal mole^{-1}. The uncertainty in these values may be even greater, because the initial data[31] were later shown[32] to be doubtful. However, we may assume that the relative magnitudes of the bond energy are correct.

A definite correlation has been reported[30,31] between the exothermicity of the elementary act, i.e. the energy of the C–X bond, and the energy of the vibrational level which is populated with the highest probability. However, recent work[32] at low pressures and high spectral resolution does not confirm this conclusion. Hence, the maxima in the distribution of the product over the vibrational levels cannot be directly related to the exothermicity of the reaction (see Table 2), and the large difference between the $K + CHCl_3$ and $K + CCl_4$ systems shows that the assumption of a common mechanism for the formation of the emitter for all reactions of a given type is an oversimplification.

b. Addition reactions. Practically all the known chemiluminescent reactions are termolecular:

$$A + B + M \rightarrow AB^* + M \tag{VI}$$

The third body M disposes of some of the energy and thus prevents the immediate decomposition of the newly formed AB molecule. Reaction (VI) can follow several paths and lead to different states of the product AB. If A and B are free atoms, the high degree of degeneracy can lead to correlation between the initial state and a number of stable states of the product (see, for example Fig. 7). The chemiluminescence is not necessarily emitted from these states: their potential energy surfaces may intersect other surfaces, and transitions to new states can take place.

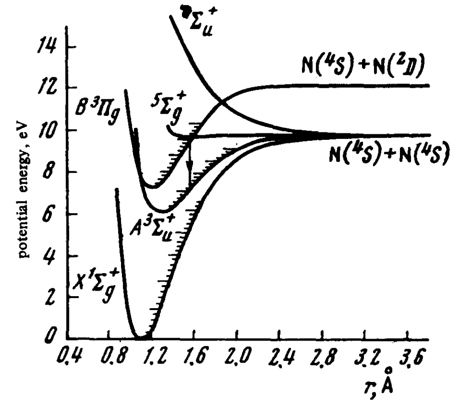


Figure 7. Potential energy curves for the nitrogen molecule.

The yellow "afterglow" of nitrogen in an electrical discharge is an example of chemiluminescence of this type: the emission comes from electronically excited N_2 molecules produced by the recombination of N atoms. Emission occurs after transition of the nitrogen molecule from the states $A^3\Sigma_u^+$ and $^5\Sigma_g^+$ to the state $B^3\Pi_g$, which correlates with a state of the free atoms in which one of them is excited[29].

The third body M also can act as the emitter of chemiluminescence, particularly if it is a metal atom with a low excitation potential, e.g.[33-35]

$$H + H + Na \rightarrow H_2 + Na^* \quad (590\ nm)$$
$$H + H + Tl \rightarrow H_2 + Tl^* \quad (535\ nm)$$
$$H + OH + Pb \rightarrow H_2O + Pb^* \quad (406\ nm)$$
$$H + X + Pb \rightarrow HX + Pb^*$$

(where X is a halogen atom). In the reaction

$$O + O + O \rightarrow O_2 + O(^1S)$$

one of the oxygen atoms acts as the third body, by accepting some of the energy of the reaction (5.1 eV) and going into a ^1S excited state (4.17 eV). This process can occur only at very low pressures, and it has been detected (postulated. Sci. Ed.) in the upper atmosphere. The well known "green atmospheric line" at 557.7 nm is due to the transition of an O atom from a ^1S level to another (also excited ^1D level located 1.96 eV above the ^3P ground state[17,36,37].

Other examples of chemiluminescent addition reactions include NO + O + M ("air afterglow"), N + O + M, H + NO + M, O + SO + M, O + CO + M, O + H + M, and others.

None of these gas-phase chemiluminescent reactions has been investigated as extensively as the air afterglow reaction. But even the latter has not yet been fully interpreted: clearly, its mechanism is very complex. The main difficulty is to account, at the same time, for the influence of the nature of the third body M on the luminescence intensity and for the independence of the luminescence intensity on the concentration of M over a wide range of pressures.

Many workers[38-40] have treated the reaction of NO and O as a bimolecular radiative association, but most workers now incline to the view that this reaction is termolecular (see discussion in Ref. 41); it has also been suggested that vibrational relaxation[42,43] (energy redistribution) and redissociation by collision[43] of the electronically excited nitrogen dioxide play a significant role.

Under some experimental conditions the well known tendency of NO to associate may be important. When the gas is allowed to expand adiabatically into a low-pressure chamber, the equilibrium

$$n\mathrm{NO} \rightleftharpoons (\mathrm{NO})_n$$

is shifted towards the right by the cooling effect[44]. Most of the associated species are dimeric, but clusters with a mass number up to 600 have been detected mass spectrometrically[45]. Excitation is more likely in the reaction $(NO)_n + O \rightarrow NO_2^* + (NO)_{n-1}$ than with the monomer; in the case of the dimer, between 1 and 10 collisions of the dimer with an oxygen atom are needed[45] to form an electronically excited NO_2^* molecule. This explains the anomalously high (by 3–4 orders of magnitude) chemiluminescence intensity of nitric oxide in the upper atmosphere[46,47]. Under normal (non-adiabatic) conditions the excitation probability is low (of the order of 10^{-5} excited molecules[41] per collision between NO and O). However, the probability of the overall reaction $NO + O \rightarrow NO_2$ is also of the same order, and therefore not less than one-half of the molecules of product are formed via an electronically excited state[48], and most of the collisions do not lead to a reaction.

The great importance of chemiluminescent reactions stems from that fact that they occur both in artificial and in natural processes. Many reactive particles are formed in the upper atmosphere under the influence of u.v. radiation from the sun. Their chemiluminescence provides information on the composition of the atmosphere, on the movement of air masses, and on solar activity. An interesting new method of investigation is the slow release of an active material from a rising rocket, and observation of the bright chemiluminescence produced by the reaction between this material (nitric oxide, triethylboron, trimethylaluminium, sodium or aluminium vapour) and atoms present in the atmosphere[46,47,49]. "Air afterglow" is observed in the wake of bodies moving at supersonic speeds: atoms and radicals are produced by thermal dissociation of the oxygen in the compressed layers of air ahead of the moving body, and the resulting chemiluminescence gives information on the streamline properties of the body, on the transition from laminar to turbulent flow, etc.[50,51] Lastly, observations of chemiluminescence can lead to numerical values of chemical bond energies, rate constants, and to spectroscopic information on the structure of molecules and radicals[27].

5. *Excitation of singlet oxygen*

The chemical excitation of molecular oxygen calls for a special discussion, because it has recently been shown to play an important role in some liquid-phase chemiluminescent reactions as well as in the gas phase.

O atoms can be produced by an electrical discharge in O_2. Under favourable conditions up to 10% of the O_2 molecules formed by recombination are obtained in the $^1\Delta_g$ state, and up to 0.1% in the $^1\Sigma_g^+$ state[52]. Emission from singlet states is both spin- and parity-forbidden and has a very low probability. For example, the radiative life time τ_0 for the magnetic-dipole $^1\Delta \rightarrow {}^3\Sigma$ transition (1270 nm band) is 5.3×10^3 s.

It has recently been shown[52-54] that, in addition to isolated singlet molecules, double molecules as a collision pair (but not forming a complex) are able to emit light. Careful study of the emission spectra has revealed bands corresponding to transitions between vibrational sublevels of the electronic states of O_2 molecules and O_4 dimers (Fig. 8).

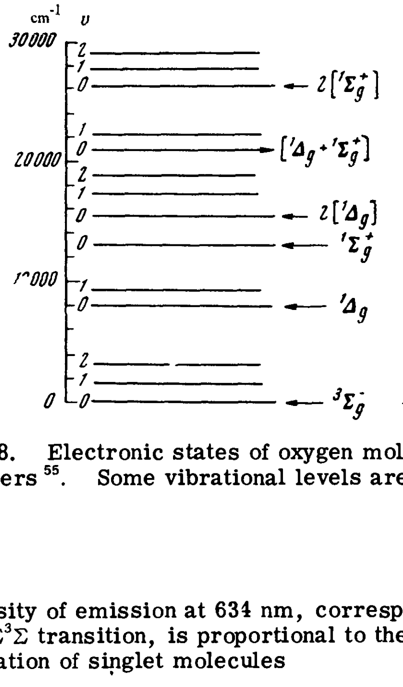


Figure 8. Electronic states of oxygen molecules and dimers[55]. Some vibrational levels are indicated.

The intensity of emission at 634 nm, corresponding to the $^1\Delta{}^1\Delta \rightarrow {}^3\Sigma{}^3\Sigma$ transition, is proportional to the square of the concentration of singlet molecules

$$I_{634} = k[O_2{}^1\Delta]^2$$

where $k = 0.28$ litre mole^{-1} s^{-1}.[54] (According to Falick and Mahan[56], this constant has the value 0.03 litre mole^{-1} s^{-1}.) From the scheme

$$2O_2{}^1\Delta \underset{k_2}{\overset{k_1}{\rightleftharpoons}} (O_2{}^1\Delta)_2 \xrightarrow{k_3} (O_2{}^3\Sigma)_2 + h\nu \qquad \text{(VII)}$$

we easily obtain formula (7), with $k = k_1k_3/k_2$. Hence, taking $k_1 = 10^{11}$ litre mole^{-1} s^{-1} and $k_2 = 10^{13}$ s^{-1}, we obtain $k_3 = 28$ s^{-1}, or $1/k_3 = 3.6 \times 10^{-2}$ s for the lifetime of the radiation, which is 5 orders of magnitude shorter than for the transition in an isolated molecule. Since the pair $O_2^*O_2^*$ exists only as a collision state, $1/k_2 \simeq 10^{-13}$ s, and only one collision between excited oxygen molecules in $k_2/k_3 \simeq 10^{11}$ leads to emission. The $O_2{}^1\Delta$ molecule is fairly stable: collisional deactivation by oxygen and nitrogen molecules occurs with rate constants of 10^3 and 10^1 litre mole^{-1} s^{-1} respectively[57]. Hence, only one in 10^8 collisions between singlet and non-excited O_2 molecules causes deactivation of $O_2{}^1\Delta$, and the concentration of singlet oxygen can reach relatively high values. From the ratio of the emission intensities from dimeric and monomeric O_2 molecules

$$\frac{I_{634}}{I_{1270}} = \frac{k[O_2{}^1\Delta]^2}{\tau_0^{-1}[O_2{}^1\Delta]} = k\tau_0[O_2{}^1\Delta] \qquad (12)$$

combined with the above values of k and τ_0, we conclude that the ratio becomes greater than unity when the pressure of singlet oxygen exceeds a few tens of mmHg. In low-pressure experiments the quantum intensity of the 634 nm emission is always lower than the quantum intensity of the 1270 nm emission, but the former is easier to detect because photoelectric cells are much more sensitive in the visible than in the infrared region.

Evidently, this emission mechanism allows the photon energy to be much greater than the energy evolved in the elementary chemical act. This is the exception to the rule outlined at the beginning of this article.

B. Reactions in the Liquid Phase (Electronic Excitation)

The quantitative study of the elementary excitation acts in solutions is very much harder than the study of chemiluminescent gas-phase reactions.

Most liquid-phase reactions involve polyatomic molecules. The quantum-mechanical description of polyatomic molecules relies on approximate computational methods, in which the transition from the simplest one-electron system to more complex systems is made by various means. There is no exact theory of the elementary act in condensed systems. Neither the transition state theory nor the collision theory is able, in practice, to predict reaction rates from the structure of the reacting species. A direct calculation of the motion of the representative point of the system along the potential energy surface, such as has been done for the H + $H_2 \rightarrow H_2$ + H reaction, is impossible in a more complicated system. The same is true of an exact calculation of the influence of the solvent.

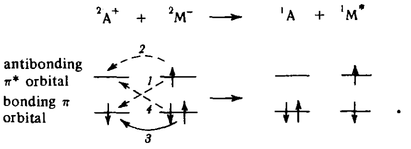
Most chemiluminescent liquid-phase reactions in solutions are complicated processes involving many intermediate steps whose mechanism is as yet far from clear. Both the reactions themselves and their chemiluminescence are characterised by complex kinetics, and quantitative data on chemiluminescence and excitation yields are very difficult to obtain.

For this reason, the standards and the criteria used in liquid-phase chemiluminescence studies are quite different from those used in gas-phase systems. Workers studying simple gas reactions aim to understand every detail of their mechanism—a realistic albeit laborious objective. On the other hand, with the complex molecules involved in liquid-phase reactions one must be content with a simple, qualitative interpretation. Workers rely heavily on analogies: on the one hand, with the simpler gas-phase systems, on the other hand with photochemical and photophysical processes. (Note that chemiluminescence is "photochemistry in reverse".)

Relatively few of the steadily increasing number of papers on liquid-phase chemiluminescence have attempted to study the phenomenon in reactions where the mechanism is known. However, a number of well chosen model systems have been described in recent years, and several types of excitation mechanism have been shown to have wide application. We shall consider a few examples of these mechanisms below. A more detailed description of the specific features of chemiluminescence in solutions can be found in various reviews[57-66] and in Gundermann's monograph[67].

1. *Electron transfer*

Consider the transfer of an electron from an anion-radical M^- (or $^2M^-$, where the left-hand superscript denotes the multiplicity) to a cation-radical A^+ (or $^2A^+$). A^+ has a deficiency of one electron with respect to the molecule A, and M^- has one electron in excess; the last bonding orbital and the first antibonding orbital are filled, as shown below:



$$^2A^+ + {}^2M^- \longrightarrow {}^1A + {}^1M^* \qquad \text{(VIII)}$$

The transition can occur in several ways. Transition *1* gives only non-excited products (not shown). However, if the excitation potential of at least one of the product molecules is less than the difference between the ionisation potential and the electron affinity (or, if M^- and A^+ have the same solvation energy, less than the difference between the oxidation and the reduction potential), it is possible to obtain an excited and a non-excited molecule (path *2* and path *3*, the latter shown in the diagram), or even two electronically excited molecules (path *4*)†.

Excitation by the mechanism of radical-cation and radical-anion annihilation was first demonstrated by Chandross and Sonntag[68]. These workers observed singlet–singlet emission from 9,10-diphenylanthracene (DPA) during the reaction between potassium diphenylanthracene (source of DPA^-) and the 9,10 dichloride of DPA (source of DPA^{2+}). Weller and Zachariasse[69] observed chemiluminescence during the reaction of the anion-radicals (M^-) of chrysene, picene, pyrene, 1,2-benzanthracene, anthracene, perylene, and tetracene with the cation of Würster Blue (D^+). Chemiluminescence had been predicted by the authors before the experiment: since the fluorescent state of the aromatic hydrocarbons M^* is quenched by electron donors D through the formation of a charge-transfer complex M^-D^+, the authors suggest that the opposite process—the interaction of M^- and D^+—can lead to chemical excitation.

The electrochemical production of ion-radicals is an effective way of studying the chemiluminescence associated with electron transfer. Chemiluminescence accompanying electrolysis has been reported by several workers (see review in Ref. 65), but the recent work by Hercules[70] on the chemiluminescent annihilation of aromatic ion-radicals has produced a veritable avalanche of reports of electrochemiluminescence. Electrochemical excitation using a.c. is particularly revealing, because both cations and anions are produced at any one site of the layer adjacent to the electrode during each half cycle (by the reactions $M + e^- \rightarrow M^-$, $M \rightarrow M^+ + e^-$, and $M^- \rightarrow M^+ + 2e^-$). The electrochemiluminescence is particularly intense if the voltage applied to the electrodes is sufficient to produce both types of ion-radical. When one type only is produced, the observed chemiluminescence is weaker by several orders of magnitude. The mechanism of this "pre-annihilation"[71] electrochemiluminescence is still unclear (see discussion in Ref. 72), and so are also many other features of the phenomenon such as the roles of the solvent, of impurities, of the products, etc. (see discussion of Hoytink's paper at a Discussion of the Faraday Society[73]).

Hoytink[73] summarises current views on the thermodynamics and kinetics of electrochemiluminescence by discussing the annihilation of the radical-ions of aromatic hydrocarbons (M). The heat of reaction ΔH does not differ significantly from the difference between the oxidation and the reduction potential of M, which are themselves close to the oxidation and the reduction half-wave potential respectively. It is evident from Table 3 that the exothermicity is sufficient to populate the triplet states, and in some cases also the singlet excited states. The formation of either state during reaction is determined by the relative rates, which can be assessed by considering the intersection of the potential energy surfaces (where the initial and the final state have the same nuclear conformation). The energy change accompanying electron transfer depends mainly on the change in the orientation of the solvent: according to Marcus' theory[74], this change can be characterised by the average distribution of the electron (m) between the participants to the reaction. For example, for the initial state $M^+ + M^-$ the energy minimum corresponds to $m = 0$, whereas for the final state M + M, to $m = 1$. The energy change is proportional to m^2, i.e. it has a parabolic form, which differs for the various combinations of states of the products (singlets, triplets, excimers). The position of the parabolas (Fig. 9) for strongly exothermic reactions shows that the energy barriers separating the initial state ($M^+ + M^-$) from the electronically excited products (curves *3* and *4*) are much lower than the barrier between the initial reactants and the non-excited products (curve *2*). Hence, excitation occurs with 100% probability at the intersection points (to the approximation of the statistical spin factor). On the other hand, the rate of formation of the non-excited product is low, because of tunnelling transition is required (the intersection point is not reached in practice). This transition is similar to the transition involved in the internal conversion from the S_1 state to the S_0 state (see Ref. 4, p. 82–84).

Table 3. Energy balance during cation–anion annihilation[73].

Hydrocarbon	Half-wave potential, V		$-\Delta H$, eV	Energy, eV	
	oxidation	reduction		singlet	triplet
Benzene	2.26	(—3.16)	5.4	4.7	3.6
Naphthalene	1.57	—2.60	4.2	3.9	2.6
Phenanthrene	1.49	—2.48	4.0	3.6	2.7
Pyrene	1.14	—2.10	3.2	3.3	2.1
Anthracene	1.10	—1.98	3.1	3.3	1.8
Perylene	(0.77)	—1.67	2.4	2.9	—
Tetracene	0.80	—1.58	2.4	2.6	1.3

This phenomenon has a clear physical meaning. The elementary act of electron transfer does not involve a change in the nuclear coordinates: therefore, it is fast, and the slower processes of energy dissipation among the bonds cannot compete with the faster processes in which the reaction energy is set free in the form of electronic excitation energy[68]. A somewhat different explanation can also be given[75]: when the product is formed in the ground state the whole of the (electronic!) energy of the reaction must be converted into vibrational energy. This process has a low probability, as shown by the low rate

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†For examples, see Fig. 9 below.

constant for the internal conversion illustrated in Fig. 2 (of the order of 10^5 s^{-1}). On the other hand, when the electronically excited state is populated the greater part of the electronic energy of the reaction is converted into electronic energy of the product.

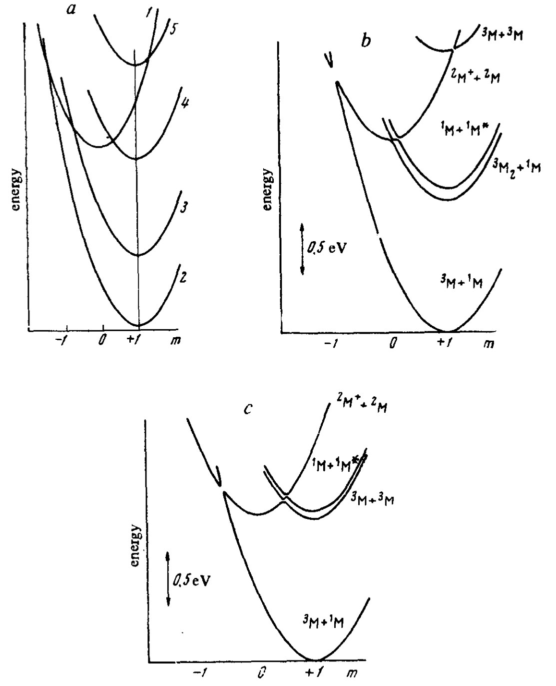


Figure 9. Potential energy curves for a typical radical-ion annihilation (*a*) and for the annihilation of naphthalene (*b*) and tetracene (*c*) radical-ions. Figs. *b* and *c* show the non-intersection ("repulsion") of the curves. *1*) Initial state, *2*) non-excited products, *3*–*5*) electronically excited products.

As regards the emission stage, we can say the following. The life time of the triplets (^3M) is large, and in liquids these species are effectively quenched. Hence, their contribution to the electrochemiluminescence results from triplet–triplet annihilation, yielding a singlet excited molecule $^1M^*$:

$$^3M + {}^3M \rightarrow {}^1M^* + {}^1M\,.$$

Direct emission from the triplet state has a low intensity in solutions, although in principle it can be enhanced by exchange interaction between the triplet molecule and radical-ions or other triplet molecules. The main contribution to the electrochemiluminescence comes from directly excited singlets ($^1M^*$) and singlet excimers ($^1M_2^*$). The electrochemiluminescence spectrum is qualitatively similar to the photofluorescence spectrum[76], but the relative importance of monomers and excimers is different in these two different types of excitation.

It is evident from Fig. 9 that the barrier to the reverse reactions of the type

$$^3M + {}^3M \rightarrow M^- + M^+$$

can be relatively low. Processes of this type have been observed in the photoexcitation of fluorescein[77], eosin[78], and Methylene Blue[79].

The rapid progress made in the study of electrochemiluminescence is largely due to the practical advantages of the method: the particles whose interaction produces the elementary excitation act can be prepared at a known and controllable rate.

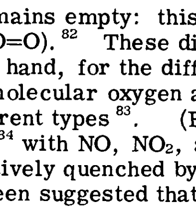
Electrochemiluminescence can be characterised by its yield, defined as the average number of photons emitted per electron transferred from one electrode to the other[71]. Its value can be calculated from the absolute luminescence intensity and the electrolysis current. For example, in the electrolysis of *N*-methyl-1,3-di-*p*-anisyl-4,7-diphenylisoindole in dimethylformamide solution the emission amounts to 3×10^{-3} photon per electron. Allowing for the fluorescence yield, this is equivalent to 0.6% conversion of the electrical energy into excitation.

2. *Excitation of molecular oxygen*

The formation of singlet oxygen molecules in liquid-phase as well as in gas-phase reactions has recently been demonstrated. For example, when a stream of molecular chlorine is passed through an alkaline aqueous solution of hydrogen peroxide, oxygen in the $^1\Delta$ state is obtained in at least 10% yield[80]. The chemiluminescence of reactions of this type has been successfully investigated, mainly because the emitter is a simple molecule in which the nature and the energetics of the excited states are well known. The electronic configuration of the O_2 molecule is obtained by combination of the atomic orbitals of the O atoms:

$$2O\,(1s^22s^22p^4) \rightarrow O_2\,(KK\,(\sigma 2s)^2\,(\sigma^*2s)^2\,(\sigma 2p)^2\,(\pi_y 2p)^2\,(\pi_z 2p)^2\,(\pi_y^* 2p)\,(\pi_z^* 2p));\ {}^3\Sigma_g^-.$$

Thus, we obtain eight bonding and four antibonding orbitals, and the bond order is two. The nature of the $^3\Sigma$, $^1\Delta$, and $^1\Sigma$ states is determined by the occupancy of the upper antibonding orbitals[81]:



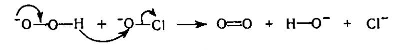
(IX)

In the $^1\Sigma$ state the unpaired electrons reside in different orbitals, spatially distinct, and this state (like the $^3\Sigma$ ground state) can be thought to have the properties of a biradical (·O–O·). On the other hand, in the $^1\Delta$ state the two electrons occupy the same antibonding orbital, while the other orbital remains empty: this structure is similar to that of ethylene (O=O).[82] These differences are responsible, on the one hand, for the different reactivities of the three states of molecular oxygen and their participation in reactions of different types[83]. (For example, the $^1\Delta$ state does not react[84] with NO, NO_2, and H_2O, whereas the $^1\Sigma$ state is effectively quenched by water[53].) On the other hand, it has been suggested that the different states of O_2 are produced in reactions of different types[82].

According to McKeown and Waters[82], the production of "biradical" oxygen is most likely in one-electron elementary acts involving free radicals, for example

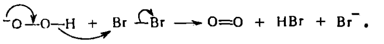
$$[Fe(CN)_6]^{3-} + {}^{\cdot}O{-}OH \rightarrow [Fe(CN)_6]^{4-} + {}^{\cdot}O{-}O^{\cdot} + H^+\,.$$

The formation of "ethylene-like" singlet oxygen is more likely in heterolytic reactions, i.e. in elementary acts involving the participation of electron pairs, as in the reaction between H_2O_2 and alkaline hypochlorite solutions:



$$^{-}O{-}O{-}H + {}^{-}O{-}Cl \longrightarrow O{=}O + H{-}O^{-} + Cl^{-} \qquad (X)$$

or in the reaction between H_2O_2 and halogens:



$$^{-}O{-}O{-}H + Br{-}Br \longrightarrow O{=}O + HBr + Br^{-}. \qquad (XI)$$

As in the case of gas-phase reactions, the emission spectra of liquid-phase reactions contain bands due to both free molecules and dimers of oxygen.

It follows from Eqn. (12) that the ratio of the photocurrents at 634 and 1270 nm in the chemiluminescence spectrum is proportional to the concentration of singlet oxygen:

$$i_{634}/i_{1270} = a\,[O_2^1\Delta] \qquad (13)$$

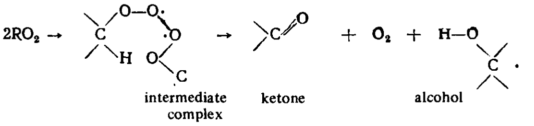
where a is a coefficient depending on the spectral sensitivity of the detector but independent of the geometry of the apparatus and of quenching by collisions. This coefficient can be evaluated by calibrating the apparatus for the 1270 and 634 nm bands using an electrical discharge in gaseous O_2. Hence, the concentration of singlet oxygen and the yield (10%) of $O_2{}^1\Delta$ in the reaction between hydrogen peroxide and chlorine can be determined experimentally[80]. It should be noted, however, that in this liquid-phase reaction the emission occurs from the gas bubbles (chlorine) rising through the solution. In these circumstances the fate of the singlet O_2 molecules is determined by the same rate constants as in the gas-phase reaction (section III.5). The rate constants of processes involving singlet oxygen as a true solute have not yet been measured.

The discovery of chemiluminescence was responsible for the interest in the problem of singlet oxygen and its participation in physical, chemical, and biological processes‡.

The "double" energy of the dimers (from 45 kcal mole^{-1} for $^1\Delta^1\Delta$ to 75 kcal mole^{-1} for $^1\Sigma^1\Sigma$) can facilitate reactions with a large activation energy. Khan and Kasha[55] attempted to formulate a general theory of chemiluminescence in reactions leading to the production of singlet oxygen. They assume that the emitter can be either the O_2O_2 pair or an acceptor species carrying the energy of the excited dimer. However, they were unable to produce a quantitative proof of these views: undoubtedly, this is because the kinetics and the mechanism of the overall reaction are complex, and the elementary excitation act cannot be isolated for study.

3. *Excitation of carbonyl compounds during the oxidation of organic materials*

The oxidation of organic compounds in solution by molecular oxygen is often accompanied by weak chemiluminescence[60,61,88]. Excitation occurs in one of the elementary steps of the complex chain reaction involved: during the disproportionation of peroxidic radicals (RO_2):



(XII)

The emitter of chemiluminescence in the visible region of the spectrum is a ketone in the triplet state.

This reaction can be studied conveniently because its rate w, and therefore also the chemiluminescence intensity I (see Eqn. 2), can be controlled by adding chain oxidation initiators (peroxides or azo compounds). In the presence of strongly luminescent energy acceptors A, formula (2) applies exactly, and the emission yield η_P of the ketone can be determined by varying the concentration of A (and thus varying the efficiency η_{PA} of the energy transfer). The low value of η_P (19^{-5}–10^{-3}) is due to the low probability of triplet–singlet emission and to strong deactivation by molecular collisions with the solvent. The excitation yields can be evaluated by formula (2) once the absolute chemiluminescence intensity I, the rate w, and the yield η_P are known. The values 10^{-3}–10^{-2} were obtained[89,90] for the excitation yield of ketones (acetophenone, cyclohexanone, benzophenone, diacetyl) in the oxidation of the hydrocarbons ethylbenzene, cyclohexane, diphenylmethane, and ethyl methyl ketone respectively.

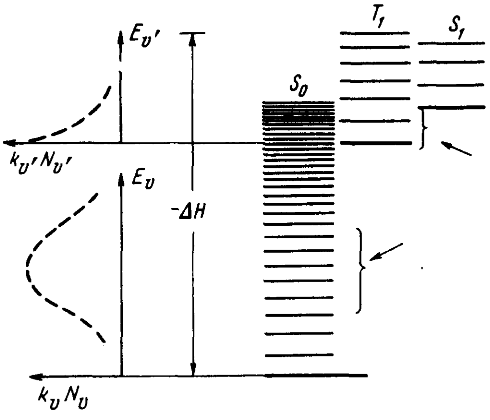


Figure 10. Population of the energy states of a ketone during the disproportionation of peroxide radicals. Probable energy dependences of the rate at which the vibrational levels are populated are shown on the left for the S_0 and T_1 electronic states. The arrows denote the levels with the highest occupancy probability.

Hence, the excitation yields are fairly large, considering that an energy of between 55 and 75 kcal mole^{-1} (depending on the structure), or 60–70% of the heat of reaction (XII), needs to be concentrated on the ketone (one of the three products) in order to excite it. The quantity η_P^{exc} can be treated[88,90] as the ratio of the rates at which the S_0 and T_1 states of the ketone are populated (Fig. 10):

$$\eta_P^{exc} = \left(\sum_{v'=0}^{\infty} k_{v'}N_{v'}\right) \Big/ \left(\sum_{v=0}^{\infty} k_vN_v\right)$$

where $k_{v'}$ and k_v are the rate constants which describe the population of the vibrational levels of the T_1 and S_0 states respectively, and N_v is the number of configurations of the intermediate complex for which the ketone molecule acquires an energy equal to the energy of the vibrational

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‡These problems attracted lively discussion in the literature of the 1930's and 1940's (see Section 79 and others in Terenin's monograph[3]). More recent reviews can be found in Refs. 85–87.

level v (or v'). Using rate constants averaged over the number of configurations, we arrive at

$$\eta_P^{\mathrm{exc}} = (\bar{k}_{v'}/\bar{k}_v)\left(\sum_{v'=0}^{\infty} N_{v'}\right)\Big/\left(\sum_{\bar{v}=0}^{\infty} N_v\right) = \frac{k_{v'}}{\bar{k}_v} n_T$$

where n_T denotes the fractional number of the states of the intermediate complex for which the energy acquired by the ketone is at least equal to the energy of the triplet state of the ketone. This fraction is evidently very small, since electronic excitation of the ketone requires much more than half the energy of reaction (XII). Yet, the low value of n_T is compensated by the ratio $\bar{k}_{V'}/k_V$; there are grounds for expecting this ratio to be much larger than unity:

1. The energy of the reaction is, essentially, electronic, since the rearrangement of the intermediate complex to give the final products involves a change in the electronic structure of the given combination of atoms. Studies of the radiationless deactivation of electronically excited organic molecules have shown that Franck–Condon factors play an important role in the conversion of electronic energy into vibrational energy. These factors inhibit the conversion to an extent which varies inversely with the energy (see Section 4–3 of Ref. 4). The rate constants $k_{V'}$ and k_V relate, on the average, to processes in which a small and a large fraction respectively of the energy of the reaction are converted into vibrations (Fig. 10).

2. If we accept the analogy with gas-phase exchange reactions (Section III.A.2), and assume that the bonds formed in reaction (XII) are not ionic, and are more similar to those of reaction (II) than to those of reaction (III), we again conclude that the conversion of a large fraction of the energy of reaction (XII) into vibrational energy has a low probability, and hence its rate constant is low.

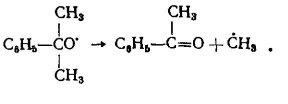
3. Lastly, as was stated above (Section III.B.1), the high yields of electrochemiluminescence are due to the fact that the conversion of large amounts of electronic energy into vibrational energy is unnecessary.

The low occupation probabilities of the upper vibrational levels of the electronic ground state indicate that in the overwhelming majority of elementary acts of type (XII), when the energy acquired by the ketone is insufficient to cause electronic excitation, the reaction does not take place and the peroxide radicals simply separate after an encounter. This may be one of the reasons why the absolute rate constant for the disproportionation of peroxide radicals is much lower than the rate constant for diffusion, even though the radicals experience tens or even hundreds of collisions at each encounter, and the activation energy for disproportionation is equal to the activation energy for diffusion.

It should be noted that detailed studies of chemiluminescence have been made only on hydrocarbons whose oxidation involves secondary peroxide radicals, so that disproportionation takes place in a six-membered complex (reaction XII). With tertiary radicals this complex cannot form, and chain termination is brought about by the reactions

$$2\mathrm{ROO}^{\cdot}\rightarrow\mathrm{ROOOOR}\begin{array}{l}\nearrow \mathrm{ROOR}+\mathrm{O_2}\\ \searrow 2\mathrm{RO}^{\cdot}+\mathrm{O_2}\end{array}. \qquad \mathrm{(XIII)}$$

In the oxidation of cumene, for example, the oxy-radical can dissociate as follows:



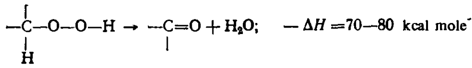
$$\mathrm{C_6H_5{-}\overset{\overset{\displaystyle CH_3}{|}}{\underset{\underset{\displaystyle CH_3}{|}}{C}}O^{\cdot}} \rightarrow \mathrm{C_6H_5{-}\overset{\overset{\displaystyle CH_3}{|}}{C}{=}O + \dot{C}H_3}\,.$$

This reaction is exothermic by about 10 kcal mole^{-1}, and the suggestion[91] that it is the source of excitation of acetophenone at 150° is clearly untenable. In this temperature region the decomposition products of tertiary peroxides have been shown to contain ethers, whose presence is ascribed[92] to the disproportionation of oxy-radicals e.g.

$$2\,(\mathrm{CH_3})_3\mathrm{CO}^{\cdot} \rightarrow (\mathrm{CH_3})_2\mathrm{C{=}O} + \mathrm{CH_3{-}O{-}C\,(CH_3)_3}\ .$$

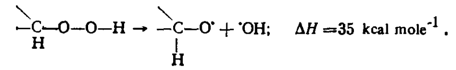
If a reaction of this type is possible in the case of cumyl oxy-radicals, it may indeed give rise to excitation of acetophenone, since its enthalpy change is at least 80 kcal mole^{-1}.

Alternative excitation mechanisms are suggested in the current literature for the chemiluminescence of oxidation reactions. Bowen and Lloyd[93-95] and Reich and Stivala[96] assume that the ketone is excited by the molecular decomposition of a hydroperoxide (a reaction product):

 (XIV)

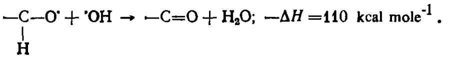
$$\mathrm{{-}\overset{|}{\underset{\underset{\displaystyle H}{|}}{C}}{-}O{-}O{-}H \rightarrow {-}\underset{|}{C}{=}O + H_2O}; \quad -\Delta H = 70{-}80\ \mathrm{kcal\ mole^{-1}}. \qquad \mathrm{(XIV)}$$

Reaction (XIV) has a relatively large activation energy, and could be significant at high temperatures. However, there is no direct proof that it takes place as a single elementary act[97]. Many peroxides decompose by a radical mechanism rather than by the molecular mechanism (XIV):



$$\mathrm{{\setminus}\!\!{-}\underset{H}{C}{-}O{-}O{-}H \rightarrow {\setminus}\!\!{-}\underset{\underset{\displaystyle H}{|}}{C}{-}O^{\cdot} + {}^{\cdot}OH}; \quad \Delta H = 35\ \mathrm{kcal\ mole^{-1}}.$$

Disproportionation of the radicals produced by this reaction gives the same final products as reaction (XIV):



$$\mathrm{{-}\underset{\underset{\displaystyle H}{|}}{C}{-}O^{\cdot} + {}^{\cdot}OH \rightarrow {-}C{=}O + H_2O}; \quad -\Delta H = 110\ \mathrm{kcal\ mole^{-1}}.$$

The radicals can also behave as oxidation initiators, and the observed chemiluminescence could simply be the result of the disproportionation of peroxide radicals.

Two more mechanisms are noteworthy. Stauff and coworkers[98] described the reaction

$$2\mathrm{RO_2} \rightarrow \mathrm{R_2} + \mathrm{O_2^*{-}O_2^*} \qquad \mathrm{(XV)}$$

and Lloyd[95] postulated the reaction

$$\mathrm{ROOH} \rightarrow \mathrm{RH} + \mathrm{O_2^*} \qquad \mathrm{(XVI)}$$

as paths for the formation of singlet oxygen. Unfortunately, no evidence whatever is quoted of the reality of these processes. It is hard to believe that deeply oxygenated compounds can lose the whole of their oxygen in elementary processes of the type of (XV) or (XVI). Reaction (XVI) could conceivably take place at high temperatures and in the presence of a powerful catalyst, but not on a glass wall at 80°.

Partial excitation of molecular oxygen in reactions of type (XII) has been proposed[60,61], and more recently Howard and Ingold[99] have confirmed this view by a chemical argument. The initial spin state in reactions (XII) and (XIII) is singlet or triplet (combination of two doublet states of free radicals), and the spin conservation rule predicts the formation of products in both the singlet and the triplet state, although the final system is profoundly affected by the energy distribution factors.

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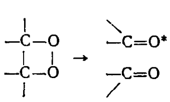
In spite of the uncertainties still present in chemiluminescence problems, particularly as regards liquid-phase reactions, there are indications that the generality (or, conversely, the specificity) of the factors leading to efficient excitation in various reactions will become better understood during the next few years. We may assume that one of these factors will be shown to be the participation of ions, radical-ions, or charge-transfer complexes: as the data discussed in this review suggest, these species favour the retention of the reaction energy as internal energy of the products.

Whilst this paper was in press, new calculations of the energy distribution of the products of exchange reactions have been published[100,101], and also a review[102] and new work on chemical lasers including the first report of purely chemical laser action[103,104] and of continuously operating chemical lasers[105,106]. Luminescence of nitrogen dioxide has been observed in crossed molecular beams[107]. In addition to the fully characterised electronic and vibrational excitation, chemical reactions can also generate non-equilibrium occupancy of nuclear spin states: studies of chemical pumping of this type were started[108] in 1967 and are attracting considerable attention at the moment[109]. Many of the recent results point to the decomposition of a cyclic peroxide group, e.g.



as the commonest elementary excitation act in liquid-phase chemiluminescence.

A process of this type is characteristic of the chemiluminescence produced by the oxidation of the light-emitting substance found in the firefly and its analogues (e.g. lophine),[110-114] of organic anhydrides and amides[115] (in this case the strongly fluorescent molecule acts as "catalyst" and as emitter by gaining electronic energy from the products which are not amenable to excitation), and other reactions. The high excitation efficiency accompanying the decomposition of the peroxide ring follows from the rule of orbital symmetry conservation[116]. Different views on the mechanism of the chemiluminescence attending the oxidation of organic compounds have been critically discussed[117], and Kellogg[118] comes to the surprising conclusion that the excitation yield of the ketone approaches 100%, with quenching by oxygen retained in the solvent cage. Interesting new data are presented in a review of the physical aspects of chemiluminescence[119].

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Institute of Chemical Physics
of the USSR Academy of
Sciences, Moscow

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Reaction of Fluorine and Non-metal Fluorides in an Electric Discharge

I.V.Nikitin and V.Ya.Rosolovskii

Fluorine reacts readily with the majority of substances at room or moderately elevated temperatures. Only in a few cases is special activation of the reactants necessary. An electric discharge may be used for this purpose. This review deals with studies of reactions involving elemental fluorine and fluorides in a gas discharge. Reactions which may be of preparative value are mainly considered.
The bibliography includes 113 references.

CONTENTS

I. INTRODUCTION

The use of electrical discharges in gases for preparative purposes in inorganic chemistry is generally known. The activating effect of the discharge makes possible reactions which cannot be achieved by thermal activation of the starting material or in the absence of a discharge by high temperatures and pressures alone.

Fluorine readily interacts with the majority of substances at room or moderately elevated temperatures. An exception are the reactions of fluorine with its nearest neighbours in the Periodic System: nitrogen, oxygen, and noble gases. In those cases where thermal activation of the starting materials does not lead to reaction or the expected products are unstable at high temperatures and therefore cannot be isolated, factors acting upon the reactant, such as an electric discharge or irradiation, become particularly important.

At low pressures and currents the plasma of a glow discharge is characterised by a low molecular temperature, amounting usually to several hundred degrees Kelvin, and a considerably higher electronic temperature. When the reaction is carried out in a discharge, the walls of the reactor may be cooled to very low temperature. Thus in syntheses in a discharge two conditions necessary for the formation of thermally unstable compounds are immediately fulfilled; in a low-temperature discharge plasma high concentrations of active species are established and the possibility of rapid quenching prevents the decomposition of the compounds formed.

The present review deals with studies on the reactions of fluorine with nitrogen, oxygen, krypton, xenon, and chlorine in an electric discharge. At normal temperatures and pressures molecular fluorine does not react with the above elements. In a discharge fluorine becomes more active due to its dissociation into atoms. The excited $^1\Pi_u$ state of the F_2 molecule has a repulsive potential curve[1]. The transition $^1\Sigma_g^+ \rightarrow {}^1\Pi_u$ leads to the dissociation of F_2 into two non-excited fluorine atoms (in the $^3P_{3/2}$ state). One cannot exclude the possibility that ionised atoms and fluorine molecules present in the discharge participate in the reaction. For example, the emission spectrum of fluorine excited by an electric discharge[2] shows emission bands which were assigned to the F_2^+ ion.

The inclusion in the review of a section dealing with the reactions of nitrogen fluorides was dictated by the considerable interest which the reactions of this group of fluorides have attracted in recent years.

II. INTERACTION OF FLUORINE WITH NITROGEN

Many reactions leading to the formation of both binary† nitrogen fluorides and those containing other elements have been investigated. A characteristic feature of these reactions is the synthesis of nitrogen fluorides from nitrogen-containing compounds[3-5]. This review deals with the reactions of fluorine with elemental nitrogen.

The synthesis of nitrogen fluorides from the elements is thermodynamically possible. A mixture of fluorine and nitrogen constitutes a system in a state of metastable equilibrium which must overcome a high activation barrier for reaction to occur. If the reaction between fluorine and nitrogen occurs then, in accordance with the large negative free energy of nitrogen trifluoride ($\Delta G^\circ_{298} = -21.38$ kcal mole^{-1}) [6], a stoichiometric mixture of fluorine and nitrogen will be fully converted at room temperature into nitrogen trifluoride. The equilibrium constants[6] for the reaction $\frac{1}{2}N_2 + \frac{3}{2}F_2 \rightleftharpoons NF_3$ at a pressure of 1 atm at 298°K is of the order of 10^{14}. The absence of an appreciable reaction between fluorine and nitrogen is evidently due to kinetic factors.

Attempts were made as early as the beginning of the century to obtain nitrogen fluoride in a discharge[7]. A study was made of the effect of an arc on a mixture of gaseous fluorine and nitrogen and also of a spark discharge on a liquid mixture of the same substances. However, the formation of nitrogen fluoride in these experiments could not be established[7].

The synthesis of nitrogen trifluoride in a glow discharge with a yield of about 30% was reported in 1964 [8]. Mixtures of fluorine and nitrogen were passed through the discharge at a pressure of 20–40 mmHg, the walls of the tube being cooled with liquid nitrogen. Variation of the ratio $F_2:N_2$ in the initial mixture did not lead to the synthesis of nitrogen fluorides other than NF_3. The compound was obtained also in a discharge at a current of 10–15 mA and a pressure of 10–17 mmHg, the reactor being maintained at temperatures ranging from –150 to –196°C.[9]

The synthesis of nitrogen fluoride in a discharge-flow apparatus at a pressure of 15 mmHg has been described[10]. The volume flow rate of the fluorine–nitrogen mixtures was varied from 0.09 to 1.20 litre h^{-1} (the volumes of the gases at s.t.p. are indicated). The nitrogen trifluoride formed in the discharge condensed on the walls of the discharge tube immersed in liquid nitrogen. The conversion of the fluorine–nitrogen mixture rises to 60–70% as the volume flow rate is reduced to about 0.1 litre h^{-1} at a current of 10 or 25 mA. The conversion is almost independent of the composition of the initial fluorine–nitrogen mixtures.

The authors of the review[11] carried out experiments with a stoichiometric mixture ($F_2:N_2 = 3:1$). The gases were passed through a discharge tube and the NF_3 formed was condensed in a trap at –196°C at a distance of 12 cm from the discharge zone. After the removal of the cold trap from the discharge, the yield of NF_3 fell. An increase of the current from 4 to 12 mA entails an increase of conversion, which, however, falls as the current is raised further to 25 or 40 mA. This phenomenon may be explained by an increase in the importance of the reverse reaction with increasing power of the discharge[11].

Since a high conversion of fluorine–nitrogen mixtures in a glow discharge is attained at low flow rates, the absolute yield of NF_3 per unit time is low. The synthesis of nitrogen trifluoride in a discharge is scarcely practicable for the preparation of the substance in large amounts. Usually the compound is obtained by the electrolysis of an ammonium hydrogen fluoride melt. Nitrogen fluoride was in fact, first synthesised in this way[12]. The electric discharge method has a certain advantage in that the compound obtained in a glow discharge is free from impurities, which are present in the substance synthesised electrolytically.

Nitrogen trifluoride is formed in very low yields (1.5–2%) in a silent (electrodeless) discharge when a mixture of fluorine and nitrogen is circulated through an ozoniser[13].

$\Delta G^\circ_{298} = 18.72$ kcal mole^{-1} for the formation of tetrafluorohydrazine from the elements, ΔG°_T becoming negative only at temperatures below –243°C [6]. However, when the experiments in a gas discharge are carried out under conditions of rapid flow, it is possible to obtain a low yield of tetrafluorohydrazine from the elements. The NF_2 radicals formed as an intermediate in the reaction between fluorine and nitrogen are stabilised to N_2F_4 as a result of the rapid cooling of the reaction mixture on quenching. Thus a stream of nitrogen was passed[14] through an arc discharge (300 A, 40 V) at a rate of 15 litre min^{-1} and mixed with gaseous fluorine. The reaction products entered a trap cooled with liquid nitrogen. The yield of nitrogen trifluoride and tetrafluorohydrazine did not exceed 1%.

About 1% of bound nitrogen was obtained on mixing carbon tetrafluoride with nitrogen plasma[15]. The quenching products contained nitrogen trifluoride, tetrafluorohydrazine, and traces of difluorodiazines. The reaction of sulphur hexafluoride with a nitrogen plasma also gives about 1% of bound nitrogen, largely in the form of the trifluoride[15]. The synthesis of nitrogen trifluoride under the action of an arc rotated by a magnetic field in a mixture of carbon tetrafluoride and nitrogen has been described[16]. The syntheses of nitrogen fluorides in plasma devices are considered in detail in the book edited by Baddour and Timmins[17].

The energy losses per unit volume of the reacting gases in the synthesis of NF_3 in a discharge are very large. Thus a conversion of 54% was achieved[11] at a specific energy[18] of 325 W h litre^{-1}. The high energy losses are evidently due to the need to activate the nitrogen molecules. The published data are as yet insufficient to decide which active forms of nitrogen participate in the synthesis of nitrogen trifluoride. The intermediates in the reaction of fluorine with nitrogen may be the radicals NF and NF_2. NF radicals have been detected both in the emission spectrum of nitrogen fluoride which has passed through a microwave discharge[19,20] and in the emission spectrum of the flame formed when hydrogen burns in nitrogen trifluoride[21]. However, it is difficult to state definitely as a result of which process NF radicals might have been generated in the synthesis of NF_3 in a discharge.

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† Binary nitrogen fluorides are defined as those which consist only of fluorine and nitrogen: NF_3, N_2F_4, N_2F_2, FN_3.

To determine the mechanism of the synthesis of nitrogen trifluoride from the elements, spectroscopic studies on the interaction between fluorine and nitrogen in a discharge would be useful. The reaction of active nitrogen and molecular fluorine has not apparently been investigated[22].

In an electric discharge it is possible to obtain substances in greater yields than those corresponding to thermodynamic equilibrium[18]. For example, nitric oxide synthesised from the elements is formed in amounts greatly exceeding the thermodynamic equilibrium value[18,23]. As already mentioned, at low temperatures the equilibrium $\frac{1}{2}N_2 + \frac{3}{2}F_2 \rightleftharpoons NF_3$ is fully displaced to the right. Electric discharge in a mixture of fluorine and nitrogen displaces the system from a state of metastable equilibrium and brings it closer to thermodynamic equilibrium, i.e., the effect of the discharge is in this case comparable to that of a catalyst.

III. REACTIONS OF NITROGEN FLUORIDES IN A DISCHARGE

Nitrogen trifluoride is decomposed into its elements in a glow discharge. At low flow rates a steady-state degree of decomposition is attained, amounting to about 80% at a current of 15 or 25 mA. [10] The dissociation of NF_3 may be represented by the following sequence of reactions:

$$NF_3 \rightleftarrows F + NF_2 \rightleftarrows 2F + NF \rightleftarrows {}^3/_2F_2 + {}^1/_2N_2.$$

Tetrafluorohydrazine was not detected in the NF_3 decomposition products[10]. The NF_2 radicals, which are suggested by this decomposition mechanism, either undergo further defluorination or combine with a fluorine atom regenerating the nitrogen trifluoride. When the fluorine formed in the decomposition of NF_3 is removed, for example by reaction with mercury vapour, it is possible to obtain tetrafluorohydrazine and difluorodiazines from nitrogen trifluoride[24]. According to the literature[24], the yields of N_2F_4 and N_2F_2 relative to the unreacted nitrogen trifluoride were respectively 51–67 and 12–16%. The discharge tube was maintained at a temperature of about 200°C. At a higher temperature (320–330°C) the reaction

$$2NF_3 + 2Hg = N_2F_4 + Hg_2F_2$$

also takes place without an electric discharge. [25]

The synthesis of tetrafluorohydrazine in the decomposition of nitrogen trifluoride in a discharge may be compared with the synthesis of hydrazine from ammonia in a discharge[26-29]. One of the reasons for the low yield of hydrazine in its synthesis from ammonia is the breakdown of the N_2H_4 formed by hydrogen atoms. Acceleration of the recombination of atomic hydrogen leads to an increased yield of hydrazine. Tetrafluorohydrazine is obtained from nitrogen trifluoride in a discharge provided that the fluorine formed reacts with mercury, which is a fluorine acceptor.

The synthesis of hydrazine from ammonia and of tetrafluorohydrazine from nitrogen trifluoride is described by the following general equation:

$$2AX_3 = A_2X_4 + X_2.$$

Other reactions described by the same general equation occur in an electric discharge: the synthesis of P_2Cl_4 from phosphorus trichloride[30] and of B_2Cl_4 from boron trichloride[31,32]. However, B_2F_4 has not been obtained in a discharge from boron trifluoride[33].

Tetrafluorohydrazine is obtained by heating nitrogen trifluoride in the presence of fluorine acceptors, for example metals[34]. The possibility of synthesising N_2F_4 from NF_3 arises because of the relative stability of NF_2 radicals and the absence of high concentrations of fluorine atoms. On the other hand, in a glow discharge tetrafluorohydrazine is unstable in relation to its decomposition products – nitrogen trifluoride and nitrogen. Tetrafluorohydrazine readily decomposes, with a small expenditure of energy, forming nitrogen trifluoride[11]:

$$N_2F_4 = {}^4/_3NF_3 + {}^1/_3N_2.$$

With increase in the energy density, more far-reaching breakdown takes place:

$$N_2F_4 \rightarrow NF_3;\ NF_3 \rightleftarrows {}^1/_2N_2 + {}^3/_2F_2.$$

The low stability of tetrafluorohydrazine in a glow discharge prevents the occurrence of difluoroamination reactions in a discharge using N_2F_4.

The first reports on the synthesis of the compound F_3NO appeared in 1966.[35-38] The compound is called nitrogen oxytrifluoride or trifluoroamine oxide. The latter name emphasises the formal similarity of F_3NO to the amine oxides $R_3N \rightarrow O$ and is used more often. The possibility of synthesising F_3NO provides evidence as to the valency, coordination unsaturation of the nitrogen atom in nitrogen trifluoride.

Trifluoroamine oxide is formed when a discharge acts upon the following mixtures: fluorine–air[39], fluorine–nitrogen oxides[39], and nitrogen trifluoride–oxygen difluoride[40,41]. The synthesis of F_3NO by the action of a discharge on an equimolar mixture of nitrogen trifluoride and oxygen has been reported and the method has been described in greater detail in a later paper[42]. The mixture of starting materials is passed at a rate of 1.7–3.4 litre h^{-1} through a discharge tube in liquid nitrogen. A pressure of 10–15 mmHg and a current of 30–50 mA are maintained in the apparatus. Under these conditions, about 70% NF_3 reacts, the yield of F_3NO amounting to 10–15%. The reaction products are also nitrogen oxides and dioxygen difluoride. When the discharge tube is thermostatted at –78°C, trifluoroamine oxide is not formed.

The mechanism of the synthesis of F_3NO from nitrogen trifluoride and oxygen in a discharge is obscure. Since nitrogen trifluoride readily dissociates, one cannot exclude the possibility that trifluoroamine oxide is in fact one of the decomposition products of nitrogen trifluoride, formed, for example, in the following way:

$$NF_3 = {}^1/_2N_2 + {}^3/_2F_2;\ {}^1/_2N_2 + {}^1/_2O_2 = NO \qquad NO + F = NOF;\ NOF + 2F = F_3NO.$$

In this case nitrogen trifluoride serves simply as a source of fluorine and nitrogen. One can also imagine a direct synthesis of F_3NO—by the reaction of activated (atomic) oxygen with nitrogen trifluoride activated in a discharge:

$$NF_3 + O = F_3NO.$$

Molecular oxygen and certain other oxidants do not interact with nitrogen trifluoride in the absence of a discharge[42-44]. Other reactions[35-37,45-52] leading to the formation of trifluoroamine oxide do not involve the use of an electric discharge. Although it is at present difficult to state a preference for any one of the methods described for the synthesis of F_3NO, the synthesis in a discharge from nitrogen trifluoride and oxygen appears to be fairly simple and the starting materials are available.

The formation of the cation NF_4^+ also indicates the coordination unsaturation of nitrogen in the NF_3 molecule. In 1966 reports were published[52,53,54] on the preparation of two salts with this hitherto unknown cation: hexafluoroarsenate ($NF_4^+AsF_6^-$) and hexafluoroantimonate ($NF_4^+SbF_6^-$). The first compound has been obtained both in a discharge[53,55] and by heating the same starting materials under pressure[56]. In the electric-discharge synthesis of $NF_4^+AsF_6^-$ a mixture of NF_3, AsF_5, and F_2 in molar proportions of 1 : 1 : 2 was passed into a glass reactor cooled to –78°C. The initial pressure of the gaseous mixture in the reactor was about 80 mmHg. After 35–42 h, about 1 g of $NF_4^+AsF_6^-$ was obtained in the circulation system. The formation of this salt may be represented by the equation

$$NF_3 + F_2 + AsF_5 = NF_4^+AsF_6^-,$$

which postulates a heterolytic dissociation of the fluorine molecule.

IV. SYNTHESIS OF OXYGEN FLUORIDES

Oxygen fluorides with the general formula O_nF_2 (n = 2–6) are extremely reactive. They react with many substances at temperatures as low as –196°C. Polyoxygen difluorides are obtained from fluorine and oxygen in a glow discharge. Since the compounds are stable only at very low temperatures, the discharge reactor must be cooled during the synthesis.

In the preparation of dioxydifluoride O_2F_2, a mixture of gases with a ratio $F_2 : O_2 = 1 : 1$ by volume or containing a small excess of fluorine is admitted into a discharge tube cooled with liquid air or liquid nitrogen[57–60]. A current of several tens of milliamperes is maintained in the discharge. The O_2F_2 produced is condensed on the walls of the discharge tube in the form of a solid, the vapour pressure of which is 0.01 mmHg at –168°C [44]. The yield of O_2F_2 falls with increasing flow rate of the fluorine–oxygen mixture but more than half of the mixture passed through the discharge is converted into dioxygen difluoride even at specific energies of 5–7 W h litre^{-1} [11]. The synthesis of dioxygendifluoride in a glow discharge may be accompanied by the formation of ozone[44,58]. It has been shown[61] that ozone is formed in an appreciable amount only at high specific energies.

Dioxygendifluoride is not formed solely by the reaction of fluorine with oxygen in a glow discharge. The photochemical reaction of fluorine with ozone on irradiation with light of wavelength 3650 Å at –153°C yields dioxygendifluoride and oxygen difluoride[62]. On the other hand, when a mixture of fluorine and ozone is irradiated at a higher temperature (0° and 20°C), ozone decomposes with formation of oxygen[63]:

$$F_2 + O_3 + h\nu\ (3650\,\text{Å}) \rightarrow F_2 + {}^3/_2O_2.$$

Trace amounts of O_2F_2 are formed when a mixture of F_2 and O_2 is irradiated with light from a mercury lamp at a temperature of –42°C [64].

The compound with the formula O_3F_2 was apparently obtained for the first time in 1938. [65] The synthesis of O_3F_2 in a glow discharge was described in 1959. [66] The conditions for the preparation of trioxygen difluoride ("ozone fluoride") did not essentially differ in any way from the conditions for the synthesis of O_2F_2 with the exception that the initial mixture of gases for the synthesis of O_3F_2 contained three volumes of oxygen and two volumes of fluorine. Trioxygendifluoride frozen at –196°C was converted into O_2F_2 under the action of fluorine activated in the discharge. Trioxygendifluoride did not react with molecular fluorine at –196°. [66]

In 1961 the synthesis of the oxygen fluoride O_4F_2 was described[67]. To prepare this compound, a mixture of two volumes of oxygen and one volume of fluorine was introduced into a discharge tube cooled to –196°C. Tetraoxygendifluoride is a reddish-brown substance melting at –191° ± 2°C and a vapour pressure of 0.25 mmHg at –183°C. [68] On increase in temperature to –163°C, O_4F_2 decomposes into oxygen and dioxygendifluoride; rapid heating results in the explosion of tetraoxygendifluoride. An improved method for the synthesis of O_4F_2 has been described[68]. In a discharge tube, made partly of copper to improve the removal of heat, a yield of 180 mg of O_4F_2 per hour was achieved. The discharge tube was maintained at temperatures between –203 and –213°C.

The oxygen fluorides O_5F_2 and O_6F_2 were obtained from fluorine–oxygen mixtures with the reactant ratios $O_2 : F_2$ = 5 : 2 (for O_5F_2) and 3 : 1 (for O_6F_2). The discharge tube was cooled to –213°C and the power of the discharge was varied in the range 1.6–6 W. [69] Apart from fluorine–oxygen mixtures, a mixture of oxygen difluoride and oxygen was employed for the synthesis of O_2F_2, O_3F_2, and O_4F_2 in a discharge[70].

Thus the results published up till 1967 show that fluorine and oxygen react in an electric discharge with formation of oxygen fluorides O_nF_2 (n = 2–6). The preparation of a particular compound is determined by the composition of the initial fluorine–oxygen mixture and the conditions of the synthesis. Higher members of the family of polyoxygendifluorides are formed at a low current and a low discharge power, a low reactor wall temperature, and a low flow rate of the starting materials into the discharge. Subsequent investigations altered somewhat the postulates established by 1967.

The existence of the compound with the formula O_3F_2 and the possibility of its synthesis in a glow discharge were questioned. Nebgen et al.[71] concluded that trioxygendifluoride is dioxygendifluoride with "intermediate" oxygen, which is retained in dioxygendifluoride too tenaciously to be regarded as dissolved but at the same time too weakly to postulate the formation of a chemical bond. Malone and McGee[72] regarded O_3F_2 as a mixture of weakly bound radicals FO and O_2F. In his review Turner[73] expressed well founded doubts concerning the existence of trioxygendifluoride and substances with the empirical formulae O_5F_2 and O_6F_2.

It has been shown[74] that the so-called trioxygendifluoride is a mixture of O_2F_2 and O_4F_2 in equilibrium with the radicals O_2F, which decompose on raising the temperature:

$$\begin{array}{l} [O_2F_2,\quad O_4F_2] \\ \qquad\quad \downarrow\downarrow \\ \qquad\quad 2OOF \rightarrow O_2F_2 + O_2 \cdot \end{array}$$

An additional study[75] on the existence of the species O_3F_2 by ^{19}F and ^{17}O NMR spectroscopy and also the study of the formation of dioxygenyl tetrafluoroborate from boron trifluoride and trioxygendifluoride confirmed these conclusions of Solomon et al.[74] It was shown[75] that the models[71,72] proposed for O_3F_2 are incorrect.

Another important result obtained recently is a development of a method for the synthesis of dioxygendifluoride not involving an electric discharge. The preparation of O_2F_2 by the radiolysis of a mixture of liquid fluorine and oxygen at –196°C was reported[76]. The synthesis was described in detail in a later communication[77]. The starting materials were subjected to the action of 3 Mev bremsstrahlung. Goetschel et al.[77] were probably the first to obtain pure dioxygendifluoride. The pure compound in the solid state is coloured yellow and not orange as usually stated in earlier communications. The melting point of O_2F_2 (–154.1°C) [76,77] differs appreciably from the value found previously (–163.5°C) [56]. Dioxygendifluoride without an admixture of O_2F radicals is diamagnetic. Data have been presented[77] indicating the possible existence of the radical O_4F.

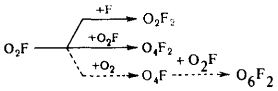
The synthesis of dioxygendifluoride in a glow discharge in large amounts does not require any special equipment apart from a single-phase high-voltage transformer. The synthesis in an electric discharge has the advantage of simplicity over the radiolysis of liquid fluorine and oxygen.

The synthesis of oxygen fluorides in an electric discharge involves the intermediate formation of the O_2F radical. The existence of the O_2F radical (dioxygenmonofluoride) has now been reliably established[78–87]. The radical is relatively long-lived at –180°C [82], its average lifetime at temperatures between –180 and –160°C has been estimated[85] as 20 min. The study where it was shown that the O_2F radical exists in the gas phase at room temperature is of great interest[88]:

$$O_2BF_4(\text{solid}) \rightleftharpoons O_2F(\text{gas}) + BF_3(\text{gas}).$$

The available data[61,75,77–79] can be rationalised in general terms by the following mechanism for the synthesis of oxygen fluorides:

$$F_2 + \text{energy} \longrightarrow 2F;\ \ F + O_2 \longrightarrow O_2F$$



The energy necessary for the dissociation of fluorine is imparted to the F_2 molecule by photolysis, radiolysis, or in a discharge. The reaction pathway indicated by a dashed line is regarded as probable.

The synthesis in a discharge of OF_2, which is thermally stable up to 200–250°C, has not been described. The action of a glow discharge on fluorine–oxygen mixtures at a low pressure with the reactor cooled in liquid nitrogen does not apparently lead to success. The synthesis of O_2F_2, which has the advantage that its occurrence does not require the dissociation of molecular oxygen, competes with the synthesis of OF_2, which does require such dissociation.

V. SYNTHESIS OF NOBLE GAS FLUORIDES

In 1962 the existence of noble gas compounds was discovered[89]. Certain noble gas fluorides were obtained in an electric discharge soon after this discovery. In the synthesis of xenon fluorides the walls of the discharge reactor or an insert introduced into the reactor are cooled to –78°C. The compounds obtained are synthesised on the cold surface in the reaction zone.

In the synthesis of XeF_2 using a discharge produced by an induction coil, mixtures of gases with $Xe : F_2$ ratios ranging from 1 : 1 to 1 : 3 were employed. The yield of the product reached 0.1 g h^{-1}. [90,91] XeF_2 is obtained in higher yields from a mixture with $Xe : F_2 = 1 : 1$ (by volume) in a glow discharge[92]. For a mixture flow rate of about 1 litre h^{-1} and a current of 30–90 mA, 3.4–3.7 g of xenon difluoride may be obtained after 1 h in the discharge[92]. Xenon difluoride has been obtained[93] by passing mixtures containing approximately equal volumes of Xe and CF_4 through a glow discharge. In this case the yield of XeF_2 was 0.05–0.15 g h^{-1} for a gas flow rate of 1–2 litre h^{-1}.

In the synthesis of xenon tetrafluoride a mixture with $Xe : F_2 = 1 : 2$ (by volume) was introduced into the discharge at a rate of about 0.14 litre h^{-1}. [94] The yield of XeF_4 reached 1.5 g after 3.5 h in the discharge at a current of 12–31 mA. Xenon hexafluoride has been synthesised from a mixture with $Xe : F_2 = 1 : 3$ (by volume)[94]. The mixture was passed into the discharge at a rate of 0.016 litre h^{-1}. [95] The possibility of synthesising xenon oxide fluorides by reacting xenon with oxygen difluoride in a discharge has been reported[44,95].

Apparently in the synthesis of xenon fluorides in a discharge the composition of the product is determined to some extent by that of the initial mixture of reactants, since in the synthesis of XeF_2, XeF_4, and XeF_6, mixtures with $Xe : F_2 = 1 : 1$, 1 : 2, and 1 : 3 respectively were employed. Probably the xenon difluoride formed initially is fluorinated to XeF_4 or XeF_6 if the fluorine content in the initial mixture exceeds 50 vol.% and the gases are passed into the discharge at a sufficiently low rate.

In the synthesis of xenon fluoride the dissociation of fluorine is a process requiring activation. The excitation of xenon atoms in the discharge[96] is not an essential condition for the synthesis of the fluorides.

Xenon difluoride may be synthesised photochemically by irradiating mixtures of xenon and fluorine or oxygen difluoride with sunlight or ultraviolet light[97–101]. Gaseous fluorine begins to absorb in the visible region, and this absorption reaches a maximum in the near ultraviolet at 2845 ± 5 Å. [102] The excitation of noble gas atoms requires a very high expenditure of energy. For example, the energies required to excite xenon atoms to metastable and resonance states are respectively 8.32 and 8.45 eV, [103] i.e. in order to excite 1 g-atom of xenon into either of these states more than 190 kcal would be required. Radiation with an energy of about 190 kcal per einstein has a wavelength of about 1500 Å, corresponding to the Schumann ultraviolet region, which is difficult to attain experimentally. The synthesis of XeF_2 by irradiating with daylight mixtures of fluorine and xenon in Pyrex reaction vessels[98,99,101] confirms the possibility of the reaction of fluorine atoms with unexcited xenon atoms. The fluorination of xenon at low temperatures with the aid of O_2F_2 [104,105] or O_4F_2 [68] in all probability also constitutes a reaction of atomic fluorine, formed as a result of the breakdown of oxygen fluorides, with unexcited xenon atoms.

When a high-frequency (25 MHz) discharge acts on mixtures of xenon, fluorine, and silicon or carbon tetrachloride, xenon difluoride, identified by mass spectrometry, is formed[106]. According to Meinert[106], the XeF_2 formed initially exchanges halogen atoms with $SiCl_4$ or CCl_4. When a mixture of xenon with chlorine and fluorine is exposed to a high-frequency (25 MHz) discharge or ultraviolet light, chlorine tri- and penta-fluorides are formed and not xenon halides[107].

In the fluorination of krypton the discharge reactor must be cooled to –183° or –196°C. Krypton fluoride was obtained in a discharge at a current of 24–37 mA and a pressure of 7–12 mmHg [95,108]. A mixture with $Kr : F_2 = 1 : 2$ (by volume) was employed for the synthesis and it was thought[95,108] that the product was krypton tetrafluoride. It soon became known[109] that, under conditions corresponding to those described above[108], krypton difluoride and not tetrafluoride is obtained. Krypton difluoride was synthesised in a circulation apparatus with a Pyrex discharge tube[109]. A mixture of fluorine and krypton with $Kr : F_2 = 1 : 2$ or 1 : 1.1 was admitted into the apparatus, the current being 15–20 mA. The yield of

KrF_2 reached 75% relative to the krypton taken for the synthesis, 0.25 g of KrF_2 being obtained after 1 h. To avoid the contamination of krypton tetrafluoride by silicon tetrafluoride, it has been suggested that KrF_2 be synthesised in a metallic discharge reactor[110].

The synthesis of krypton difluoride in a glow discharge is the only convenient method for the preparation of this compound. The photochemical reaction of krypton and fluorine[111] is very slow: after 1 day 2–3 mg of KrF_2 is formed from a mixture of the gases in a 2 litre vessel at atmospheric pressure.

VI. SYNTHESIS OF CHLORINE PENTAFLUORIDE.

The halogen derivatives of fluorine are obtained from the appropriate elements in the cold or with moderate heating. During the search for methods of synthesising higher chlorine fluorides, the possibility of preparing chlorine pentafluoride in a discharge was investigated. Chlorine pentafluoride is formed when a mixture of chlorine and fluorine or certain chlorine- or fluorine-containing compounds are exposed to an electric discharge (an a.c. or d.c. discharge or a discharge produced by a radiofrequency oscillator)[112]. In the synthesis of ClF_5 from fluorine and chlorine, mixtures were employed in which the fluorine content exceeded the stoichiometric proportion. An example of the synthesis of ClF_5 in a glow discharge where the initial mixture contained 10 volumes of fluorine for one volume of chlorine has been described[112,113]. The mixture of gases was passed at a rate of 1.5 litre h^{-1} through a discharge tube cooled to −78°C. A pressure of 30 mmHg was maintained in the apparatus. The reaction products—chlorine mono-, tri-, and penta-fluoride—were condensed in a trap at −196°C. The yield of ClF_5 was approximately 1 cm^3 (probably 1 cm^3 of gaseous ClF_5 is meant) in 4 litres of the initial mixture of gases[113]. The synthesis of ClF_5 in a discharge is interesting only as yet another example of reactions with participation of fluorine.

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The literature available on gas-discharge reactions deals mainly with traditional problems in gas electrochemistry, such as the synthesis of ozone, oxidation of nitrogen, and the cracking of hydrocarbons. The number of studies dealing with the reactions of halogens and halogen-containing compounds in a discharge has increased considerably in the last decade, but these reactions nevertheless still remain relatively little investigated.

Little attention has been devoted to the kinetics of the reactions of fluorine and fluorides in a discharge. The description in certain papers of "typical" experiments frequently illustrates only the reaction occurring in the discharge, providing information about the results of an individual experiment but not about the course of the reaction under conditions other than "typical". Non-metal fluorides are obtained mainly in a.c. glow discharges at mains frequency. The preparative scope of discharges of other types is virtually unknown.

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Institute of New Chemical Problems,
USSR Academy of Sciences,
Chernogolovka

U. D. C. 547.284

Autocondensation of Cyclic Ketones

S.V.Svetozarskii and E.N.Zil'berman

The reactions of cyclohexanone and 2-, 3-, and 4-methylcyclohexanones, cyclopentanone, and cycloheptanone, mainly under the action of acid and alkaline reagents, have been examined. The conditions governing the formation and the structures of the dimeric, trimeric, and polymeric autocondensation products—αβ-, βγ-, and other unsaturated ketones, hydroxyketones, compounds with furan or hydrogenated furan rings, dihydropyrans, hydrocarbons such as dodecahydrotriphenylene, and other compounds—have been discussed.
The bibliography includes 102 references.

CONTENTS

I. INTRODUCTION

Cyclohexanone is the starting material in the manufacture of ϵ-caprolactam. Under the conditions of the synthesis[1] of cyclohexanone by catalytic dehydrogenation of cyclohexanol[2] or the oxidation of cyclohexane, and during storage[3], and in subsequent conversion of cyclohexanone into ϵ-caprolactam[4], side reactions occur, including autocondensation reactions. As a result impurities appear in the ϵ-caprolactam which impair its quality[5] as a monomer for the manufacture of polyamide resins. Moreover, cyclohexanone has found wide applications in organic synthesis as a solvent in the processing of polymers. Here too, when cyclohexanone is heated or comes into contact with various chemical reagents, side autocondensation reactions are possible.

The cyclohexanone autocondensation products have also found some applications. For example, it has been suggested that they be used for the stabilisation of poly(vinyl chloride)[6] and as intermediates[7] or starting materials[8] in the manufacture of plastics, herbicides[9,10], insecticides[11], and polystyrene plasticisers[12].

In the present review an attempt is made to give a general account of the conditions governing the formation and structure of the cyclohexanone autocondensation products. The autocondensation of other cyclic ketones, many of which have found practical application although on a more restricted scale than cyclohexanone, is also considered.

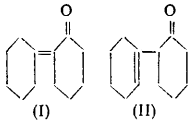
Among cycloalkanones, cyclohexanone is the most reactive, as can be seen, for example, from the rate of formation of oximes or cyanohydrins in the reactions of these cyclic ketones with hydroxylamine and hydrogen cyanide respectively. The differences in the reactivities of cycloalkanones with 5,6, and 7 carbon atoms are associated with their stereochemical structures. While cyclohexanone exists predominantly in the unstrained chair form, cyclopentanone and cycloheptanone molecules are extremely strained systems which in the case of rings with 7 and more members is due to the interaction between hydrogen atoms and the carbonyl oxygen (not linked directly) and in 5-membered rings there is classical (Baeyer) ring strain. The characteristics of the structure of cycloalkanones are reflected in their behaviour in autocondensation reactions. Indeed the autocondensation reactions of cyclohexanone are more varied than those of cyclopentanone and cycloheptanone. There are no literature data on the autocondensation of cyclic ketones with higher molecular weights.

II. DIMERIC AUTOCONDENSATION PRODUCTS

The autocondensation of cycloalkanones takes place predominantly under the influence of condensing agents. Those employed are substances with acid or basic properties.

I. Ketones

Cyclohexanone. In the autocondensation of cyclohexanone a liquid unsaturated product A with the composition $C_{12}H_{18}O$ is formed most readily. The unsaturated ketone A was obtained for the first time by Wallach[13] in 1896 by allowing cyclohexanone to stand for a long time with sodium ethoxide. Since the ketone A can have the structure of either 2-cyclohexylidenecyclohexanone (I) or 2-Δ^1-cyclohexenylcyclohexanone (II), the structure of the liquid ketone A began to be investigated from that time and a search was made for other methods of its synthesis.

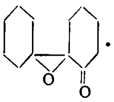

(I) (II)

The liquid ketone A is obtained by the autocondensation of cyclohexanone in the presence of sodamide[14,15], by heating with potassium hydroxide[16-19], on prolonged standing with sodium methoxide in methanol[20], on refluxing with concentrated sulphuric acid[17,21] and *p*-toluenesulphonic acid, and by reaction with 60% sulphuric acid[22] or 70% perchloric acid[23]. It is also formed from cyclohexanone on prolonged refluxing[24], on heating under pressure[25], on heating with lithium phosphate[26], calcium hydride[27,28], zinc chloride[29], lead dioxide[30], alumina (under pressure)[31], aluminium chloride[32], boron chloride[33], boron trioxide[34], aluminium phenoxide[35], tri-isobutylaluminium[36], acetoxydi-isobutylaluminium[37], and phosphorus pentoxide[16], by interaction with titanium tetraisopropoxide[38], dibromogermane, or polymeric dichlorogermane[39], by heating with cyclohexanone azomethines[8] and ion-exchange resins[7,40-42], by ultraviolet irradiation (in the presence or absence of hydrogen chloride) in monochloroacetone solution[43], etc.

The ketone A is also formed as a side product in various reactions of cyclohexanone, for example in the condensation with methanol[44], trichlorogermane[38], acrylonitrile[45], 4-vinyl pyridine[46], etc.

Either structure (I) or (II) has been attributed to the liquid ketone A or it was regarded as a mixture of ketones (I) and (II). Various reactions have been employed to establish the structure. In the hydrogenation in the presence of solid catalysts[47], reaction with benzaldehyde[29], condensation with ethyl sodiocyanoacetate[48], and in the Wolf–Kishner reaction[49], the liquid ketone A reacts as an $\alpha\beta$-unsaturated ketone (I). In the reaction with nascent hydrogen[47,50], in oxidation with ozone[48] or potassium permanganate[51], and in methylation with methyl iodide[48], the ketone A reacts as a $\beta\gamma$-unsaturated ketone (II). The absence of appreciable exaltation of molecular refraction[42,51] was regarded as proof of the endocyclic position of the double bond in the ketone.

In 1942 Reese[51] obtained a solid ketone B (m.p. 57°C) with the same composition as the liquid ketone A. There is no doubt about the position of the double bond in the $\alpha\beta$-position in the ketone B and therefore Reese believed that the liquid ketone A is a $\beta\gamma$-unsaturated compound; however, when the ketone A was oxidised with hydrogen peroxide, a small amount of compound (III), which is a product of the addition of oxygen to the exocyclic double bond, was isolated. The same compound is formed in a quantitative yield when the ketone B is oxidised with hydrogen peroxide[51]:



(III)

Kon and Nutland[48] showed that the products of the reaction of the liquid ketone A with semicarbazide is a mixture of two semicarbazones with high (main substance) and low (small amount) melting points, which they believe to differ in the position of the double bond. However, these investigators[48] did not succeed in obtaining the ketone in any one form from the high-melting semicarbazone: on reaction with semicarbazide, the regenerated liquid ketone again gave a mixture of semicarbazones. The product of the reaction of the liquid ketone A with 2,4-dinitrophenylhydrazine is also a mixture[52] of two hydrazones: orange (a colour characteristic of a ketone with an endocyclic double bond) and red (corresponding to an $\alpha\beta$-unsaturated carbonyl compound). When this mixture of hydrazones is allowed to stand with a solution of sodium hydroxide in methanol, the red form of the hydrazone is completely converted into the orange form.

Spectroscopic studies on the ketones A and B showed that their ultraviolet spectra have the same absorption maximum at 254.0–257.5 nm,[53–58] which is characteristic of $\alpha\beta\beta$-trisubstituted $\alpha\beta$-unsaturated carbonyl compounds[59]. However, the extinction coefficients of the two ketones differ—the value for the solid ketone B [56] is 6500 and that for the liquid ketone A is smaller[19,55,58], amounting to 680–800.

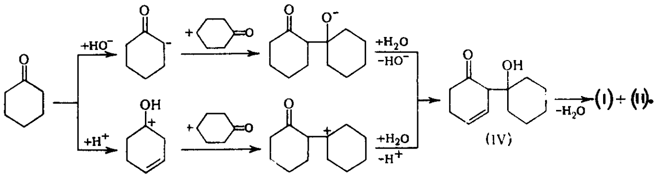
The infrared spectrum of the solid ketone B shows only one maximum[56,57] at 1670–1680 cm^{-1}, corresponding to the $\alpha\beta$-unsaturated ketone (I). At the same time the infrared spectrum[57] of the liquid ketone A has an intense band at 1710 cm^{-1}, characteristic of the $\beta\gamma$-unsaturated ketone (II), and a weak band at 1680 cm^{-1}.

The NMR study of the ketones A and B showed[57] that the spectrum of the solid ketone B contains no signals due to vinylic protons, which the spectrum of the liquid ketone A revealed the presence of a vinylic proton.

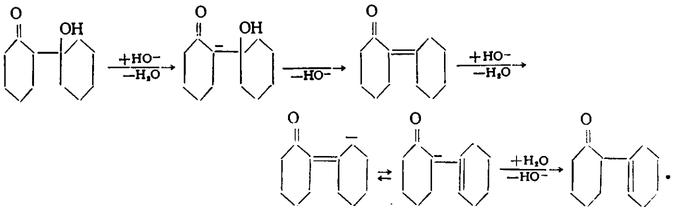
Thus the available data on the chemical and physicochemical properties of the liquid ketone A lead to the conclusion that it is a mixture not of two stereoisomers[54] but of two structural isomers with structures (I) and (II). The content of the solid ketone in this mixture is various—55% according to some data[52] and 7–20% according to others[19,57,60], which can be explained by the use of different methods of synthesis and identification. The variable composition of the liquid ketone A is evidently responsible for the wide variation of the published literature values of the constants for the product: b.p. [8,33], 142–150°C at 15 mmHg, refractive index[16,45] n_{D}^{20} = 1.5048–1.5112, and specific gravity[32,61] d_4^{20} = 1.0010–1.0072.

The fact that the liquid ketone A behaves in many reactions as a ketone with structures (I) or (II) can probably be accounted for by the migration of the double bond in the course of the reaction.

The formation of a mixture of ketones (I) and (II) in the autocondensation of cyclohexanone under the influence of bases and acids can be represented by the following mechanism:

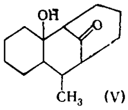


The $\alpha\beta$-unsaturated ketone (I) formed initially by the dehydration of the hydroxyketone (IV) isomerises[19] to the $\beta\gamma$-ketone (II):



Owing to the similarity of the boiling points of ketones (I) and (II), they cannot be separated by vacuum distillation. Bibo[19] subjected the liquid product A to low-temperature crystallisation and isolated a compound with m.p. 9°C and an ultraviolet absorption maximum at 291 nm ($\epsilon_{\max}$ = 46), which is characteristic of an isolated C=O group. The ultraviolet spectrum of this compound did not show the presence of bands corresponding to the C=C–C=O group and the product is probably the pure $\beta\gamma$-unsaturated ketone (II).

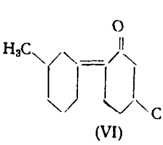
The autocondensation of aliphatic ketones is known to give rise together with unsaturated carbonyl compounds also to stable hydroxyketones, for example, acetone gives the diacetone alcohol[62] and triacetone dialcohol[38], which can be readily converted into $\alpha\beta$-unsaturated ketones—mesityl oxide and phorone. It might have been expected that, under the cyclohexanone autocondensation conditions, the hydroxyketone (IV) forms as an intermediate in the synthesis of ketones (I) and (II). However, until recently the hydroxyketone (IV) could not be isolated from the cyclohexanone autocondensation products. The first mention of the hydroxyketone (IV) appeared in 1934 when the reaction of cyclohexanone with Grignard reagents (phenylmethyl aminomagnesium bromide[63] and t-butylmagnesium bromide[64]) was achieved. The compound isolated from the reaction products melted at 56°C and on reaction with semicarbazide yielded the semicarbazone[63] of the hydroxyketone (IV) or the liquid product A. In 1952 Stanek[16] reported that, in the autocondensation of cyclohexanone in the presence of alcoholic potassium hydroxide, he isolated a solid hydroxyketone (m.p. 160°C)—2-(1-hydroxycyclohexyl)cyclohexanone (IV). However, Plešek and Munk[65] showed convincingly that this compound is in fact 2-hydroxy-4-methyl-2,3-cyclohexanobicyclo [1,3,3] nonan-9-one (V)--the product of the interaction of two cyclohexanone molecules with one acetaldehyde molecule formed from ethanol under the reaction conditions:

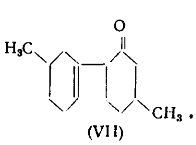

(V) .

Bibo[19] isolated from the products of the reaction of cyclohexanone with powdered potassium hydroxide (20°C) a crystalline compound (m.p. 32–33°C) with the composition $C_{12}H_{20}O_2$, which may be vacuum-distilled (0.1 mmHg) almost without decomposition. An isolated carbonyl group (λ_{max} = 290 nm, ϵ_{max} = 21), a hydrogen-bonded OH group (3528 cm^{-1} band in the infrared spectrum), and a hydrogen-bonded C=O group (1695 cm^{-1} band) were found in this compound. On the basis of these data, the structure of the hydroxyketone (IV) was attributed to the compound $C_{12}H_{20}O_2$. In addition, Bibo[19] repeated the reaction of cyclohexanone with t-butylmagnesium bromide described by Ivanoff and Spassoff[64] and isolated from the reaction mixture a compound $C_{12}H_{20}O_2$ with m.p. 32–33°C, which did not depress the melting point when mixed with the compound having the same composition synthesised by the action of powdered potassium hydroxide on cyclohexanone.

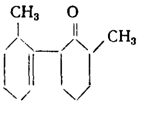
Bibo showed[19] by thin-layer chromatography that in the autocondensation of cyclohexanone in the presence of potassium hydroxide at 20°C the reaction mixture contained the hydroxyketone (IV), while in the autocondensation of cyclohexanone in the presence of the same condensing agent but in boiling toluene solution with continuous removal of the water formed in the reaction the hydroxyketone (IV) was already absent from the reaction product in the very early stages and only the ketones (I) and (II) could be detected.

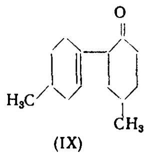
Alkylcyclohexanones can also undergo autocondensation with formation of dimeric products. When 3-methylcyclohexanone was allowed to stand with sodium ethoxide, on heating with calcium hydride[27] and potassium hydroxide[66], and on irradiation of 3-methylcyclohexanone in the presence of hydrogen chloride in chloroacetone solution[43], a liquid ketone with the composition $C_{14}H_{22}O$ was obtained, to which the structure of either the αβ-unsaturated carbonyl compound (VI) [27,67] or the βγ-unsaturated carbonyl compound (VII) [51,66,68] was attributed. At the same time Reese[51] synthesised a solid (m.p. 71°C) ketone with the composition $C_{14}H_{20}O$, in which the carbon–carbon double bond is in the αβ-position relative to the carbonyl group [compound (VI)]:

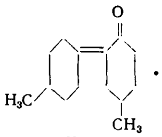

(VI)


(VII)

The corresponding liquid ketones, to which structures (VIII) and (IX) were attributed, were synthesised by heating 2-methylcyclohexanone with potassium hydroxide[66] and 4-methylcyclohexanone with barium hydroxide[66] or when the ketones were exposed to ultraviolet light and hydrogen chloride in monochloroacetone solution[43]:


(VIII)

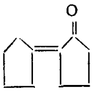

(IX)

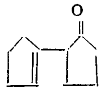

(X)

It has been stated[36] that the dimeric product of the autocondensation of 4-methylcyclohexanone has the structure of the αβ-unsaturated ketone (X). However, it should be noted that the liquid dimeric products of the autocondensation of 2-, 3-, and 4-methylcyclohexanones as well as the liquid product A of the autocondensation of cyclohexanone are mixtures of ketones with αβ- and βγ-double bonds. The infrared spectra of these compounds have bands at 1718–1720 and 1692–1695 cm^{-1} characteristic of the C=O and C=C–C=O groups respectively.

Cyclopentanone. One dimeric product of the autocondensation of the ketone is known. The liquid dimeric autocondensation product C with the composition $C_{10}H_{14}O$ is formed from cyclopentanone on heating under the conditions of its synthesis from adipic acid[69], in the presence of sodium ethoxide[13,70,71] and methoxide[72], potassium t-butoxide[73,74], potassium hydroxide[16,71,75-77], and alcoholic potassium hydroxide[16], on prolonged standing with sodium hydroxide[78], on reaction with aqueous alcoholic sodium hydroxide[79], on heating with a complex of n-butyllithium and trimethylboron[72], on saturating cyclopentanone with hydrogen chloride[71,80], on heating with sulphuric acid[81], calcium hydride[27] or carbide[27,82], lithium phosphate[26], and tri-isobutylaluminium[36], and on passing cyclopentanone vapour over alumina[75,77]. The liquid product C is obtained also by the reaction of cyclopentanone with aluminium chloride[83], t-butylmagnesium chloride[84], isopropylmagnesium halides[85,86], aluminium and magnesium amalgam[87], phosphorus pentoxide or polyphosphoric acid[70], etc. The product C is formed when cyclopentanone is reduced with aluminium isopropoxide[88], under the conditions of the reaction with acetone[89], etc.

The exaltation of the molar refraction of the liquid product C, calculated for 2-cyclopentylidenecyclopentanone (XI) [48,82] has the normal value. Nevertheless on ethylation the product C behaves as a βγ-unsaturated carbonyl compound (XII),[48] while the reaction with ethyl sodiocyanoacetate and oxidation with oxone lead to the formation of compounds characteristic of the αβ-unsaturated ketone (XI):[48]


(XI)


(XII)

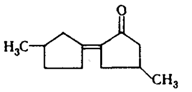
Moreover, Kon and Nutland[48] showed that, when the product C interacts with semicarbazide, a mixture of high-melting and low-melting semicarbazones in proportions of 20 : 1 is formed, and they suggest that the semicarbazones differ in the position of the double bond. The liquid carbonyl compound isolated from the high-melting semicarbazone was converted on treatment with semicarbazide into the same mixture of semicarbazones in the same proportions.

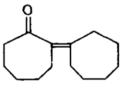
The ultraviolet spectrum of the liquid product C has an absorption maximum (at 254–259 nm)[53,56,79], characteristic of $\alpha\beta\beta$-trisubstituted $\alpha\beta$-unsaturated carbonyl compounds[59]. The extinction coefficient is high[53,56,79] ($\epsilon_{\max}$ = 10 700–12 600) and corresponds to $\alpha\beta$-unsaturated ketones[59]. The infrared spectrum shows an intense band[56] (1700 cm^{-1}) due to an $\alpha\beta$-unsaturated ketone. At the same time the literature values of the specific gravity[75,76] d_4^{20} vary in the range 1.0172–1.0217 and the refractive indices[75,76] n_D^{20} vary in the range 1.5098–1.5211.

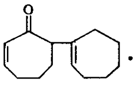
With rare exceptions[26], the structure of 2-cyclopentylidenecyclopentanone (XI) is attributed to product C. However, on the basis of the data quoted one cannot exclude the possibility that it contains also a small amount of 2-Δ'-cyclopentenylcyclopentanone (XII).

It has been stated that in the interaction of cyclopentanones with phenylmethyl aminomagnesium bromide[63], t-butylmagnesium bromide, or isopropylmagnesium bromide[64], the primary autocondensation product is a dimeric hydroxyketone. However, there are no reliable analytical data confirming the structure of this hydroxyketone.

Under the action of hydrochloric acid[13] or on heating with calcium hydride[27], 3-methylcyclopentanone is converted into the unsaturated ketone (XIII):


(XIII)

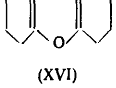

(XIV)

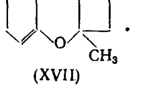

(XV)

When cycloheptanone is heated with lithium phosphate[26], potassium t-butoxide[73], or potassium hydroxide[90], an autocondensation product with the composition $C_{14}H_{22}O$ is obtained, which is regarded as a mixture of 2-cycloheptylidenecycloheptanone (XIV) and 2-Δ'-cycloheptenylcycloheptanone (XV), since the infrared spectrum showed absorption bands at frequencies of 1720 and 1692 cm^{-1} (see p. 555).

2. Oxygen-containing Heterocyclic Compounds

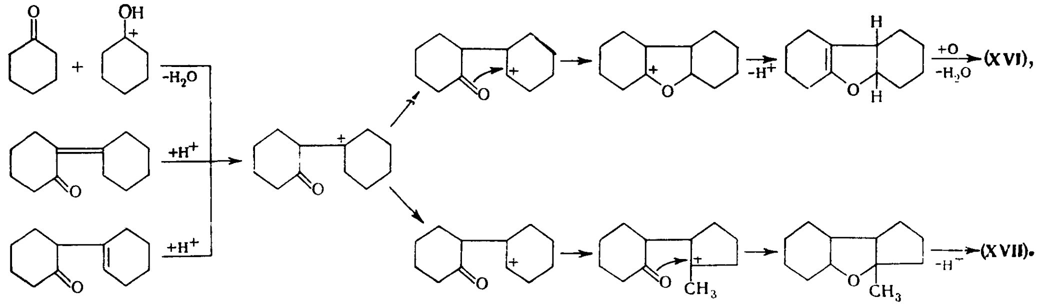
In 1964 Svetozarskii et al.[90] showed that oxygen-containing heterocycles may be formed in the autocondensation of cyclohexanone. 1,2,3,4,5,6,7,8-Octahydrodibenzofuran (XVI) and 2-methyl-2,3-cyclopentano-4,5-cyclohexeno-(Δ^5)-2,3,4,5-tetrahydrofuran (XVII) were isolated from the products of the reactions of cyclohexanone, the ketone (I),[91] or the liquid mixture[66] of the ketones (I) and (II) (product A) with a large amount of concentrated sulphuric acid in the absence of a solvent[90] or in the presence of benzene[66]:


(XVI)


(XVII)

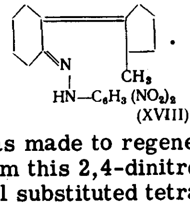
The substituted tetrahydrofuran (XVII) and octahydrodibenzofuran (XVI) are formed in small amounts as side products under conditions of the Beckmann rearrangement of cyclohexanone oxime under the influence of oleum and when the product of the rearrangement comes into contact subsequently with cyclohexanone[4]. Compound (XVI) is obtained in small amounts[92] also when a mixture of the $\alpha\beta$- and $\beta\gamma$-unsaturated ketones (I) and (II) is passed over a zinc–iron catalyst at 450°C.

The formation of compounds (XVI) and (XVII) under the conditions of the autocondensation of cyclohexanone under the influence of concentrated sulphuric acid can be explained by the following mechanism[90,91]:



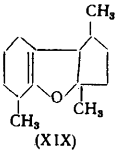
In this reaction the oxidising agent is probably sulphuric acid.

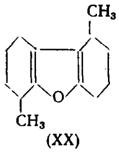
On reaction with 2,4-dinitrophenylhydrazine, compound (XVII) gives rise[90] to the hydrazone of an $\alpha\beta$-unsaturated ketone (XVIII):

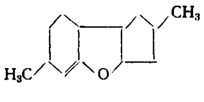

(XVIII)

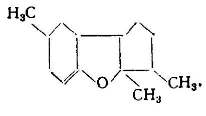
When an attempt was made to regenerate the $\alpha\beta$-unsaturated ketone from this 2,4-dinitrophenylhydrazone (XVIII), only the initial substituted tetrahydrofuran (XVII) was isolated[90]. Probably the steric positions of the groups in 2-(2-methylcyclopentylidene)cyclohexanone are so unfavourable that ring closure to the more stable tetrahydrofuran derivative (XVII) takes place readily. The instability of this ketone is in all probability due to the powerful interaction of the carbonyl oxygen with the methyl group, which entails a considerable deformation of the $\pi-\pi$ conjugated system leading to the migration of the double bond with simultaneous cyclisation to the substituted tetrahydrofuran (XVII).

2-, 3-, and 4-Methylcyclohexanones undergo similar reactions. Two compounds (XIX) and (XX) were isolated[66] from the products of the reaction of 2-methylcyclohexanone with concentrated sulphuric acid[66], while in the case of 3-methylcyclohexanone[66,91] and 4-methylcyclohexanone[66], only the substituted tetrahydrofurans (XXI) and (XXII) respectively were obtained:


(XIX)

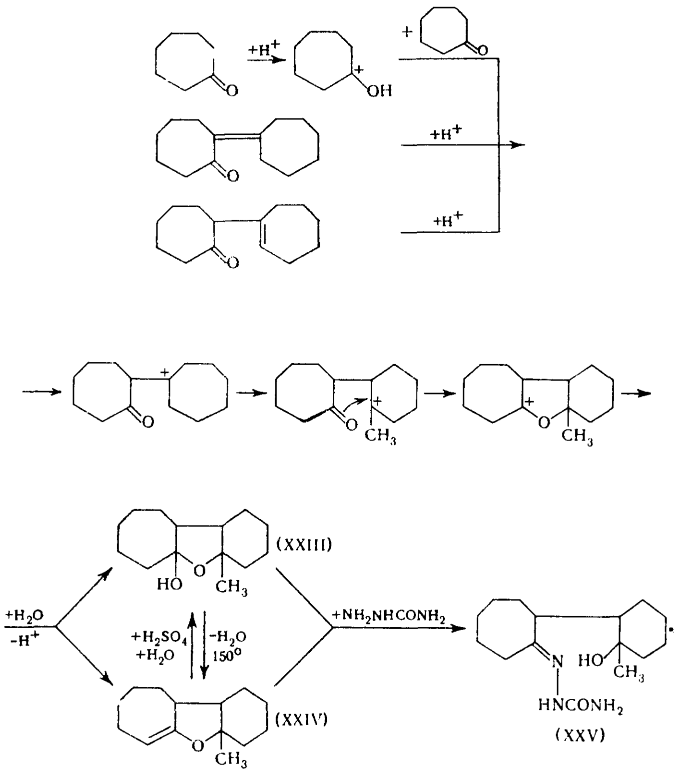

(XX)


(XXI)


(XXII)

When cycloheptanone or the dimeric product of its autocondensation in the presence of sulphuric acid is allowed to stand[93], rearrangement with intramolecular cyclisation also takes place. A distinctive feature of this reaction is the formation together with the liquid unsaturated tetrahydrofuran derivative (XXIII) of a solid substituted tetrahydrofuran derivative (XXIV) without a double bond but containing an associated hydroxy-group.

The scheme below shows that compounds (XXIII) and (XXIV) can be interconverted and yield the same semicarbazone (XXV) on reaction with semicarbazide:



It is noteworthy that the contraction of one of these rings on autocondensation of cycloheptanone may lead to the formation not of a six-membered ring, as shown in the mechanism [compounds (XXIII) and (XXIV)], but a five-membered ring[93]. To determine more accurately the structure of compounds (XXIII) and (XXIV), additional studies are necessary.

Thus the common reaction of the cycloalkanones considered in this section is autocondensation with formation of dimeric unsaturated carbonyl compounds, which are mixtures of ketones with endocyclic and exocyclic carbon–carbon double bonds.

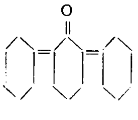
Cycloalkanones behave differently in reactions with concentrated sulphuric acid: cyclohexanone, 2-, 3-, and 4-methylcyclohexanones, and cycloheptanone are converted into tetrahydrofuran derivatives, while cyclopentanone and 2-ethylcyclohexanone do not enter into this reaction[66]. The inertness of cyclopentanone is probably due to the fact that the conversion of five-membered rings into four-membered rings is unfavourable owing to energy factors. A product of type A also was not obtained from 2-ethylcyclohexanone, probably because of the hindrance of the carbonyl oxygen by the ethyl group[66] in the 2-position.

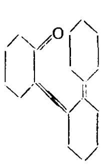
III. TRIMERIC AND POLYMERIC AUTOCONDENSATION PRODUCTS

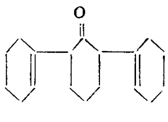
1. Ketones

As early as 1896 Wallach[13] isolated from the products of the reaction of cyclohexanone with sodium ethoxide a steam-involatile liquid substance, which set on standing into a yellow crystalline mass. Wallach suggested that the substance is an unsaturated ketone with the formula $C_{18}H_{26}O$ formed by the condensation of three cyclohexanone molecules with evolution of two water molecules. On heating cyclohexanone in methanol solution with concentrated sulphuric acid, Mannich[21] obtained a liquid product D with the composition $C_{18}H_{26}O$, from which no solid compound of any kind could be obtained even after prolonged standing. The product D was also synthesised by the autocondensation of cyclohexanone under the influence of zinc chloride[29], alumina[31], titanium tetraisopropoxide[38], ion-exchange resins[40], 60% sulphuric acid[91], etc.

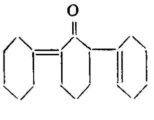
The liquid product D has been regarded[21,31,38] as an unsaturated ketone—2,6-dicyclo hexylidenecyclohexanone (XXVI):

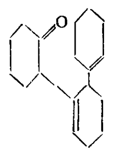

(XXVI)


(XXVII)


(XXVIII)

The structures of the $\alpha\beta$- $\gamma\delta$-unsaturated ketone[29] (XXVII) and 2,6-dicyclohexenylcyclohexanone (XXVIII)[16] have also been attributed to the trimeric autocondensation product of cyclohexanone. It has been stated[18,36] that the product D is a mixture of the ketones (XXVI) and (XXIX):


(XXIX)

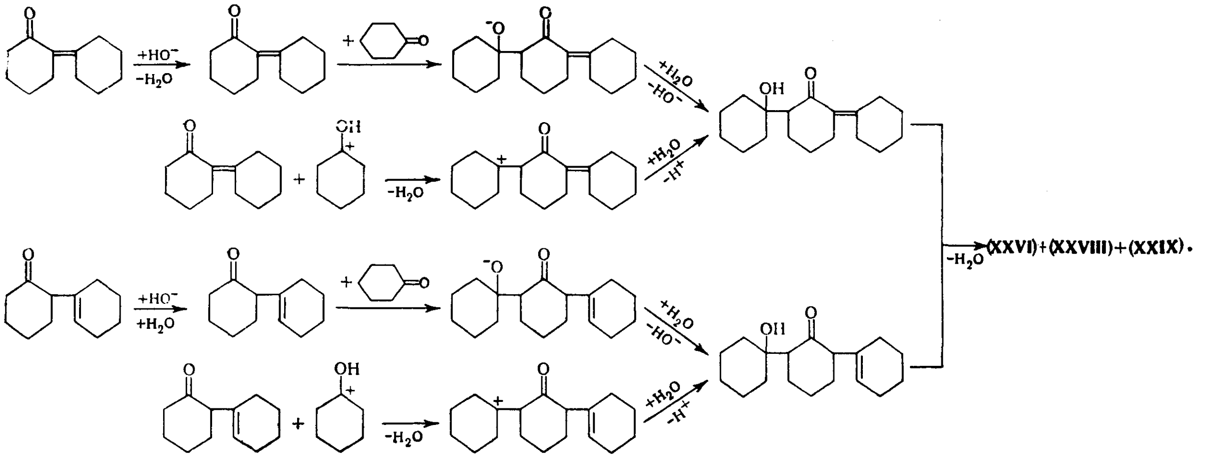

(XXX)

Among the structures quoted, that of compound (XXVII) is quite unacceptable, since this ketone cannot exist owing to steric hindrance[94]. The other hypothesis also proved to be incorrect. The most correct appears to be the view of Munk and coworkers[56,95], who showed that the liquid product D is a mixture of the ketones (XXVIII) and (XXIX). The infrared spectrum of this product does not show a band at 1662 cm^{-1}, which would have been characteristic of the ketone (XXVI), but bands at 1716 cm^{-1} (isolated C=O group) and 1685 cm^{-1} (C=C–C=O group) have been found.

Further studies on the composition of the liquid product D, obtained by refluxing cyclohexanone in toluene solution with sodium hydroxide, with continuous removal of the water formed, showed[19] that it is a mixture of three ketones: *cis*-(XXVIII) (m.p. 79°C), *trans*-(XXVIII) (colourless liquid), and (XXIX) with a very small amount of the ketone (XXVI).

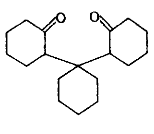
The *cis*-isomer of the ketone (XXVIII) was obtained as a pure solid compound also by other investigators[17,18]. It is noteworthy that Mleziva[17], who was the first to isolate this ketone, erroneously attributed to it the structure of compound (XXX). 2,6-Dicyclohexylidenecyclohexanone (XXVI) (m.p. 144.5–146.5 °C) was synthesised[95] by eliminating hydrogen chloride from the products of the addition of hydrogen chloride to a liquid mixture of ketones D or to 2,6-dicyclohexenylcyclohexanone (XXVIII).

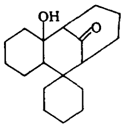
The liquid trimeric product D is also formed[17,29] on heating a mixture of cyclohexanone with the mixed dimeric ketones (I) and (II) or the product A alone[18] in the presence of condensing agents. Therefore, one may assume[17,29] that in the synthesis of a mixture of trimeric ketones D directly from cyclohexanone the intermediates are the dimeric ketones (I) and (II). On the other hand, the formation of the product D from the liquid mixture of ketones (I) and (II) alone[18] must be preceded by their hydrolysis[96]. The formation of a liquid mixture of trimeric ketones in the autocondensation of cyclohexanone or its condensation with the liquid product A may be represented by the following mechanisms:



The interaction of 4-methylcyclohexanone with tri-isobutylaluminium gives a mixture[36] of trimeric autocondensation products, the structure of which was not investigated.

Prolonged standing of cyclohexanone with sodium methoxide in methanol or heating the ketone with sodium hydroxide in methanol lead to the formation of a solid product (m.p. 182°C), to which the structure of compound (XXXI) was attributed[20]. However, more detailed studies showed[97] that the 1,5-diketone formed initially readily cyclises and exists as a tetracyclic hydroxyketone with the structure (XXXII):

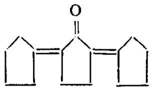

(XXXI)

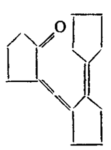

(XXXII)

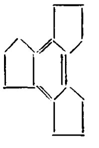
The reaction of cyclohexanone or the liquid mixture of ketones (I) and (II) with concentrated sulphuric acid in the presence of water, methanol, or butanol leads to a product of the autocondensation of six cyclohexanone molecules with the composition $C_{36}H_{52}O_2$, which is a diketone with three double bonds, two of which are conjugated with the carbonyl group and one is isolated[98].

Cyclopentanone. When cyclopentanone is heated with potassium hydroxide[16,71,75-77], sodium methoxide, or a complex of butyl-lithium with trimethylboron[72], potassium t-butoxide[73], potassium n-butoxide[74], and tri-isobutylaluminium[36], when it reacts with sodium ethoxide[13,70] and solid sodium hydroxide[78], or when its vapour is passed over alumina[75,77], an unsaturated trimeric autocondensation product E with the composition $C_{15}H_{20}O$ is obtained as a yellow solid[56,78] with m.p. 83–84°C.

The structure of 2,5-dicyclopentylidenecyclopentanone (XXXIII) has been attributed to product E.[13,16,70-74,78] It has been suggested[76,77] that the product E (m.p. 83–84°C) is a ketone with the structure (XXXIV). However, Mayer[70] and Plešek[71] disproved this hypothesis on the basis of numerous observations and in particular the following findings: (a) the saturated ketone 2,5-dicyclopentylcyclopentanone obtained in the reduction of the ketone (XXXIII) does not react with benzaldehyde[70], while the product of the reduction of the unsaturated ketone (XXXIV), which has an active methylene group, does react with this reagent; (b) heating of the ketone (XXXIII) in acids or alkalis does not lead to the formation of the hydrocarbon 1,2,3,4,5,6-tricyclotrimethylenebenzene (XXXV), which should have formed from the ketone with the structure (XXXIV):


(XXXIII)


(XXXIV)


(XXXV)

The infrared spectrum of 2,5-dicyclopentylidenecyclopentanone (XXXIII) has a band at 1692 cm⁻¹ and the ultraviolet spectrum has an absorption maximum at 300 nm $(\epsilon_{max} = 20900)$[56].

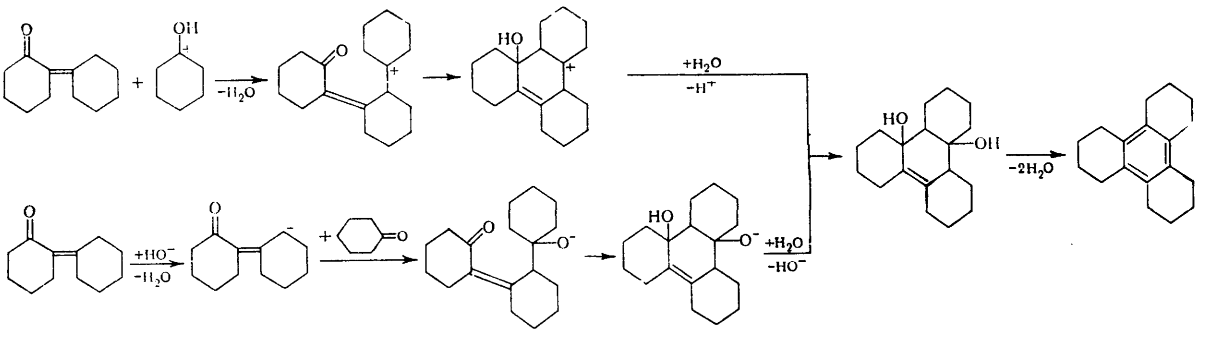
The ketone (XXXIII) is also formed[71] when the unsaturated ketone (XI) is heated with potassium hydroxide in toluene, as a result of a reversible aldol condensation (hydrolysis of 2-cyclopentylidenecyclopentanone).

2. Hydrocarbons

Cyclohexanone. When cyclohexanone is allowed to stand with concentrated sulphuric acid in methanol[98] and with 60% sulphuric acid[91], on heating cyclohexanone with concentrated sulphuric acid[17], *p*-toluenesulphonic acid[18], zinc chloride[29], polymeric dichlorogermane[39], polyphosphoric acid[99], activated aluminosilicate[100], alumina (under pressure)[31], thorium oxide, and a mixture of calcium, aluminium, and cerium (or thorium) oxides[101], or simply on heating under pressure without any condensing agent[27], a hydrocarbon—1,2,3,4,5,6,7,8,9,10,11,12-dodecahydrotriphenylene (XXXVI)—is obtained in a yield not exceeding[101] 13%. This hydrocarbon (m.p. 232°C) is formed as a side product in the reaction of cyclohexanone with acetic anhydride in nitromethane in the presence of perchloric acid[23].

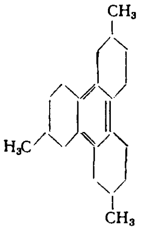
It has been shown[96] that dodecahydrotriphenylene (XXXVI) can be obtained in a low yield by heating under pressure a mixture of the dimeric ketones (I) and (II) with aqueous potassium hydroxide. The formation of the hydrocarbon (XXXVI) is probably preceded by the hydrolysis of the ketones (I) and (II). Compound (XXXVI) is also formed on heating a mixture of the ketones (I) and (II) with cyclohexanone in the presence of zinc chloride[29] or when a mixture of the ketones (I) and (II) is allowed to stand with sulphuric acid in methanol[96].

As in the synthesis of the mixture of the trimeric ketones (product D), in the synthesis of dodecahydrotriphenylene (XXXVI) the intermediates are probably the ketones (I) and (II):

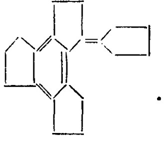


(XXXVI)

On heating with sulphuric acid in methanol or with a mixture of thorium and aluminium oxides, 4-methylcyclohexanone is converted into 2,6,10-trimethyl-1,2,3,4,5,6-7,8,9,10,11,12-dodecahydrotriphenylene (XXXVII):[101]



(XXXVII)



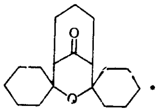
(XXXVIII)

When hydrogen chloride is passed into cyclopentanone[70,71,80] and when the latter is heated with potassium hydroxide[76] or with concentrated sulphuric acid[81], triscyclotrimethylenebenzene (XXXV) is obtained (m.p. 97.5–98.0°C). It is also formed when a mixture of cyclopentanone and 2-cyclopentylidenecyclopentanone (XI) is saturated with hydrogen chloride[70,71].

When the ketone (XI) is heated with *p*-toluenesulphonic acid, a hydrocarbon with the composition $C_{20}H_{24}$ is formed, to which the structure (XXXVIII) is attributed[71].

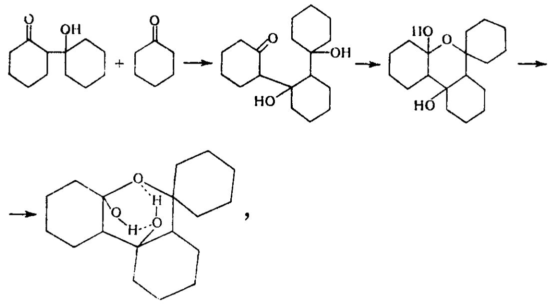
3. Oxygen-containing Heterocyclic Compounds

After the reaction of cyclohexanone with sodamide[14], a compound with the composition $C_{18}H_{28}O_2$ (m.p. 186°C) was isolated and was assigned the structure of the saturated heterocyclic ketone (XXXIX):

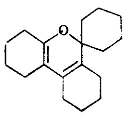


(XXXIX)

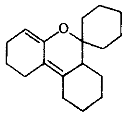
It was shown[94] that, when cyclohexanone is kept for a long time in contact with powdered sodium hydroxide, a solid compound with the composition $C_{18}H_{30}O_3$ (m.p. 175°C), having the structure of an internal cyclic hydrogen-bonded hemiacetal (XL)[102], is formed. The maximum yield (75%) of compound (XL) was achieved[102] at 10°C when the duration of the reaction was 24 h. Under the influence of catalytic amounts of sulphuric acid[102], this cyclohexanone trimer (see the mechanism below) splits off two molecules of water and is converted into a mixture[19] of the pyran (XLI) and the dihydropyrans (XLII) and (XLIII) which are its isomers:



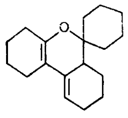
(XL)



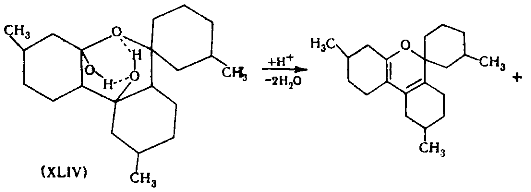
(XLI)



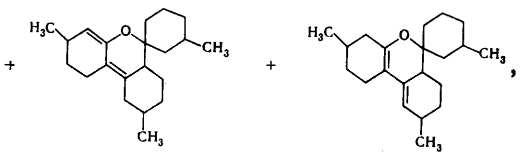
(XLII)

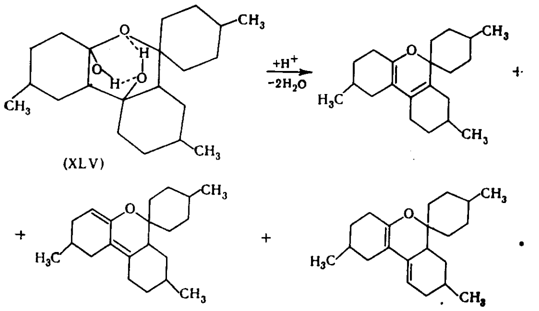


(XLIII)



(XLIV)





(XLV)

Compound (XL) and also the mixture of (XLI), (XLII), and (XLIII), are converted on heating into dodecahydrotriphenylene (XXXVI) in high yields.

It is noteworthy that initially the structure of an $\alpha\beta$–$\delta\epsilon$-unsaturated ketone, and not the pyran (XLI) or the dihydropyrans (XLII) and (XLIII), was attributed to the product formed on elimination of two water molecules from compound (XL).

It has been shown[78] that the interaction of 3- and 4-methylcyclohexanones with solid sodium hydroxide leads to the formation of the analogous trimeric products (XLIV) and (XLV). 2-Methylcyclohexanone does not trimerise owing to steric hindrance. In the presence of sulphuric acid the trimeric compounds (XLIV) and (XLV) are dehydrated to compounds which on heating yield the same hydrocarbon—2,6,10-trimethyl-1,2,3,4,5,6,7,8,9,10-11,12-dodecahydrotriphenylene (XXXVII). By analogy with the products formed in the reaction of cyclohexanone with sodium hydroxide[102], the trimeric compounds (XLIV) and (XLV) should also be internal cyclic hemiacetals and the products of their dehydration by sulphuric acid should consist of a mixture of the corresponding pyrans and dihydropyrans.

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Organophosphorus Compounds with an Active Methylene Group

A.N.Pudovik and G.E.Yastrebova

The review deals with the present state of the chemistry of organophosphorus compounds with an active methylene group: esters and nitriles of phosphonoacetic acids, phosphonoacetone, and other compounds in which the methylene group is linked directly to the P=O and any other electronegative group. Compounds of this type are analogues of acetoacetic, malonic, cyanoacetic, and phenylacetic esters, the importance of which for theoretical and synthetic organic chemistry is well known. The methods for the synthesis of phosphorus-containing compounds with an active methylene group are considered in the first part of the review, while their chemical properties associated with the mobility of the hydrogen atoms of the methylene group (alkylation, addition, condensation, P(O)-activated olefin formation, and certain other reactions) are dealt with in the second part.

The bibliography includes 292 references.

CONTENTS

I. INTRODUCTION

The chemistry of organophosphorus compounds has been developing very rapidly recently. This is primarily due to the considerable theoretical and especially practical importance which organophosphorus compounds have acquired in various branches of the national economy and modern engineering. The applications of organophosphorus compounds as insecticides in agriculture, medicinal preparations (particularly for eye infections), extractants, flotation agents in mining, plasticisers and stabilisers for polymers, and antioxidants for lubricating oils and the manufacture of non-combustible fabrics and materials are well known. The range of practical uses of organophosphorus compounds increases every year. Among the numerous types of organophosphorus compounds those with an active methylene group are of great interest. The first representative of this class of compound—ethyl diethoxyphosphonoacetate—was obtained by A. E. Arbuzov and Dunin in 1914 by the Arbuzov rearrangement. They established for the first time that the hydrogen atoms of the methylene group may be substituted by sodium and the reaction of the sodio-derivative of the diethoxyphosphonoacetate ester with alkyl halides can yield alkyl derivatives. Since then a number of organophosphorus compounds with an active methylene group have been obtained by the Arbuzov and Michaelis–Becker reactions and other methods.

The hydrogen atoms of the methylene group linked to the phosphorus atom and any other electron-accepting group exhibit considerable mobility which is responsible for the capacity of these compounds to undergo alkylation, acylation, addition, condensation, P(O)-activated olefin formation, and halogenation reactions. Thus we see an analogy between these organophosphorus compounds and esters of ketoacids and dicarboxylic acids such as the acetoacetic and malonic esters, which have played an extremely important role in theoretical and synthetic organic chemistry. Problems associated with the structure and tautomerism of this type of organophosphorus compounds are also of definite interest. The present review is a first attempt at a general account of the extensive and interesting data available in world chemical literature on the synthesis, structure, and reactivity of organophosphorus compounds with an active methylene group. Soviet chemists have made a very large contribution to the development of this branch of the chemistry of organophosphorus compounds.

II. SYNTHESIS OF ORGANOPHOSPHORUS COMPOUNDS WITH AN ACTIVE METHYLENE GROUP

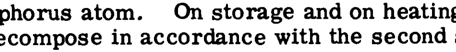
1. Derivatives of Phosphorylated Acetic Acid and Its Nitrile

Ethyl diethoxyphosphonoacetate was obtained for the first time by A. E. Arbuzov and Dunin more than half a century ago by the reaction of ethyl bromoacetate with triethyl phosphite[1]:

$$(C_2H_5O)_3P + BrCH_2COOC_2H_5 \rightarrow (C_2H_5O)_2P(O)CH_2COOC_2H_5 + C_2H_5Br.$$

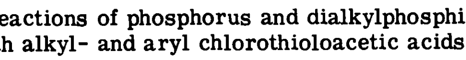
Subsequently the Arbuzov–Dunin method was successfully used for the synthesis of the ethyl esters of higher dialkoxyphosphonoacetic acids[2-7] and phosphonoacetic esters containing unsaturated substituents both at the phosphorus atom and in the carboxy-group[8-10].

The fully esterified alkylphosphonous and dialkylphosphinous acids enter into the Arbuzov rearrangement with esters of halogenoacetic acids more vigorously than trialkyl phosphites[11-15]. After the reaction of the ethyl esters of dialkylphosphinous acids with iodoacetic ester, Razumov and Zabusova isolated crystalline intermediates of the quasiphosphonium type, in accordance with the first step of the Arbuzov reaction[16]:



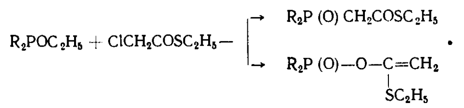
$$R_2POC_2H_5 + ICH_2COOC_2H_5 \rightarrow \left[R_2P\begin{matrix} \diagup OC_2H_5 \\ \diagdown CH_2COOC_2H_5 \end{matrix}\right]^+ I^-.$$

Their stability depends on the nature of the groups joined to the phosphorus atom. On storage and on heating, the products decompose in accordance with the second step of the Arbuzov reaction, forming ethyl iodide and dialkylethoxycarbonylmethylphosphine oxide[17,18]:



$$\left[R_2P\begin{matrix} \diagup OC_2H_5 \\ \diagdown CH_2COOC_2H_5 \end{matrix}\right]^+ I^- \rightarrow R_2P(O)CH_2COOC_2H_5 + C_2H_5I.$$

The reactions of phosphorus and dialkylphosphinous acids with alkyl- and aryl chlorothioloacetic acids follow two pathways: via the classical mechanism of the Arbuzov rearrangement and with formation of alkenyl esters of phosphorus acids, i.e. via the Perkow mechanism[19-22]:



$$R_2POC_2H_5 + ClCH_2COSC_2H_5 - \left[\begin{array}{l} \rightarrow R_2P(O)CH_2COSC_2H_5 \\ \rightarrow R_2P(O){-}O{-}\underset{SC_2H_5}{\underset{|}{C}}{=}CH_2 \end{array}\right. .$$

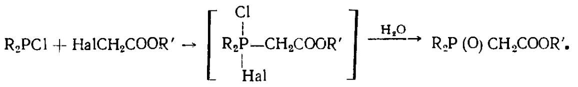
Nylen successfully used the Michaelis–Becker method for the preparation of phosphonoacetic esters. Thus ethyl diethoxyphosphonoacetate was obtained in high yield by the reaction of sodium diethyl phosphite with ethyl chloroacetate[23,24]:

$$(C_2H_5O)_2PONa + ClCH_2COOC_2H_5 \rightarrow (C_2H_5O)_2P(O)CH_2COOC_2H_5 + NaCl\,.$$

A large number of various phosphonoacetic acid esters[25-31] and dialkylcarboxymethylphosphine oxides[32] were obtained by this method, usually referred to as the Michaelis–Becker–Nylen method. Phosphonoacetic acid esters can be obtained by the reaction of dialkylphosphorous acids themselves with diazoacetic ester[33,34]:

$$(C_2H_5O)_2POH + N_2CHCOOC_2H_5 \rightarrow (C_2H_5O)_2P(O)CH_2COOC_2H_5.$$

Apart from the above general methods, a number of specific reactions leading to the formation of phosphorylated derivatives of carboxylic acids of the type of tertiary phosphine oxides have been described. The starting materials in these reactions are the chlorides of phosphinous acids. Dialkylalkoxycarbonylmethylphosphine oxides have been obtained by the addition of α-halogeno-substituted acid esters to dialkylchlorophosphines with subsequent hydrolysis of the addition products[35,36]:



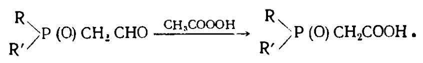
$$R_2PCl + HalCH_2COOR' \rightarrow \left[R_2\overset{Cl}{\underset{Hal}{P}}{-}CH_2COOR'\right] \xrightarrow{H_2O} R_2P(O)CH_2COOR'.$$

In the method proposed by Lutsenko and coworkers dialkylchlorophosphines, alkyldichlorophosphines, and aryldichlorophosphines are allowed to react with trichlorostannylacetic acid[37,38]:

$$\rangle P{-}X + R'_3SnCH_2COOR \rightarrow \rangle P{-}CH_2COOR + R'_3SnX.$$

The alkoxycarbonylmethylphosphines and di(alkoxycarbonylmethyl)phosphines are oxidised further by atmospheric oxygen with formation of the corresponding phosphine oxides.

Phosphorylated acids may be obtained also by the oxidation of the corresponding phosphorylated aldehydes by peracetic acid[39]:



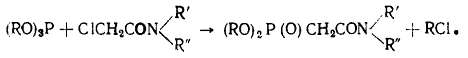
$$\begin{matrix}R\\R'\end{matrix}\!\!>P(O)CH_2CHO \xrightarrow{CH_3COOOH} \begin{matrix}R\\R'\end{matrix}\!\!>P(O)CH_2COOH\,.$$

They are converted by esterification into esters of dialkylphosphonoacetic acids.

The first example of phosphonoacetonitriles was obtained in 1952 by Dawson and Burger[40] as a result of the reaction between chloroacetonitrile and triethyl phosphite[40]:

$$(C_2H_5O)_3P + ClCH_2CN \rightarrow (C_2H_5O)_2P(O)CH_2CN + C_2H_5Cl\,.$$

The method based on the Arbuzov rearrangement was successfully employed subsequently also for the synthesis of phosphorylated acetonitriles[19,41-43]. The reactions of trialkyl phosphites with chloroacetamide and its substituted derivatives leads to the formation of phosphonoacetamide or its *N*-alkyl and *N*-aryl derivatives[2,3,19,21,44-52]:



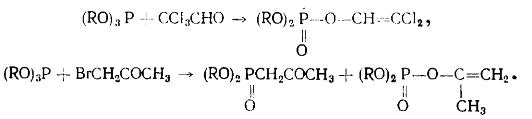
$$(RO)_3P + ClCH_2CON\begin{matrix}R'\\R''\end{matrix} \rightarrow (RO)_2P(O)CH_2CON\begin{matrix}R'\\R''\end{matrix} + RCl\,.$$

Apart from phosphites, phosphoroamidites and esters of phenylphosphonous acid were employed in these reactions[49].

2. Phosphorylated Ketones

The Arbuzov rearrangement was used as the first synthetic procedure for esters and other derivatives of β-ketophosphonic acids, which are phosphorus analogues of the corresponding derivatives of β-ketocarboxylic acids. A. E. Arbuzov and Razumov obtained diethoxyphosphonoacetophenone in 1934 by the reaction of triethyl phosphite with ω-bromoacetophenone[25]. In a similar reaction with bromoacetone Razumov and Petrov established that two products are then formed, which they suggested are tautomers of diethoxyphosphonoacetone[54].

This problem was elucidated much later when Perkow[55] showed for α-halogenoaldehydes and then Pudovik[56,57] and Allen and Jonson[58] for α-halogenoketones that the reactions of esters of phosphorus(III) acids with α-halogenocarbonyl compounds can take place in two ways: with formation of ketophosphonates, unsaturated phosphoric acid esters, or both simultaneously; diethyl isopropenyl phosphate was isolated by one of the authors of this review[57]:



$$(RO)_3P + CCl_3CHO \rightarrow (RO)_2\underset{O}{\underset{\|}{P}}{-}O{-}CH{=}CCl_2,$$

$$(RO)_3P + BrCH_2COCH_3 \rightarrow (RO)_2\underset{O}{\underset{\|}{P}}CH_2COCH_3 + (RO)_2\underset{O}{\underset{\|}{P}}{-}O{-}\underset{CH_3}{\underset{|}{C}}{=}CH_2\,.$$

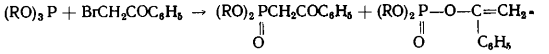
The relative amounts of the ketophosphonic esters and unsaturated phosphates or phosphonates formed by the reaction of phosphites or phosphinites with α-halogenoketones are significantly influenced by the nature and amounts of halogen atoms and also by the structure of the halogenoketones and the reaction conditions. Pudovik and Aver'yanova showed that the relative yield of ketophosphonic esters increases appreciably on going from chloro- to bromo- and iodo-acetone[59].

With increase in the number of halogen atoms in the halogenoketone, the formation of ketophosphonates becomes more difficult and the yield of unsaturated phosphates increases. The reactions with asymmetric dichloro- and dibromo-acetones[56,60,61] and tribromoacetone[62] lead to the formation of unsaturated phosphates only.

Ketophosphonic esters are formed in high yields from primary monobromo-[62,64] and iodo-ketones[59,63]. When secondary and particularly tertiary[64] halogenoketones are employed, their yield is considerably reduced or they are not formed at all.

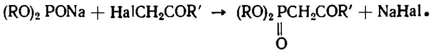
The yield of ketophosphonic esters is significantly affected also by the reaction temperature and the solvent. An increase of temperature favours the formation of the ketophosphonate[56,59]. When iodoacetone is allowed to react with triethyl phosphite in ethyl ether as solvent[59], the ketophosphonic ester is formed with a higher yield than, for example, in aqueous alcohol[63].

Mixed esters of phosphorous acid[61], phosphoroamidites[61], and esters of phenylphosphonous[59] and diphenylphosphinous[53,65] acids have been allowed to react with halogenocarbonyl compounds in order to synthesise various derivatives of ketophosphonic acids. The reactions of α-halogenoacetophenones with phosphites[25,66-69], mixed phosphites[70,72], and diphenylphosphinous acid esters[53,65] take place similarly. In all cases both products—the phosphonate and vinyl phosphate—are formed in different proportions:



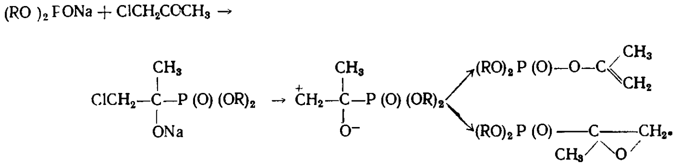
$$(RO)_3P + BrCH_2COC_6H_5 \rightarrow (RO)_2P(O)CH_2COC_6H_5 + (RO)_2P(O){-}O{-}C(C_6H_5){=}CH_2.$$

The Michaelis–Becker reaction has been used for the synthesis of ketophosphonic esters. Nylen, who was the first to investigate the reactions of α-chloro- and α-bromo-acetones with sodium diethyl phosphite, concluded that they take place in a complex manner and did not obtain the ketophosphonic esters[24]. Subsequently B. A. Arbuzov and coworkers showed that this reaction leads to a mixture of products consisting of esters of β-ketophosphonic acids and epoxyphosphonic acids and unsaturated esters of phosphoric acid[64,67,73–83]. They suggest[78] that the reactions can involve both the α-carbon atom and the carbonyl group. In the first case the ester of a β-ketophosphonic acid is formed:



$$(RO)_2PONa + HalCH_2COR' \rightarrow (RO)_2P(O)CH_2COR' + NaHal.$$

The reaction via the carbonyl group leads to the formation of a dipolar ion, which rearranges to an unsaturated phosphate or is stabilised as an epoxyphosphonic ester[78,84]:

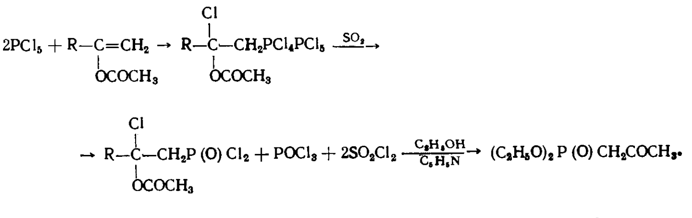


While α-chloro- and α-bromo-cyclohexanones and α-bromoacetophenone form with sodium diethyl phosphite mixtures of phosphoric and epoxyphosphonic acids[78], the reaction with chloro- and bromo-acetones leads to a mixture of esters of β-keto- and epoxy-phosphonic acids[76,79,85].

The esters of chloro- and trichloro-acetylphosphonic acids and diethoxyphosphonoacetyl- and diethoxyphosphonodichloroacetyl-phosphonic acids have been obtained by the reaction of sodium dialkyl phosphites with chloro- and trichloro-acetyl chlorides [86,87]:

$$(RO)_2PONa + ClCH_2COCl \rightarrow (RO)_2P(O)COCH_2Cl + (RO)_2P(O)CH_2C(O)P(O)(OR)_2 + NaCl.$$

The above results show that esters of β-ketophosphonic acids are formed by the Michaelis–Becker reaction either in very low yields or not at all. Among other reactions leading to the formation of esters of β-ketophosphonic acids, the interaction of phosphorus pentachloride with enol acetates is of considerable interest. This reaction, developed by Lutsenko and Kirillov, leads to the formation initially of the chlorides of β-acetoxy- β-chloroalkylphosphonic acids, which are converted into diethoxyphosphonoacetone by treatment with alcohol[88]:



$$2PCl_5 + R{-}C(OCOCH_3){=}CH_2 \rightarrow R{-}CCl(OCOCH_3){-}CH_2PCl_4PCl_5 \xrightarrow{SO_2}$$
$$\rightarrow R{-}CCl(OCOCH_3){-}CH_2P(O)Cl_2 + POCl_3 + 2SO_2Cl_2 \xrightarrow[C_5H_5N]{C_2H_5OH} (C_2H_5O)_2P(O)CH_2COCH_3.$$

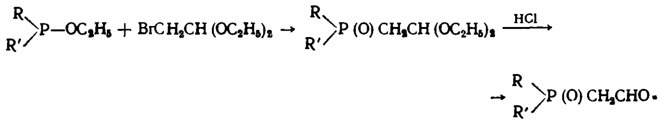
Diethoxyphosphonoacetaldehyde[88,89] and diethoxyphosphonoacetophenone[90] were obtained by the same method. The latter is also formed in the reaction between diazomethane and benzoylphosphonic ester[90]:

$$(C_2H_5O)_2P(O)COC_6H_5 + CH_2N_2 \rightarrow (C_2H_5O)_2P(O)CH_2COC_6H_5.$$

The reaction of trialkylstannylacetone with dialkylchlorophosphines gave dialkylacetonylphosphines, the oxidation of which leads to dialkylacetylmethylphosphines[91]:

$$R_2PCl + R'_3SnCH_2COCH_3 \rightarrow R_2PCH_2COCH_3 \xrightarrow{H_2O_2} R_2P(O)CH_2COCH_3.$$

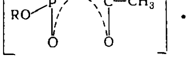
Phosphorylated acetals have been obtained by the action of halogeno-substituted acetals on phosphorus(III) acid esters; their hydrolysis leads to phosphorylated aldehydes[40 92–94]:



$$RR'P{-}OC_2H_5 + BrCH_2CH(OC_2H_5)_2 \rightarrow RR'P(O)CH_2CH(OC_2H_5)_2 \xrightarrow{HCl} RR'P(O)CH_2CHO.$$

In order to investigate the tautomerism of the keto–enol type of β-ketophosphonic esters, B. A. Arbuzov and Vinogradova employed methods involving titration with bromine and ultraviolet, infrared, and Raman spectroscopy[64,74–76,95,96]. Phosphonoacetone and methylphosphonoacetone, which are the phosphorus analogues of acetoacetic and methylacetoacetic esters, contain a small amount of the enolic form[96]. They undergo appreciable enolisation only in an alkaline medium[97]. Titration with bromine of cyclohexanone-2-phosphonic acid in alcoholic solution revealed the presence of 9% of the enolic form and in hexane solution 60% of the enolic form was found[98,99]. Comparison of the effects of the carboxy- and phosphono-groups on the capacity for the formation of the enolic form led to the conclusion that there is a definite analogy in the behaviour of β-keto acids and their phosphorus analogues, with the difference that the β-ketophosphonic esters are less enolised. A complete parallelism is not, however, observed.

The structure of metal derivatives in the molecules of which the methylene group is located between the P = O and carbonyl groups was investigated by infrared, ultraviolet, and NMR spectroscopy[100]. The results indicate the presence in the anion of phosphonoacetone of an extended π-orbital system, which is also characteristic of the acetylacetone anion:



3. Phosphorylated Alkanes

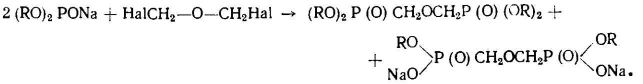
The first example of this class of compound—tetraethyl methylenediphosphonate—was obtained by Ford-Moore and Williams[101] by the reaction of methylene iodide with triethyl phosphite[101]. The yield of the diphosphonate in this reaction was, however, very low, since considerable amounts of diethyl iodomethyl- and ethyl-phosphonates are formed at the same time:

$$(C_2H_5O)_3P + CH_2I_2 \rightarrow (C_2H_5O)_2P(O){-}CH_2{-}P(O)(OC_2H_5)_2 + (C_2H_5O)_2P(O)CH_2I + (C_2H_5O)_2P(O)C_2H_5 + C_2H_5I.$$

The yield of the diphosphonate may be increased somewhat by using in the reaction an excess of trialkyl phosphite[102–104]. The yield of tetra-alkyl methylenediphosphonates is improved still further when the reaction is carried out in two consecutive stages[105]:

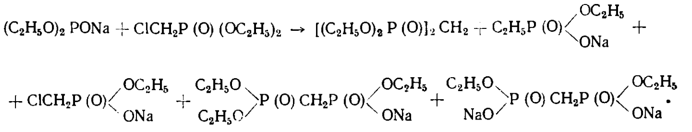
$$(C_2H_5O)_3P + CH_2I_2 \rightarrow (C_2H_5O)_2P(O)CH_2I + C_2H_5I,$$
$$(C_2H_5O)_2P(O)CH_2I + (C_2H_5O)_3P \rightarrow [(C_2H_5O)_2P(O)]_2CH_2 + C_2H_5I.$$

When an attempt was made to obtain tetra-alkyl methylenediphosphonates by the Michaelis–Becker reaction between methylene iodide or chloride and sodium diethyl or diallyl phosphite, instead of the neutral esters only the corresponding disodium salts were isolated[105–107]. The formation of salts of the acid esters is observed also in the reactions of sodium dialkyl phosphite with di-(α-bromomethyl) and di-(α-chloro methyl) esters[108–110]:



$$2(RO)_2PONa + HalCH_2{-}O{-}CH_2Hal \rightarrow (RO)_2P(O)CH_2OCH_2P(O)(OR)_2 + \frac{RO}{NaO}{>}P(O)CH_2OCH_2P(O){<}\frac{OR}{ONa}.$$

The formation of salts of acid esters is due to the alkylation of sodium dialkyl phosphite by the phosphonates[111]. When sodium dialkyl phosphite is alkylated by alkyl halides, the neutral alkylphosphonic esters are formed initially in all cases. The salts of the acid esters are formed as a result of secondary processes due to the high reactivity of the neutral alkylphosphonic esters. It has been shown for the reaction of sodium diethyl phosphite with diethyl chloromethylphosphonate that the salt-like product is a mixture of sodium chloride and salts of the acid esters of ethyl- and chloromethyl-phosphonic and methylenediphosphonic acids[112]:



$$(C_2H_5O)_2PONa + ClCH_2P(O)(OC_2H_5)_2 \rightarrow [(C_2H_5O)_2P(O)]_2CH_2 + C_2H_5P(O){<}\frac{OC_2H_5}{ONa} +$$
$$+ ClCH_2P(O){<}\frac{OC_2H_5}{ONa} + \frac{C_2H_5O}{C_2H_5O}{>}P(O)CH_2P(O){<}\frac{OC_2H_5}{ONa} + \frac{C_2H_5O}{NaO}{>}P(O)CH_2P(O){<}\frac{OC_2H_5}{ONa}.$$

Nevertheless, despite the complexity of these reactions[112–114], tetra-alkyl methylenediphosphonates are formed in high yields compared with the analogous reactions of phosphites. Until recently, methylenediphosphine dioxides were very difficult to obtain. A number of methods using organometallic compounds have been proposed for their synthesis. Thus, reactions of methylenediphosphonic dichloride with Grignard reagents have been described[114,115]:

$$[Cl_2P(O)]_2CH_2 + 4RMgX \rightarrow [R_2P(O)]_2CH_2 + 4MgXCl,$$

and also reactions of dialkylchloromethylphosphines with halogenomagnesium derivatives of dialkylphosphinous acids[116]:

$$R_2P(O)CH_2Cl + R_2POMgX \rightarrow R_2P(O)CH_2P(O)R_2 + MgXCl,$$

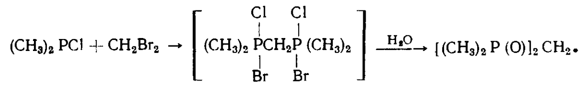
and reactions of diphenylphosphinic chloride with the lithio-derivative of methyldiphenylphosphine oxide[117]:

$$(C_6H_5)_2P(O)CH_3 \xrightarrow{n\text{-}C_4H_9Li} (C_6H_5)_2P(O)CH_2Li \rightarrow$$
$$\xrightarrow{(C_6H_5)_2P(O)Cl} (C_6H_5)_2P(O){-}CH_2{-}P(O)(C_6H_5)_2.$$

Methylenediphosphine dioxides may be obtained by the oxidation of the corresponding methylenediphosphines, which are formed in the reaction between methylene chloride or bromide with sodium diphenyl phosphite[118] or dialkylhydroxymethylphosphine[119]:

$$2(C_6H_5)_2PNa + CH_2Cl_2 \rightarrow (C_6H_5)_2PCH_2P(C_6H_5)_2 +$$
$$+ 2NaCl \xrightarrow{O_2} (C_6H_5)_2P(O)CH_2P(O)(C_6H_5)_2,$$
$$2R_2PCH_2OH + CH_2Br_2 \rightarrow R_2PCH_2PR_2 \xrightarrow{O_2} R_2P(O)CH_2P(O)R_2.$$

Among other methods for the synthesis of methylenediphosphine dioxides, the addition of chlorodimethylphosphine to methylene bromide with subsequent hydrolysis of the addition product is interesting[36]:



$$(CH_3)_2PCl + CH_2Br_2 \rightarrow \left[(CH_3)_2\overset{Cl}{\underset{Br}{P}}CH_2\overset{Cl}{\underset{Br}{P}}(CH_3)_2\right] \xrightarrow{H_2O} [(CH_3)_2P(O)]_2CH_2.$$

as well as the reaction of chlorodiphenylphosphine with diazomethane, which leads ultimately to tetraphenylmethylenediphosphine dioxide[120]:

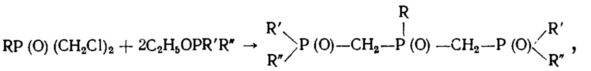
$$(C_6H_5)_2PCl + CH_2N_2 \xrightarrow[-N_2,\,-2HCl]{H_2O} (C_6H_5)_2P(O)CH_2P(C_6H_5)_2 \rightarrow$$
$$\xrightarrow{KMnO_4} (C_6H_5)_2P(O)CH_2P(O)(C_6H_5)_2.$$

However, all the methods enumerated above have not found wide practical application because of the difficulty of obtaining the reactants employed in them and the low yields of the desired products. In 1962 Kabachnik and Medved' proposed a simpler method for the synthesis of methylenediphosphine dioxides by the condensation of chloromethyldiphenylphosphine oxide with ethyl diphenylphosphinite[121]:

$$(C_6H_5)_2P(O)CH_2Cl + C_2H_5OP(C_6H_5)_2 \xrightarrow[-C_2H_5Cl]{} (C_6H_5)_2P(O)CH_2P(O)(C_6H_5)_2.$$

Subsequently this method was successfully employed for the synthesis of a number of methylenediphosphine dioxides with alkyl and substituted aromatic groups[122,123] and also methylenediphosphonic acids[124].

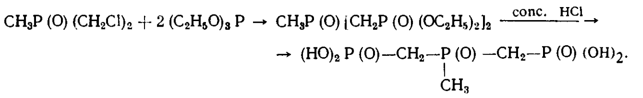
Similarly di(chloromethyl)phosphine and tri(chloromethyl)phosphine oxides and phosphorus(III) esters gave the corresponding phosphine oxides and phosphorus acid esters containing in the molecule several $>P(O){-}CH_2$ groups[125–127]:



$$RP(O)(CH_2Cl)_2 + 2C_2H_5OPR'R'' \rightarrow \frac{R'}{R''}{>}P(O){-}CH_2{-}\overset{R}{P}(O){-}CH_2{-}P(O){<}\frac{R'}{R''},$$

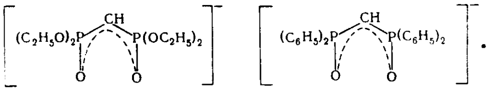
$$(ClCH_2)_3P(O) + 3R_2POC_2H_5 \rightarrow [R_2P(O)CH_2]_3P(O).$$

Certain compounds of this type, containing dialkoxyphosphono-groups, were hydrolysed to the corresponding acids[127], which proved to be extremely interesting and promising as complexones[128]:



$$CH_3P(O)(CH_2Cl)_2 + 2(C_2H_5O)_3P \rightarrow CH_3P(O)[CH_2P(O)(OC_2H_5)_2]_2 \xrightarrow{\text{conc. HCl}}$$
$$\rightarrow (HO)_2P(O){-}CH_2{-}\underset{CH_3}{P}(O){-}CH_2{-}P(O)(OH)_2.$$

In the study of the structure of sodio- and potassio-derivatives of tetraethoxydiphosphonomethane and tetraphenylmethylenediphosphine dioxide by infrared and NMR spectroscopy, Cotton and coworkers[129] in the first case and Kabachnik and coworkers[130] in the second showed that the anions of these compounds have a structure with delocalised π bonds:

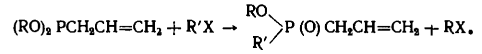


4. Phosphorylated Alkenes

The esters of allylphosphonic acid are readily obtained by the Arbuzov rearrangement when allyl chloride or bromide reacts with trialkyl[131] and triallyl[132] esters of phosphorous acid:

$$(RO)_3P + BrCH_2CH{=}CH_2 \rightarrow (RO)_2P(O)CH_2CH{=}CH_2 + RBr.$$

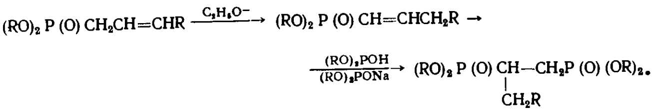
The reaction of alkyl halides with esters of allylphosphonous acid gives esters of alkylallylphosphinic acids[132,134]:


$$(RO)_2PCH_2CH{=}CH_2 + R'X \rightarrow \begin{matrix} RO \\ R' \end{matrix}\!\!>\!P(O)CH_2CH{=}CH_2 + RX.$$

Phosphonic esters can also be synthesised by the Michaelis–Becker reaction. However, Pudovik's investigation showed that the reactions of salts of dialkylphosphorous acids with halogenoallyl compounds do not always take place unambiguously. The reactions of allyl bromide, crotyl chloride[135,136], cinnamyl chloride[137,138], and 1-chloro-5-methoxypent-2-ene with sodium diethyl phosphite in benzene solutions and in the presence of an excess of diethylphosphorous acid leads to the formation of diethyl alkenylphosphonates[131,139,140]. The reactions with secondary halogenoallyl isomers take place with the allyl rearrangement[135,139,141–143]:

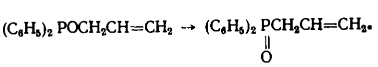
$$\left.\begin{matrix} (C_2H_5O)_2PONa + RCH{=}CHCH_2Cl \\ (C_2H_5O)_2PONa + RCHClCH{=}CH_2 \end{matrix}\right\rangle \rightarrow (C_2H_5O)_2P(O)CH_2CH{=}CHR.$$

When stoichiometric proportions of the reactants are used and the reaction is carried out without a solvent, the allylphosphonic esters undergo prototropic isomerisation to thermodynamically more stable substituted vinylphosphonic esters, to which diethylphosphorous acid adds subsequently. This results in a mixture of esters of phosphonic and diphosphonic acids[139]:

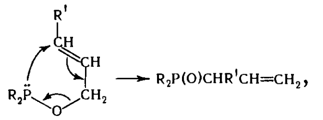

$$(RO)_2P(O)CH_2CH{=}CHR \xrightarrow{C_2H_5O^-} (RO)_2P(O)CH{=}CHCH_2R \rightarrow$$
$$\xrightarrow[(RO)_2PONa]{(RO)_2POH} (RO)_2P(O)\underset{\displaystyle CH_2R}{\underset{|}{C}H}{-}CH_2P(O)(OR)_2.$$

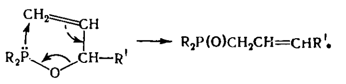
The thermal rearrangement of allyl esters of phosphorous acid[144–146] leading to allylphosphonic esters and the similar rearrangements of alkyl-, dialkyl-, aryl-, and diaryl-phosphinous acids are very interesting reactions[147]. When the diallyl ester of ethylphosphonous acid is replaced by the allyl ester of diethylphosphinous acid, the rate of thermal rearrangement increases.

The isomerisation of the allyl esters of phenylphosphonous and diphenylphosphinous acids takes place much more readily. On vacuum distillation alone, the allyl ester of diphenylphosphinous acid isomerises to allyldiphenylphosphine oxide[147,148]:


$$(C_6H_5)_2POCH_2CH{=}CH_2 \rightarrow (C_6H_5)_2\underset{\displaystyle O}{\underset{\|}{P}}CH_2CH{=}CH_2.$$

The thermal isomerisation of α- and γ-substituted allyl esters takes place with inversion of the allyl radicals[145]. For these reactions, Pudovik and Aladzheva proposed an intramolecular mechanism with intermediate formation of five-membered cyclic transition states[145]:





Esters of propargylphosphonic acids with similar structures are difficult to obtain[149]. Gordon and Griffin showed that the reaction of propargyl bromide with sodium diethyl phosphite leads to the formation of a mixture of 1-propynylphosphonate, 2-propynylphosphonate, and allenylphosphonate[150]:

$$(C_2H_5O)_2PONa + BrCH_2C{\equiv}CH \rightarrow (C_2H_5O)_2P(O)C{\equiv}C{-}CH_3 +$$
$$+ (C_2H_5O)_2P(O)CH_2C{\equiv}CH + (C_2H_5O)_2P(O)CH{=}C{=}CH_2.$$

The content of 2-propynylphosphonate in the mixture is less than 1% according to NMR data. Similar results were obtained when an attempt was made to prepare 2-propynylphosphonate by the Arbuzov rearrangement[150,151].

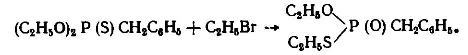
5. Derivatives of Substituted Methylphosphonic Acids containing Aryl, Carbocyclic, and Heterocyclic Groups

Methods based on the Arbuzov rearrangement and the Michaelis–Becker reaction have been successfully employed to synthesise the esters of unsubstituted and ring-substituted benzylphosphonic acids[84,152–154] and alkyl(aryl)benzylphosphinic acids[155,156]:

$$\left.\begin{matrix} (C_2H_5O)_3P + ClCH_2C_6H_4{-}R \xrightarrow{-C_2H_5Cl} \\ (C_2H_5O)_2PONa + ClCH_2C_6H_4{-}R \xrightarrow[-NaCl]{} \end{matrix}\right] \rightarrow (C_2H_5O)_2P(O)CH_2C_6H_4{-}R.$$

The second method was used to prepare unsubstituted benzylphosphonates[156–159] and benzylphosphonates with alkyl[157], ethoxycarbonyl, and cyano-groups[154] in the benzene ring. The sodium salts of ethylphosphonous[160], benzylphosphonous[161], and diphenylphosphinous acids[162] can also be successfully employed in these reactions. Sodium diethylphosphorothioite reacts with benzyl chloride to form diethyl benzylphosphonothionate[163]. When it was heated with ethyl bromide, *OS*-diethyl benzylphosphonothiolate was obtained[164]:

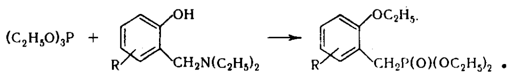
$$(C_2H_5O)_2PSNa + ClCH_2C_6H_5 \rightarrow (C_2H_5O)_2P(S)CH_2C_6H_5 + NaCl,$$


$$(C_2H_5O)_2P(S)CH_2C_6H_5 + C_2H_5Br \rightarrow \begin{matrix} C_2H_5O \\ C_2H_5S \end{matrix}\!\!>\!P(O)CH_2C_6H_5.$$

A modified Michaelis–Becker method, in which benzyl acetate is used in the reaction with sodium diallyl phosphite instead of benzyl chloride, has been successfully employed for the synthesis of diallyl benzylphosphonate[165]:

$$(CH_2{=}CHCH_2O)_2PONa + CH_3COOCH_2C_6H_5 \rightarrow (CH_2{=}CHCH_2O)_2P(O)CH_2C_6H_5 + CH_3COONa.$$

Esters of ethoxybenzylphosphonic acids are formed in the reaction between diethylaminomethylphenols and triethyl phosphites[166]:



An interesting method for the synthesis of substituted tribenzylphosphine oxides has been developed by Kirsanov and coworkers; it is based on the reaction of substituted benzyl chlorides with red phosphorus and iodine with subsequent treatment of the reaction products with sodium sulphite. Dibenzylphosphinic and benzylphosphonic acids are formed in these reactions in small amounts in addition to substituted tribenzylphosphine oxides[167]:

$$P + ClCH_2C_6H_4{-}R + I_2 \xrightarrow{Na_2SO_3} (R{-}C_6H_4CH_2)_3P(O) +$$
$$+ RC_6H_4CH_2P(O)(OH)_2 + (R{-}C_6H_4CH_2)_2P(O)OH.$$

The synthesis of methylphosphonic acids with carbocyclic and heterocyclic substituents has been achieved by the reaction of trialkyl phosphites and sodium dialkyl phosphites with a wide variety of carbocyclic[168] and heterocyclic derivatives of methyl halides[169–174]. α-Furyl-[169], α-tetrahydrofuryl-[169,170], α-thienyl-[171], α-pyridyl-[172], and phthalimidomethyl-phosphonates[173,174], and phosphonates containing polycyclic substituents[157,168,175] were obtained.

6. Esters of Halogenomethyl-, Aminomethyl-, Hydroxymethyl-, and Alkoxymethyl-Phosphonic Acids

Esters of chloromethylphosphonic acids can be readily obtained by the reaction of chloromethylphosphonic dichloride with alcohols[112,176,177]. The dichlorides themselves became available after the discovery and development by Kabachnik and Shepeleva of the reaction between phosphorus trichloride and paraformaldehyde[176]:

$$PCl_3 + CH_2O \rightarrow ClCH_2P(O)Cl_2,$$
$$ClCH_2P(O)Cl_2 + 2\,ROH \rightarrow (RO)_2P(O)CH_2Cl + 2\,HCl.$$

A number of diarylchloromethylphosphine oxides[122,123] and the chlorides of alkyl- and aryl- chloromethylphosphinic acids were obtained similarly by the reaction of diarylchlorophosphines and alkyl- and aryl-dichlorophosphines with paraformaldehyde:

$$(R{-}C_6H_4)_2PCl + CH_2O \rightarrow (R{-}C_6H_4)_2P(O)CH_2Cl.$$

While the esters of bromomethyl-[101,179,180] and iodomethyl-phosphonic acids[30,101,105,180] and the free acids themselves[180] have been described in fair detail, the esters of fluoromethylphosphonic acid were difficult to obtain until recently. The reactions of the fluorides of dialkylphosphorous acids with diazomethane[158] or of the sodium salts of dialkylphosphorous with bromofluoromethane have been suggested for their synthesis[181]:

$$(RO)_2P(O)F + CH_2N_2 \rightarrow (RO)_2P(O)CH_2F + N_2\,,$$
$$(RO)_2PONa + BrCH_2F \rightarrow (RO)_2P(O)CH_2F + NaBr.$$

A simple method for the preparation of the chloride of di(chloromethyl)phosphinic acid, consisting in the reaction of phosphorus pentachloride with di(hydroxymethyl)phosphinic acid, was recently developed by Ivanov and coworkers[182]:

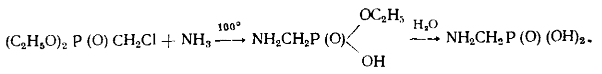
$$(HOCH_2)_2P(O)OH + 3\,PCl_5 \rightarrow (ClCH_2)_2P(O)Cl + 3\,HCl + 3\,POCl_3.$$

Numerous derivatives of di(chloromethyl)phosphinic[183] and di(chloromethyl)phosphinothionic acids[184-187] have been obtained from this acid chloride by substituting the chlorine at the phosphorus atom. These reactions may be represented by the following general equation:

$$(ClCH_2)_2P(O)Cl + RX \rightarrow (ClCH_2)_2P(O)X + RCl,$$

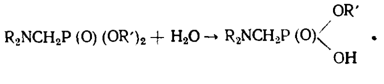
where X = OH, OAlk, OAr, $N(Alk)_2$, and others.

A number of methods have been proposed for the synthesis of aminomethylphosphonic acids and their various derivatives. When aqueous ammonia acts upon the esters of chloro- or iodo-methylphosphonic acids under severe conditions, the monoester of aminomethylphosphonic acid is formed. Its hydrolysis yielded the free aminomethylphosphonic acid[177]:



$$(C_2H_5O)_2P(O)CH_2Cl + NH_3 \xrightarrow{100^\circ} NH_2CH_2P(O)\begin{matrix} OC_2H_5 \\ OH \end{matrix} \xrightarrow{H_2O} NH_2CH_2P(O)(OH)_2.$$

Acid esters of dialkylaminomethylphosphonic acids may be obtained also as a result of the partial hydrolysis of the diesters[188]:

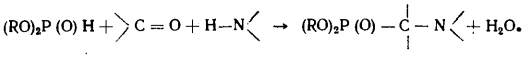


$$R_2NCH_2P(O)(OR')_2 + H_2O \rightarrow R_2NCH_2P(O)\begin{matrix} OR' \\ OH \end{matrix}\,.$$

An *N*-substituted aminomethylphosphonic acid was obtained by the reaction of benzoyl chloride with aminomethylphosphonic acid[177]:

$$NH_2CH_2P(O)(OH)_2 + C_6H_5COCl \rightarrow C_6H_5CONHCH_2P(O)(OH)_2.$$

In 1952 Kabachnik and Medved'[189,190] and somewhat later Fields[191] developed a simple method for the preparation of esters of α-aminoalkylphosphonic acids by the condensation of aldehydes and ketones with dialkylphosphorous acids and ammonia or amines[189-191]:

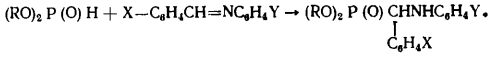


$$(RO)_2P(O)H + {>}C{=}O + H{-}N{<} \rightarrow (RO)_2P(O){-}\overset{|}{\underset{|}{C}}{-}N{<} + H_2O.$$

The reactions of dialkylphosphorous acids with formaldehyde and primary amines or ammonia give, depending on the proportions of the initial reactants, mono-, di-, and tri-(dialkylphosphonomethyl)amines[191-193]. Tertiary aminomethylphosphine oxides were obtained from secondary phosphine oxides, formaldehyde, and the amines[194,195]:

$$(CNCH_2CH_2)_2P(O)H + CH_2O + (C_4H_9)_2NH \rightarrow (CNCH_2CH_2)_2P(O)CH_2N(C_4H_9)_2.$$

Also in 1952 Pudovik found that substituted aminophosphinic esters can be readily obtained in high yields by the addition of partially esterified phosphorus acids to Schiff bases[196-198]:



$$(RO)_2P(O)H + X{-}C_6H_4CH{=}NC_6H_4Y \rightarrow (RO)_2P(O)\underset{\displaystyle C_6H_4X}{\underset{|}{C}}HNHC_6H_4Y.$$

This reaction was subsequently extended to carbodiimides, dibenzylidenediamines, and polymeric Schiff bases[199,200].

Esters of aminomethylphosphonic and di(aminomethyl)phosphinic acids are also formed by the reaction of alkyl hypophosphites with diethylaminomethyl esters and di(diethylamino)methane[201]:

$$ROP(O)H_2 + (C_2H_5)_2N{-}CH_2{-}N(C_2H_5)_2 \rightarrow ROP(O)[CH_2N(C_2H_5)_2]_2.$$

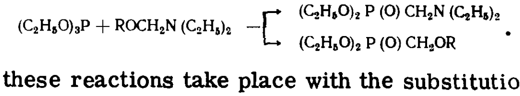
The reactions of trialkyl phosphites, diethyl phosphoroamidites, and phosphorous triamides with esters and ethers of aminomethanol and diethylaminoacetylnitrile give rise to esters and other derivatives of dialkylaminomethylphosphonic acids[202]:

$$(C_2H_5O)_3P + CNCH_2N(C_2H_5)_2 \rightarrow (C_2H_5O)_2P(O)CH_2N(C_2H_5)_2.$$

Böme and coworkers[203] showed that the reactions of aminoacetates with triethyl phosphite and diethyl phosphoroamidite take place even at room temperature forming the diethyl ester of dimethylaminomethylphosphonic acids and the ethyl ester of dimethylaminomethylphosphonoamidic acid:

$$(C_2H_5O)_3P + (CH_3)_2NCH_2OCOCH_3 \rightarrow (C_2H_5O)_2P(O)CH_2N(CH_3)_2.$$

The reactions of aminomethyl ethers with triethyl phosphite are not unambiguous. In the presence of acetic acid the C–O bond in the aminomethyl ether is broken and diethyl diethylaminomethylphosphonate is formed, while alkyl halides lead to the formation of diethylalkoxymethylphosphonates[204]:



$$(C_2H_5O)_3P + ROCH_2N(C_2H_5)_2 \rightarrow \begin{cases} (C_2H_5O)_2P(O)CH_2N(C_2H_5)_2 \\ (C_2H_5O)_2P(O)CH_2OR \end{cases}.$$

All these reactions take place with the substitution of amino-, acetate, and alkoxy-groups by a phosphono-group and have a common mechanism based on the Arbuzov rearrangement.

Similar reactions of *N*-hydroxymethylamides of acetic and benzoic acids with trialkyl phosphites lead to esters of acetamido- and benzamido- methylphosphonic acids[208]:

$$(RO)_3P + R'CONHCH_2OH \rightarrow (RO)_2P(O)CH_2NHCOR' + ROH.$$

The reaction of the *N*-hydroxymethylamide of chloroacetic acid with triethyl phosphite is much more complicated, forming a mixture of products consisting of the ester, amide, and nitrile of diethoxyphosphonoacetic acid[51]:

$$(C_2H_5O)_3P + ClCH_2CONHCH_2OH \rightarrow (C_2H_5O)_2P(O)CH_2COOC_2H_5 + \\ + (C_2H_5O)_2P(O)CH_2CONH_2 + (C_2H_5O)_2P(O)CH_2CN.$$

The reaction of phosphorus trichloride with an *N*-hydroxymethylamide followed by hydrolysis of the products gave *N*-alkylaminomethylphosphonic acid[206,207]:

$$PCl_3 + RCONR'CH_2OH \rightarrow RCONR'CH_2OPCl_2 \rightarrow RCONR'CH_2P(O)Cl_2 \rightarrow \\ \rightarrow RCONR'P(O)(OH)_2 \rightarrow NHR'CH_2P(O)(OH)_2.$$

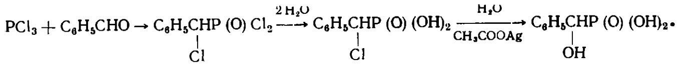
When aminomethylphosphonic acid was acted upon by nitrous acid, hydroxymethylphosphonic acid was obtained[177]:

$$NH_2CH_2P(O)(OH)_2 + HNO_2 \xrightarrow{H_2O} HOCH_2P(O)(OH)_2.$$

Earlier hydroxymethylphosphonic acid had been synthesised by the hydrolysis of the intermediate formed in the reaction between phosphorus trichloride and paraformaldehyde[208]:

$$PCl_3 + (CH_2O)_3 \xrightarrow{H_2O} HOCH_2P(O)(OH)_2.$$

Similarly the reaction of phosphorus trichloride and benzaldehyde gave the dichloride of α-chlorobenzylphosphonic acid, the hydrolysis of which can yield both α-chlorobenzylphosphonic and α-hydroxybenzylphosphonic acids, depending on the conditions[209]:



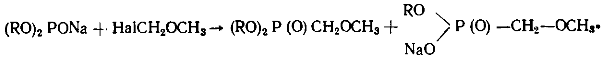
$$PCl_3 + C_6H_5CHO \rightarrow C_6H_5\underset{\mid \atop Cl}{C}HP(O)Cl_2 \xrightarrow{2H_2O} C_6H_5\underset{\mid \atop Cl}{C}HP(O)(OH)_2 \xrightarrow[CH_3COOAg]{H_2O} C_6H_5\underset{\mid \atop OH}{C}HP(O)(OH)_2.$$

Abramov[210] showed for the first time that esters of hydroxymethylphosphonic acid are formed as a result of the addition of dialkylphosphorous acid to formaldehyde[211]. A large number of derivatives of both hydroxymethyl- and hydroxyalkyl-phosphonic acids have been obtained by the addition of partially esterified phosphorus acids to various carbonyl compounds.

Esters of alkoxymethylphosphonic[212], methylthiomethylphosphonic[213], and alkoxymethylphenylphosphinic[214] acids are formed in high yields when alkylchloromethyl and chloromethylthiomethyl ethers react with trialkyl phosphites and diethyl phenylphosphonite:

$$(RO)_3P + ClCH_2OR' \rightarrow (RO)_2P(O)CH_2OR' + RCl.$$

Depending on the conditions, the reaction of α-chloro- or α-bromo-methyl ethers with sodium dialkylphosphites gives rise either to esters of alkoxymethylphosphonic or an involatile mixture of ester salts[109,215,216]:



$$(RO)_2PONa + HalCH_2OCH_3 \rightarrow (RO)_2P(O)CH_2OCH_3 + {RO \atop NaO}\rangle P(O)-CH_2-OCH_3.$$

The sodium salt of diethylphosphinous acid reacts similarly with butyl chloromethyl ether[217].

III. REACTIONS OF ORGANOPHOSPHORUS COMPOUNDS WITH AN ACTIVE METHYLENE GROUP BASED ON THE MOBILITY OF ITS HYDROGEN ATOMS

The hydrogen atoms of the methylene group in organophosphorus compounds, located between two electron-accepting groups, become so mobile that the proton is readily eliminated with formation of carbanions even in reactions with weak organic bases.

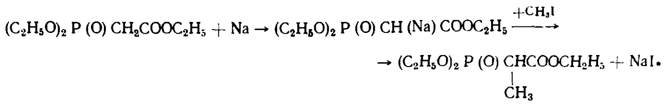
A method has been proposed recently for a quantitative determination of mobile hydrogen atoms in compounds of this type[218]. It is a modification of the standard Chugaev–Tserevitinov method for the determination of mobile hydrogen and consists in the reaction of methylmagnesium iodide with the test compound. It was shown that, when the substituent X in the compound $\rangle P(O)-CH_2-X^-$ is an electron-accepting group, both hydrogen atoms in the methylene group become mobile (esters and nitrile of diethoxyphosphonoacetic acid, diethoxyphosphonoacetone, and diethoxyphosphonoacetophenone). When the substituents X are various hydrocarbon residues or other groups without electron-accepting properties or with weak properties of this kind, only one hydrogen atom is mobile (esters of ethyl-, benzyl-, and propoxymethyl-phosphonic acids). Mobile hydrogen is found also in phosphonium salts of the type[219] $[(C_6H_5)_3\overset{+}{P}CH_2COAr]X^-$.

According to the data of Kabachnik and coworkers, the hydrogen atoms of the methylene group located between two diphenylphosphine oxide groups exhibit distinct proton mobility[220]. Thus tetraphenylmethylenediphosphine dioxide in aniline solution enriched with deuterium undergoes hydrogen isotope exchange at an appreciable rate even at room temperature. It has been confirmed by ^{1}H NMR that only the hydrogen atoms of the methylene group are involved in the isotope exchange.

Among the reactions of organophosphorus compounds with an active methylene group based on the mobility of the hydrogen atoms, the most important and the most interesting are the alkylation and acylation reactions, reactions involving addition to αβ-unsaturated compounds with activated multiple bonds, and reactions with carbonyl compounds.

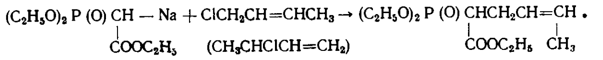
1. Alkylation and Acylation Reactions

A. E. Arbuzov and Dunin[221-223] were the first to show that the reaction of alkyl halides with the sodio-derivative of diethoxyphosphonoacetic ester results in the formation of alkyl-substituted ethyl diethoxyphosphonoacetates[25,30 224-232]:



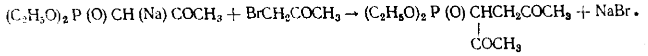
$$(C_2H_5O)_2P(O)CH_2COOC_2H_5 + Na \rightarrow (C_2H_5O)_2P(O)CH(Na)COOC_2H_5 \xrightarrow{+CH_3I} \\ \rightarrow (C_2H_5O)_2P(O)\underset{\mid \atop CH_3}{C}HCOOCH_2H_5 + NaI.$$

Alkyl halides, esters of α-halogenocarboxylic acids, α-halogenoethers, and α-halogenoketones have been used as alkylating agents in the alkylation of esters of diethoxyphosphonoacetic acid[230]. Pudovik and coworkers[233] showed that the alkylation of diethoxyphosphonoacetic ester with isomeric butadiene hydrochlorides gives in both cases the same product, corresponding to the structure of the primary chloride—the ester of but-2-enyldiethoxyphosphonoacetic acid. The reaction with the secondary chloride takes place with complete allyl rearrangement:

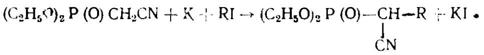


$$(C_2H_5O)_2P(O)\underset{\mid \atop COOC_2H_5}{C}H-Na + \underset{(CH_3CHClCH=CH_2)}{ClCH_2CH=CHCH_3} \rightarrow (C_2H_5O)_2P(O)\underset{\mid \atop COOC_2H_5}{C}HCH_2CH=\underset{\mid \atop CH_3}{C}H.$$

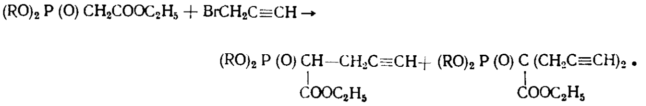
Apart from the alkylation of diethoxyphosphonoacetic esters, the alkylation of diethoxyphosphonoacetone[74,76,97, 231,232] and diethoxyphosphonoacetonitrile[41,230] has been investigated in fair detail. The alkylation of diethoxyphosphonoacetone can be achieved fairly readily when its sodio-derivative is acted upon both by alkyl halides[74,76,231] and the ethyl esters of bromoacetic and α-bromo-propionic acids and bromoacetone[230]:


$$(C_2H_5O)_2P(O)CH(Na)COCH_3 + BrCH_2COCH_3 \rightarrow (C_2H_5O)_2P(O)\underset{\displaystyle COCH_3}{CH}CH_2COCH_3 + NaBr.$$

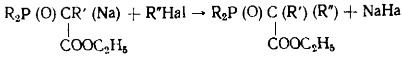
The alkylation of diethoxyphosphonoacetonitrile with alkyl halides takes place most readily when its potassio-derivative in ether–dioxane solution is employed. In this case alkyl iodides are the most effective[41]:


$$(C_2H_5O)_2P(O)CH_2CN + K + RI \rightarrow (C_2H_5O)_2P(O)-\underset{\displaystyle CN}{CH}-R + KI.$$

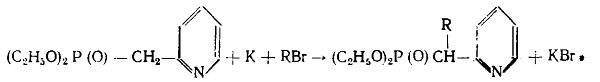
In the alkylation of the esters and nitrile of diethoxyphosphonoacetic acid and of diethoxyphosphonoacetone with equimolar amounts of alkylating agents, monoalkylation products were obtained in all cases. However, when propargyl bromide acts upon sodio- or potassio-derivatives of the ethyl ester or nitrile of diethoxyphosphonoacetic acid, a mixture of products of the substitution of one and two hydrogen atoms for a propargyl group is formed[234]. Evidently the introduction of a third electron-accepting group increases the mobility of the remaining hydrogen atom to such an extent that even with an equimolar ratio of the initial reactants the dialkylation product is formed preferentially:


$$(RO)_2P(O)CH_2COOC_2H_5 + BrCH_2C{\equiv}CH \rightarrow$$
$$(RO)_2P(O)\underset{\displaystyle COOC_2H_5}{CH}-CH_2C{\equiv}CH + (RO)_2P(O)\underset{\displaystyle COOC_2H_5}{C}(CH_2C{\equiv}CH)_2.$$

The dialkylation products of esters of diethoxy-[225], diethyl-[16], and diphenyl-phosphonoacetic acids[16] were obtained by the action of alkyl halides on the sodio- or potassio-derivatives of the corresponding monoalkylated products:


$$R_2P(O)\underset{\displaystyle COOC_2H_5}{C}R'(Na) + R''Hal \rightarrow R_2P(O)\underset{\displaystyle COOC_2H_5}{C}(R')(R'') + NaHal.$$

Among other organophosphorus compounds with an active methylene group, diethyl 2-pyridylmethylphosphonate[235] and tetraethyl methylenediphosphonate[100,102] were alkylated with alkyl bromides:

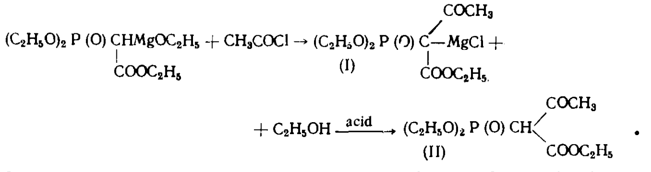


The alkylation of the diphosphonate takes place with much more difficulty[236]. The reaction of butyl bromide with the potassio-derivative of tetraethoxydiphosphonomethane gave butyl(tetraethoxydiphosphono)methane in a yield of only about 15%[102]:

$$(C_2H_5O)_2P(O)CH_2P(O)(OC_2H_5)_2 + K + C_4H_9Br \xrightarrow[-KBr]{} [(C_2H_5O)_2P(O)]_2CH-C_4H_9.$$

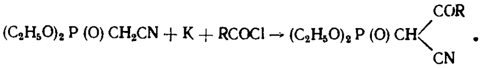
In the alkylation of metallated derivatives of methylenediphosphine dioxides with alkyl iodides, it was shown that sodium iodide is firmly retained by the alkylated dioxide[237-239]. A tetrasubstituted product was obtained in the alkylation with allyl bromide of ethyl dimethylenetriphosphonate, which has two active methylene groups, as a result of the successive substitution of their mobile hydrogen atoms[125].

The acylation of organophosphorus compounds with an active methylene group has been investigated in less detail. It has not proved possible to obtain *C*-acylated products from diethoxyphosphonoacetic ester by the action of acetyl chloride on the alkali metal salts[240]. However, when the ethoxymagnesium salt of diethoxyphosphonoacetic ester was employed, ethyl diethoxyphosphonoacetoacetate (II) was obtained in a good yield:

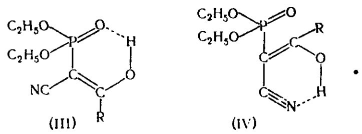

$$(C_2H_5O)_2P(O)\underset{\displaystyle COOC_2H_5}{CH}MgOC_2H_5 + CH_3COCl \rightarrow \underset{(I)}{(C_2H_5O)_2P(O)\overset{\displaystyle COCH_3}{\underset{\displaystyle COOC_2H_5}{C}}-MgCl} +$$
$$+ C_2H_5OH \xrightarrow{acid} \underset{(II)}{(C_2H_5O)_2P(O)CH}\begin{matrix}COCH_3\\COOC_2H_5\end{matrix}.$$

Diethoxyphosphonomalonic ester is obtained similarly.

The acylation of diethoxyphosphonoacetonitrile is achieved by the reaction of its potassio-derivative with the chlorides of acetic, propionic, n-butyric, and benzoic acids[241]:

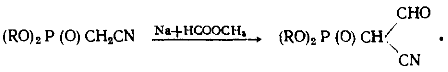

$$(C_2H_5O)_2P(O)CH_2CN + K + RCOCl \rightarrow (C_2H_5O)_2P(O)CH\begin{matrix}COR\\CN\end{matrix}.$$

The authors suggest on the basis of infrared spectroscopy that the *C*-acyl derivatives of diethoxyphosphonoacetonitrile can have structures (III) or (IV):

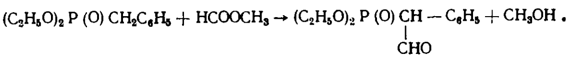

(III) (IV)

The preferred structure is (III), in which the formation of a hydrogen bond involving the P=O group is postulated, since the displacement of the P=O absorption band is much greater (by 90 cm^{-1}) compared with the band due to the CN-group (by 50 cm^{-1}).

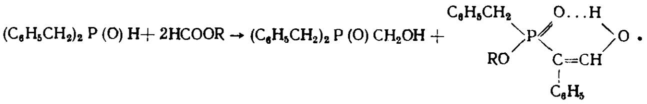
Recently it proved possible to formylate dialkoxyphosphonoacetonitriles[242]:


$$(RO)_2P(O)CH_2CN \xrightarrow{Na+HCOOCH_3} (RO)_2P(O)CH\begin{matrix}CHO\\CN\end{matrix}.$$

The formylation of the esters of dialkoxyphosphonoacetic[243], benzylphosphonic[244], and dibenzylphosphinous[245] acids has also been described:


$$(C_2H_5O)_2P(O)CH_2C_6H_5 + HCOOCH_3 \rightarrow (C_2H_5O)_2P(O)\underset{\displaystyle CHO}{CH}-C_6H_5 + CH_3OH.$$

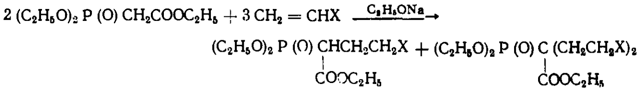
However, in the last case the reaction takes place in a more complex manner: instead of the expected product, dibenzylhydroxymethylphosphine oxide and an enol are formed[245]:



2. Addition Reactions

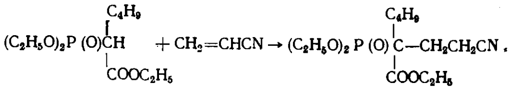
Reactions involving the addition of partially esterified phosphorus acids and organophosphorous compounds with an active methylene group to unsaturated electrophilic compounds, which were first achieved by Pudovik, serve as the basis of a new method for the synthesis of various derivatives of phosphonic and phosphinic acids[246].

The addition of diethoxyphosphonoacetic ester to the nitrile and the methyl ester of acrylic acid takes place readily in the presence of a small amount of sodium ethoxide. Products of addition to one and two molecules of the unsaturated compound have been isolated[224,231,247]:



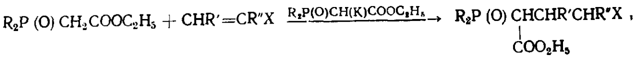
$$2(C_2H_5O)_2P(O)CH_2COOC_2H_5 + 3CH_2=CHX \xrightarrow{C_2H_5ONa} (C_2H_5O)_2P(O)\underset{COOC_2H_5}{C}HCH_2CH_2X + (C_2H_5O)_2P(O)\underset{COOC_2H_5}{C}(CH_2CH_2X)_2,$$

where X = CN or $COOCH_3$. The addition of homologues of diethoxyphosphonoacetic ester—methyl and butyl diethoxyphosphonoacetates—to electrophilic compounds—acrylonitrile, methyl acrylate, and methyl methacrylate—also takes place readily[224,247]:



$$(C_2H_5O)_2P(O)\overset{C_4H_9}{\underset{COOC_2H_5}{C}}H + CH_2=CHCN \rightarrow (C_2H_5O)_2P(O)\overset{C_4H_9}{\underset{COOC_2H_5}{C}}-CH_2CH_2CN.$$

When alkylalkoxy-, dialkyl-, and diphenyl-phosphonoacetic acids and their homologues, in which the methylene group is less reactive, were added to unsaturated compounds, the potassio-derivatives of the esters were employed[248]:

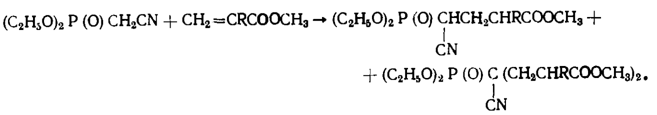


$$R_2P(O)CH_2COOC_2H_5 + CHR'=CR''X \xrightarrow{R_2P(O)CH(K)COOC_2H_5} R_2P(O)\underset{COO_2H_5}{C}HCHR'CHR''X,$$

Later the addition of phosphonoacetic esters to nitroisopentene, ethyl vinyl sulphone[249], divinyl sulphone, and *p*-di-(β-nitrovinyl)benzene[250] to esters of maleic[251], cinnamic[231], crotonic[252], and propynylphosphonic[253] acids, and also unsaturated polyesters[254] was achieved. The esters of αβ-unsaturated carboxylic acids can be arranged in the following sequence in terms of their reactivity in reactions involving the addition of diethoxyphosphonoacetic ester: acrylates > crotonates > methacrylates > cinnamates[247].

The addition of diethoxyphosphonoacetone and its homologues to acrylonitrile[255], methyl acrylate, diethyl maleate, diethyl acetylenedicarboxylate, and ethylideneacetone[231] has been achieved. In most cases these reactions take place with greater difficulty and are accompanied by very small heat change. In order to drive the reactions to completion, the reaction mixtures must be heated for a long time.

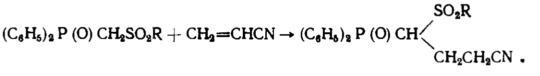
The addition of diethoxyphosphonoacetonitrile and its homologues[41,247,256] takes place much more readily compared with that of diethoxyphosphonoacetic ester and diethoxyphosphonoacetone:



$$(C_2H_5O)_2P(O)CH_2CN + CH_2=CRCOOCH_3 \rightarrow (C_2H_5O)_2P(O)\underset{CN}{C}HCH_2CHRCOOCH_3 + (C_2H_5O)_2P(O)\underset{CN}{C}(CH_2CHRCOOCH_3)_2.$$

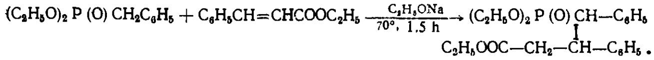
Diethoxyphosphonoacetonitrile is somewhat more reactive and ethyl diethoxyphosphonoacetate somewhat less reactive than dibutylphosphorous acid, as shown by experiments on "competing addition" and confirmed by the results of a kinetic study of the addition of a number of organophosphorus compounds with a mobile hydrogen atom to acrylonitrile. The introduction of an alkyl residue into the methylene group of diethoxyphosphonoacetic ester results in a lowering of its reactivity in addition reactions[257].

The addition of (alkylsulphonyl)methyldiphenylphosphine oxide[258] and butyl (ethylsulphonyl)methylphenylphosphinate[259] to acrylonitrile has also been achieved:



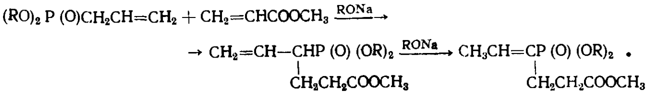
$$(C_6H_5)_2P(O)CH_2SO_2R + CH_2=CHCN \rightarrow (C_6H_5)_2P(O)CH\begin{matrix} SO_2R \\ CH_2CH_2CN \end{matrix}.$$

When benzylphosphonic ester was added to acrylonitrile and ethyl acrylate, it proved impossible to isolate the addition product in a pure form[260]; in the reaction with ethyl cinnamate the addition product was isolated and characterised[261]:



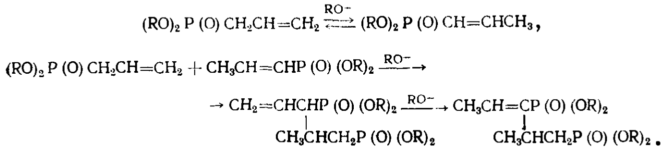
$$(C_2H_5O)_2P(O)CH_2C_6H_5 + C_6H_5CH=CHCOOC_2H_5 \xrightarrow[70^\circ,\ 1.5\ h]{C_2H_5ONa} (C_2H_5O)_2P(O)\underset{C_2H_5OOC-CH_2-\underset{}{C}H-C_6H_5}{CH}-C_6H_5.$$

The addition of dialkyl esters of allylphosphonic acid to methyl acrylate yields the methyl esters of 3-(dialkoxyphosphono)pentene-3-carboxylic acid. The addition products formed initially, in the presence of sodium alkoxide, undergo prototropic isomerisation[262]:



$$(RO)_2P(O)CH_2CH=CH_2 + CH_2=CHCOOCH_3 \xrightarrow{RONa} \rightarrow CH_2=CH-\underset{CH_2CH_2COOCH_3}{C}HP(O)(OR)_2 \xrightarrow{RONa} CH_3CH=\underset{CH_2CH_2COOCH_3}{C}P(O)(OR)_2.$$

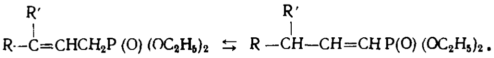
In the presence of sodium ethoxide, diethyl allylphosphonate is converted into a dimeric product—1,3-di(diethoxyphosphono)-2-methylpent-3-ene[263]. Evidently the first stage in this reaction is prototropic isomerisation of the allylphosphonic ester to the diethyl ester of propenylphosphonic acid, which then adds on a second molecule of the allylphosphonic ester at the double bond. In the presence of alkoxide anions, the addition products undergo further prototropic isomerisation with formation of the final products[262]:



$$(RO)_2P(O)CH_2CH=CH_2 \overset{RO^-}{\rightleftarrows} (RO)_2P(O)CH=CHCH_3,$$

$$(RO)_2P(O)CH_2CH=CH_2 + CH_3CH=CHP(O)(OR)_2 \xrightarrow{RO^-} \rightarrow CH_2=CH\underset{CH_3CHCH_2P(O)(OR)_2}{C}HP(O)(OR)_2 \xrightarrow{RO^-} CH_3CH=\underset{CH_3CHCH_2P(O)(OR)_2}{C}P(O)(OR)_2.$$

The possibility of the prototropic isomerisation of allylphosphonic esters to the propenyl isomers has been demonstrated by Ionin and Petrov for diethyl allylphosphonate and its methyl-, chloromethyl-, and phenyl-substituted derivatives[137]:



$$R-\overset{R'}{C}=CHCH_2P(O)(OC_2H_5)_2 \rightleftarrows R-\overset{R'}{C}H-CH=CHP(O)(OC_2H_5)_2.$$

Analysis of infrared, ultraviolet, and NMR (^1H and ^{31}P) spectroscopic data established that the isomerisation goes to completion only in the case of the allylphosphonic ester. Crotylphosphonic ester isomerises to the extent of 25% and cinnamylphosphonic ester does not isomerise at all. In the case of γ-chlorocrotylphosphonic ester the chlorine is replaced by an ethoxy-group without isomerisation. The above data led to the conclusion that the diethoxyphosphono-group interacts very weakly with a double bond. Conjugation with this group is less stable than hyperconjugation between a methyl group and a double bond. The conjugation between a double bond and a benzene ring is incomparably more favourable than the possible conjugation of this bond with a diethoxyphosphono-group[137].

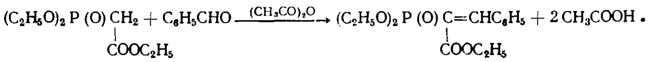
Recently Kirilov and coworkers found that the ethyl esters of diethoxy- and di-isopropoxy-phosphonoacetic acids and diethoxyphosphonoacetonitrile add to the C=N double bonds of Schiff bases—benzylideneaniline, benzylidene-*p*-chloroaniline, etc.[264] The reactions take place in the presence of aluminium chloride, sodamide, and sodium alkoxides. The yields of the addition products are 30–60% and depend on the catalyst; the highest yields were obtained with aluminium chloride[265]:

$$(RO)_2P(O)CH_2X + C_6H_5CH=N-C_6H_4-R \rightarrow (RO)_2P(O)CH(X)CH(C_6H_5)NHC_6H_4-R,$$

where X = $COOC_2H_5$ or CN.

3. Condensation and P(O)-activated Olefin Synthesis

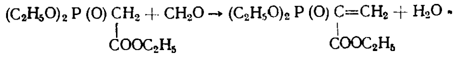
Condensation reactions. The possibility of the condensation of organophosphorus compounds having an active methylene group with aldehydes was demonstrated for the first time by Pudovik and Lebedeva in 1953. By heating diethoxyphosphonoacetic ester with benzaldehyde in acetic anhydride solution, they obtained the diethyl ester of α-ethoxycarbonyl-β-phenylvinylphosphonic acid[255]:



$$(C_2H_5O)_2P(O)\underset{\displaystyle COOC_2H_5}{\underset{|}{CH_2}} + C_6H_5CHO \xrightarrow{(CH_3CO)_2O} (C_2H_5O)_2P(O)\underset{\displaystyle COOC_2H_5}{\underset{|}{C}}{=}CHC_6H_5 + 2\,CH_3COOH\,.$$

Later in the condensation of diethoxyphosphonoacetic ester with benzaldehyde under somewhat different conditions and in the presence of piperidine the yield of the condensation product was greatly increased[266,267]. The product of the condensation of benzaldehyde with two moles of diethoxyphosphonoacetic ester was also obtained in low yield[266].

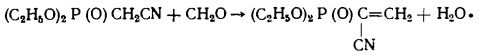
Diethoxyphosphonoacetic ester reacts with aliphatic aldehydes and in particular formaldehyde under milder conditions, in methanol solution in the presence of piperidine. The esters of α-ethoxycarbonylvinylphosphonic acid have been obtained by this method[268]:



$$(C_2H_5O)_2P(O)\underset{\displaystyle COOC_2H_5}{\underset{|}{CH_2}} + CH_2O \rightarrow (C_2H_5O)_2P(O)\underset{\displaystyle COOC_2H_5}{\underset{|}{C}}{=}CH_2 + H_2O\,.$$

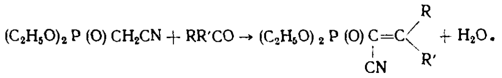
The synthesis of esters of α-alkoxycarbonyl- and α-cyanovinylphosphonic acids by the condensation reaction has significant advantages both as regards yields and the availability of the starting materials over the methods for the preparation of these compounds described previously[264,270].

In the presence of piperidine, diethoxyphosphonoacetonitrile readily condenses with both aliphatic[271-273] and aromatic aldehydes[42,274]:



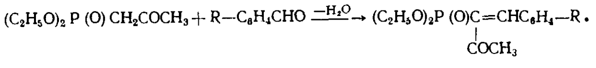
$$(C_2H_5O)_2P(O)CH_2CN + CH_2O \rightarrow (C_2H_5O)_2P(O)\underset{\displaystyle CN}{\underset{|}{C}}{=}CH_2 + H_2O\,.$$

In the presence of ammonium acetate and acetic acid, reaction with ketones also take place[275]:



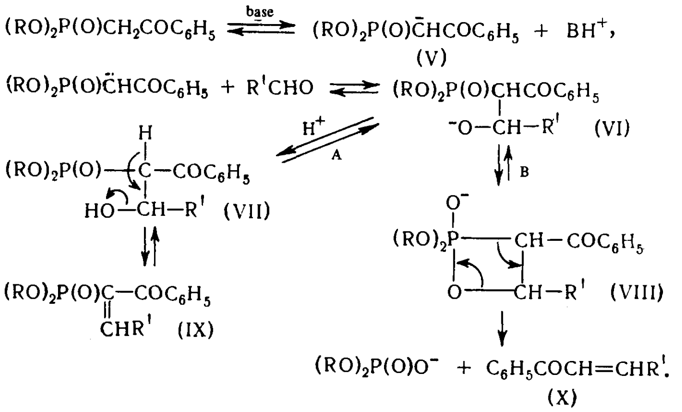
$$(C_2H_5O)_2P(O)CH_2CN + RR'CO \rightarrow (C_2H_5O)_2P(O)\underset{\displaystyle CN}{\underset{|}{C}}{=}C\begin{matrix} R \\ R' \end{matrix} + H_2O\,.$$

Recently we showed that diethoxyphosphonoacetone[274,276,277] and diethoxyphosphonoacetophenone[278,279] are also capable of condensing with aliphatic and aromatic aldehydes. The reactions occur in benzene or toluene solutions in the presence of piperidine with simultaneous azeotropic distillation of the water formed:



$$(C_2H_5O)_2P(O)CH_2COCH_3 + R{-}C_6H_4CHO \xrightarrow{-H_2O} (C_2H_5O)_2P(O)\underset{\displaystyle COCH_3}{\underset{|}{C}}{=}CHC_6H_4{-}R\,.$$

The reactions of aldehydes with dialkoxyphosphonoacetophenones are of considerable theoretical interest[279]. We established that the reaction with p-nitrobenzaldehyde can involve simultaneously either condensation or P(O)-activated olefin formation:



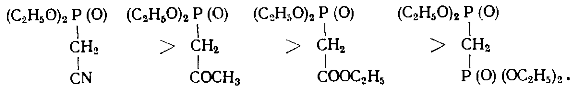
The carbonion (V), formed when a basic reagent acts upon the organophosphorus compound with an active methylene group, interacts further with the carbonyl compound and is converted into the anion (VI). Both stages are common to the condensation and P(O)-activated olefin formation reactions. By combining with a proton, the anion (VI) is converted into the alcohol (VII) and its dehydration gives the condensation product (IX) (pathway *A*). The P(O)-activated olefin formation reaction (pathway *B*) probably takes place via the intermediate formation of an unstable four-membered cyclic product or transition state (VIII) (by analogy with the Wittig reaction); the bond redistribution in (VIII) leads to a phosphoric acid and an unsaturated ketone.

The rate and mode of this complex and multistage reaction depend both on the nature and amount of the catalysts and solvents employed and on the structure of the organophosphorus compounds and aldehydes[279].

Tetraethoxydiphosphonomethane, which has a less active methylene group, condenses with benzaldehyde only after prolonged heating of the reactants in xylene with simultaneous azeotropic distillation of the water formed[280]:

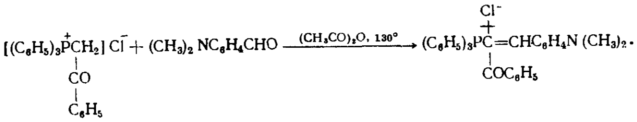
$$[(C_2H_5O)_2P(O)]_2CH_2 + C_6H_5CHO \rightarrow C_6H_5CH{=}C[P(O)(OC_2H_5)_2]_2 + H_2O\,.$$

Organophosphorus compounds with an active methylene group can be arranged in the following sequence in terms of their relative reactivities in condensation reactions with aldehydes[274]:



$$\underset{\displaystyle CN}{\underset{|}{\overset{\displaystyle (C_2H_5O)_2P(O)}{\overset{|}{CH_2}}}} > \underset{\displaystyle COCH_3}{\underset{|}{\overset{\displaystyle (C_2H_5O)_2P(O)}{\overset{|}{CH_2}}}} > \underset{\displaystyle COOC_2H_5}{\underset{|}{\overset{\displaystyle (C_2H_5O)_2P(O)}{\overset{|}{CH_2}}}} > \underset{\displaystyle P(O)(OC_2H_5)_2\,.}{\underset{|}{\overset{\displaystyle (C_2H_5O)_2P(O)}{\overset{|}{CH_2}}}}$$

Phosphonium salts also condense with aldehydes; thus dyes analogous to styryl dyes have been obtained by the condensation of phosphonium salts with p-dimethylaminobenzaldehyde[281]:



$$[(C_6H_5)_3\overset{+}{P}\underset{\displaystyle \underset{\displaystyle C_6H_5}{\underset{|}{CO}}}{\underset{|}{CH_2}}]\,\overset{-}{Cl} + (CH_3)_2NC_6H_4CHO \xrightarrow{(CH_3CO)_2O,\ 130^\circ} (C_6H_5)_3\overset{\displaystyle \overset{Cl^-}{+}}{P}\underset{\displaystyle COC_6H_5}{\underset{|}{C}}{=}CHC_6H_4N(CH_3)_2\,.$$

The P(O)-activated olefin formation reaction. The P(O)-activated olefin formation reaction, discovered by Horner in 1958, is characteristic of and specific to organophosphorus compounds with an active methylene group. It is of great preparative importance in organic chemistry, since it permits the syntheses of a wide variety of unsaturated hydrocarbons and their various derivatives.

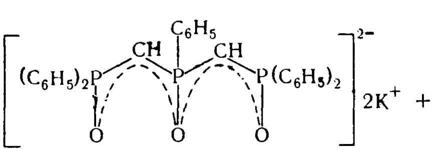
The use of reagents for the P(O)-activated synthesis of olefins is more effective than the Wittig reaction involving various phosphoranes. In relation to carbonyl compounds and in particular to ketones, reagents for P(O)-activated olefin synthesis are more reactive by virtue of their more pronounced nucleophilic properties compared with phosphoranes. The isolation of olefins is greatly facilitated when the P(O)-activated olefin formation method is employed. The unsaturated compounds obtained can be readily separated from the readily water-soluble alkali metal salts of alkylphosphoric acids, while in the Wittig reactions it is necessary to resort to special procedures for the separation of the olefin from triphenylphosphine oxide. Moreover, reagents for P(O)-activated olefin synthesis are more readily available than the Wittig reagents.

A detailed review has been published on the P(O)-activated olefin formation reaction in organic synthesis[282]. Here we shall confine ourselves to a discussion of studies which have been published recently and in which diphosphono-derivatives were used as for P(O)-activated olefin synthesis reagents. Reactions of this type are of considerable interest also because they permit a fairly simple synthesis of various unsaturated organophosphorus compounds.

The possibility of synthesising vinylphosphonates by the P(O)-activated olefin formation reaction was first demonstrated by Wadsworth and Emmons[283]. They obtained the diethyl ester of β-phenylvinylphosphonic acid by the reaction of tetraethoxydiphosphonomethane with benzaldehyde in the presence of sodium hydride[283]:

$$[(C_2H_5O)_2P(O)]_2CH_2 + C_6H_5CHO \xrightarrow{NaH} (C_2H_5O)_2P(O)CH{=}CHC_6H_5 .$$

Similarly, even with the potassio-derivative of tetraphenylmethylenediphosphinedioxide, Kabachnik and coworkers obtained also unsaturated phosphine oxides[130]. Phosphine oxides with two unsaturated substituents may be obtained by using in the reaction with aldehydes the dipotassio-derivative of pentaphenyldimethylenetriphosphine trioxide[127]:

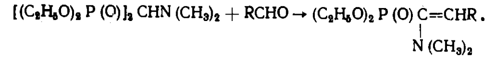


$$+\ 2C_6H_5CHO \xrightarrow{-2(C_6H_5)_2P(O)OK} (C_6H_5CH{=}CH)_2P(O)C_6H_5 .$$

The P(O)-activated olefin formation reaction permits the synthesis of organophosphorus compounds with a substituent at the phosphorus atom containing several conjugated double bonds. For example, cinnamaldehyde is allowed to react for this purpose with the potassio-derivative of tetraethoxydiphosphonomethane[284]:

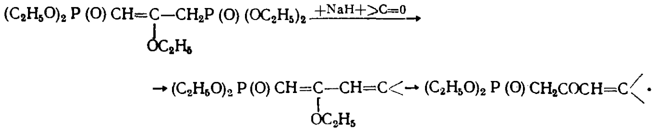
$$[(C_2H_5O)_2P(O)]_2CHK + C_6H_5CH{=}CHCHO \rightarrow (C_2H_5O)_2P(O)CH{=}CHCH{=}CHC_6H_5 .$$

Diphosphonomethane derivatives in which the hydrogen has been replaced by another group readily enter into the P(O)-activated olefin formation reaction. Thus esters of unsaturated phosphonic acids containing the dimethylamino-group at the α-carbon atom have been obtained from di(diethoxyphosphono)dimethylaminomethane[285]:



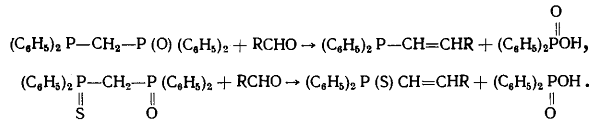
$$[(C_2H_5O)_2P(O)]_2CHN(CH_3)_2 + RCHO \rightarrow (C_2H_5O)_2P(O)C(N(CH_3)_2){=}CHR .$$

Unsaturated ketophosphonic esters were obtained by Normant by the reaction of carbonyl compounds with the sodio-derivative of 2-ethoxy-1,3-diphosphonopropene[265]:



$$(C_2H_5O)_2P(O)CH{=}C(OC_2H_5){-}CH_2P(O)(OC_2H_5)_2 \xrightarrow{+NaH+{>}C{=}0} (C_2H_5O)_2P(O)CH{=}C(OC_2H_5){-}CH{=}C{<} \rightarrow (C_2H_5O)_2P(O)CH_2COCH{=}C{<} .$$

$\alpha\beta$-Unsaturated phosphines and phosphine sulphides have been obtained with the aid of the P(O)-activated olefin formation reaction[286]. In this case compounds containing simultaneously ter- and quinque-valent phosphorus atoms or diphenylphosphine oxide and diphenylphosphine sulphide groups were used in this case as reagents for P(O)-activated olefin synthesis:

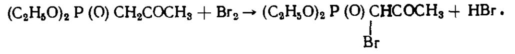


$$(C_6H_5)_2P{-}CH_2{-}P(O)(C_6H_5)_2 + RCHO \rightarrow (C_6H_5)_2P{-}CH{=}CHR + (C_6H_5)_2P(O)OH,$$
$$(C_6H_5)_2P(S){-}CH_2{-}P(O)(C_6H_5)_2 + RCHO \rightarrow (C_6H_5)_2P(S)CH{=}CHR + (C_6H_5)_2P(O)OH .$$

4. Reactions of Other Types

Among other reactions of organophosphorus compounds with an active methylene group in which the methylene hydrogen atoms are involved, bromination, chlorination, and azo-coupling reactions are known.

The bromination of diethoxyphosphonoacetone and diethoxyphosphonoacetaldehyde with elemental bromine takes place readily and rapidly in ethereal solution[40]:



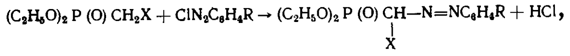
$$(C_2H_5O)_2P(O)CH_2COCH_3 + Br_2 \rightarrow (C_2H_5O)_2P(O)CH(Br)COCH_3 + HBr .$$

Chlorination of diethoxyphosphonoacetone with sulphuryl chloride gave a high yield of α-chlorodiethoxyphosphonoacetone[287]. When an excess of chlorine is allowed to react with dialkoxyphosphonoacetonitriles with simultaneous ultraviolet irradiation of the reaction mixture, both hydrogen atoms are substituted[288]:

$$(RO)_2P(O)CH_2CN + 2Cl_2 \xrightarrow[25-30^\circ]{h\nu} (RO)_2P(O)CCl_2CN + 2HCl .$$

Without ultraviolet irradiation, the chlorination does not take place but at a higher temperature not only the methylene group but also the alkoxy-group and the phosphorous atoms are chlorinated.

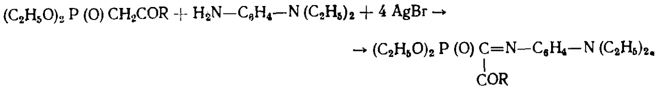
The azo-coupling of aromatic diazo-compounds with diethoxyphosphonoacetic ester, diethoxyphosphonoacetone, and diethoxyphosphonoacetonitrile has been achieved. The reactions were carried out under mild conditions in the absence of catalysts[289]:



$$(C_2H_5O)_2P(O)CH_2X + ClN_2C_6H_4R \rightarrow (C_2H_5O)_2P(O)CH(X){-}N{=}NC_6H_4R + HCl,$$

where X = $COOC_2H_5$, $COCH_3$, or CN.

There are data showing that the reaction of diethylaminoaniline with organophosphorus compounds having an active methylene group in the presence of silver bromide leads to the formation of azomethylene dyes containing the phosphono-group[290]:



$$(C_2H_5O)_2P(O)CH_2COR + H_2N{-}C_6H_4{-}N(C_2H_5)_2 + 4\,AgBr \rightarrow$$

$$\rightarrow (C_2H_5O)_2P(O)\underset{\displaystyle COR}{\underset{|}{C}}{=}N{-}C_6H_4{-}N(C_2H_5)_2.$$

However, later it was shown that in the case of diethoxyphosphonoacetophenone the yields of dyes in this reaction are very low and they cannot be isolated in a pure form[291,292].

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Kazan University

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Organosilicon Ketones

N.V.Komarov and V.K.Roman

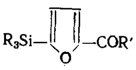
One of the most important fields in the chemistry of organosilicon compounds at the present time is the chemistry of organic silanes and siloxanes with carbon-containing functional groups[1-6]. Polysiloxanes with vinyl, nitrile, hydroxy- and other functional groups in the silane exhibit enhanced mechanical strength compared with alkylsiloxanes, are satisfactorily compatible with many materials, and have already found industrial application. Organic silanes and siloxanes with carbonyl groups in the organic substituents are also used in the manufacture of new products[7-11]. Patent data show that polyketoalkylsiloxanes exhibit improved adhesion to metallic surfaces[12]. The aim of the review is to describe methods for the preparation and the properties of silicon-containing ketones. In earlier monographs[3,13] and a review[14] on organic silanes with carbon-containing functional groups, the sections dealing with organosilicon ketones are very fragmentary and incomplete.
The bibliography includes 180 references.

CONTENTS

I. INTRODUCTION

The first information about organosilicon compounds with carbonyl groups appeared in 1903.[15] However, vigorous studies in this field were begun only after 1950 by Sommer, Andrianov, Petrov, Brook, Gilman, and many other investigators. The names of these compounds are usually derived from the name of the organic ketone with an indication of the position of the silyl group. For example, the compound $(CH_3)_3SiCH_2COCH_3$ is called 1-trimethylsilyl-2-propanone or trimethylsilylacetone. Sometimes the silane serves as a basis for the name, for example, benzoyltrimethylsilane $(CH_3)_3SiCOC_6H_5$.

Depending on the relative positions of silicon and the carbonyl group, silyl-substituted ketones of the type R_3SiCOR', R_3SiCH_2COR', $R_3Si(CH_2)_2COR'$, $R_3Si(CH_2)_3COR'$, $R_3Si(CH_2)_4COR'$, etc. are called respectively α-, β-, γ-, δ-, ϵ-, etc. organosilicon ketones. An aromatic or a heterocyclic group may also be interposed between the silyl and keto-groups, for example:

$R_3Si(CH_2)_nC_6H_4COR'$, $n = 0, 1, 2 \ldots$ or 

Silicon-containing β-diketones and ketoesters of the type

$$R_nSi[OC(R')=CHCOR']_{4-n} \text{ and } R_nSi[CH(COCH_3)COOR']_{4-n}, n = 1, 2, 3.$$

are also known.

II. METHODS OF SYNTHESIS OF ORGANOSILICON KETONES

The majority of the synthetic methods do not differ fundamentally from those for the preparation of organic ketones, although the presence of a silicon atom undoubtedly influences the type of reaction. The only general method, whereby organosilicon ketones with a wide variety of structures may be obtained, is organometallic synthesis. Among other methods, the Friedel–Crafts reaction, the acetoacetic ester synthesis, the Kharasch reaction, and the oxidation of silicon-containing alcohols and hydrocarbons have been widely employed.

1. Organometallic Synthesis

Organosilicon ketones are obtained with the aid of organolithium, organosodium, organopotassium, organocadmium, and organomagnesium compounds, the organomagnesium synthesis being most widely used.

As early as 1947 Whitmore et al.[16] attempted to prepare trimethylsilylacetone by the reaction of acetyl chloride with trimethylsilylmethylmagnesium chloride. However, only the decomposition products, including acetone, were obtained. The compound was later prepared by Hauser and Hance[17] by the reaction of acetic anhydride with trimethylsilylmethylmagnesium bromide under milder conditions:

$$(CH_3)_3SiCH_2MgBr \xrightarrow[2.\ H_2O,\ NH_4Cl]{1.\ (CH_3CO)_2O,\ -70^\circ} (CH_3)_3SiCH_2COCH_3.$$

4-Trimethylsilyl-2-butanone was synthesised from the chloride of trimethylsilylpropionic acid and methylmagnesium bromide in the presence of ferric chloride[18]:

$$(CH_3)_3SiCH_2CH_2COCl \xrightarrow[FeCl_3]{CH_3MgBr} (CH_3)_3SiCH_2CH_2COCH_3.$$

This ketone was also obtained using an organocadmium compound[19]:

$$(CH_3)_3SiCH_2CH_2COCl \xrightarrow{(CH_3)_2Cd} (CH_3)_3SiCH_2CH_2COCH_3.$$

γ-Silylketones are also obtained in high yields by the action of organomagnesium compounds on the nitriles of silicon-containing carboxylic acids[20-23]:

$$Cl_3SiCH_2CH_2CN \xrightarrow{RMgHal} R_3SiCH_2CH_2COR,$$

where R = CH_3 and C_6H_5.

δ- and ϵ-Silyl-substituted ketones[24,25], silicon-containing ethynyl ketones[26,27], and aromatic and heterocyclic silyl-substituted ketones[28,29] have been obtained similarly. At the same time the reaction of chloro-α-cyanoisopropopoxydimethylsilane $(CH_3)_2ClSiOC(CH_3)_2CN$ with Grignard reagents involves not only the CN group but also the Si–Cl and Si–O bonds and leads to the formation of a complex mixture of substances from which it is impossible to isolate the individual products[30]. Komarov and Yarosh[31,32] obtained α-silylethynyl ketones by the reaction of trialkylsilylethynylmagnesium bromides with acetic anhydride:

$$R_3SiC{\equiv}CMgBr + (CH_3CO)_2O \rightarrow R_3SiC{\equiv}CCOCH_3,$$

where R = CH_3 or C_2H_5.

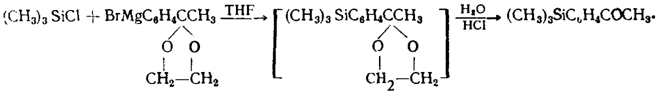
The same reaction with acetyl and benzoyl chlorides leads to the exclusive formation of tertiary diethynylsilylalcohols.

The reactions of *p*-triethylsilylphenylmagnesium bromide with acid anhydrides gave alkyl(aryl) *p*-triethylsilylphenyl ketones[33]:

$$p\text{-}(C_2H_5)_3SiC_6H_4MgBr + (RCO)_2O \rightarrow p\text{-}(C_2H_5)_3SiC_6H_4COR,$$

where R = CH_3, C_2H_5, n-C_3H_7, or C_6H_5.

p-Trimethylsilylacetophenone is formed in high yield by the reaction between the magnesium derivative of the ethyleneketal of 4-bromoacetophenone and trimethylchlorosilane in tetrahydrofuran (THF)[34]:



$$(CH_3)_3SiCl + BrMgC_6H_4C(OCH_2CH_2O)CH_3 \xrightarrow{THF} \left[(CH_3)_3SiC_6H_4C(OCH_2CH_2O)CH_3\right] \xrightarrow[HCl]{H_2O} (CH_3)_3SiC_6H_4COCH_3.$$

Silicon-containing ketoalcohols are obtained by the addition of benzil to an ethereal solution of trimethylsilylmethylmagnesium chloride[35]:

$$(CH_3)_3SiCH_2MgCl + C_6H_5COCOC_6H_5 \rightarrow (CH_3)_3SiCH_2C(OH)(C_6H_5)COC_6H_5.$$

Treatment of benzoyl chloride with a suspension of triphenylsilylpotassium in ether leads to the synthesis of benzoyltriphenylsilane in 4% yield[36]:

$$C_6H_5COCl + (C_6H_5)_3SiK \rightarrow (C_6H_5)_3SiCOC_6H_5 + KCl.$$

When triphenylsilyl-lithium reacts with an excess of acetyl chloride, acetyltriphenylsilane is also formed in a low yield[37]:

$$(C_6H_5)_3SiLi + CH_3COCl \rightarrow (C_6H_5)_3SiCOCH_3 + LiCl.$$

On the other hand, the reaction of triphenylsilyl-lithium with acetic anhydride does not yield the expected ketone[38]. A di-ϵ-silylketone was obtained unexpectedly as a side product in the synthesis of an ϵ-silylcarboxylic acid by the following reaction[39]:

$$(C_6H_5)_3Si(CH_2)_4Li \xrightarrow[-25°]{CO_2} \xrightarrow{H_2O} (C_6H_5)_3Si(CH_2)_4COOH + [(C_6H_5)_3Si(CH_2)_4]_2CO.$$

2. Synthesis with the Aid of Acetoacetic Ester

The first information about the sodioacetoacetic synthesis of organosilicon ketones was obtained in 1947 when Gilman[40] attempted to prepare triethylsilylacetoacetate by the reaction of sodioacetoacetic ester with triethylchlorosilane according to the following scheme:

$$(CH_3COCHCOOC_2H_5)^- Na^+ + (C_2H_5)_3SiCl \rightarrow (C_2H_5)_3SiCH(COCH_3)COOC_2H_5.$$

However, the only product isolated under these conditions proved to be ethyl β-triethylsiloxyorotonate $(C_2H_5)_3SiOC(CH_3){=}CHCOOC_2H_5$.

Andrianov[41], who achieved a similar reaction with chlorodiethoxymethylsilane, succeeded in obtaining silylacetoacetate:

$$CH_3(C_2H_5O)_2SiCl + NaCH(COCH_3)COOC_2H_5 \rightarrow CH_3(C_2H_5O)_2SiCH(COCH_3)COOC_2H_5 + NaCl.$$

When this compound is hydrolysed in an alkaline medium, the ester group is not split off from silicon and there is only partial hydrolysis of the ethoxy-groups linked to silicon. On the other hand, in an acid medium the ester group is almost completely split off and an infusible, insoluble powder is formed.

Later it was shown that silylacetoacetates can be more conveniently obtained by the condensation under mild conditions of organochlorosilanes with acetoacetic ester in the presence of triethylamine:[11]

$$(CH_3)_3SiCl + CH_2(COCH_3)COOC_2H_5 \xrightarrow[C_6H_6,\,-5°]{(C_2H_5)_3N} (CH_3)_3SiCH(COCH_3)COOC_2H_5.$$

Acetoacetic ester reacts with $SiCl_4$ in the cold with formation of the hydrochloride of tri(acetylethoxycarbonylmethyl)chlorosilane as prisms[42,43]:

$$3\,CH_3COCH_2COOC_2H_5 + SiCl_4 \rightarrow (CH_3COCHCOOC_2H_5)_3SiCl \cdot HCl + 2HCl.$$

On the other hand, when the mixture is heated to 100°C and at the same time dry air is passed through it the reaction leads to the formation of the yellow crystals of di(acetyl ethoxycarbonylmethyl)dichlorosilane[44].

Organosilanes containing a halogen in the organic substituent proved to be more suitable for the sodioacetoacetic ester synthesis of organosilicon ketones. Thus Sommer[19,45] obtained 4-trimethylsilyl-2-butanone by the following reaction:

$$(CH_3)_3SiCH_2I + CH_3COCH_2COOC_2H_5 + Na \rightarrow (CH_3)_3SiCH_2CH(COCH_3)COOC_2H_5 \rightarrow$$

$$\xrightarrow[\text{or 10\% NaOH}]{HCl} (CH_3)_3SiCH_2CH_2COCH_3.$$

The reaction of monobromohexamethyldisiloxane with sodioacetoacetic ester and subsequent hydrolysis of the ketoester produced gave a mixture of ketosiloxanes[46]:

$$(CH_3)_3SiOSi(CH_3)_2CH_2Br \xrightarrow[Na]{CH_3COCH_2COOC_2H_5} (CH_3)_3SiOSi(CH_3)_2CH_2CH(COCH_3)COOC_2H_5 \rightarrow$$

$$\xrightarrow[8\ h]{10\%\ NaOH} (CH_3)_3SiOSi(CH_3)_2CH_2CH_2COCH_3 + O[Si(CH_3)_2CH_2CH_2COCH_3]_2.$$

The ϵ-silylketone[24] $(CH_3)_3Si(CH_2)_4COCH_3$ and the aliphatic-aromatic organosilicon ketoester[47] $(CH_3)_3SiC_6H_4CH_2CH(COCH_3)COOCH_3$ were synthesised similarly.

In the reaction with sodioacetoacetic ester primary γ-silyl-substituted ethynyl chlorides also form organosilicon ketoesters[48]. When the latter are heated with 10% hydrochloric acid, silylethynylketoacids are formed. More prolonged refluxing leads to the rupture of the Si–C bond with formation of hexaethyldisiloxane as the principal product:

$$(C_2H_5)_3SiC{\equiv}CCH_2Cl + CH_3COCHNaCOOC_2H_5 \rightarrow (C_2H_5)_3SiC{\equiv}CCH_2CH(COCH_3)COOC_2H_5 \rightarrow$$

$$\xrightarrow[C_2H_5OH]{HCl} (C_2H_5)_3SiC{\equiv}CCH_2CH(COCH_3)COOH \xrightarrow[90°]{HCl} (C_2H_5)_3SiOSi(C_2H_5)_3 + CO_2 + \text{resin}.$$

The expected silylethynyl ketones $R_3SiC{\equiv}CCH_2COCH_3$ could not be isolated.

Secondary γ-silylethynyl chlorides behave similarly in sodioacetoacetic ester synthesis[27].

3. The Friedel–Crafts Reaction

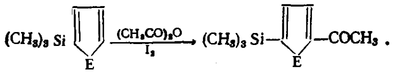
The Friedel–Crafts reaction constitutes a convenient method for the preparation of aromatic and heterocyclic organosilicon ketones, although it does not always take place successfully in consequence of the instability of the Si–Caryl bond in relation to acid reagents[49]. For example, the reaction of triethylphenylsilane[50] and also arylhalogenosilanes[51] with acid chlorides in the presence of aluminium chloride usually yields organic ketones and hexa-alkyldisiloxane instead of the expected organosilicon ketones:

$$R_3SiC_6H_5 + R'COCl \xrightarrow{AlCl_3} C_6H_5COR' + R_3SiOSiR_3.$$

Successful acylation of phenylsilanes by the Friedel–Crafts reaction[52] was achieved under mild conditions by the action of acetyl and benzoyl fluorides on trimethylphenylsilane in the presence of boron trifluoride:

$$(CH_3)_3SiC_6H_5 + RCOF \xrightarrow{BF_3} (CH_3)_3SiC_6H_4COR \quad (R{=}CH_3C_6H_5).$$

Acylation of 2-thienyltrimethylsilane and 2-furyltrimethylsilane with acetic anhydride takes place readily in the presence of iodine[53]:



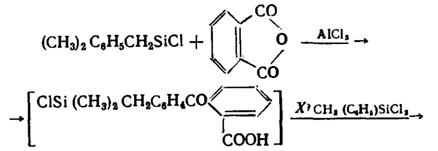
In contrast to phenylsilanes, the acylation of benzylsilanes[54] and trialkyl-β-phenylethylsilanes[55] with acyl chlorides using aluminium chloride takes place without the dissociation of the Si–C bond:

$$R_3Si(CH_2)_nC_6H_5 + R'COCl \xrightarrow{AlCl_3} R_3Si(CH_2)_nC_6H_4COR' \quad (n = 1,\ 2).$$

It has been established that, because of the conjugation of the Si–C bond with the aromatic ring, benzyltrimethylsilane is approximately 24 times more reactive than benzene in the acylation reaction and trimethyl-β-phenylethylsilane is 16 times more reactive.

The Friedel–Crafts reaction has been successfully used by Andrianov for the synthesis of various benzylsiloxane derivatives[10,56–59]:

$$(CH_3)_2C_6H_5CH_2SiCl + (CH_3CO)_2O \xrightarrow{AlCl_3} \xrightarrow{H_2O} [CH_3COC_6H_4CH_2(CH_3)_2Si]_2O,$$



$$\rightarrow HOOCC_6H_4COC_6H_4CH_2Si(CH_3)_2O[Si(CH_3)(C_6H_5)O]_xSi(CH_3)_2CH_2C_6H_5COC_6H_4COOH.$$
$$(x = 1-5,10)$$

Organosilicon ketones are also obtained by the Friedel–Crafts reaction from the chlorides of organosilicon carboxylic acids. Thus toluene and anisole are acylated in the *p*-position with *m*- and *p*-trimethylsilylbenzoyl chlorides[60]:

$$(CH_3)_3SiC_6H_4COCl + C_6H_5R \xrightarrow{SnCl_4} (CH_3)_3SiC_6H_4R,$$

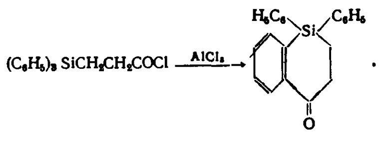
where R = CH_3 or OCH_3.

The chlorides of organosilicon carboxylic acids with alkoxy-groups at the silicon atom may be used as acylating agents. For example, the condensation of trimethoxysilylundecanoyl chloride with benzene in the presence of aluminium chloride leads to the formation of the corresponding ketone[61]:

$$(CH_3O)_3Si(CH_2)_{10}COCl + C_6H_6 \xrightarrow{AlCl_3} (CH_3O)_3Si(CH_2)_{10}COC_6H_5.$$

Ketosilanes with the composition $X_mR_{3-m}Si(CH_2)_nCOR'$, where $m = 0-3$ and $n = 2-10$, are obtained similarly[62].

It is interesting to note[63] that 3-triphenylsilylpropionyl chloride cyclises under the action of aluminium chloride to 2,3-benzo-1,1-diphenyl-1-silacyclohex-2-en-4-one:



A similar cyclisation is observed also with 4-triphenylsilylbutyryl chloride.

The condensation of β-trimethylsilylpropionyl chloride with ferrocene in the presence of aluminium chloride led to the isolation of a 76% yield of β-trimethylsilylpropionylferrocene[64]:

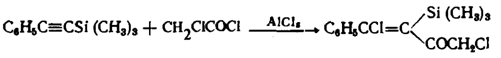
$$(CH_3)_3SiCH_2CH_2COCl + C_5H_5FeC_5H_5 \xrightarrow{AlCl_3} (CH_3)_3SiCH_2CH_2COC_5H_4FeC_5H_5.$$

A very interesting reaction was discovered by Birkofer et al.[65], who observed that the reaction of acid chlorides or anhydrides with di(trimethylsilyl)acetylene in the presence of aluminium chloride results in the formation of silylated alkynones:

$$(CH_3)_3SiC{\equiv}CSi(CH_3)_3 + RCOCl \xrightarrow{AlCl_3} (CH_3)_3SiC{\equiv}CCOR + (CH_3)_3SiCl,$$

where R = CH_3, C_2H_5, $C_6H_4NO_2$, or CH_2Cl. The yields of the ketones reached 90%.

The following reaction takes place similarly:



$$C_6H_5C{\equiv}CSi(CH_3)_3 + CH_2ClCOCl \xrightarrow{AlCl_3} C_6H_5CCl{=}C\begin{matrix} \diagup Si(CH_3)_3 \\ \diagdown COCH_2Cl \end{matrix}.$$

4. The Kharasch Reaction[66]

Sommer[67] and then Petrov and Chernyshev[68,69] obtained silicon-containing ketones by the addition of butyraldehyde and benzaldehyde to vinyl- and γ-butenyl-silanes in the presence of diacetyl and benzoyl peroxides:

$$R_3SiCH{=}CH_2 + R'CHO \xrightarrow{\text{peroxide}} R_3SiCH_2CH_2COR',$$

where R = CH_3 or C_2H_5 and R^1 = C_3H_7 or C_6H_5.

Organosilicon ketones are also formed in low yields on heating equimolar mixtures of tri(trimethylsiloxy)vinylsilane with aldehydes in an autoclave in the presence of t-butyl peroxide[70]:

$$[(CH_3)_3SiO]_3SiCH{=}CH_2 + RCHO \xrightarrow[185°,\ 4\ h]{\text{peroxide}} [(CH_3)_3SiO]_3SiCH_2CH_2COR,$$

where R = CH_3, C_6H_5, or *o*-HOC_6H_4.

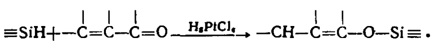
Brook[71] added benzaldehyde to triphenylvinylsilane with ultraviolet irradiation and obtained a corresponding ketone in 12% yield. We showed that the photochemical reaction of aldehydes with alkylvinyl- and alkoxyvinyl-silanes is general and may serve as a convenient method for the synthesis of γ-silyl-substituted ketones with various structures, including ketones containing readily hydrolysable alkoxy-groups at the silicon atom[72–73]:

$$R_3SiCH{=}CH_2 + R'CHO \xrightarrow{h\nu} R_3SiCH_2CH_2COR',$$

where R = CH_3, C_2H_5, or C_2H_5O and R′ = CH_3, C_2H_5, C_3H_7, iso-C_4H_9, C_6H_5, etc. The yields of ketones reach 90%. On the other hand, the reaction involving the radical addition of aldehydes to allylsilanes could not be achieved.

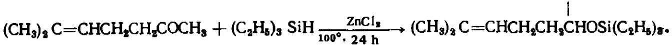
5. Interaction of Silanes Containing Unsubstituted Hydrogen Atoms with Unsaturated Ketones

Petrov and Sadykh-Zade[74,75] showed that the addition of partially substituted silanes bearing organic substituents to αβ-unsaturated ketones in the presence of a Speier catalyst does not yield the expected organosilicon ketone. The reaction involves the 1,4-position with formation of silicon-containing vinyl ethers:



$$\equiv SiH + -\overset{|}{C}{=}\overset{|}{C}-\overset{|}{C}{=}O \xrightarrow{H_2PtCl_6} -CH-\overset{|}{C}{=}\overset{|}{C}-O-Si\equiv.$$

Calas[76] investigated the reaction between silanes with free hydrogen atoms and unsaturated ketones having an isolated double bond. The reaction of triethylsilane with 2-methylhept-2-en-6-one in the presence of zinc chloride as a catalyst does not lead to the formation of a ketone:



$$(CH_3)_2C{=}CHCH_2CH_2COCH_3 + (C_2H_5)_3SiH \xrightarrow[100°,\ 24\ h]{ZnCl_2} (CH_3)_2C{=}CHCH_2CH_2\overset{\overset{CH_3}{|}}{C}HOSi(C_2H_5)_3.$$

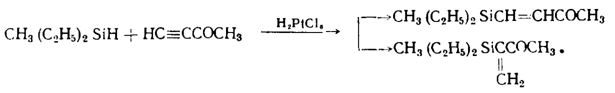
We investigated[77,78] the reaction between silanes with free hydrogen atoms and allylacetone under the influence of chloroplatinic acid and showed that it is suitable for the synthesis of ϵ-silyl-substituted ketones:

$$\mathrm{R_3SiH + CH_2{=}CHCH_2CH_2COCH_3 \xrightarrow{H_2PtCl_6} R_3Si\,(CH_2)_4\,COCH_3}.$$

The yields of ketones reached 75–85%. Recently Khudobin and Kharitonov[79] obtained ϵ-silyl-substituted ketones by the addition of trisubstituted silanes to unsaturated ketones with an isolated double bond, the mixture being heated in the presence of colloidal nickel. Klotz and Kuckertz[12] synthesised siloxanes with two keto-groups in the ϵ-positions in 42% yield by the reaction of *sym*-tetramethyldisiloxane with allylacetonylacetone in the presence of platinum in an autoclave:

$$\mathrm{2H(CH_3)_2\,SiOSi\,(CH_3)_2\,H + 2CH_2{=}CHCH_2CH\,(COCH_3)_2 \xrightarrow[160^\circ]{Pt}}$$
$$\mathrm{\rightarrow (CH_3CO)_2\,CH\,(CH_2)_3\,Si\,(CH_3)_2\,OSi\,(CH_3)_2\,(CH_2)_3\,CH\,(COCH_3)_2}.$$

Mashlyakovskii and Chelpanova[80] investigated the reaction of 2-butynone with diethylmethylsilane and established that, in contrast to methyl vinyl ketone, the reaction involves the 1,2-position with formation of a mixture of the *cis*- and *trans*-isomers. On the basis of infrared and PMR-spectroscopic studies, gas–liquid and thin-layer chromatography, and also by synthesis, Komarov and Pukhnarevich[81] showed that, under the conditions of this reaction, a mixture of β- and γ-silylvinyl ketones is in fact obtained:



$$\mathrm{CH_3\,(C_2H_5)_2\,SiH + HC{\equiv}CCOCH_3 \xrightarrow{H_2PtCl_6}} \begin{cases} \mathrm{\rightarrow CH_3\,(C_2H_5)_2\,SiCH{=}CHCOCH_3} \\ \mathrm{\rightarrow CH_3\,(C_2H_5)_2\,SiC({=}CH_2)COCH_3}. \end{cases}$$

The use of polar aprotic solvents (tetrahydrofuran, dioxane) permits the selective hydroxylation of ethyl methyl ketone and the isolation of chromatographically pure γ-substituted ketone derivatives[82].

6. Oxidation of Silicon-containing Alcohols and Hydrocarbons

Organosilicon ketones may be obtained by the oxidation of silicon-containing secondary alcohols and aliphatic-aromatic silicon-containing hydrocarbons. Potassium permanganate, the chromic acid mixture, anddicyclohexylcarbodi-imide are used as oxidising agents. α-Silyl-substituted ketones[83-87] $\mathrm{R_3SiCOR'}$ and β-silyl-substituted ketones[71,87] $\mathrm{R_3SiCH_2COR'}$ have been obtained in this way. By oxidising secondary silicon-containing ethynyl- and vinyl-alcohols with chromium trioxide, one of the present authors[88,89] synthesised for the first time organosilicon ethynyl ketones:

$$\mathrm{(CH_3)_3\,SiC{\equiv}CCHOHR \xrightarrow{CrO_3} (CH_3)_3\,SiC{\equiv}CCOR},$$

where $\mathrm{R = CH_3}$, $\mathrm{C_2H_5}$, or $\mathrm{CH{=}CH_2}$. Organosilicon ketones of the ethylene series $\mathrm{R_3SiCH{=}CHCOR^1}$ were obtained similarly[90].

The oxidation of *o*-, *m*-, and *p*-trimethylsilylethylbenzenes with oxygen in the presence of chromium trioxide and calcium carbonate gives a mixture of trimethylsilylacetophenones with trimethylsilylbenzoic acids[91]:

$$\mathrm{(CH_3)_3\,SiC_6H_4C_2H_5 \xrightarrow[200^\circ]{O_2/CrO_3+CaCO_3} (CH_3)_3\,SiC_6H_4COCH_3 + (CH_3)_3\,SiC_6H_4COOH}.$$

The yields of ketones are 15–20%.

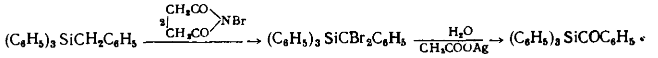
When secondary silicon-containing aromatic alcohols were heated with an excess of acetone in the presence of aluminium t-butoxide, the corresponding ketones were isolated in yields of 19–42% (Oppenauer reaction)[33]:

$$p\text{-}\mathrm{R_3SiC_6H_4CHOHR' + CH_3COCH_3 \underset{200^\circ}{\overset{Al(OC_4H_9\text{-}t)_3}{\rightleftarrows}}} p\text{-}\mathrm{R_3SiC_6H_4COR' + CH_3CHOHCH_3},$$

where $\mathrm{R = CH_3}$ or $\mathrm{C_2H_5}$ and $\mathrm{R' = CH_3}$, $\mathrm{C_2H_5}$, $\mathrm{C_3H_7}$, or $\mathrm{C_6H_5}$.

7. Hydrolysis of Organosilicon Dihalogeno-derivatives

The hydrolysis of silicon-containing dihalogeno-derivatives of hydrocarbons is an important method for the synthesis of α-silyl-substituted ketones. The first α-silyl-substituted ketones was obtained in 1957 by Brook[36] from benzyltriphenylsilane by the reaction



$$\mathrm{(C_6H_5)_3\,SiCH_2C_6H_5 \xrightarrow{2\,(CH_2CO)_2NBr} (C_6H_5)_3\,SiCBr_2C_6H_5 \xrightarrow[CH_3COOAg]{H_2O} (C_6H_5)_3\,SiCOC_6H_5}.$$

Benzoylhydroxy- and benzoylmethoxy-silanes $\mathrm{C_6H_5COSi(C_6H_5)_2OR}$ ($\mathrm{R = H}$ or $\mathrm{CH_3}$), benzoyl(halogenobenzyl)silanes $\mathrm{C_6H_5COSi(C_6H_5)_2CXYC_6H_5}$ ($\mathrm{Y = Cl}$ or Br: $\mathrm{X = H}$, Cl, or Br), dibenzoylsilanes $\mathrm{(C_6H_5CO)_2SiR_2}$ ($\mathrm{R = CH_3}$ or $\mathrm{C_6H_5}$), and benzoylmethyl-α-naphthylphenylsilane $\mathrm{CH_3(C_6H_5)(C_{10}H_7)SiCOC_6H_5}$ were synthesised analogously[92,93]. All the reactions take place with satisfactory yields. The synthesis of a γ-silyl-substituted ketone was achieved similarly[71]:

$$\mathrm{(C_6H_5)_3\,SiCl + Li\,(CH_2)_3\,C_6H_5 \rightarrow (C_6H_5)_3\,Si\,(CH_2)_3\,C_6H_5 \xrightarrow[H_2O]{Br_2} (C_6H_5)_3\,SiCH_2CH_2COC_6H_5}.$$

A β-silyl-substituted ketone could not be obtained by this method, only the decomposition products being isolated.

8. Hydration of Silylacetylenes

The attempts to hydrate trialkylsilylacetylenes and di(trialkylsilyl)acetylenes proved unsuccessful. The reaction apparently leads to the formation of silyl-substituted ketones with the carbonyl group in the β-position, which decompose according to the mechanism[94,95]:

$$\mathrm{R_3SiC{\equiv}CR' + H_2O \rightarrow [R_3SiCH_2COR'] \rightarrow 2R_3SiOH + CH_3COR'},$$

where $\mathrm{R = CH_3}$ or $\mathrm{C_2H_5}$ and $\mathrm{R' = C_6H_5}$, $\mathrm{(CH_3)_3Si}$, etc.

The attempt at the Kucherov hydration of the triple bond in trialkylvinylethynylsilanes $\mathrm{R_3SiC{\equiv}CCH{=}CH_2}$ and dialkyldi(vinylethynyl)silanes $\mathrm{R_2Si(C{\equiv}CCH{=}CH_2)_2}$ was also unsuccessful: under mild conditions there was only partial polymerisation of the compound and under severe conditions the Si–C bond was broken[96,97]. The corresponding ketones were obtained only from monosubstituted alkynylsilanes with the triple bond in the γ-position relative to the silicon atom:

$$\mathrm{R_3SiCH_2CH_2C{\equiv}CH \xrightarrow[HgSO_4]{H_2O} R_3SiCH_2CH_2COCH_3},$$

where $\mathrm{R = CH_3}$ or $\mathrm{C_2H_5}$.

Silyl-substituted α-ketoalcohols[99] and alkenyl alkoxyalkyl ketones[100] were also synthesised from the corresponding silyl-substituted ethynyl and vinylethynyl-alcohols:

$$\mathrm{R_3Si\,(CH_2)_{\mathit{n}}\,COH\,(CH_3)\,C{\equiv}CH \xrightarrow[HgSO_4]{H_2O} R_3Si\,(CH_2)_{\mathit{n}}\,COH\,(CH_3)\,COCH_3},$$
$$\mathrm{R_3Si\,(CH_2)_{\mathit{n}}\,COH\,(CH_3)\,C{\equiv}CCH{=}CH_2 \xrightarrow[HgSO_4+H_2SO_4]{CH_3OH} R_3Si(CH_2)_{\mathit{n}}C(CH_3){=}CHCOCH_2CH_2OCH_3},$$

where $n = 2$–4 and R is an alkyl group.

9. Condensation of Silanes Containing Functional Groups with β-Diketones

Dilthey[15] found in 1903 that acetylacetone readily reacts with silicon tetrachloride to form a crystalline hydrochloride. The reaction usually results in the substitution of three chlorine atoms according to the mechanism:

$$3\,(CH_3CO)_2CH_2 + SiCl_4 \rightarrow [(CH_3CO)_2CH]_3SiCl\cdot HCl + 2HCl.$$

The fourth chlorine atom is not substituted even in the presence of an excess of the diketone. Subsequently this reaction was extended to benzoylacetone and dibenzoylmethane[101] and also silicon tetrabromide[102].

The condensation of tetra-acetoxysilane with acetylacetone in molar proportions of 1 : 2 leads to the formation of diacetoxydi-(2,4-dioxopentyl)silane $[CH_2(CH_3CO)_2]_2.$ $.Si(OCOCH_3)_2$.[103,104] West[105] obtained a number of mono-, di-, and tri-alkylsilyl derivatives of acetylacetone:

$$R_nSiCl_{4-n} + (4-n)\,CH_3COCH_2COCH_3 \rightarrow R_nSi\,[CH\,(COCH_3)_2]_{4-n} + (4-n)\,HCl,$$

where n = 1–3 and R = CH_3, C_2H_5, or C_6H_5. The trimethylsilyl derivative of acetylacetone is also obtained by the following reaction[106]:

$$R_3SiN\,(C_6H_5)\,CONHC_6H_5 + CH_3COCH_2COCH_3 \rightarrow R_3Si\,[CH(COCH_3)_2] + C_6H_5NHCONHC_6H_5.$$

The reaction of chlorodiethylmethoxysilane with sodium acetylacetonate gave a silyl ether of the enolic form of acetylacetone[107]:

$$(C_2H_5)_2\,(CH_3O)\,SiCl + CH_3COCHNaCOCH_3 \rightarrow (C_2H_5)_2\,(CH_3O)\,SiOC\,(CH_3){=}CHCOCH_3.$$

10. Ester, Crotonic, and Benzoin Condensations

Esters of the type $R(CH_3)_2Si(CH_2)_nCOOR'$ condense in the presence of sodamide, sodium alkoxides[108], di-isopropylaminomagnesium bromide[108,109], and $(CH_3)_2NMgBr$[110] to silicon-containing β-ketoesters. The latter are hydrolysed to ketones on treatment with a strong inorganic acid[108-111,180]:

$$2R\,(CH_3)_2Si(CH_2)_nCOOR' \xrightarrow{C_2H_5ONa}$$
$$\rightarrow R\,(CH_3)_2\,Si\,(CH_2)_{n-1}CH(COOR')CO\,(CH_2)_nSiR\,(CH_3)_2 \xrightarrow{H_2SO_4} [R(CH_3)_2Si(CH_2)_n]_2\,CO.$$

Ethyl trimethylsilylpropionate condenses with acetone in the presence of sodamide to the corresponding β-diketone[18]:

$$(CH_3)_3\,SiCH_2CH_2COOC_2H_5 + CH_3COCH_3 \xrightarrow{NaNH_2} (CH_3)_3\,SiCH_2CH_2COCH_2COCH_3.$$

The condensation of *p*-trimethylsilylbenzaldehyde with acetone, pinacol, acetophenone, and cyclohexanone has been achieved[28,112]. When the ketone contains one active methylene group, the reaction takes place unambiguously according to the mechanism:

$$p\text{-}(CH_3)_3SiC_6H_4CHO + CH_3COR \xrightarrow{-H_2O} p\text{-}(CH_3)_3\,SiC_6H_4CH{=}CHCOR,$$

where R = C_6H_5 or $C(CH_3)_3$. In the presence of two active methylene groups, further condensation involving this group is possible.

When an alcoholic solution of *p*-trimethylsilylbenzaldehyde is heated with potassium cyanide, benzoin condensation takes place and leads to the formation of a disilyl-substituted aromatic ketoalcohol[28]:

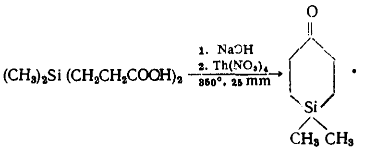
$$(CH_3)_3SiC_6H_4CHO + OHCC_6H_4Si(CH_3)_3 \xrightarrow{CN^-} (CH_3)_3SiC_6H_4COCH(OH)C_6H_4Si(CH_3)_3.$$

11. Pyrolysis of Salts of Organosilicon Acids

Dry distillation of the calcium salts of organosilicon acids and their mixtures with organic acid salts leads to the formation of silicon-containing ketones with symmetrical and asymmetric structures[113]:

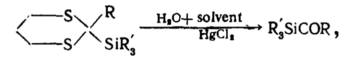
$$(R_3SiCH_2CH_2COO)_2\,Ca \rightarrow (R_3SiCH_2CH_2)_2\,CO + CaCO_3,$$
$$(R_3SiCH_2CH_2COO)_2\,Ca + (R'COO)_2\,Ca \rightarrow R_3SiCH_2CH_2COR' + CaCO_3,$$

where R = CH_3 or C_2H_5 and R′ = $(CH_3)_2CH$. The yields of ketones amount to 13–28%. Dimethylsilacyclohexanone was obtained in 35% yield by the pyrolysis of the thorium salt of a dibasic organosilicon acid[114]:



12. Other Methods

Many α-silyl-substituted ketones have been prepared by the hydrolysis of 2-silyl-1,3-dithianes[84,115]:

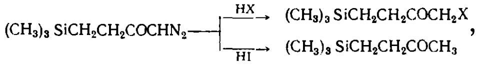


where R = R′ = CH_3, C_6H_5, etc.

The reaction of the chloride of β-(trimethylsilyl)propionic acid with diazomethane results in the formation of diazomethyl β-(trimethylsilyl)ethyl ketone[116,117]:

$$(CH_3)_3SiCH_2CH_2COCl + CH_2N_2 \rightarrow (CH_3)_3SiCH_2CH_2COCHN_2.$$

The latter reacts with hydrogen halides and acetic acid to form halogeno- and acetoxy-substituted organosilicon ketones and these can be converted into 4-trimethylsilyl-2-butanone:



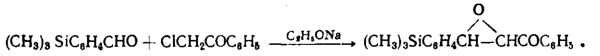
$$(CH_3)_3\,SiCH_2CH_2COCHN_2 \begin{cases} \xrightarrow{HX} (CH_3)_3\,SiCH_2CH_2COCH_2X \\ \xrightarrow[HI]{} (CH_3)_3\,SiCH_2CH_2COCH_3 \end{cases},$$

where X = Cl, Br, or $OCOCH_3$.

The diazo-method can also be used to synthesise a di[oxoalkyl(alkyl)]siloxane by the reaction

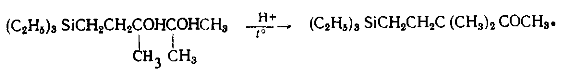
$$ClSi\,(CH_3)_2CH_2CH_2COCl \xrightarrow{CH_2N_2} ClSi\,(CH_3)_2CH_2CH_2COCHN_2 \xrightarrow[H_2O]{HI}$$
$$\rightarrow O[Si(CH_3)_2CH_2CH_2COCH_3]_2.$$

The synthesis of 2-benzoyl-1-(*p*-trimethylsilylphenyl)-epoxyethane by the Darzens condensation has been reported[118]:



$$(CH_3)_3\,SiC_6H_4CHO + ClCH_2COC_6H_5 \xrightarrow{C_2H_5ONa} (CH_3)_3SiC_6H_4\overset{O}{CH{-}CH}COC_6H_5.$$

The present authors synthesised a δ-silyl-substituted ketone by the pinacol rearrangement of an organosilicon glycol[99]:



$$(C_2H_5)_3\,SiCH_2CH_2\underset{CH_3}{C}OH\underset{CH_3}{C}OHCH_3 \xrightarrow[t^\circ]{H^+} (C_2H_5)_3\,SiCH_2CH_2C\,(CH_3)_2\,COCH_3.$$

Silicon-containing ketones can also be obtained by the silylation of hydroxyketones[119]:

$$(CH_3)_3\,SiCl + C_2H_5CHOHCOC_2H_5 \xrightarrow{C_5H_5N} (CH_3)_3\,SiOCH\,(C_2H_5)\,COC_2H_5.$$

III. PROPERTIES OF ORGANOSILICON KETONES

The properties of organosilicon ketones depend to a large degree on the relative positions of the silicon atom and the carbonyl group. A characteristic feature of α- and β-silyl-substituted ketones is the instability of the Si–C bond in relation to the majority of the nucleophilic and electrophilic reagents. Silicon-containing ketones in which the silicon atom is further away from the C=O group enter into various reactions involving the carbonyl group without the dissociation of the silicon–carbon bond.

These features of organosilicon ketones are reflected in their ultraviolet and infrared spectra. The study of the spectra showed that the characteristic absorption of the carbonyl group in these compounds is determined, on the one hand, by the structure of the molecule as a whole and, on the other hand, depends on the relative positions of the carbonyl group and the silicon atom. The carbonyl groups of α-silyl-substituted ketones exhibit an anomalous polarity, resembling that of a carboxylate ion rather than a β-diketone (6.2–6.45 μm).[120]

Polarity of C=O bond, μm (infrared spectra)

CH_3COCH_3—5.81

$C_6H_5COC_6H_5$—6.01

$(C_6H_5)_3SiCOCH_3$—6.08

$\left.\begin{matrix}(C_6H_5)_3SiCOC_6H_5\\(CH_3)_3SiCOCH_3\end{matrix}\right\}$—6.18

It has been suggested[71,121] that the anomalous spectroscopic effects of α-silyl-substituted ketones can be explained by the interaction of the unpaired electron of the oxygen atom in the carbonyl group with the vacant *d*-orbitals of silicon. As the silicon atom is removed further away from the carbonyl group, the effect of the silyl group diminishes and the absorption band associated with the carbonyl group in α-silyl-substituted ketones (1618 cm^{-1} for benzoylsilanes and 1645 cm^{-1} for acetyl- and propionylsilanes) rises to 1667 cm^{-1} in the spectra of β-silyl-substituted ketones and reaches 1716 cm^{-1} in the case of γ-silyl-substituted ketones, a value which is usual for aliphatic ketones[116,122–124]. Yates and Agolini[125] believe that the fundamental cause of the lower absorption frequency of the carbonyl group in α-silyl-substituted ketones is the inductive effect of the silicon atom, which increases the electron density at the carbonyl oxygen, thereby enhancing the basicity of the carbonyl group in ketones of the $R_3SiCOC_6H_5$ series compared with their hydrocarbon analogues.

Since the properties of α- and β-silyl-substituted ketones differ appreciably from those of ketones with the silicon atom more remote from the carbonyl group, we combined them into separate classes. Aromatic silyl-substituted ketones, silylethynylketones with the formula $R_3SiC{\equiv}CCOR'$, and complexes of silicon halides with β-diketones and β-ketoesters also exhibit a number of characteristic features because of the mutual effects of the silicon atom and the carbonyl group.

1. α-Silyl-substituted Ketones

In contrast to their hydrocarbon analogous, α-silyl-substituted ketones are coloured yellow, orange, or red[36,83]. Evidently the silicon atom behaves as a chromophore[120]. These ketones are thermally stable. For example, benzoyltriphenylsilane scarcely changes on heating to 250°C. At 365°C there is some decomposition, but 70% of the initial compound is recovered[36]. Alkylsilyl ketones and alkylarylsilyl ketones are liquid, while arylsilyl ketones are solid crystalline substances.

The chemical properties of α-silyl-substituted ketones were investigated Brook. The principal characteristic feature is high lability in relation to chemical reagents. The majority of benzoylsilanes are readily hydrolysed in air[92]. In consequence of the interaction of the unshared electrons of the oxygen atoms in the carbonyl group with the vacant *d*-orbitals of silicon, nucleophilic reagents usually cause the decomposition of the ketone molecule at the Si–C bond. Similar decomposition takes place also when benzoylsilanes are irradiated with ultraviolet light. Only hydrogenation and reactions with phenylhydrazine and certain Grignard reagents take place without the rupture of the carbon–silicon bond.

When α-silyl-substituted ketones are treated with ethanol in the presence of aqueous alkali, the yellow colour of the ketone disappears after several minutes and silanol and an aldehyde are formed[36,126]:

$$(C_6H_5)_3SiCOC_6H_5 \xrightarrow[H_2O]{\bar{O}H} (C_6H_5)_3SiOH + C_6H_5CHO.$$

A similar reaction takes place in the chromatographic separation of α-silyl-substituted ketones on activated alumina.

When sodium ethoxide is allowed to act upon benzoyltriphenylsilane, the main product is ethoxydiphenyl(diphenylmethoxy)silane $(C_6H_5)_2CHOSi(OC_2H_5)(C_6H_5)_2$ together with small amounts of cleavage products—diphenylmethanol and diethoxydiphenylsilane[126,127].

Treatment of benzoyltriphenylsilane with phenyl-lithium does not lead to the expected alcohol: only the decomposition products, including triphenylsilanol and tetraphenylsilane, were isolated[36]. Methyl–magnesium iodide and benzylmagnesium chloride interact with benzoyltriphenylsilane in a normal manner with formation of alcohols[120,128]:

$$(C_6H_5)_3SiCOC_6H_5 \xrightarrow{CH_3MgI} (C_6H_5)_3SiC(OH)(CH_3)C_6H_5.$$

At the same time Grignard reagents with β-hydrogen atoms (C_2H_5MgBr, C_3H_7MgBr) behave mainly as reducing agents. There is no reaction between benzoyltriphenylsilane and t-butylmagnesium chloride and only cleavage at the Si–C bond takes place when this ketone interacts with phenylmagnesium bromide.

The attempts to prepare the oxime of benzoyltriphenylsilane were unsuccessful because of its decomposition into triphenylsilanol and benzaldehyde[36]. However, benzoyltriphenylsilane does form crystalline hydrazones[129]. It is readily reduced by lithium aluminium hydride[120] to the carbinol $(C_6H_5)_3SiCHOHC_6H_5$. On being irradiated with ultraviolet light in methanol solution for 2 h, benzoyltriphenylsilane is converted into methoxytriphenylsilane[130,131]:

$$(C_6H_5)_3SiCOC_6H_5 \xrightarrow[CH_3OH]{h\nu} (C_6H_5)_3SiOCH_3 + C_6H_5CH(OCH_3)_2.$$

The treatment of α-silyl-substituted ketones with diazomethane leads to the formation of a mixture of β-silyl-substituted ketones with isomeric siloxyalkenes[132]:

$$R_3SiCOR' + CH_2N_2 \rightarrow R_3SiCH_2COR' + R_3SiOCR'{=}CH_2.$$

The Wittig reaction with α-silyl-substituted ketones has been investigated[133]. Benzoylsilanes form siloxyalkenes and alkyl silyl ketones undergo the normal Wittig reaction.

2. β-Silyl-substituted Ketones

A distinctive feature of β-silyl-substituted ketones is also chemical instability. They decompose under the action of both nucleophilic and electrophilic reagents[18]. β-Silyl-substituted ketones formed on hydration of trialkylsilylacetylenes cannot be isolated because of their decomposition into trialkylsilanol and a non-silylated ketone[95]:

$$R_3SiC{\equiv}CR' \xrightarrow{H_2O} [R_3SiCH_2COR'] \xrightarrow{H_2O} R_3SiOH + CH_3COR'.$$

β-Ketosilanes isomerise to siloxyalkenes on heating to 80–175°C and also in the presence of mercuric iodide[134–137]:

$$R_3SiCH_2COR' \rightarrow R_3SiOCR'{=}CH_2.$$

When trimethylsilylacetone is treated with 2,4-dinitrophenylhydrazine in 85% ethanol containing sulphuric acid, the Si–C bond is ruptured and a 2,4-dinitrophenylhydrazone of acetone is formed[17]. This ketone also decomposes on being refluxed with ethanol:

$$(CH_3)_3SiCH_2COCH_3 \xrightarrow[t^\circ]{C_2H_5OH} (CH_3)_3SiOC_2H_5 + CH_3COCH_3\ .$$

Trimethylsilylphenylacetone $(CH_3)_3SiCH(C_6H_5)COCH_3$ is more stable and does form a 2,4-dinitrophenylhydrazone. Triphenyl(phenylacetyl)silane $(C_6H_5)_3SiCH_2COC_6H_5$, obtained by the oxidation of the corresponding carbinol with a mixture of chromium trioxide and sulphuric acid, is even more stable[71].

3. γ-, δ-, and ε-Silyl-substituted Ketones

The Si–C bonds in γ-, δ-, and ε-silyl-substituted ketones are stable in relation to nucleophilic and electrophilic reagents, in contrast to the α- and β-substituted ketones. In oxidation, reduction, and condensation reactions they behave similarly to non-silylated ketones. In addition they undergo certain specific reactions due to the presence of the silicon atom.

The reduction of γ-silyl-substituted ketones with lithium aluminium hydride leads to the formation of silicon-containing secondary alcohols[71,138–140]. The oxidation of 4-trimethylsilyl-2-butanone[19] and 5-trimethylsilyl-2-pentanone[24] with sodium hypobromite yields organosilicon acids:

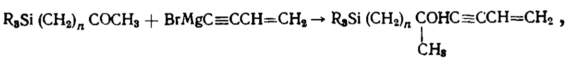
$$(CH_3)_3Si(CH_2)_nCOCH_3 \xrightarrow{NaBrO} (CH_3)_3Si(CH_2)_nCOOH\ (n = 2\text{–}3).$$

The reaction with alkylmagnesium bromides results in the formation of tertiary organosilicon alcohols[19,20,22,24,140]:

$$(CH_3)_3Si(CH_2)_nCOR \xrightarrow{R'MgBr} (CH_3)_3Si(CH_2)_nCR'(OH)R',$$

where R = CH_3 or C_6H_5, R′ = CH_3, C_2H_5, or C_6H_5, and n = 2 and 4.

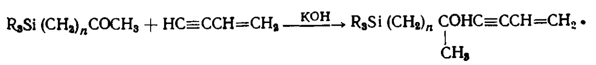
The reaction of vinylethynylmagnesium bromide with γ-, δ-, and ε-silyl-substituted ketones takes place normally with formation of silicon-containing vinylethynylalcohols[100]:



$$R_3Si(CH_2)_nCOCH_3 + BrMgC{\equiv}CCH{=}CH_2 \rightarrow R_3Si(CH_2)_n\underset{\displaystyle CH_3}{\underset{|}{C}}OHC{\equiv}CCH{=}CH_2\ ,$$

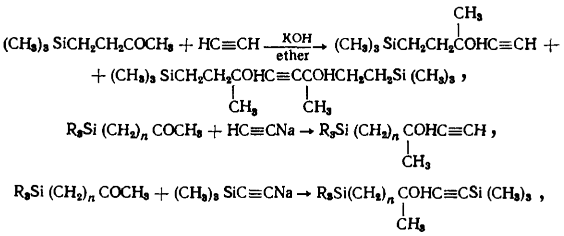
where R = CH_3 or C_2H_5 and n = 2–4.

These alcohols have also been synthesised in yields up to 80% by the reaction of organosilicon ketones with vinylacetylene in the presence of potassium hydroxide:



$$R_3Si(CH_2)_nCOCH_3 + HC{\equiv}CCH{=}CH_2 \xrightarrow{KOH} R_3Si(CH_2)_n\underset{\displaystyle CH_3}{\underset{|}{C}}OHC{\equiv}CCH{=}CH_2\ .$$

γ-, δ-, and ε-Silyl-substituted ketones enter into the Favorskii reaction with acetylene and also react with sodioacetylene and its derivatives to form silylethynylmethanols and silylethynylglycols[99,141–142] in high yields:



$$(CH_3)_3SiCH_2CH_2COCH_3 + HC{\equiv}CH \xrightarrow[ether]{KOH} (CH_3)_3SiCH_2CH_2\overset{\displaystyle CH_3}{\overset{|}{C}}OHC{\equiv}CH\ +$$

$$+\ (CH_3)_3SiCH_2CH_2\underset{\displaystyle CH_3}{\underset{|}{C}}OHC{\equiv}\underset{\displaystyle CH_3}{\underset{|}{C}}COHCH_2CH_2Si(CH_3)_3\ ,$$

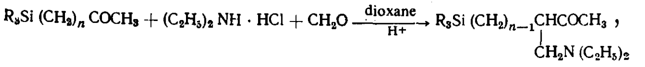
$$R_3Si(CH_2)_nCOCH_3 + HC{\equiv}CNa \rightarrow R_3Si(CH_2)_n\underset{\displaystyle CH_3}{\underset{|}{C}}OHC{\equiv}CH\ ,$$

$$R_3Si(CH_2)_nCOCH_3 + (CH_3)_3SiC{\equiv}CNa \rightarrow R_3Si(CH_2)_n\underset{\displaystyle CH_3}{\underset{|}{C}}OHC{\equiv}CSi(CH_3)_3\ ,$$

where R = CH_3 or C_2H_5 and n = 2–4.

The reaction with 2,4-dinitrophenylhydrazine[20,22,24,68,98,113,140], 3,5-dinitrobenzoylhydrazide[143], hydroxylamine[20,108,144,145], and semicarbazide[67,68,140] leads to the formation of crystalline silicon-containing hydrazones, oximes, and semicarbazones.

The condensation of silicon-containing ketones with secondary amines and formaldehyde by the Mannich reaction requires comparatively severe conditions and the use of a solvent—dioxane or alcohol—is obligatory[146,147]:

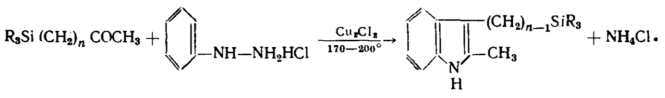


$$R_3Si(CH_2)_nCOCH_3 + (C_2H_5)_2NH\cdot HCl + CH_2O \xrightarrow[H+]{dioxane} R_3Si(CH_2)_{n-1}\underset{\displaystyle CH_2N(C_2H_5)_2}{\underset{|}{C}}HCOCH_3\ ,$$

where R = CH_3 or C_2H_5 and n = 2–4.

The yields of organosilicon aminoketones amount to 40–45%. Their water-soluble hydrochlorides are physiologically active: they reduce blood pressure, stimulate respiration, and exhibit a spasmolytic activity. Their toxicity is in the range 250–320 mg kg^{-1}.

The Fischer reaction between phenylhydrazine hydrochloride and γ-, δ-, and ε-silyl-substituted ketones leads to the formation of indole derivatives with a silyl substituent in the β-position[148]:



γ-Silyl-substituted ketones are capable of condensation with esters in the presence of sodamide, whereby they are converted into silicon-containing β-diketones[18,149,150]:

$$(CH_3)_3SiCH_2CH_2COCH_3 + RCOOC_2H_5 \xrightarrow{NaNH_2} (CH_3)_3SiCH_2CH_2COCH_2COR,$$

where R = CH_3 or $(CH_3)_3SiCH_2CH_2$.

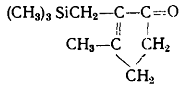
According to their dissociation constants, organosilicon β-diketones are weaker acids than acetylacetone because of the inductive effect of the trimethylsilyl group. Like their non-silylalated analogues, they are effective chelating agents and readily form complexes with copper(II), nickel, and barium salts[18,149,151,152]. The chelates usually contain two molecules of the ketone per metal ion.

When 4-trimethylsilyl-2-butanone is heated with diethyl carbonate in the presence of sodium hydride, the product is a β-ketoester the subsequent treatment of which with bromoacetone and sodium gives a silicon-containing diketoester[18,153,154]:

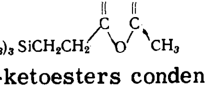
$$(CH_3)_3SiCH_2CH_2COCH_3 + (C_2H_5O)_2CO \xrightarrow{NaH} (CH_3)_3SiCH_2CH_2COCH_2COOC_2H_5 \rightarrow$$

$$\xrightarrow[Na]{BrCH_2COCH_3} (CH_3)_3SiCH_2CH_2COCH(COOC_2H_5)CH_2COCH_3\ .$$

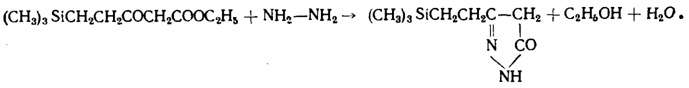
The latter, on being refluxed with aqueous sodium hydroxide, cyclises to 3-methyl-[2-(trimethylsilyl)methyl]cyclopent-2-enone:



and on treatment with a mixture of sulphuric and acetic acids gives rise to a mixture of silicon-containing furan derivative:



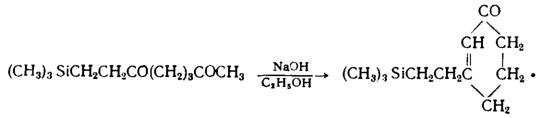
Organosilicon β-ketoesters condense with hydrazine hydrate to crystalline pyrazolones[18]:



The sodio-derivative of a silicon-containing β-ketoester adds to methyl vinyl ketone with formation of a δ-diketone (the Michael reaction):[18,155]

$$(CH_3)_3SiCH_2CH_2COCH_2COOC_2H_5 + CH_3COCH{=}CH_2 \xrightarrow{NaOC_2H_5} \rightarrow (CH_3)_3SiCH_2CH_2CO(CH_2)_3COCH_3.$$

The diketone thus obtained cyclises on treatment with alcoholic alkali to 3-[2-(trimethylsilyl)ethyl]cyclohex-2-enone:



When concentrated sulphuric acid is allowed to act upon γ- or ϵ-silyl-substituted ketones, one methyl group is split off from the silicon atom and the corresponding ketosiloxanes are formed[7-9,19,109,156-160]:

$$2(CH_3)_3SiCH_2CH_2COCH_3 \xrightarrow{H_2SO_4} \xrightarrow{H_2O} O[Si(CH_3)_2CH_2CH_2COCH_3] + 2CH_4,$$

$$n[(CH_3)_3Si(CH_2)_2]_2CO \xrightarrow{H_2SO_4} \xrightarrow{H_2O} [(CH_3)_3Si(CH_2)_2CO(CH_2)_2Si(CH_3)_2O]_n + 2n\,CH_4.$$

γ- and ϵ-Oxoalkylsiloxanes with linear and cyclic structures are readily obtained by the hydrolysis of mono-, di-, and tri-ethoxy- and mono-, di-, and tri-chloro-oxoalkylsilanes[159,160]:

$$(C_2H_5O)_n(CH_3)_{3-n}SiCH_2CH_2COCH_3 \xrightarrow[H+]{H_2O} [O_{n/2}(CH_3)_{3-n}SiCH_2CH_2COCH_3]_x,$$

$$Cl_nR_{3-n}Si(CH_2)_4COCH_3 \xrightarrow{H_2O} [O_{n/2}R_{3-n}Si(CH_2)_4COCH_3]_x.$$

When the oxoalkylsiloxanes are refluxed with dilute alkali, water-soluble oxoalkylsiliconates (monosodium salts of oxoalkylsilanetriols) are formed:

$$[CH_3CO(CH_2)_nSiO_{1.5}]_x \xrightarrow{NaOH} x[CH_3CO(CH_2)_nSi(OH)_2]ONa,$$

where $n = 2$ and 4.

The photolysis of organosilicon ketones leads to mainly cleavage[161].

4. Silylethynyl ketones with the General Formula $R_3SiC{\equiv}CCOR'$

The chemistry of these ketones was investigated by Komarov and Pukhnarevich[89,162-171]. Their characteristic feature is reduced reactivity of the triple bond in reactions with nucleophilic reagents. It is due to the conjugation of the triple bond with the 3*d*-orbitals of the silicon atom and also due to influence of the silicon and carbonyl groups. The addition of electrophilic agents and reactions involving the carbonyl group take place according to the usual mechanism characteristic of non-silylated analogues[163].

a. Reactions involving the carbonyl group. The reaction of 4-trimethylsilylbut-3-yn-2-one with methylmagnesium iodide leads to the formation of a tertiary alcohol:

$$(CH_3)_3SiC{\equiv}CCOCH_3 \xrightarrow{CH_3MgI} (CH_3)_3SiC{\equiv}CC(OH)(CH_3)_2.$$

The reaction with vinylethynylmagnesium bromide results in the formation of silylethynyl homologues of Nazarov's carbinol and those with phenylethynylmagnesium bromide give organosilicon diethynylalcohols with isolated triple bonds[164,165]:

$$R_3SiC{\equiv}CCOCH_3 + BrMgC{\equiv}CR' \rightarrow R_3SiC{\equiv}CC(OH)(CH_3)C{\equiv}CR',$$

where R = CH_3 or C_2H_5 and R′ = C_6H_5 or CH=CH_2.

Triethynyldisilylglycols with isolated triple bonds were synthesised by reaction with ethynylenedimagnesium dibromide[166]:

$$2R_3SiC{\equiv}CCOCH_3 + BrMgC{\equiv}CMgBr \rightarrow R_3SiC{\equiv}CC(OH)(CH_3)C{\equiv}CC(OH)(CH_3)C{\equiv}CSiR_3,$$

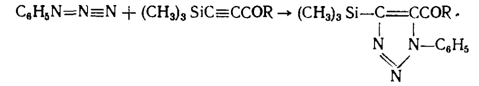
where R = CH_3 or C_2H_5.

The reaction of silyl-αβ-ethynyl ketones with magnesium derivatives of ethynylalcohols leads to the synthesis of organosilicon diethynylglycols[167]:

$$R_3SiC{\equiv}CCOCH_3 + BrMgC{\equiv}CCH_2OMgBr \rightarrow R_3SiC{\equiv}CC(OH)(CH_3)C{\equiv}CCH_2OH.$$

Silyl-α-ethynyl ketones react with 2,4-dinitrophenylhydrazine, semicarbazide, 3,5-dinitrobenzoylhydrazide, and hydrazine hydrate, forming the corresponding hydrazones[143].

The addition of phenyl azide to trimethylsilylalkynones gave silyl-substituted triazoles[65]:



b. Reactions involving the triple bond. When hydrogen chloride is passed through a solution of a silyl-α-ethynyl ketone in glacial acetic acid, silyl-substituted β-chlorovinyl ketones are formed[168,169]:

$$R_3SiC{\equiv}CCOCH_3 + HCl \rightarrow R_3SiCCl{=}CHCOCH_3,$$

where R = CH_3 or C_2H_5. They are thick oily liquids, which rapidly darken in the light with formation of viscous polymers. Chemically they are less reactive than their non-silylated analogues. They do not enter into the Diels–Alder reaction with cyclopentadiene and hexachlorocyclopentadiene and do not exchange the chlorine atom for an alkoxy-, acetoxy-, and hydroxy-group under normal conditions. When silicon-containing β-chlorovinyl ketones were allowed to react with Grignard reagents, tertiary chloroallyl alcohols were obtained in high yields[170]:

$$R_3SiCCl{\equiv}CHCOR' + R''MgX \rightarrow R_3SiCCl{=}CHCOHR'R'',$$

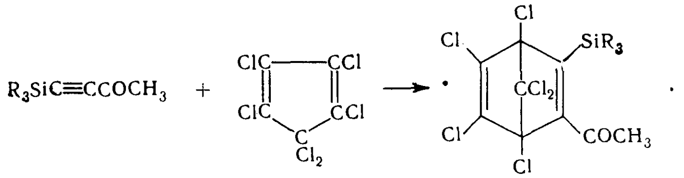
where R = R′ = CH_3 or C_2H_5, R″ = CH_3 or C_6H_5, and X = Br or I.

Silyl-α-ethynyl ketones can combine with both one and two bromine molecules at the multiple bond, but the addition of a second molecule takes place with considerable difficulty[89]:

$$R_3SiC{\equiv}CCOR' \xrightarrow{Br_2} R_3SiCBr{=}CBrCOR' \xrightarrow{Br_2} R_3SiCBr_2CBr_2COR'.$$

In contrast to their non-silylated analogues, silyl-substituted ketones do not combine with hydrogen under the usual conditions in the presence of Raney nickel and Lindlar's catalyst. Hydrogenation in an autoclave at 25 atm leads to the formation of saturated ketones without a silicon atom.

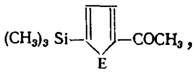
In reactions with cyclopentadiene and hexachlorocyclopentadiene adducts could be isolated only in the case of the latter and even then severe conditions were required and the yields were low, while non-silylated α-ethynyl ketones react with cyclopentadiene even at room temperature[171]:



The reaction of silyl-α-ethynyl ketones with alcohols and phenols in the presence of sodium ethoxide and with diethylamine is usually accompanied by the cleavage of the Si–C bond. They do not react with acetic and chloroacetic acids in the presence of $BF_3.O(C_2H_5)_2$–HgO and on irradiation with ultraviolet light. The reaction with mercaptans in the presence of sodium methoxide or on prolonged ultraviolet irradiation also does not occur, while non-silylated ethynyl ketones readily combine with one or two mercaptan molecules. The attempts to hydrate silyl-α-ethynyl ketones in the presence of mercuric salts led only to the formation of products of decomposition at the silicon-carbon bond.

5. Aromatic and Heterocyclic Silyl-substituted Ketones

A characteristic feature of silicon-containing aromatic ketones of the type $(CH_3)_3SiC_6H_4COR$ is the instability of the Si–C_{aryl} bond in relation to electrophilic agents such as $AlCl_3$ [50,51] and that of ketones of the type $(CH_3)_3SiCH_2C_6H_4COR$ is instability to the action of oxidising agents [56]. At the same time oxidation of heterocyclic ketones takes place without the cleavage of the Si–C bond [53,172]:



where E = O or S.

When acted upon by reducing agents, organomagnesium compounds, 2,4-dinitrophenylhydrazine, hydroxylamine, and semicarbazide and in the Mannich reaction, ketones of this class behave like their non-silylated analogues. The reduction of 4-trimethylsilylacetophenone with sodium borohydride takes place according to the usual mechanism [173]:

$$(CH_3)_3SiC_6H_4COCH_3 \xrightarrow{2H} (CH_3)_3SiC_6H_4CHOHCH_3.$$

A glycol is obtained in 91% yield by a similar procedure from the diketone $(CH_3)_2Si(C_6H_4COCH_3)_2$. The hydrogenation of the hydrochlorides of organosilicon aminoketones over Raney nickel yielded secondary aminoalcohols, the reduction being accompanied by the degradation of the aminoketones [174]:

$$(CH_3)_3SiCH_2C_6H_4COCH_2CH_2N(CH_3)_2\,HCl \xrightarrow[Ni]{H_2} (CH_3)_3SiCH_2C_6H_4CHOHCH_2CH_2N(CH_3)_2 + HCl.$$

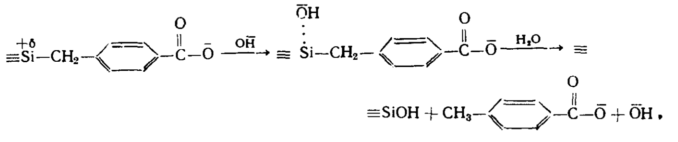
The hydrochlorides of organosilicon aminoketones react with ethylmagnesium bromide to form silicon-containing tertiary aminoalcohols. Organosilicon tertiary alcohols have also been obtained by Grignard reaction from trialkylsilylmethylphenyl and trialkylsilylethylphenyl ketones [55]:

$$R_3Si(CH_2)_nC_6H_4COCH_3 \xrightarrow{CH_3MgCl} R_3Si(CH_2)_nC_6H_4C(OH)(CH_3)_2.$$

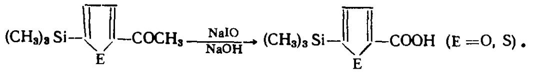
The oxidation of di(acetylbenzyl)tetramethyldisiloxane with sodium hypobromite in an alkaline medium is accompanied by the decomposition of the molecule at the silicon-carbon bond [56]:

$$[CH_3COC_6H_4CH_2(CH_3)_2Si]_2O + 6NaBrO \rightarrow 2CH_3C_6H_4COONa + [(CH_3)_2SiO]_x + 4NaOH + 2CHBr_3.$$

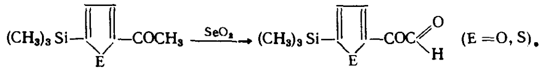
The comparatively ready elimination of the benzylcarboxy-group is probably associated with the migration of the reaction centre in a system of conjugated multiple bonds, as a result of which the electron density at the silicon atom is reduced, whereupon the Si–C bond dissociates under the action of a nucleophilic agent:



The oxidation of 2-acetyl-5-trimethylsilylfuran and 2-acetyl-5-trimethylsilylthiophen with hypoiodite takes place without the rupture of the Si–C bond and yields the corresponding acids [53]:



Selenium dioxide oxidises the above compounds to silicon-containing glyoxals in 40–70% yield [172]:



The Mannich condensation of alkyl trimethylsilylmethylphenyl ketones with dimethylamine and paraformaldehyde leads to the formation of organosilicon aminoketones [174]. However, the aminoketones were not isolated in a pure form:

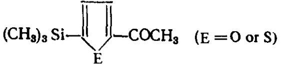
$$(CH_3)_3SiCH_2C_6H_4COR + CH_2O + (CH_3)_2NH \cdot HCl \xrightarrow[C_2H_5OH]{HCl} \rightarrow (CH_3)_3SiCH_2C_6H_4COCHR'CH_2N(CH_3) \cdot HCl,$$

where R = CH_3 or C_2H_5 and R′ = CH_3.

The aromatic silicon-containing ketones $R_3Si(CH_2)_nC_6H_4COR'$, where R = CH_3 or C_2H_5, R′ = CH_3, C_6H_5, C_5H_{11}, $C_6H_4OCH_3$, or $C_6H_4CH_3$, and $n = 0–2$, react with 2,4-dinitrophenylhydrazine to form crystalline 2,4-dinitrophenylhydrazones [33,34,52,55,60,91]. The reaction of 2,4-dinitrophenylhydrazine with the ketodisiloxanes $O[Si(CH_3)_2CH_2C_6H_4COR]_2$ may involve both carbonyl groups [56,57].

When semicarbazide is allowed to react with silicon-containing aromatic ketones, crystalline semicarbazones are obtained [34,60,91].

Heterocyclic ketones of the type



also readily form semicarbazones. A crystalline oxime has been obtained from *p*-trimethylsilylacetophenone $(CH_3)_3SiC_6H_4COCH_3$. [34]

The polycondensation of organosilicon ketodicarboxylic acids with glycol at 170–190°C in an atmosphere of nitrogen has been reported [58]:

$$HOOCC_6H_4COC_6H_4CH_2Si(CH_3)_2OSi(CH_3)_2CH_2C_6H_4COC_6H_4COOH + n\,HOCH_2CH_2OH \rightarrow$$
$$\rightarrow [OCOC_6H_4COC_6H_4CH_2Si(CH_3)_2OSi(CH_3)_2CH_2C_6H_4COC_6H_4COOCH_2CH_2]_nOH + (n-1)\,H_2O.$$

The polycondensation of organosilicon ketoacids with more than two dimethylsiloxane rings may involve a rearrangement into cyclic polydimethylsiloxanes and polyesters with a disiloxane unit:

$$m\,HOOCC_6H_4COC_6H_4CH_2Si(CH_3)_2O[Si(CH_3)_2O]_nSi(CH_3)_2CH_2C_6H_4COC_6H_4COOH +$$
$$+ m\,HOCH_2CH_2OH \rightarrow H_2O + m[-Si(CH_3)_2O-]_n +$$
$$+ n[OCH_2CH_2OCOC_6H_4COC_6H_4CH_2Si(CH_3)_2OSi(CH_3)_2CH_2C_6H_4COC_6H_4CO]_mOH.$$

These polyesters are vitreous low-melting products readily soluble in organic solvents.

The polycondensation of silicon-containing diketodicarboxylic acids with di-(β-hydroxyethoxymethyl)tetramethyldisiloxane takes place according to the mechanism [10]:

$$x\,HOOCC_6H_4COC_6H_4CH_2Si(CH_3)_2O[Si(CH_3)_2O]_nSi(CH_3)_2CH_2C_6H_4COC_6H_4COOH +$$
$$+ x\,HOCH_2CH_2OCH_2Si(CH_3)_2OSi(CH_3)_2CH_2OCH_2CH_2OH \rightarrow (x-1)\,H_2O +$$
$$+ x\,H\{OOCC_6H_4COC_6H_4CH_2Si(CH_3)_2O[Si(CH_3)_2O]_nSi(CH_3)_2CH_2C_6H_4COC_6H_4COOCH_2-$$
$$-CH_2OCH_2Si(CH_3)_2OSi(CH_3)_2CH_2OCH_2CH_2\}OH^{\cdot\cdot}.$$

6. Complexes of Silicon Halides with β-Diketones and β-Ketoesters

West[105], Andrianov[107], and Hester[175] established by infrared and NMR spectroscopy that the complexes of acetylacetone with silicon halides have the structure of *o*-silyl derivatives:

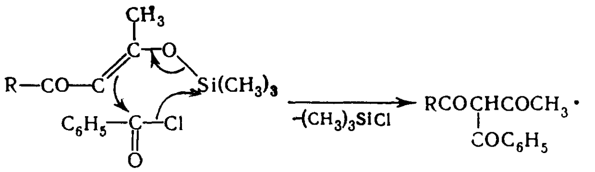
$$R_nSi[OC(CH_3){=}CHCOCH_3]_{4-n},$$

where $n = 1-3$ and R = alkyl, aryl, or a halogen. For the triethylsilyl derivative of ethyl acetoacetate, Andrianov[41] proposed a structure with a C-silyl bond, i.e. $R_3Si[CH(COCH_3)COOC_2H_5]$, and Gilman[40] and West[176] suggested an enolic structure: $R_3SiOC(CH_3){=}CHCOOC_2H_5$.

A characteristic property of compounds of this class is instability in both acid and alkaline media. In aqueous hydrochloric acid solutions they are slowly hydrolysed, while in an alkaline medium the hydrolysis is instantaneous[105,107,177,178]:

$$[CH_3COCH{=}C(CH_3)O]_3SiCl \cdot HCl \xrightarrow{H_2O} (CH_3CO)_2CH_2 + Si(OH)_4 + HCl.$$

When benzoyl chloride is allowed to act upon 2-trimethylsiloxypent-2-en-4-one, the molecule decomposes, possibly as a result of the interaction between the 3*d*-orbitals of silicon and the free electron pairs of the chlorine atom in benzoyl chloride[179]:



The interaction of complexes with heavy metal chlorides leads to the formation of crystalline double salts[15,43,102,105]:

$$[RCOCH{=}C(R)O]_3SiCl \cdot HCl + MCl_n \rightarrow [RCOCH{=}C(R)O]_3SiCl \cdot MCl_n,$$

where R = CH_3 or C_6H_5, M = Rb, Cu, Zn, Fe, Au, Pt, or Sn, and *n* is the valence of the metal.

When $[C_6H_5COCH{=}C(C_6H_5)O]_3SiCl.HCl$ is acted upon by sulphuric acid or silver nitrate, the crystalline sulphate $[C_6H_5COCH{=}C(C_6H_5)O]_3Si(HSO_4)$ and the nitrate $[C_6H_5COCH{=}C(C_6H_5)O]_3SiNO_3$ are formed respectively[101].

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Irkutsk Institute of Organic Chemistry,
Siberian Division of the USSR
Academy of Sciences

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The Electronic Structure of Radical-anions

S.P.Solodovnikov and A.I.Prokof'ev

The ESR spectroscopic data relating to studies on the chemical and electronic structures of radical-anions derived from organic compounds have been examined. These studies include those on the distribution of unpaired electron density in radical-anions, the effect of substituents on such distribution, the hindered motion of groups and fragments in radical-anions, the effect of the solvent on the distribution of unpaired electron density, and the nature of the association of radical-anions with metal cations. Among problems of the chemical behaviour of radical-anions, electron-exchange reactions between the radical-anions and the initial molecules have been considered.
The bibliography includes 124 references.

CONTENTS

I. INTRODUCTION

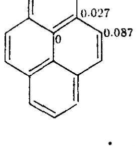
Electron-transfer hypotheses are nowadays widely used to account for the mechanisms of certain chemical reactions. These include the metallation, Wurtz, Grignard, hydrogenation, and certain other reactions [1]. In these reactions radical-anions (RA) are either detected experimentally or are postulated as intermediates. Although the true role of radical-anions in these processes has not been always completely established, their very presence necessitates a careful study of their chemical behaviour.

The application of radiospectroscopic, optical polarographic, quantum-chemical, and other methods yielded extensive data on the physicochemical properties of these species. These techniques have greatly expanded our knowledge of the electronic structure of molecules capable of being reduced with the formation of radical-anions.

The formation of ionic species in the interaction between liquid potassium and naphthalene was noted as early as 1867 by Berthelot [2]. However, systematic studies in this field began with the work of Schlenk [3] in the first quarter of the twentieth century. Schlenk observed that aromatic ketones and hydrocarbons react with alkali metals in ethereal solutions forming coloured free-radical products. The free-radical nature of metal ketyls was confirmed in 1934 by Sugden [4], who showed them to be paramagnetic. In the nineteen-thirties, studies on the reactions of alkali metals with aromatic hydrocarbons were continued by Scott [5], who began the general use of 1,2-dimethoxyethane (DME) as a solvent and demonstrated its exceptional effectiveness in the reaction between aromatic hydrocarbons and alkali metals. A number of studies have been made [6-8] to elucidate the composition of complexes of aromatic hydrocarbons with alkali metals. It has been shown for complexes of anthracene with lithium, sodium, and potassium that, depending on the amount of metal M introduced into the reaction, the composition of the complex with anthracene (A) varies from AM to AM_2. An important property of solutions of these complexes is their high electrical conductivity.

The electronic structure of the products of the reaction of aromatic hydrocarbons with alkali metals has been established by electron spin resonance (ESR) and electronic spectroscopy. Analysis of these data showed that one of the first products of the interaction in solution between aromatic compounds and alkali metals are mono- and di-anions of these compounds linked to some extent to the metal cations. The hyperfine structure (HFS) of the ESR spectra indicates complete transfer of the unpaired electron from the alkali metal to the aromatic hydrocarbon molecule and a high degree of delocalisation of the electron. The simple approximation of the molecular orbital (MO) method is frequently sufficient to describe the nature of the delocalisation of the unpaired electron. Analysis of ESR spectra of numerous hydrocarbon π-electron radicals shows that the magnitude of hyperfine coupling (HFC) to protons (a_H) is proportional to the density of the unpaired electron at the corresponding hydrogen nucleus [9]. Fig. 1 shows the variation of a_H with the unpaired electron density at the carbon atom (ρ_C) in the lowest non-bonding orbital of the radical-anion calculated by the simple MO method. This linear relation constitutes the basis of the familiar McConnell formula [10]: $a_H = Q\rho_C$ ($-Q = 22.5$–30 gauss).

However, there are cases where the simple molecular orbital theory predicts zero unpaired electron densities at carbon atoms, while the ESR spectra show a hyperfine structure due to hydrogen atoms bound to these carbon atoms. As an example, the diagram below shows the distribution of unpaired electron density in the pyrene radical-anion [9,11] based on the simple molecular orbital theory:



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The diagram shows that zero unpaired electron densities occur at the terminal protons of pyrene. Nevertheless the ESR spectra of this radical-anion show a hyperfine structure due to these protons with hyperfine coupling constants of 1 gauss.

This discrepancy between the simple molecular theory and the ESR data is due to the fact that the molecular orbital theory yields charge densities of the unpaired electron, while the hyperfine structure of the ESR spectra is due to the interaction of the unpaired electron spin density (SD) with the paramagnetic nuclei in the radical.

Practical methods for the calculation of spin density in π-electron radicals were proposed by McLachlan[11]. Since a detailed description of the essential features of these methods is outside the scope of this review, we shall only mention that they allow for the interaction of the unpaired electron with the filled π-electron shells. This interaction leads to partial "unpairing" of the electrons with α- and β-spins in filled electron shells, as a result of which they move in orbitals which differ from those predicted by the molecular orbital theory. In this case the spin density at the carbon atom is the sum of the unpaired electron density calculated by the simple molecular orbital theory and the spin densities of electrons corresponding to the α- and β-spins. When the molecular orbital theory yields zero unpaired electron densities, the overall spin density may have a "negative" sign relative to the direction of the spin of the unpaired electron.

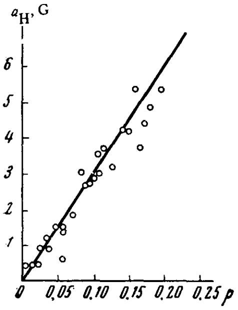


Figure 1. Variation of the proton hyperfine coupling constants in the ESR spectra of the radical-anions of benzene, cyclo-octatetraene, naphthalene, anthracene, naphthacene, pentacene, perylene, coronene, phenanthrene, and biphenyl with unshared electron density at a given carbon atom calculated by the molecular orbital method.

Further studies showed that there exists also a relation between the hyperfine coupling to the carbon-13 and nitrogen-14 nuclei and the distribution of spin density[12]. These relations are more complex but are nevertheless satisfactorily consistent with the concepts of the delocalisation of the unpaired electron in the lowest non-bonding orbital of the radical-anion.

The electronic absorption spectra of anions and dianions may be treated from this standpoint[13-15]. The electronic spectra of these species have characteristic bands in the visible region and the ultraviolet absorption is analogous to that of the initial hydrocarbon. Absorption in the visible region is due to transitions of the unpaired electron in the lowest non-bonding orbital.

An enormous amount of work has been done in the last decade on radical-anions, mostly using the ESR method. One of the most important results of the application of this method in the chemistry of free radicals has been the detection of radical-anions in polarographic reduction carried out directly in an ESR spectrometer[16]. This method, developed by Maki and Geske, greatly extended the possibilities of the synthesis of radical-anions. While reduction with alkali metals is carried out mainly in ethereal solutions, electrochemical reduction allows the use of a larger number of solvents. In many cases it proved possible to employ solvents such as alcohol and water[17], in addition to aprotic solvents such as dimethylformamide (DMF), dimethyl sulphoxide (DMSO), and acetonitrile (AC).

The range of problems solved with the aid of ESR is very wide: the distribution of spin density in various radical-anions, the effect of substituents on the distribution of spin density, the effect of solvent and the hindered rotation of individual groups on hyperfine coupling, electron-exchange reactions, ion association, stability of radical-anions and the way it is influenced by the nature of the metal and the solvent, and chemical reactions involving radical anions.

We decided to isolate only a few main trends in studies on radical-anions without attempting a complete description of the enormous scientific literature which has accumulated recently. One may include here the electronic structure of radical-anions of various classes of chemical compounds, the effect of substituents and medium on the electronic structure of radical-anions, and the formation of ionic association complexes. Among problems related to the chemistry of radical-anions, only electron-exchange reactions will be considered in detail, since extensive and interesting data have accumulated in this field. Until recently there have been no reviews or monographs on this problem in the Soviet literature. Among the reviews published outside the Soviet Union, particular mention should be made of those of Geske[18] and Szwarc[19] and the compilation on radical-ions[20].

II. ELECTRONIC STRUCTURE OF RADICAL-ANIONS

The ESR spectra of the radical-anions derived from an enormous number of organic compounds have now been investigated: polyenes, aromatic compounds with various functional groups, heterocyclic compounds, and organic derivatives of the elements. In describing these extensive experimental data, we decided to separate the most important classes of chemical compounds whose radical-anions have been investigated in detail and also certain trends in this field.

The review of the experimental data should be begun with butadiene as the simplest example. The radical-anion from butadiene was obtained electrochemically in liquid ammonia by Levy and Myers[21]. The ESR spectrum of this radical-ion is presented in Fig. 2 and consists of a quintet of triplets with the following hyperfine proton coupling constants (a_i) in the 1- and 4-positions and 2- and 3-positions: $a_1 = a_4 = 7.617$ gauss and $a_2 = a_3 = 2.791$ gauss.

$$^{\bullet}H_2\overset{1}{C}{=}\overset{2}{C}H{-}\overset{3}{C}H{=}\overset{4}{C}H_2 .$$

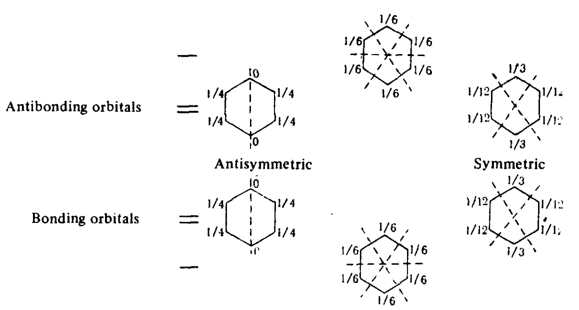
The distribution of spin density is described satisfactorily by the wave function $\Psi_3 = 0.600\ \varphi_1 - 0.371\ \varphi_2 - 0.371\ \varphi_3 + 0.600\ \varphi_4$ obtained by Hückel's simple molecular orbital method. The ratio of the coupling constants is $a_1/a_2 = 2.729$ and that of the spin densities is $\rho_1/\rho_2 = 0.600^2 : 0.371^2 = 2.615$. The distribution of spin density in the butadiene radical-anion is confirmed by the analysis of the spectra of the radical-anions obtained from butadiene derivatives[22]: $(CH_3)_2C{=}CH{-}CH{=}(CH_3)_2$ and $H_2C{=}C(CH_3){-}C(CH_3){=}CH_2$.

Numerous studies have been made on the radical-anions of benzene derivatives. These include alkyl, cyano-, carbonyl, nitro-, and also certain organometallic derivatives. The distribution of spin density in some of these radical-anions may be interpreted using the properties of the molecular orbitals of benzene [9]. Six molecular orbitals may be formed from the six $2p_z$ atomic orbitals of carbon: three bonding and three antibonding orbitals.

Figure 2. ESR spectrum of the butadiene radical-anion in liquid ammonia at −78°C.

The relative energies of these orbitals and the electron densities are presented in Scheme 1.

Scheme 1



The dashed lines indicate the positions of the nodes of the π-orbitals. The highest bonding and the lowest antibonding orbitals are degenerate. In the benzene radical-anion the unshared electron is equally distributed between two degenerate orbitals. The distribution of the electron in the degenerate orbitals is indicated in the Scheme. These two orbitals may be classified as symmetric and antisymmetric according to their behaviour on reflection in a plane perpendicular to the benzene ring and passing through opposite atoms. The spin density at each carbon atom in the benzene radical-anion is 1/6 and the ESR spectrum consists of 7 lines with binomial intensity ratios and with spacings of 3.75 gauss.[23] In the radical-anions of substituted benzene where the symmetry is less than threefold the degeneracy is removed. If the perturbation introduced by the substitutent is not too great, then the distribution of the unshared electron proves to be similar to the distribution in one of the degenerate benzene orbitals. The effect of substituents may be examined most simply when the perturbation is purely inductive [9]. If the substituent is electropositive, the unshared electron will occupy the antisymmetric orbital and the ESR spectrum of the radical-anion will consist of a quintet due to the interaction of the unshared electron with the *ortho*- and *meta*-protons with a coupling constant of about 5 gauss. The Scheme shows that the spin density in the antisymmetric antibonding orbital is distributed equally between the four carbon atoms. The hyperfine coupling to the proton in the *para*-position and the nuclei of the substituent should be small.

When the substituent is electronegative, the unshared electron will occupy the symmetric orbital. Here the ESR spectrum will be complex, since it must involve considerable doublet splitting (about 8 gauss) due to the proton in the *para*-position with additional splitting of the doublet components due to the *ortho*- and *meta*-protons. The application of these simple concepts to certain mono- and di-*para*-substituted benzenes gives a good agreement with experiment. Similar concepts were developed for *ortho*- and *meta*-derivatives of benzene [9].

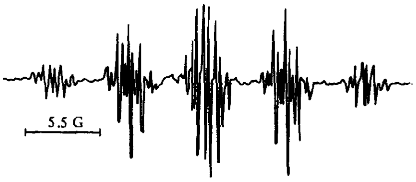
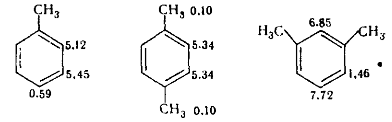
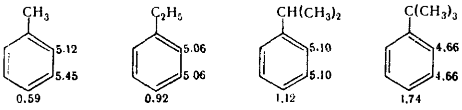


Figure 3. ESR spectrum of the toluene radical-anion in dimethoxyethane containing potassium.

The experimental data on the ESR spectra of the radical-anions of alkylbenzenes clearly illustrate these ideas. Fig. 3 presents as an example the ESR spectrum of the toluene radical-anion. The coupling constants for the toluene and *p*-xylene radical-anions [23-26] indicated in the Scheme below proved to be similar to those predicted by considering the antisymmetric orbital, while in the *m*-xylene radical-anion the distribution of spin density agrees better with the symmetric orbital [24-26]:

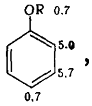


Interesting features are revealed when the ESR spectra of the following radical-anions are compared:



It is seen that, on transition from toluene to t-butylbenzene, there is an appreciable increase of the coupling constant for protons in the *para*-position and a decrease of the constants for the *ortho*- and *meta*-protons [9]. Three causes responsible for this change in the distribution of spin density may be indicated: configuration interaction, vibrational interaction, and thermal equilibrium between two states close to degeneracy. These mechanisms should lead to an admixture of a symmetric wave function with the antisymmetric wave function in the wave function of the unpaired electron. The high value of the coupling constant for the *para*-hydrogen in the radical-anion of t-butylbenzene is regarded as a result of the mixing of two states. The role of the vibrational interaction between the antisymmetric and symmetric states decreases with increasing distance between these two states. If the distance between the levels become comparable to *kT*, thermal population of the highest vacant orbital at room temperature becomes possible. When this condition applies, the coupling constants should depend on temperature. Such a variation has been observed by Tuttle[27] and de Boer and Colpa[28]. The sum of the coupling constants $a_H(para) + a_H(CH_3)$ diminishes as the temperature is lowered, while the sum $a_H(ortho) + a_H(meta)$ increases by the same amount. The hyperfine coupling constants for the *p*-xylene radical-anion are independent of temperature, which may be accounted for by long distances between the levels[28]. Estimates of the distance between the two states yield 384 cm^{-1} for toluene and 868 cm^{-1} for *p*-xylene.

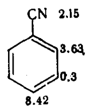
Another example illustrating the effect of electropositive substituents on the degenerate benzene orbitals is the ESR spectra of the radical-anions of alkoxybenzenes investigated by Grandberg et al.[29]:

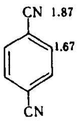


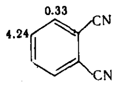
,

where R = CH_3 or C_2H_5.

The cyano-group has a filled π-bonding and a vacant antibonding orbital the interaction of which with the π-orbitals of benzene must be considered in the analysis of the ESR spectra of the radical-anions of cyanobenzenes. However, here too the concepts developed above are applicable to the analysis of the ESR data for the radical-anions of benzonitrile, terephthalonitrile, and phthalonitrile:







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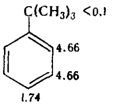
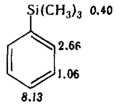
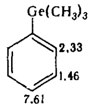
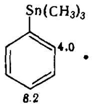
The cyano-group in the radical-anion of benzonitrile and terephthalonitrile lowers the energy of the symmetric orbital and in the radical-anion of phthalonitrile the energy of the antisymmetric orbital is reduced[9].

The concept of the orbital degeneracy of the benzene levels proved useful in the examination of a number of other substituted benzenes[30,31]:









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Above it was shown that the unshared electron in the radical-anions of monoalkylbenzenes occupies the antisymmetric orbital. Analysis of the hyperfine structures of the ESR spectra of the radical-anions of benzene derivatives containing silicon, germanium[30], and tin[31] shows that in these radical-anions the symmetric orbital lies below the antisymmetric orbital. The simple concepts developed above permit the classification of these substituents as electronegative. However, one must not disregard certain features in the ESR spectra which may be associated with conjugation. Thus the high values of the hyperfine coupling constants for methyl protons in the radical-anion of trimethylsilylbenzene may reflect the occurrence of some interaction between the vacant *d*-orbitals of silicon and the π-electrons in the benzene ring.

The examples examined illustrate the removal of degeneracy in cases where the unshared electron is located either in the symmetric or the antisymmetric orbital. However, weak perturbation by a substituent may lead to only a slight redistribution of spin density between these orbitals. Such a situation was observed by Fraenkel and coworkers[32] in the radical-anion of monodeuterobenzene in which one hydrogen atom was replaced by deuterium. In contrast to the benzene radical-anion for which a hyperfine coupling constant of 3.75 gauss was found, the following hyperfine coupling constants were obtained for monodeuterobenzene: $a_H^2 = a_H^3 = a_H^5 = a_H^6 = 3.92 \pm 0.01$ gauss, $a_H^4 = 3.41$ gauss, and $a_D^1 = 0.55 \pm 0.01$ gauss. The introduction of deuterium leads to a somewhat greater population of the antisymmetric orbital compared with the symmetric orbital. Köhnlein et al.[33] succeeded in removing the degeneracy in the benzene radical-anion itself by a suitable choice of conditions. The ESR spectrum of the benzene radical-anion in a 2 : 1 tetrahydrofuran (THF)—dimethoxyethane mixture changes on raising the temperature above −20°C—the seven lines with a binomial distribution of intensities are replaced by a main triplet ($a_H^1 = 6.5$ gauss) with further splitting of each triplet component into a quintet ($a_H^2 = 1.75$ gauss). The authors suggest that the removal of degeneracy is due to exchange interaction with the metal cation, as a result of which the unshared electron occupies the symmetric orbital.

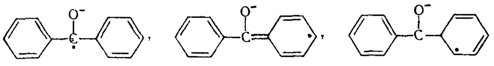
Apart from benzene, the radical-anions of a number of compounds with D_{3h}, D_{6h}, and D_{8h} symmetries having degenerate electronic states have been investigated: triphenylene, *sym*-tricyanotriazole[34], *sym*-trimethylsilylbenzene[35], trinitrobenzene[36], coronene[37], and cyclo-octatetraene[38]. When the radical-anions of *sym*-tricyanotriazole, *sym*-trimethylsilylbenzene, and trinitrobenzene are generated chemically, the distribution of spin density shows a deviation from the symmetry of the initial molecules. These deviations are attributed to the removal of orbital degeneracy and to the distribution of spin density in each of the degenerate orbitals. The interaction of the metal cation with one of the functional groups is regarded as a possible cause of the removal of degeneracy[36].

Cyclo-octatetraene (COT) readily accepts two electrons and is converted into a dianion. The ESR spectrum of the cyclo-octatetraene radical-anion consists of nine lines with a binomial intensity distribution and a hyperfine coupling constant of 3.2 gauss.[38] It has been suggested that the addition of one electron results in a flattening of cyclo-octatetraene, so that the radical-anion has a planar structure with D_{8h} symmetry. The electronic structure of planar COT$^{\dot{-}}$ should exhibit orbital degeneracy. However, the study of the ESR spectrum of the radical-anion of monodeuterated cyclo-octatetraene does not show any signs of the removal of degeneracy[39]. McLachlan[39] explains the absence of such signs by the fact that the vibrations of the C–C bonds, which leads to the extension or compression of the molecule, interact more effectively with the motion of electrons than do other types of vibrations. These interactions lead to the appearance of orbitals corresponding to a fully symmetrical distribution of spin density.

The above concepts proved unsatisfactory in the study of the ESR spectra of the radical-anions of substituted benzenes with substituents having their own π electrons. In these radical-anions the unshared electron orbitals differ markedly from the benzene orbitals and an independent calculation is necessary for the interpretation of the ESR spectra. Such substituents include the carbonyl, nitroso-, nitro-, and certain other complex functional groups. A satisfactory description of the distribution of spin density in the radical-anions of the above compounds may be achieved by the McLachlan method[11] with a suitable choice of parameters for the Coulombic and exchange integrals (MO parameters).

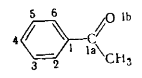
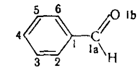
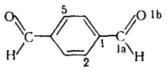
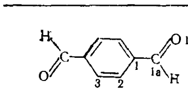
The ESR spectra of *p*-benzosemiquinone[40], *o*-benzosemiquinone[41], 1,4-naphthosemiquinone, 9,10-anthrasemiquinone, *o*-phenanthraquinone, etc.[42] can be satisfactorily described within the framework of the McLachlan method when the following values are adopted for the MO parameters: $\alpha_0 = \alpha_C + 1.2\beta$ and $\beta_{CO} = 1.56\beta$.

The principal features of the distribution of spin density in the radical-anions of the carbonyl compounds may be examined on the basis of the following valence bond schemes for the benzophenone radical-anion:



from which it follows that in the ESR spectrum of the benzophenone radical-anion there should be a main hyperfine structure due to the protons in the *ortho*- and *para*-position with subsidiary hyperfine structure due to the *meta*-protons. Indeed, Kazakova and Syrkin[43] obtained hyperfine coupling constants of 2.1 gauss for the *ortho*- and *para*-protons and 0.7 gauss for the *meta*-protons.

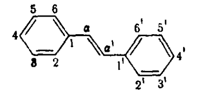
Table 1. Hyperfine coupling constants and spin densities in the radical-anions of carbonyl compounds.

Radical-anion	Position	a_H, G	Spin density (expt.)	Spin density (calc.)
 Acetophenone	1a (CH_3)	6.73	0.2476	0.2540
	1b	—	—	0.1323
	1	—	—	0.090
	2	4.251	0.1794	0.1775
	3	1.070	−0.0451	−0.0554
	4	6.397	0.2784	1.2605
	5	0.875	−0.0369	−0.0446
	6	3.712	0.1566	0.1591
 Benzaldehyde	1a (CHO)	8.507	0.3589	0.3555
	1b	—	—	0.1155
	1	—	—	0.0525
	2	4.685	0.1977	0.1904
	3	1.307	−0.0551	−0.0632
	4	6.471	0.2730	0.2425
	5	0.750	−0.0316	−0.0365
	6	3.393	0.1432	0.1433
 *cis*-Terephthalic aldehyde	1a (CHO)	3.81	0.1607	0.1602
	1b	—	—	0.0871
	1	—	—	0.1434
	2	1.16	0.0489	0.0451
	5	1.54	0.065	0.0641
 *trans*-Terephthalic aldehyde	1a (CHO)	3.89	0.1641	0.1590
	1b	—	—	0.0869
	1	—	—	0.1444
	2	2.08	0.0878	0.0799
	3	0.70	0.0295	0.0298

The ESR spectra of the radical-anions of certain carbonyl compounds show interesting features. A breakdown of the symmetry of the hyperfine interaction relative to the axis passing through the carbonyl carbon atom and the carbon atom in the *para*-position has been observed in the radical-anions of acetophenone, benzaldehyde[44], terephthalic aldehyde[45,46], and 1,4-diacetylbenzene[46]. Table 1 lists the hyperfine coupling constants for the ESR spectra of certain carbonyl radical-anions.

Such non-equivalence of the hyperfine coupling constants for the *ortho*- and *meta*-positions is caused by the interaction of the benzene ring protons with the carbonyl groups. The rotation of the carbonyl group is hindered and its frequency is probably less than the characteristic frequency for relaxation of the ESR spectra (10^7–10^6 Hz). The retardation of the rotation of the carbonyl group results in the existence of *cis*- and *trans*-forms of the radical-anion of terephthalic aldehyde and 1,4-diacetylbenzene[46]. The free energy of the conversion of the *cis*-form into the *trans*-form is $\Delta F_{293^\circ} = -200 \pm 25$ cal mole^{-1} for the terephthalic aldehyde radical-anion and $\Delta F_{293^\circ} = 210 \pm 90$ cal mole^{-1} for the 1,4-diacetylbenzene radical-anion with $N_{cis}/N_{trans} = 1/4$. A satisfactory agreement between the experimental and theoretical spin densities was achieved with the following choice of MO parameters: $\alpha_0 = \alpha_C + 1.55\beta$, $\beta_{CO} = 1.5\beta$, and $\beta_{CC^*} = 1.1\beta$, where β_{CC^*} is the exchange integral between the carbonyl carbon atom and the carbon atom in the benzene ring. The asymmetry in the distribution of spin density was achieved by introducing a negative correction to the Coulombic integral for the carbon atom in the 6-position [$\delta = (-0.05)$–(-0.15)].

A similar asymmetry in the hyperfine coupling constant was observed in the ESR spectra of the *trans*-stilbene[47] and *trans*-azobenzene[48] radical-anions:



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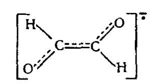
	2	3	4	5	6	α	
Stilbene	3.03	0.83	4.00	0.80	1.94	4.51	gauss
Azobenzene	2.81	0.78	2.81	0.78	2.03	4.84	gauss

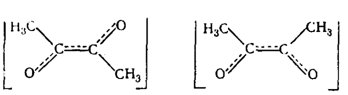
When account is taken of the interaction between the atoms in the 2- and α-positions and also in the 2′- and α′-positions, which alters the Coulombic integrals for the atoms in the 2- and 2′-positions, it is possible to obtain agreement between the theoretical and experimental spin densities. However, as for the carbonyl radical-anions, the physical significance of this interaction remains unexplained. Maki[45] suggested that the asymmetry may be due to the polarisation of the π-electron cloud by the electrical dipole of the carbonyl group.

Rieger and Fraenkel[46] described the ESR spectra of a series of radical-anions containing the carbonyl group. These radical-anions are aromatic resonance-stabilised paramagnetic species. However, the less stable aliphatic ketyls, obtained in particular from hexamethylacetone, pentamethylacetone[49], and diethylpinacol[50], have also been investigated.

Recently Russell and coworkers[20] made a large-scale study of the paramagnetic species formed on reduction of conjugated diketones, which have been called semidiones. The reduction of conjugated tri- and tetra-ketones leads to the corresponding radical-anions: semitriones and semitetraones. The simplest representative of semidiones is the radical-anion formed on reduction of glyoxal[51]:

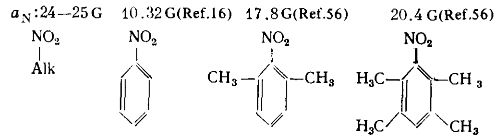


The spectrum of this radical-anion consists of a triplet due to the interaction of the unshared electron with two hydrogen atoms. Analysis of the spectrum permits an estimation of the spin density distribution, according to which the maximum spin density is located at the carbonyl carbon atoms. ESR spectra revealed the formation of two paramagnetic species in the reduction of diacetyl[52]:



with a signal intensity ratio of 20:1. The study of the temperature variation of these signals made it possible to determine the difference between the stabilities of the isometric semidiones. It was found that the *trans*-isomer is more stable than the *cis*-isomer. The higher values of the hyperfine interaction constants for the *cis*-isomer can be accounted for by the formation of a "more compact" ion pair and the consequent increase of spin density at the carbonyl carbon atoms. The introduction of bulky substituents (isopropyl, t-butyl) leads to the formation of *trans*-isomers only[53]. The study of numerous derivatives of semidiones shows clearly how the hyperfine coupling constants for β-protons depend on the conformation, bond angles, and other factors. These problems will be discussed in greater detail in the next section.

The ease of the electrochemical generation of radical-anions containing the nitro-group permitted a detailed study of the ESR spectra of the radical-anions of a large number of nitro-compounds. The localisation of the unshared electron at the nitro-group is caused by its high electronegativity. The diagrams quoted below show how the structure of the nitro-compounds affects the hyperfine coupling to the nitrogen nucleus in the nitro-group:



where Alk = CH_3,[54] C_2H_5, C_3H_7, or C_4H_9.[55]

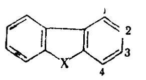
While in the radical-anions of aliphatic nitro-compounds the spin density is wholly localised at the nitro-group, in the nitrobenzene radical-anions approximately half the spin density is withdrawn into the benzene ring as a result of conjugation. The decrease of this conjugation caused by the displacement of the nitro-group from the plane of the benzene ring in the radical-anions of *o*-dimethylnitrobenzene and nitrodurene leads to greater localisation of the unshared electron at the nitrogroup as compared with nitrobenzene. Satisfactory agreement between the theoretical spin densities in the radical-anions of nitro-compounds and the experimental values was achieved with the following parameters found by Rieger and Fraenkel[57]: $\alpha_N = \alpha + 2.2\beta$, $\beta_{CN} = 1.2\beta$, $\alpha_0 = \alpha + 1.7\beta$, and $\beta_{NO} = 1.67\beta$. The hyperfine coupling constant for the nitrogen atom (a_N) is described by the expression $a_N = A\rho_N^\pi + 2B_0\rho_O^\pi$, where A = 99 ± 10 gauss, $B_0 = -35.8 \pm 5.9$ gauss, and ρ_N^π and ρ_O^π are the spin densities at the nitrogen and oxygen atoms.

Aliphatic nitro- and polynitro-compounds behave differently on reduction. While mononitroalkanes yield relatively stable primary radical-anions, polynitro-compounds are capable of forming paramagnetic dianions on reduction. Thus in the reduction of tetranitromethane with dithionite in an alkaline medium, Lagercrantz[58] observed the formation of the nitroform radical-dianion $[C(NO_2)_3^{\cdot}]^{2-}$. The formation of such a dianion was confirmed by the reduction of the potassium salt of nitroform. The ESR spectrum of the nitroform dianion consists of seven lines with a hyperfine coupling constant for the nitrogen nuclei of 8.4 gauss and intensity ratios corresponding to the interaction of the unshared electron with 3 equivalent nitrogen nuclei. In the reduction of the potassium salt of nitroform the formation of a new radical-dianion $[CH(NO_2)_2^{\cdot}]^{2-}$ with the hyperfine coupling constants a_N = 9.6 gauss and a_H = 4.1 gauss is observed in addition to $[C(NO_2)_3^{\cdot}]^{2-}$. The dissociation of the C–C or C–X bonds with formation of the corresponding radical-dianions is observed in the electrochemical reduction of various derivatives of dinitroalkanes[59]. Syrkin and coworkers observed the formation of paramagnetic dianions in the reduction of *p*-dinitrodiphenylmethane[60].

A number of studies have been made on the radical-anions of diaryl systems of the type Ar–Ar and Ar–X–Ar. One of the problems associated with the structure of these compounds is the degree of breakdown of the conjugation between the aromatic rings joined by a single C–C bond. Such breakdown is possible due to the repulsion of the hydrogen atoms and the displacement of the aryl groups from the planes for conjugation. The study of biphenyl[61], 1,1′-binaphthyl[62], and 9,9′-bianthryl[63], in which the angle between the arene planes is ~30°, ~70°, and ~90° respectively, showed that in the biphenyl and binaphthyl radical-anions the unshared electron is delocalised over both aromatic fragments, while in the bianthryl radical-anion it is delocalised over only one fragment.

The study of bridged radical-anions is interesting from the standpoint of the transmission of effects via various –X– groups. The radical-anions of diphenylmethane[64–66], diphenylethane[64–66], phenyl ether[66], *p*-cyclophanes[66,67], di-(*p*-nitrophenyl)methane[68,69], *p*-nitrophenyl ester[68], and di-(*p*-nitrophenyl) sulphide[68] were studied for this purpose. Syrkin and coworkers[65] showed that the initial conclusion[64] that the unshared electron in the radical-anions of diphenylmethane and diphenylethane may be delocalised was based on erroneous experimental data obtained in the measurement of the ESR spectra of secondary radical-anions. The data on *p*-cyclophanes and di-(*p*-nitrophenyl)methane are not unambiguous. The differences in the spectra of the radical-anions obtained from di-(*p*-nitrophenyl)methane are due to the mobility of the hydrogen atoms in the $-CH_2-$ group. Syrkin and coworkers[69] state that, depending on the conditions, it is possible to observe the ESR spectrum of a radical-monoanion in which, according to their data, there is no conjugation, and of the radical-dianion of di-(*p*-nitrophenyl)methane in which the unshared electron is fully delocalised over the entire molecule. An unambiguous conclusion may be arrived at concerning the delocalisation of the unshared electron between the nitro-groups via the $-CF_2-$ group in the radical-anion of difluorodinitromethane on the basis of an analysis of a simple ESR spectrum[70], which consists of a triplet of quintets due to the interaction of the unshared electron with two nitrogen nuclei (a_N = 12.9 gauss) and two fluorine nuclei (a_F = 14.8 gauss). The delocalisation of the unshared electron was observed in the radical-anion of diphenyl sulphone by Kaiser et al.[71] and also by Gerdil and Lucken[72]. The distribution of spin density in the phenyl rings of this radical-anion is similar to that in the radical-anion of biphenyl.

The intensive studies on the radical-anions of aromatic hydrocarbons and aromatic compounds containing oxygen and nitrogen atoms are largely due to the simplicity of the theoretical analysis of their ESR spectra. The inclusion in the aromatic systems of many-electron atoms such as those of sulphur, phosphorus, and selenium leads to certain difficulties in the interpretation of the spectra. One of the few approaches whereby account can be taken of the effect of these atoms on the electronic structure of organic derivatives of elements of this kind involves the consideration of the *d* orbitals. The quantum-mechanical method for taking into account the interaction of *d* electrons with *p* electrons proposed by Longuet-Higgins[73] permits the treatment of the sulphur atom as an analogue of the double bond in ethylene. According to Longuet-Higgins, such treatment makes it possible to understand the aromatic nature of thiophen. Since thiophen itself is not reduced, dibenzothiophen and related compounds were chosen to test these hypotheses. The hyperfine coupling constants for protons in benzene rings are presented below[74]:



X	a_1	a_2	a_3	a_4, gauss
O	4.87	0.98	4.87	1.96
S	4.48	0.86	5.16	1.46
Se	4.27	1.02	5.27	1.02
$-CH=CH-$	0.32	2.88	0.72	3.60 .

The calculation of the hyperfine coupling constants within the framework of the Longuet-Higgins scheme, which takes into account the interaction of *p* and *d* electrons, gave the following values for benzothiophen: $a_1 =$ 1.36 gauss; $a_2 =$ 2.30 gauss; $a_3 =$ 0.02 gauss; $a_4 =$ 2.63 gauss (*d* model). At the same time a second calculation was made including the interaction of the π electrons of the aromatic part of the molecule with the lone pair of *p* electrons of sulphur and oxygen. The hyperfine interaction constants obtained agree with experiment better than in the case where account is taken of *d* electrons:

	a_1	a_2	a_3	a_4, gauss	
Dibenzothiophen	3.99	−1.23	5.03	0.75	(*p*-model).
Dibenzofuran	4.78	−1.41	4.80	1.86	

On the basis of these results, Gerdil and Lucken concluded that the interaction of the *d* orbitals of the sulphur atom with the π orbitals of the aromatic system is slight.

Urberg and Kaiser[20] compared the involvement of various valence states of sulphur in conjugation using as an example thioxanthone and its sulphone. The data show that in both cases the sulphur atom is only weakly involved in conjugation compared with the carbonyl group. Analysis of the ESR spectra of the radical-anions of di-(*p*-nitrophenyl) sulphide, sulphoxide, and sulphone led to the conclusion that the distribution of unshared electron density in these compounds depends little on the valence state of sulphur.

The problem of the $d-\pi$ conjugation was discussed in the study of the radical-anions of 2,1,3-benzothiadiazole and 2,1,3-benzoselenadiazole by Strom and Russell[75] and by Solodovnikov and Todres[76]. However, data in favour of $d-\pi$ interaction were not obtained. This problem also arises in the study of the radical-anions containing a phosphorus atom, such as aromatic and aliphatic phosphines and phosphine oxides[77]. The search for more distinctive effects of the involvement of *d* orbitals in conjugation led to the study of the ESR spectra of non-aromatic radical-anions[78,79] such as $[R_2Si]_n$. The ESR spectra of the radical-anions of the cyclic compounds $[(CH_3)_2Si]_6$ and $[(C_2H_5)_2Si]_6$ provide evidence of the interaction of the unshared electron with six silicon atoms and 12 carbon atoms. This delocalisation is attributed[78] to the interaction of the silicon *d* orbitals, which the authors believe to contain the unshared electron.

III. EFFECT OF SUBSTITUENTS AND THE MEDIUM ON THE ELECTRONIC STRUCTURE OF RADICAL-ANIONS

The review of studies on the effect of substituents, the solvent, and the hindered motion of the functional groups in radical-anions on their ESR spectra requires special consideration. Some of these problems were considered for a number of examples in the preceding section. In particular, it was shown that semiempirical quantum-chemical methods permit a satisfactory description of the effect of substituents on the distribution of spin density. In this section we shall consider certain special methods for the treatment of the effect of substituents.

Rieger and Fraenkel[80] showed that the ratio of the spin densities in the *ortho*- and *para*-positions of the radical-anions is associated with the π energy of the unshared electron:

$$\rho^{\pi}_{\text{ortho}}/\rho^{\pi}_{\text{para}} = 1/4\,(x_0^2-2)^2$$

where x_0 is the root of the secular equation. In the case of a weak interaction between the substituent and the ring $x_0 \to 1$ and the ratio $\rho^{\pi}_{\text{ortho}}/\rho^{\pi}_{\text{para}}$ approaches 1/4, i.e. the orbital of the unshared electron comes close to the symmetrical benzene orbital. For powerful electron-accepting groups, x_0 tends to zero and the ratio $\rho^{\pi}_{\text{ortho}}/\rho^{\pi}_{\text{para}}$ tends to unity. For nitrobenzene and the benzonitrile radical-anions, this ratio is 0.83 and 0.43 respectively. Thus the ratio of the spin densities in the *ortho*- and *para*-positions is a quantitative characteristic of the electronegativity of the substituent. However, this method does not seem to be widely used.

Table 2. Nitrogen hyperfine coupling constants and Hammett's σ_p constants for the radical-anions of *p*-substituted nitrobenzenes.

Substituent	a_N, G	σ_p	Substituent	a_N, G	σ_p
NH_2	12.18	−0.172	Br	9.70	0.238
OCH_3	11.57	−0.111	$CONH_2$	8.37	—
CH_3	10.79	−0.129	$COOCH_3$	7.73	0.385
F	10.76	−0.056	CN	7.15	0.674
H	10.32	0.00	$COCH_3$	7.02	0.502
C_6H_5	9.84	—	SO_3CH_3	6.90	—
Cl	9.83	0.238	CHO	5.83	0.50
			NO_2	1.74	0.778

Attempts have been made to take into account the effect of substituents on the hyperfine coupling constants using the Hammett equation. Table 2 lists the hyperfine coupling constants for nitrogen nuclei (a_N) in the radical-anions of *para*-substituted nitrobenzenes[81] and Hammett's σ_p constants (after Van Bekkum[82]).

The analysis of such data carried out by Bowers[20] yielded the following values of ρ in the Hammett equation $\lg\,(a^X_N/a^H_N) = \rho\sigma_n$ for different solvents: −0.833 in dimethylformamide, 0.888 in dimethyl sulphoxide, and −0.750 in acetonitrile. The correlation between a_N and σ_n is not adequate, but is nevertheless a definite correspondence between these quantities.

Brokskii and coworkers[83,84] found that the relation between a_N and σ_n for the radical-anions of *para*-substituted nitrobiphenyls is described satisfactorily by the equation

$$a^H_N - a^X_N = \Delta a^X_N = 3.60\,\sigma - 0.3$$

where a correlation coefficient $r = 0.958$. Having expressed a_N for the radical-anions of nitrobiphenyls as a function of a'_N for the radical-anions of *p*-nitrobenzene using the results of Maki and Geske[81], these investigators estimated the weakening of the effect of the substituent on a_N when a second benzene ring is introduced:

$$a_N = 5.61 + 0.424\,a'_N,$$

whence it follows that the ratio of the slopes (ρ) of the plots based on the Hammett equations for these two series of compounds is about 0.4. This corresponds to a weakening by a factor of 2.5 of the effect of the substituent in the radical-anions when a second benzene ring is introduced.

Certain examples of the effect of the hindered rotation of functional groups on the ESR spectra of radical-anions were considered in the first section of the review. The asymmetry of the spectra of the carbonyl compounds of azobenzene and stilbene is evidence that there is no free interconversion of the *cis*- and *trans*-forms. These examples relate to "static" cases where the barrier between two conformations is fairly high and the transitions take place at a low frequency and do not affect the ESR spectra. However, there exist examples where in the analysis of ESR spectra it is necessary to take into account the nature of the motion of different groups in the radical-anions. This has been clearly shown by Stone and Maki[85] in the analysis of the hyperfine coupling constants for the radical-anions of nitroalkanes $RR'CHNO_2$.[17,18,85]

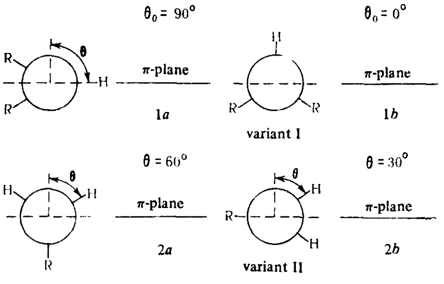
Table 3. Hyperfine coupling constants for the radical-anions of certain nitroalkanes.

R	R′	a_N, G	a_H^β, G	Variant
CH_3	H	25.5	9.75	II
C_2H_5	H	24.8	9.98	II
n-C_3H_7	H	24.2	9.76	II
n-C_5H_{11}	H	25.1	10.1	II
CH_3	CH_3	25.2	4.6	I
C_2H_5	CH_3	24.7	3.19	I
C_2H_5	CH_2OH	24.7	3.26	I

Table 3 shows that the hyperfine coupling constants for the nitrogen nucleus (a_N) are almost independent of the substituents R and R′. In those cases where R′ = H, $a_H^\beta = 9.9 \pm 0.14$ gauss and is independent of R. In radical-anions with one β-proton, a_H^β is much smaller than in the case of two β-protons. The sharp change in the hyperfine coupling constants for the β-proton on transition from RCH_2NO_2 to $RR'CHNO_2$, where R and R′ are alkyl substituents, is attributed to the effect of the hindered rotation of the RR′CH group about the C–N bond. The dependence of the hyperfine coupling constant for β-hydrogen atoms in RR′CH–X on the angle θ is described by the expression $a_H^\beta = Q(\theta)\rho_X^\pi$,[86] where $Q(\theta) = B_0 + B_2\cos^2\theta$, ρ_X^π is the spin density in the $2p_z$-orbital, and θ is the angle between the $2p_z$-orbital and the CH bond projected on a plane perpendicular to the C–X bond. Horsfield et al.[87] determined the constants B_0 and B_2 for the radical $CH_3CHCOOH$ and found them to be 3.2 and 43.5 gauss respectively. Since $B_0 \ll B_2$, it follows that $Q(\theta) \simeq B\cos^2\theta$. In the liquid phase the alkyl groups are not rigidly fixed and Q varies with their rotation. In this case the equation describing the dependence of the hyperfine coupling constants for β-protons on the angle θ must be modified: $a_H^\beta = \langle Q(\theta)\rangle \rho_X^\pi$, where $\langle Q(\theta)\rangle$ is the average value of Q. In the general case $\langle Q(\theta)\rangle$ is the quantum-mechanical average of $\cos^2\theta$ with respect to the rotational wave functions $\Psi(\theta)$. In the limit corresponding to free rotation, $\langle Q(\theta)\rangle = \frac{1}{2}B$ and $a_H^\beta = \frac{1}{2}B\rho_C^\pi$.

It is possible to distinguish several equilibrium conformations (Scheme 2):

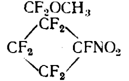
Scheme 2



Qualitative examination of these conformations showed that $a_H^\beta(1b) > a_H^\beta(1a)$ and $a_H^\beta(2b) > a_H^\beta(2a)$.

The differences in the hyperfine coupling constants are probably associated with the existence of different equilibrium conformations and with different effects of hindered rotation on $\langle Q(\theta)\rangle$. Averaging in the classical quantum-mechanical approximation leads to qualitatively identical results. An increase in the amplitude of vibrations in the classical case causes a decrease of $\langle Q(\theta)\rangle$ for equilibrium positions in the vicinity of 0° and 30°C and an increase for angles of 60° and 90°. A similar effect causes the barrier height to be reduced in a quantum-mechanical treatment.

Table 4. Splitting constants for the radical-anions of certain organic fluoronitro-compounds.

R	R′	a_N, G	a_F^β, G	Variant
H	F	20.05	28.8	II
CF_3	F	19.25	24.85	II
CF_2OCH_3	F	19.7	49.0	II
		15.9	93.3	I
CF_3	Cl	21.6	42.1	I

Analysis of the data in Table 3 shows that for variant I $a_H^\beta \neq 0$ and $\theta \neq 90°$, which leads to conformation 1*b*. It follows from the conformations quoted that $a_H^\beta(1b) > a_H^\beta(2a)$, but this is inconsistent with experiment, i.e. it is necessary to suppose that β-protons are not fixed but possess a certain freedom of rotation.

Hindered rotation probably has a significant effect on the hyperfine coupling constants in the ESR spectra of the radical-anions of organic fluoronitro-compounds[88] $RR'CFNO_2$. It may be supposed that the following expression is valid for such anions:

$$a_F^\beta \simeq (B_0 + B\cos^2\theta)\rho_N^\pi + Q_F\rho_F^\pi.$$

For the majority of the radical-anions quoted in Table 4, a_N is constant within the limits of 2 gauss; it is therefore probable that the term $Q_F\rho_F^\pi$ makes a constant contribution to the splitting by β-fluorine atoms in CF_2.

An interesting example of the conformational differences in the structural of the radical-anions of 2,3,5,6-tetraisopropylnitrobenzene was observed by McKinney and Geske[89].

Hyperfine lines corresponding to two different "rotational isomers" A and B appear in the ESR spectrum of this radical-anion. Fig. 4 shows the ESR spectrum which arises when tetraisopropylnitrobenzene is reduced in acetonitrile. The species A and B are characterised by a nitrogen nucleus hyperfine coupling constant of 23.6 and 22.0 gauss respectively. Since the g-factors of A and B are identical, the central components of their spectra merge. The equilibrium constant $K = B/A = 2.3$ and $\Delta G_{298°} = -500 \pm 100$ cal mole^{-1}.

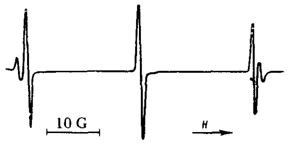


Figure 4. ESR spectrum of the tetraisopropylnitrobenzene radical-anion in acetonitrile.

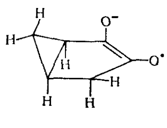
The hindered motion of portions of cyclohexane-1,2-semidione was observed by Lown[90]. At 25°C the ESR spectrum of this radical-anion contains five lines due to the interaction of the unshared electron with four equivalent α-protons ($a_H = 10.34$ gauss is dimethoxyethane). However, on cooling to −96°C, a spectrum consisting of seven lines and corresponding to the two pairs of equivalent protons with $a_H = 14.2$ gauss and $a_H = 6.9$ gauss appears. Hence it follows that a reduction of temperature entails a retardation of inversion and the equatorial and axial protons become distinguishable. At 25°C the inversion frequency is $(14.2 - 6.9) \times 2.8 \times 10.6 = 2 \times 10^7$ Hz, i.e. the lifetime of the radical-anion in one conformation is less than 5×10^{-8} s. Russell and Strom[91] showed that in the ESR spectra of the radical-anions in the series ranging from cycloheptane-1,2-semidione to cyclopentadecane-1,2-semidione at 25°C the signals due to both conformations are present. This is evidence that at this temperature the lifetime of one conformation is $> 10^{-7}$ s.

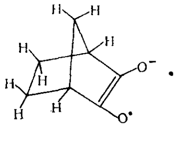
Talaty and Russell[92] found that the introduction of substituents into cyclohexane-1,2-semidione alters significantly the hyperfine coupling constant for equatorial and axial protons. However, the sum of these constants is virtually invariant (Table 5). These data lead to the conclusion that the observed hyperfine coupling constants (a_{eq} and a_{ax}) are correlated with the true constants ($a^0_{ax} = 13.18$ gauss and $a^0_{eq} = 6.59$ gauss) by the simple equation

$$a_{ax} = 13.18f + 6.69(1 - f),$$
$$a_{eq} = 6.59f + 13.18(1 - f),$$

where f is the fraction of molecules in one of the stable conformations. Calculation with the aid of these equations showed that, with increase in the size of the substituents, an increasing proportion of the molecules are in a stable state and the fraction undergoing ring inversion falls.

Semidiones obtained from bicyclic diketones are of particular interest:





The hyperfine structure of the ESR spectra of these radical-anions contains components due to all the protons present. The assignments of the hyperfine coupling constants are based on a study of the corresponding alkyl-substituted semidiones[20,93,94]. The problems of the mechanism of the transfer of spin density to more remote protons has not been elucidated in detail, but it is suggested that homohyperconjugation takes place in this case.

Table 5. Hyperfine coupling constants (gauss) for 4-substituted cycloalkane-1,2-semidiones at 25°C in dimethyl sulphoxide.

4-Substituent	a_{ax}	a_{eq}	$a_{ax} + a_{eq}$
H	9.83	9.83	19.66
CH_3	12.33	7.34	19.67
$(CH_3)_2CH$	12.63	7.02	19.65
t-Butyl	13.02	6.64	19.66
trans-4,5-$(CH_2)_4$	13.18	6.59	19.77

Analogous effects of the steric positions of atoms on ESR spectra were observed by Russell[20] for semidiones obtained from derivatives of decalin, steroid ketones, bicyclic hydrocarbons, etc.

The hyperfine coupling constants of the radical-anions measured in the ESR spectra refer, strictly speaking, to a definite solvent and depend on its nature. Ludwig et al.[95] observed a change in the hyperfine coupling constant for the nitrogen nucleus in the radical-anion of nitrobenzene from 10.32 gauss in acetonitrile to 9.7 gauss in dimethylformamide. The radical-anions of substituted nitrobenzenes behave similarly[96]. We may note that the changes of the hyperfine coupling constants for protons in the aromatic nucleus are small. However, in the radical-anions of semiquinones the proton hyperfine coupling constants change by 1–45% on transition from dimethyl sulphoxide to aqueous alcoholic solutions[97].

One of the causes responsible for the change in the hyperfine coupling constants is probably a redistribution of spin density in the radical-anions due to the specific solvation of functional groups and the formation of hydrogen bonds. Gendell et al.[98], who suggested the existence of an equilibrium between various types of radical-anion complexes with solvents, succeeded in describing satisfactorily the relation between the hyperfine coupling constants and solution composition. In pure solvents S_A and S_B the complexes R_XS_A and R_XS_B of the radical R_X with one molecule of S_A and S_B exist. In a mixture of solvents there is the equilibrium.

$$R_XS_A + S_B \underset{k_B}{\overset{k_A}{\rightleftarrows}} R_XS_B + S_A$$

It may prove that the hyperfine coupling constant a_A for the nucleus under consideration in the complex R_XS_A differs from the value of a_B for the complex R_XS_B. The observed ESR spectra will depend on the rate of the exchange reaction. For slow exchange, the lifetime of the radical complexes $\tau \gg |\gamma(a_A - a_B)|^{-1}$ (γ is the gyromagnetic ratio for two electrons) and the spectrum will show components referring to both complex R_XS_A and R_XS_B. A case of this kind was observed by Corvaja and Giacometti[99] for the radical-anion of m-nitrophenol in water–dimethyl formamide mixtures. In the case of a rapid exchange, only a single spectrum will be observed with a hyperfine coupling constant having the mean value

$$\tilde{a} = p_A a_A + p_B a_B,$$

where p_A and p_B are the fractions of the complexes R_XS_A and R_XS_B:

$$p_A = \frac{\tau_A}{\tau_A + \tau_B} = \frac{1}{1 + K\alpha}; \qquad p_B = \frac{\tau_B}{\tau_A + \tau_B} = \frac{K\alpha}{1 + K\alpha}.$$

The lifetimes τ_A and τ_B of the complexes R_XS_A and R_XS_B depend on the rate constants and the concentrations:

$$\tau_A = \frac{1}{k_A[S_B]}; \qquad \tau_B = \frac{1}{k_B[S_A]}; \qquad \alpha = \frac{[S_B]}{[S_A]}.$$

The equilibrium constant is

$$K = \frac{k_A}{k_B} = \frac{[R_XS_B][S_A]}{[R_XS_A][S_B]}.$$

The observed mean hyperfine coupling constant $\tilde{a}$ for rapid exchange may be expressed by the somewhat rearranged formula

$$\tilde{a} = {}^1/_2(a_A + a_B) + {}^1/_2[(K\alpha - 1)/(K\alpha + 1)]\Delta,$$

where $\Delta = a_B - a_A$. A plot, based on this equation, of α against $2\delta\tilde{a}/\Delta$, where $2\delta\tilde{a} = 2[\tilde{a} - \frac{1}{2}(a_A + a_B)]$, yields for $K = 10$ the curve in Fig. 5. The value of K was chosen arbitrarily to illustrate the form of the expression[98]. It corresponds to the case where the complex with the solvent S_B is much more stable than the complex with S_A.

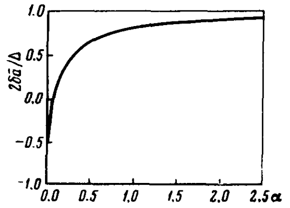


Figure 5. Variation of the hyperfine coupling constant with solvent composition (see text).

The value of $\tilde{a}$ varies rapidly from a_A in the pure solvent to S_A ($\alpha = 0$), since on addition of small amounts of a strongly complexing solvent we have for low values of K a linear relation between $\tilde{a}$ and the hyperfine coupling constants in the pure solvents:

$$\tilde{a} = a_A K\alpha(a_B - a_A).$$

When large amounts of S_B are added, $\tilde{a}$ tends asymptotically to a_B. This type of situation is observed in the variation of the hyperfine coupling constants for the nitrogen nucleus of the nitro-group in the radical-anions of nitrobenzene and *p*-nitroaniline in aqueous acetonitrile mixtures[98]. The addition of small amounts of water leads to an appreciable increase of the hyperfine coupling constant for the nitrogen nucleus. With increase in percentage content of water, this quantity changes little and at a fairly high concentration remains invariant, which is evidence of complete "solvation" of the radical-anion by water molecules.

IV. ION PAIRS

The formation of ion pairs has been investigated hitherto by electrochemical and ultraviolet spectroscopic methods and only recently radioscopic methods began to be used in this field: Symons[100] analysed different ESR spectroscopic data which provide direct or indirect information about the formation of ion pairs in solution: (1) analysis of the dependence of the hyperfine coupling constants on the diamagnetic gegenion; (2) the variation of the properties of the radical-anion, in particular the variation in the symmetry of the spin density distribution; (3) the variation of the ESR line shape; (4) analysis of the ESR spectra of paramagnetic dimers in a triplet state.

We shall consider these data separately. The hyperfine interaction with alkali metal ions is frequently reflected in the ESR spectra of radical-anions in ethereal solutions. This effect was observed by Adam and Weissman[101]. In a study of the ESR spectrum of the sodioketyl of benzophenone they noted the splitting of each component of the spectrum into four lines as a result of the interaction between the unshared electron and the magnetic moment of the ^{23}Na nucleus which has a spin of 3/2. Subsequently such interaction was observed in the ESR spectra of many radical-anions obtained by reduction with alkali metals. In all cases the spin density at the cation is low, but the detection of a small splitting nevertheless permits the conclusion that an ion pair is formed. The data on the hyperfine interaction constants for the nuclei of metal cations (a_M) in various solvents and the calculated spin densities at these nuclei (ρ_{ns}) are compiled in Table 6 taken from Symons' paper.

It was assumed that $\rho_{ns} = a_M/a_{atom}$, i.e. the ratio of the hyperfine coupling constants for the metal cation and the free metal in the gas phase. Analysis of the hyperfine coupling constants for the cations shows that the solvent plays a decisive role in the formation of ion pairs. This is associated with the particular solvating capacity of the ions. Unfortunately, this problem has not been investigated adequately on a quantitative basis, and at present one can only note, for example, that the hyperfine coupling constants for the Na^+ cations in the ion pairs with the radical-anions of naphthalene increase on going from dimethoxyethane to tetrahydrofuran and to ethyl ether.

The structure of the radical-anions also plays a significant role. The magnetic interaction depends on the overlapping of the *s* orbital of the cation with the orbital of the unshared electron of the anion. Symons noted that the preferred sites for the localisation of the cation are positions with maximum negative charges.

Atherton and Weissman[102] found an appreciable increase of the hyperfine coupling constant for sodium-23 in sodionaphthalene dissolved in various ethers when the temperature was raised. On lowering the temperature, this quantity tends to zero in tetrahydrofuran solution. The authors suggest that, when the temperature is reduced, the cation is located at the node of the wave function of the unshared electron between the 9- and 10-positions, so that the overlapping of the wave function of the unshared electron in the radical-anion with the *s* orbital of the cation is zero. On raising the temperature, the cation begins to vibrate about its equilibrium position, which leads to an increase of the overlapping and of the hyperfine coupling constants.

Another explanation of this effect is that a decrease of temperature entails an increase of the solvation of the cation and an increase of the distance between the cation and the paramagnetic ion[103]. This type of variation is regarded as a result of the equilibrium $A \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} B$, where A is an ion pair with a hyperfine coupling constant for the sodium nucleus $a_{Na} = 1.5$ gauss and B an ion pair with $a_{Na} = 0$. For higher values of k_1 and k_{-1}, an averaged spectrum will be observed. If two different ion pairs have different hyperfine coupling constants a_A^{Na} and a_B^{Na} and the probabilities of the existence of forms A and B are p_A and p_B, the equilibrium constant K may be expressed in terms of these quantities:

$$K = \frac{p_B}{p_A} = \frac{\tau_B}{\tau_A} = \frac{k_1}{k_{-1}},$$

where τ_A and τ_B are the lifetimes of forms A and B. In the case of rapid exchange between the two forms, a_{Na} will depend on temperature in accordance with the formula

$$a_{Na} = p_A a_A^{Na} + p_B a_B^{Na} = \frac{a_A^{Na} + K a_B^{Na}}{1+K}.$$

The heats and entropies of reaction have been determined for a number of systems using this expression (Table 7).

Table 6. Cation hyperfine coupling constants (a_M) for ion pairs including paramagnetic anions (M^+A^-).

Anion	Cation	Solvent	a_M, G	ρ_{as}
Naphthalene	Li	THP	0.37	0.26
	Na	THP	1.26	0.40
	Rb	THP	0.09	0.026
	Cs	THP	1.81	0.14
	Na	THF	1.05	0.32
Biphenyl	Li	THP	0.136	0.095
	Na	THP	0.079	0.025
	K	THP	0.083	0.101
	Rb	THP	0.33	0.091
	Cs	THP	1.16	0.142
Anthracene	Li	EE	1.7	0.0
	Na	TMED	2.083	0.66
	K	TMED	0.157	0.19
	Na	MeTHF	1.5	0.47
	Na	MeTHF (-100°)	0.5	0.16
	Na	THP	0.08	0.025
	Cs	THP	0.54	0.066
Azulene	Li	THF	0.174	0.12
	Na	THF	0.538	0.17
	K	THF	0.2	0.24
Pyracene	Na	MeTHF (-80°)	0.176	0.056
	Cs	THF (-100°)	−0.2	−0.024
	Cs	THF (-20°)	−0.7	+0.085
Duroquinone	Li	t-PeOH	0.22	0.15
	Na	t-PeOH	0.85	0.27
p-Benzoquinone	Na	t-BuOH	0.2	0.06
o-Benzoquinone	Li	t-BuOH	0.3	0.21
	Na	t-BuOH	0.2	0.06
Hexamethylacetone	$(Na)_2$	THF (-70°)	1.7	0.54
Benzophenone	Li	DME	0.67	0.47
	$(Li)_2$	DME	1.125	0.79
m-Dinitrobenzene	Na	THF	0.26	0.082
	K	THF	0.2	0.24
	Rb	THF	0.9	0.25
	Cs	THF	2.45	0.30

Note. THP = tetrahydropyran, EE = ethyl ether, TMED = tetramethylethylenediamine, MeTHF = 2-methyltetrahydrofuran, DME = dimethoxyethane, THF = tetrahydrofuran, t-PeOH = t-pentyl alcohol, and t-BuOH = t-butyl alcohol. The temperature of the measurement is indicated in brackets in the second column; in all other cases the experiments were performed at room temperature.

The constants k_1 and k_{-1} and the activation energies for the formation of ion pairs have been determined from the temperature variation of the ESR line widths (Table 8).

Table 7.

	Sodioanthracene in MeTHF	Sodioanthracene in 1:1 THF-MeTHF	Sodionaphthalene in THF	Sodionaphthalene in 1:1 THF-EE
a_A^{Na}, G	1.55	1.55	1.15	1.00
a_B^{Na}, G	0	1.15	0	0
$\Delta H°$, kcal mole^{-1}	−4.6±0.3	−6.2±0.5	−4.8±0.5	−6.4±0.8
$\Delta S°$, e.u.	−23±3	−25±3	−20±4	−33±4

The condition for rapid exchange between ion pairs does not always hold. Thus the ESR spectrum of sodionaphthalene in ethyl ether at low temperatures (below −80°C) corresponds to two different ion pairs with different hyperfine coupling constants for the sodium nucleus: $a_{Na} = 0.8$ gauss and $a_{Na} = 0.06$ gauss. Hirota[103] attributes the higher hyperfine coupling constants to contact ion pairs and the lower values to ion pairs separated by solvent molecules.

Table 8.

	Sodioanthracene in MeTHF	Sodionaphthalene in 1:3 THF-EE
k_1, s^{-1}	$5 \cdot 10^7$ (−60°)	$1 \cdot 10^8$ (−80°)
k_{-1}, s^{-1}	$4 \cdot 10^8$ (−80°)	$7 \cdot 10^8$ (−80°)
ΔE_1, kcal mole^{-1}	3·0	6·0
ΔH_{-1}, kcal mole^{-1}	7.4	11.5

The formation of ion pairs is also reflected in a variation of the hyperfine coupling constants for the radical-anion nuclei as a function of the nature of the cation and the solvent or in relation to the free ion. The free anion is understood to be the paramagnetic species obtained by electrochemical reduction using tetra-alkylammonium salts as a supporting electrolyte. In this case one can neglect the formation of ion pairs with a considerable degree of justification. In some cases, for example, for protons in the 9- and 10-positions of the anthracene anion (the Na^+ and K^+ cations, tetrahydrofuran and tetramethylethylenediamine as solvents) the variation of the hyperfine coupling constant amounts to only a few per cent[100]. In other cases these changes may be much greater. The ESR spectrum of the lithium salt of durosemiquinone in t-pentyl alcohol is characterised by two different hyperfine coupling constants for methyl protons. Thus one may suppose that the lithium cation resides for a relatively long time at one oxygen atom[104]. A similar situation arises in the radical-anion of *m*-dinitrobenzene on formation of an ion pair with the alkali metal cation. As a result of the perturbation introduced by the cation, the hyperfine coupling constant for one nitrogen nucleus is about 10 gauss, while for the other it is about 0.2 gauss.[100]

Interesting information about the kinetic characteristics of ionic association complexes may be obtained by studying the specific broadening of their hyperfine structure lines. We shall examine separately the broadening associated with the change in the hyperfine coupling constants for the alkali metal and radical-anion nuclei. The changes in the hyperfine coupling constants for the metal nuclei may be caused by the reaction[100]

$$(M^+A^-) \rightleftarrows M^+ + A^-,$$
$$(M^+A^-) + M^+ \rightleftarrows M^+ + (A^-M^+),$$
$$(M^+A^-)_1 \rightleftarrows (M^+A^-)_2.$$

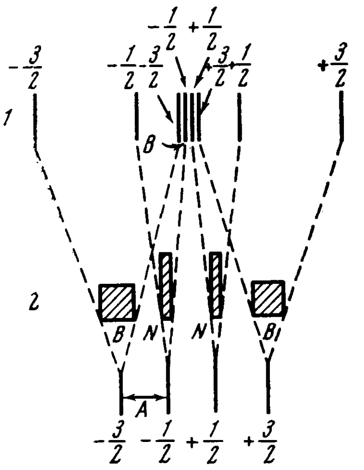


Figure 6. Splitting due to the metal cation ($I = 3/2$) in the ESR spectra of two ion pairs with hyperfine coupling constants A_1 and A_2: 1) slow exchange; 2) intermediate case; 3) rapid exchange.

These reactions affect the lifetime of the paramagnetic species in a definite spin state, which in turn leads to line broadening. The first two reactions cause uniform broadening of all the lines. Hirota and Weissman[105] found that the addition of sodium iodide to the sodioketyl of xanthone leads to an appreciable line broadening. The third reaction represents the conversion of ion pair 1 with a hyperfine coupling constant A_1 into ion pair 2 with a constant A_2. Here the significant factor is that the transition from one type of ion pair to another takes place with participation of one cation. The splitting due to the metal does not disappear in this process. Fig. 6 illustrates the broadening of the lines caused by the third reaction for ion pairs which are in equilibrium and which have metal hyperfine coupling constants a_1 and a_2.[100] In the case of a slow exchange two sets of lines will be observed, as can be seen in Fig. 6 (lines *1*). With increase in the rate of exchange, each pair of lines will become wider until they overlap, and as a result we obtain a single broad line corresponding to each spin state. Since the ±3/2 lines (Fig. 6) are separated in the field considerably more than the ±1/2 lines, the widening of the ±3/2 lines will be much greater compared with the ±1/2 lines (lines *2*). In rapid exchange only a quartet of narrow lines will be observed (lines *3*). Fig. 7 (Hirota[103]) illustrates clearly this type of broadening of the components of the sodium hyperfine structure in sodionaphthalene in a mixed tetrahydrofuran–ethyl ether solvent at different temperatures. It is clearly seen that the two extreme components due to sodium undergo marked broadening at −100°C.

The dynamic nature of solvation is indicated by the specific broadening in the hyperfine structure of the radical-anion itself. It is expressed in an alternation of the hyperfine structure line widths. One of the reasons for the alternation may be the migration of the cation between two equivalent functional groups in the anion. The steady-state pattern associated with this process is determined by the non-equivalence of the hyperfine coupling constants for the nuclei in these functional groups. For example, in the ion pairs of the radical-anions of *m*-dinitrobenzene with alkali metal cations the hyperfine coupling constant for one nitrogen nucleus is 10 gauss and that for the other is 0.2 gauss.[100] Here the situation is complicated by the fact that the same effects can be produced either by the fluctuation of the solvation shell or by conformational transitions in the molecule[106].

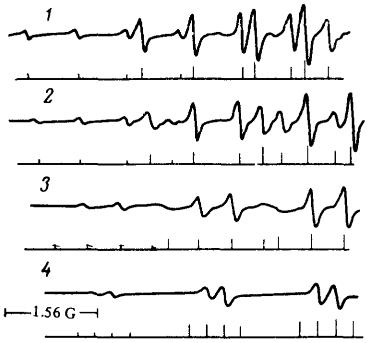


Figure 7. Temperature variation of the line width in the ESR spectrum of the naphthalene radical-anion in the presence of potassium in the mixed solvent tetrahydrofuran (25%)–ethyl ether (75%); the expected relative line intensities in the absence of broadening effects associated with exchange processes are indicated under the spectra: temperature (°C): 1) −60; 2) −75; 3) −85; 4) −95.

Another ionic association process is the formation of paramagnetic dimers observed by Weissman and coworkers[107,108]. A clear example of such structures is the formation of the complexes of the radical-anions of 2,2′-bipyridyl and related ligands with divalent cations (Be^{2+}, Ba^{2+}, and Zn^{2+}). The ESR spectra of these systems in the solid phase at −196°C are characterised by the presence of triplet states corresponding to the structure of the chelate complexes of two radical-anions with a divalent metal cation. The determination of the zero splitting constants from the ESR spectra of the paramagnetic dimers permitted the estimation of the average distance between the anions in the dimers. In the complexes of the radical-anion dimers of 4,7-biphenyl-1,10-phenanthroline, 2,2′-biquinoline, and 2,2′-bipyridyl with the cations Be^{2+}, Mg^{2+}, Zn^{2+}, Ca^{2+}, Ba^{2+}, and Sr^{2+} this distance is approximately 7 Å.[108] The distance between the radical-anions of hexamethylacetone in the complex with sodium cations is 5.6 Å.[107] Comparison of these distances with the radii of the cations suggests that the dimers have either the structure $A^-M^{2+}A^-$ or $A^-M_2^+A^-$.

V. ELECTRON EXCHANGE REACTIONS

Ward and Weissman[109] observed a pronounced broadening of the hyperfine structure components in the ESR spectrum of the naphthalene radical-anion on addition of free naphthalene to the solution of the radical-anion.

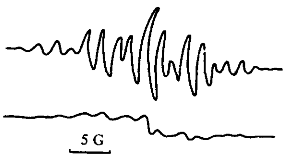


Figure 8. ESR spectrum of the naphthalene radical-anion in the presence of potassium in dimethoxyethane; concentration of radical-anion 1.4 × 10^{-3} M; upper spectrum recorded in the absence of neutral naphthalene; lower spectrum recorded after the addition of naphthalene to a concentration of 0.218 M.

Fig. 8 presents the original ESR spectra of the naphthalene radical-anions obtained by these investigators before and after the addition of free naphthalene. They attributed this phenomenon to the exchange of an electron between the radical-anion and the naphthalene molecule:

$$C_{10}H_8^{\overset{\cdot}{-}} + C_{10}H_8 \rightleftarrows C_{10}H_8 + C_{10}H_8^{\overset{\cdot}{-}}.$$

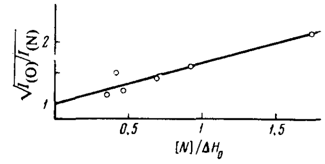


Figure 9. Variation of $I(O)/I(N)$ with $[N]/\Delta H_0$ for naphthalene in the presence of sodium in tetrahydrofuran.

The position of the hyperfine line in the spectrum is determined by the spin quantum numbers of the protons m_α and m_β in the α- and β-positions in the molecule. The transition of an electron from the radical-anion to the neutral molecule alters m_α and m_β to m'_α and m'_β. This process is accompanied by a shift of the resonance line in accordance with the new values m'_α and m'_β. According to Anderson's theory[110], the contribution of such an exchange process to line width is given by the expression $1/\tau = 2\pi\delta\nu$, where $\delta\nu$ is the contribution to line width by the exchange and τ the period between the exchange steps. It is suggested that the line has the Lorentzian shape and the frequency of the exchange is small compared with the difference $\nu_i - \nu_j$ between the frequencies of adjacent hyperfine lines. On the other hand, when $1/\tau > \nu_i - \nu_j$, the exchange results in narrowing of the line.

In practice it proved more convenient to measure not the line width but the intensity, since the two are related:

$$\frac{I_{(N)}}{I_{(O)}} = \left(\frac{\Delta H_0}{\Delta H_0 + \Delta H_N}\right)^2; \quad \sqrt{\frac{I_{(O)}}{I_{(N)}}} = 1 + \frac{\Delta H_N}{\Delta H_0},$$

where $I_{(O)}$ and ΔH_0 are the intensity and line width before the addition of neutral molecules, $I_{(N)}$ is the intensity after the addition, and ΔH_N is the contribution to line width by electron exchange. Simple rearrangement leads to an expression relating k_{exch} (the rate constant for the bimolecular exchange reaction) to line intensity and naphthalene concentration $[N]$:

$$\sqrt{\frac{I_{(O)}}{I_{(N)}}} = 1 + \frac{k_{exch}[N]}{\sqrt{3}\pi\, 2.83 \cdot 10^6 \Delta H_0},$$

where ΔH_0 is the width of the ESR line between the points of maximum slope. Fig. 9 shows the variation of $\sqrt{I_{(O)}/I_{(N)}}$ with $N/\Delta H_0$ for sodionaphthalene in tetrahydrofuran. Table 9 lists the exchange rate constants (k_{exch}) in various solvents with different counterions. The data in this Table confirms that the nature of the solvent and the metal have a significant influence on the rate of exchange reactions[109].

Table 9. Rate constants for the exchange between metal-naphthalene and naphthalene.

Cation	Solvent	k_{exch}, litre mole^{-1} s^{-1}
K^+	DME	$(7.6 \pm 3)10^7$
K^+	THF	$(5.7 \pm 1)10^7$
Na^+	DME	$\sim 10^9$
Na^+	THF	$\sim 10^7$
Li^+	THF	$(4.6 \pm 3)10^8$

Further studies by Zandstra and Weissman[111] showed that the rate of the exchange reaction is very different for free ions and ion pairs. Their studies of the reactions

$$C_{10}H_8^{\overset{\cdot}{-}} + C_{10}H_8 \rightleftarrows C_{10}H_8 + C_{10}H_8^{\overset{\cdot}{-}}, \qquad (A)$$

$$C_{10}H_8^{\overline{\cdot}}Na^+ + C_{10}H_8 \rightleftarrows C_{10}H_8 + Na^+C_{10}H_8^{\overline{\cdot}}, \qquad (B)$$

in tetrahydrofuran, tetrahydropyran, and 2-methyltetrahydrofuran show that reaction (A) is much faster than reaction (B). Table 10 lists the rate constants and activation energies for these reactions. Remarkable changes in the rate of reaction (B) in tetrahydrofuran are observed when the temperature is reduced. On lowering the temperature below 300°K, the rate of reaction begins to increase and then at 280°K it becomes higher than reaction (A) at the same temperature. To account for this effect, the association of ion pairs with naphthalene is postulated. According to Szwarc[19], the activation energies in Table 10 are too high, the explanation of the anomalous behaviour of the rate constant for the exchange reaction (B) in tetrahydrofuran at a low temperature is not satisfactory, and the effect requires further study.

A similar situation was observed by Hirota[103] in the study of the rates of exchange in sodioanthracene in dimethoxyethane, 2-methyltetrahydrofuran, and in 2-methyltetrahydrofuran–tetrahydrofuran mixtures. To determine the rates of reactions (A) and (B) in the same solvent with the same gegenion, there must be equilibrium between the free ions and ion pairs and the rate of exchange between these species must be sufficiently low to preclude the formation of an average pattern.

Table 10. Rate constants and activation energies for the exchange reaction between sodionaphthalene and naphthalene.

Solvent	Species	Activation energy, kcal $mole^{-1}$	Temp., °C	$10^{-6}k$, litre $mole^{-1}$ s^{-1}
Tetrahydropyran	ion pairs	17.7±0.9	21	4.4±0.1
	free pairs	18.5±2.2	—23	9.7±4.5
Methyltetrahydrofuran	ion pairs	12.8±3.2	—23	2.8±0.7
	free pairs	12.4±3.6	21	4.5±0.1
Tetrahydrofuran	ion pairs	4.6±0.5	50	34.0±0.8
		—6.8±0.5	—16	71.0±15
	free ions	13.2±1.5	13	38.0±14

Chang and Johnston[112] found that the difference in the rates may be observed with the aid of ESR also when it is impossible to distinguish between the ESR spectra of the ion pairs and free ions. Using the conditions for the so called "rapid exchange" when $1/\tau > \nu_i - \nu_j$ and the exchange leads to the narrowing of the lines, these investigators found a sharp difference in line narrowing in the spectra of free radical-anions and ion pairs. In Fig. 10 the narrow line corresponds to the free radical-anions and the broad line to the ion pairs. The exchange constants obtained from these spectra agree satisfactorily with the data of Zandstra and Weissman[111].

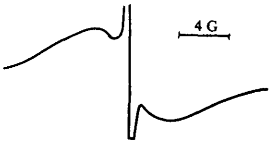


Figure 10. ESR spectrum of the naphthalene radical-anion in the presence of potassium in tetrahydrofuran after the addition of naphthalene to a concentration of 1.4 M.

The study of the rates of exchange in a wider class of compounds showed that molecular structure and the type of interaction between the radical-anion and the solvent have a marked influence on the rate of exchange in different aromatic systems[113]. Table 11 presents data illustrating the effect of the structure of the species undergoing exchange on the electron exchange rate constant.

Adams and coworkers made an interesting comparison of the splitting by nitrogen nuclei in the spectra of the radical-anions of aromatic nitro-compounds and the rates of electron exchange[113]. With increase of the hyperfine coupling constants, there is an appreciable decrease of k_{exch}. This comparison may be followed on the basis of the data in Table 12.

Table 11. k_{exch} in dimethylformamide measured for various aromatic systems.

A/$A^{\dot{-}}$ systems undergoing exchange	k_{exch}, litre $mole^{-1}$ s^{-1}
Anthracene	$4.8 \cdot 10^8$
p-Benzoquinone	$3.8 \cdot 10^8$
Duroquinone	$6.2 \cdot 10^7$
1,4-Naphthoquinone	$4.2 \cdot 10^8$
Nitrobenzene	$3.0 \cdot 10^7$
Benzonitrile	$2.9 \cdot 10^8$
m-Nitrobenzonitrile	$1.6 \cdot 10^8$
Benzophenone	10^8

The same effect on k_{exch} is observed when water is added to dimethylformamide. The increase of a_N on addition of water is accompanied by a decrease of k_{exch}. The data are presented in Table 13.

Table 12. k_{exch} in dimethylformamide for aromatic nitro-compounds.

A/$A^{\dot{-}}$ systems undergoing exchange	a_N, G	k_{exch}
Nitrobenzene	9.83	$3.0 \cdot 10^7$
p-Dinitrobenzene	1.47	$6.0 \cdot 10^8$
m-Dinitrobenzene	4.68	$5.2 \cdot 10^8$
p-Chloronitrobenzene	9.18	$7.9 \cdot 10^7$
m-Chlorodinitrobenzene	8.75	$8.8 \cdot 10^7$
3,5-Dichloronitrobenzene	7.63	$1.6 \cdot 10^8$

Interesting details of the mechanism of the electron transfer reactions were obtained by Adam and Weissman[101] in the study of the exchange between the sodium ketyl of benzophenone and benzophenone in dimethoxyethane. Two pathways may be postulated for the exchange reaction:

1. Transfer of an electron from the ion pair to the ketone molecule:

$$Na^+OC(C_6H_5)_2^{\dot{-}} + OC(C_6H_5)_2 \rightarrow Na^+ + OC(C_6H_5)_2 + OC(C_6H_5)_2^{\dot{-}},$$

$$Na^+ \text{(free ion in solution)} + OC(C_6H_5)_2^{\dot{-}} \rightarrow Na^+OC(C_6H_5)_2^{\dot{-}}.$$

2. Transfer of a sodium atom:

$$Na^+OC(C_6H_5)_2^{\dot{-}} + OC(C_6H_5)_2 \rightarrow OC(C_6H_5)_2 + Na^+OC(C_6H_5)_2^{\dot{-}}.$$

If the reaction takes place via the first pathway, then at high benzophenone concentrations a singlet line should be observed; if the reaction follows the second pathway, a quartet due to the sodium nucleus should be found. The observation of a quartet due to the sodium atom with a hyperfine coupling constant of 1.1 gauss (instead of 1.0 gauss in dilute solution of the benzophenone ketyl) is evidence of the transfer of a sodium atom and of increased spin density at the sodium nucleus as a result of the exchange.

Data on the rates of exchange between different species are of considerable interest:

$$A^{\overline{\cdot}} + B \rightarrow B^{\overline{\cdot}} + A \,.$$

The application of ESR yielded only qualitative data, since the rates of such processes are very high and direct kinetic study is extremely difficult[114]. Reactions of this kind were investigated by Arai et al.[115] using pulse radiolysis. The measured rate constants for electron transfer from the biphenyl radical-anion to naphthalene, phenanthrene, *p*-terphenyl, pyrene, and anthracene are very high and lie in the range $(0.26–6.4) \times 10^9$ litre mole^{-1} s^{-1}.

Table 13. Effect of solvation on k_{exch} for exchange between the nitrobenzene radical-anion and nitrobenzene.

Solvent	a_N, G	k_{exch}
DMF-1.6% H_2O	10.17	$9\ 9\cdot10^6$
DMF-4.8% H_2O	10.82	$2.7\cdot10^6$
DMF-8.0% H_2O	11.26	$2.7\cdot10^6$
DMF-10% H_2O	11.35	$3.2\cdot10^5$
DMF-32% ethyl acetate	9.8	$3.1\cdot10^7$

From the standpoint of the theory of electron transfer reactions, the comparison of the rate constants for the exchange between A and B (k_{AB}) with the rate constants for the exchange reactions

$$A^{\overline{\cdot}} + A \rightarrow A + A^{\overline{\cdot}}, \quad (k_A)$$

$$B^{\overline{\cdot}} + B \rightarrow B^{\overline{\cdot}} + B\,, \quad (k_B)$$

is of considerable interest. According to the theory of Marcus[116], there is a definite relation between these quantities:

$$k_{AB} = (k_A\, k_B\, K_{AB}\, f)^{1/2},$$

where K_{AB} is the equilibrium constant for the exchange reaction A and B and $f = 1$ when $K_{AB} = 1$. The applicability of this theory to the electron exchange reaction was tested by Bruning and Weissman[117] on optically pure 1-(naphthyl)-1-phenylethane and the corresponding radical-anion and also the racemic mixture. The first system yields identical rate constants for the exchange between the optical isomers and their radical-anions ($k_d = k_l$) and the second yields rate constants for the exchange between the radical-anion of one isomer and the neutral molecule of the other (k_{dl}): $A_d^{\overline{\cdot}} + A_l \rightarrow A_d + A_l^{\overline{\cdot}}$.

If the Marcus theory is correct, then $k_d = k_l = k_{dl}$. The rate constants were determined for the potassium salt: $k_d = 0.7 \times 10^8$ litre mole^{-1} s^{-1} and $k_{dl} = 1.1 \times 10^8$ litre mole^{-1} s^{-1} in dimethoxyethane and $k_d = 0.2 \times 10^8$ litre mole^{-1} s^{-1} and $k_{dl} = 0.2 \times 10^8$ litre mole^{-1} s^{-1} in tetrahydrofuran. These data show that the theory, developed largely for electron transfer reactions between variable-valence ions, is indeed applicable to electron transfer reactions between organic compounds.

It is striking that rapid exchange is observed between identical species. Electron exchange is strongly retarded when structural changes are produced by transfer of an electron to a neutral molecule. This is the situation in the radical-anion of cyclo-octatetraene (COT). The experiments of Katz and Strauss[38] showed that after the addition of small amounts of potassium to a solution of 0.7 M COT, a well resolved ESR spectrum of the COT radical-anion is observed. The low rate of exchange between the COT radical-anion and the neutral molecule,

$$\text{COT}^{\overline{\cdot}} + \text{COT} \rightleftarrows \text{COT} + \text{COT}^{\overline{\cdot}}, \tag{1}$$

is due to the fact that the radical-anion has a planar structure, in contrast to the non-planar neutral molecule. Further addition of potassium leads to the obliteration of the hyperfine structure by the reaction

$$\text{COT}^{\overline{\cdot}} + \text{COT}^{=} \rightleftarrows \text{COT}^{=} + \text{COT}^{\overline{\cdot}}. \tag{2}$$

The estimated rate constants for reactions (1) and (2) are about 10^4 litre mole^{-1} s^{-1} and about 10^9 litre mole^{-1} s^{-1} respectively. Since the radical-anion and the dianion of COT have the same planar structure, the rate constants for the exchange between them are much higher than for the exchange between the radical-anion and the neutral molecule[118].

ESR is not the only method for the measurement of rate constants for electron exchange. In many cases the NMR method has been used successfully. The application of NMR is based on the study of the effect of electron exchange on proton line width in NMR spectra. The contribution to the NMR line width (ΔT_2^{-1}) by electron exchange is described by the expression[119]

$$\Delta T_2^{-1} = \frac{f_P \tau_P a^2/4}{1 + f_D \tau_P^2 a^2/4 + 2\,\tau_P T_{1e}^{-1}},$$

where τ_P and τ_D are the lifetimes in the paramagnetic and diamagnetic states, $\tau_P = 1/k[D]$, $\tau_D = 1/k[P]$, k is the exchange rate constant, $[P]$ and $[D]$ are the concentrations of the molecules in the paramagnetic and diamagnetic states, a is the proton hyperfine coupling constant, f_P and f_D are the fractions of paramagnetic and of diamagnetic molecules, and T_{1e} is the spin–lattice electronic relaxation time. Two limiting cases of slow and rapid exchange are distinguished: slow exchange when $f_D \tau_P^2 a^2/4 \gg 1 + 2\tau_P T_{1e}^{-1}$ and rapid exchange when $f_D \tau_P^2 a^2/4 + 2\tau_P T_{1e}^{-1} \ll 1$. The formulae corresponding to these limiting cases are greatly simplified: for slow exchange $\Delta T_2^{-1} = \tau_D^{-1} = k[P]$ and for rapid exchange $\Delta T_2^{-1} = f_P \tau_P a^2/4 = [P]a^2/4[D]^2 k$. These two limiting cases should differ in the temperature variation of the line width. In the case of slow exchange an increase of temperature should entail a considerable widening of the lines, while in the case of rapid exchange the NMR line should become narrower.

Both these cases were observed by de Boer and McLean[119] in a study of the NMR spectra of *p*-xylene in the presence of the *p*-xylene radical-anions. The lines due to the ring protons became broader on raising the temperature and those due to the methyl protons became narrower. Since the hyperfine coupling constant for the methyl proton is more then ten times higher than for the benzene ring protons in the ESR spectrum of the *p*-xylene radical-anion, the condition of rapid exchange obtained for protons of the first type and the condition of slow exchange obtains for protons of the second type. Studies on the temperature variation of the line width led to the determination of the pre-exponential factor and the activation energy for electron exchange between the *p*-xylene radical-anion and the neutral molecule: $k = 10^{12.0} \exp(-6200/RT)$ litre mole^{-1} s^{-1}.

Williams[120] showed that the rate constants for electron exchange involving the *p*-benzosemiquinone and durosemiquinone radical-anions measured by the NMR method agree satisfactorily with the constants determined by the ESR method.

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One may conclude that considerable progress has been achieved in the study of the electronic and chemical structure of radical-anions. However, at present this progress is to some extent isolated from the development of the chemistry of radical-anions[1,19,121,122]. This is because the reactivity of radical-anions has still been little investigated. Nevertheless a brief survey of the few available data on the reactions of radical-anions leads to the conclusion that factors such as the distribution of the unshared electron[123], association between the anion and cation[124], and the effect of the solvent on the electronic structure and reactions of radical-anions play an important role in their chemistry. Comparison of the kinetic data for electron exchange reactions and reactions involving electron transfer from a radical-anion to a molecule with a different structure are also of considerable interest. The elucidation of the effect of these factors on the kinetic behaviour of radical-anions is undoubtedly one of the essential stages in the study of the role of electron transfer in organic reactions and the extensive data now available on the chemical and electronic structure of radical-anions should in the future make a positive contribution to the solution of this urgent chemical problem.

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Institute of Organic Derivatives
of the Elements, USSR
Academy of Sciences, Moscow

U. D. C. 539.121

Application of Mössbauer Spectroscopy in the Study of Surface Phenomena

V.I.Gol'danskii and I.P.Suzdalev

Recently there has been a considerable growth of interest in the elementary processes occurring on the surface of a solid or associated with the effect of the surface on the properties of atoms and molecules within the bulk of the solid. Mössbauer spectroscopy yields unique information about the electronic structure and the nature of the motion of atoms and therefore the use of this method is extremely effective in fundamental investigations of surface phenomena.

This review deals with the theoretical concepts of Mössbauer spectroscopy and the experimental data on its application in the physical chemistry of surface phenomena. A systematic account is given of new experimental results, which are compared with data obtained by other procedures.

The bibliography includes 70 references.

CONTENTS

I. INTRODUCTION

The development of the theory and technique of Mössbauer spectroscopy has revealed fields of research where its application is extremely effective. One such field, where the characteristics of the method give rise to a particularly large number of new possibilities, concerns surface phenomena[1,2]. During the several years of the application of the Mössbauer effect in the study of surface phenomena, many interesting and important results have been obtained in studies on the dynamics of the motion of atoms on the surface, their electronic state, the elementary steps in adsorption and catalysis, and also the physics of the highly dispersed state of matter.

Bearing in mind the differences between the types of surface effects, the surface phenomena investigated with the aid of Mössbauer spectroscopy may be conventionally divided into two classes. The first class is associated with the study of the state of atoms present directly on the surface of the solid. Here one investigates (1) the atomic vibrations on the surface, (2) surface diffusion, (3) the electronic states of atoms on the surface, (4) the magnetic properties of atoms on the surface, (5) the elementary steps in adsorption and the chemistry of surface compounds, and (6) catalysis.

The second class of phenomena is associated with the effects of the boundaries of the solid on the properties of its internal atoms. These include, for example, (1) the change in the phonon spectrum and the type of atomic vibrations in highly dispersed particles, (2) the variation of the magnetic properties of the particles (the phenomenon of superparamagnetism), and (3) topochemical reactions.

The study of all these processes involves a definite characteristic associated with the method, consisting in the fact that, in order to ensure a sufficiently large number of resonating nuclei on the surface of the solid (it is necessary to have at least 10^{17} nuclei per cm^2 when the probability of the Mössbauer effect $f' \simeq 0 - 0.3$), it is necessary to choose systems with high surface areas, amounting to hundreds of square metres per gramme. The surface density of atoms in a monomolecular layer is about 10^{15} nuclei per cm^2. However, it is possible to observe the effect for surface densities smaller by a factor of tens and hundreds (10^{13}–10^{14} nuclei per cm^2) if one uses as the test object a surface source of resonance γ-radiation, for example by depositing cobalt-57 nuclei on the test surfaces. Then the measurement of the spectra with the required statistical accuracy is determined solely by the duration of the experiment. Experiments where the test substance is employed as an absorber are simpler to perform and are more widely carried out. However, in many cases, for example in the study of the properties of atoms located on crystal boundaries, it is necessary to deposit radioactive nuclei on the surface investigated.

The necessity for the presence on the surface of a sufficiently large number of resonating nuclei in order that the Mössbauer effect may be observed naturally imposes limitations on the application of Mössbauer spectroscopy, particularly in the study of adsorption and catalysis at low surface coverages and also in the study of the surface of single crystals.

The characteristics of the results in the fields enumerated above are dealt with below.

II. PHENOMENA ON THE SURFACE OF SOLIDS

1. Atomic Vibrations on the Surface

The first theoretical calculations of Rich[3] and Maradudin[4] showed that the type of vibrations of atoms on the surface differs from that in the bulk of the solid. It was to be expected that the average of the square of the displacement of the atoms on the surface $\langle r^2 \rangle$ will be higher compared with the internal atoms and that the difference should increase with temperature. According to Rich[3], in a model comprising a cubic lattice extending to infinity at one end and in which account is taken only of the nearest neighbours, the probability of the Mössbauer effect at 90°K for the internal atoms is higher by 26% and at 284°K by 60% than for the surface atoms. Maradudin[4] drew attention to the fact that the vibrations of surface atoms are anisotropic. Thus, for the model with a cubic lattice of a central type taking into account the interactions with the nearest neighbours and the neighbours following immediately beyond them, the average of the square of displacement in a direction perpendicular to the surface exceeds by a factor of two the corresponding values for the internal atoms, while along the surface $< x^2 >$ is greater by 30% than $< x^2 >$ for internal atoms. Calculations showed that the effect of the surface extends only over five layers. Kothari[5] found by calculating the ratio of the Debye temperatures for the surface and internal layers of the cubic lattice ($\theta_{\text{eff}}/\theta_0 \simeq 0.7$) that $< r^2 >_s$ for surface atoms exceeds by a factor of two $< r^2 >_i$ for internal atoms and is almost independent of the model. Analogous results were obtained by Corciovei[6]. Clark et al.[7] calculated $< r^2 >$ as a function of the distance from the free surface of the single crystal for a face-centred cubic lattice of nickel at a high temperature. The calculations were made for (100), (110), and (111) surfaces using a model of the central type taking into account the interactions with nearest neighbours in a crystal having a thickness of 20 layers. It was esablished that $< r^2 >$ increases monotonically from the centre of the crystal to its edges.

Burton and Godwin[8] and also Suzdalev[9] noted that the nature of the anisotropy of the atomic vibrations depends significantly on whether the atoms form part of the surface layer itself, i.e. on whether they are located within the surface or whether they are distributed on top of the surface under investigation (Fig. 1).

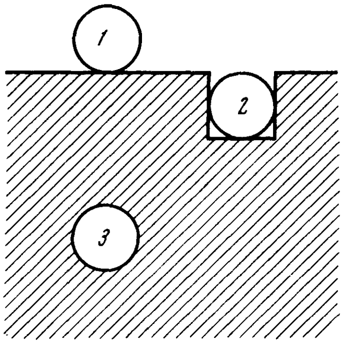


Figure 1. Atoms *on* the surface of the solid (*1*), *within* the surface (*2*), and within the solid (*3*).

Subsequently we shall use the following terminology: unless it is specified where the atoms are located, the term atoms *in* the surface will imply atoms within the surface when they are located in the interior of the surface layer and the term atoms *on* the surface will imply atoms distributed on top of the surface layer. The values of $< x^2 >$ and $< z^2 >$ on the surface have been estimated with the aid of a very simple model developed by Clark et al.[7] (Fig. 2) in which the force constants are proportional to the number of bonds between a given atom and the nearest neighbours and the next nearest neighbours (all the bonds are assumed to be of equal length and the bonds directed at right angles to the direction of the γ-radiation are disregarded). Fig. 2 presents three cases of bond location: *a* and *b*—atoms on the surface of the solid; *c* and *d*—atoms in the surface; *e*—atoms within the solid. The arrows indicate two different directions of γ-radiation. Under these conditions the force constants κ are as follows:

(*a*) $\kappa \propto 1 + 4 = 5$ bonds
(*b*) $\kappa \propto 0 + 2 = 0$ bonds
(*c*) $\kappa \propto 1 + 4 = 5$ bonds
(*d*) $\kappa \propto 2 + 6 = 8$ bonds
(*e*) $\kappa \propto 2 + 8 = 10$ bonds.

Apart from showing a general increase of $< r^2 >$ on the surface, the model permits the estimation of the anisotropic vibration of the surface atoms. For atoms *within* the surface (*c* and *d*), the amplitude of the atomic vibrations at right angles to the surface is higher than along the surface:

$$\frac{\langle z^2\rangle}{\langle x^2\rangle} = \frac{8}{5} = \frac{\varkappa_x}{\varkappa_z}.$$

On the other hand, for atoms over the surface of the solid (*a* and *b*), the amplitude of the atomic vibrations along the surface is higher than at right angles to the surface:

$$\frac{\langle z^2\rangle}{\langle x^2\rangle} = \frac{2}{5} = \frac{\varkappa_x}{\varkappa_z}.$$

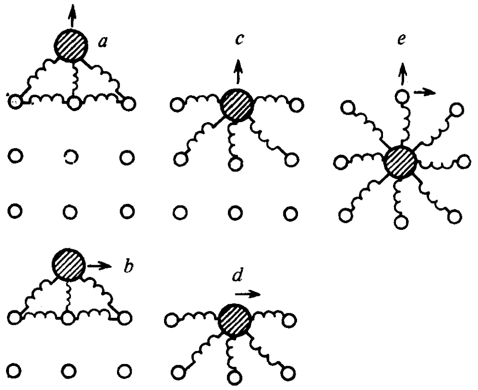


Figure 2. A model diagram illustrating the location of the atoms *on* the surface (*a*, *b*), *within* the surface (*c*, *d*), and within the solid (*e*) taking into account the interactions with nearest and next nearest neighbours.

Wallis[10] analysed the problem of the mean square velocities $< v^2 >$ of atoms on the surface of a solid and showed that on the surface these velocities are reduced, which leads to a decrease of the temperature shift of the Mössbauer spectral lines: $\delta E_D = E_\gamma < v^2 >/c^2$, where E_γ is the energy of the resonance transition.

A number of experiments have been performed to investigate the nature of the atomic vibrations on different surfaces. The type of vibrations of radioactive atoms in a planar surface of the usual kind was investigated by the surface emitter–bulk phase absorber method.

Allen[11] deposited 0.01 of a monolayer of cobalt-57 on the (100) and (111) silicon surfaces previously evacuated to 10^{-9} mmHg. The spectrum had two lines, which "merged" into one when the cobalt diffused into the silicon. For 300° and 800°K, the second-order Doppler effect resulted in a relative temperature shift $\delta E_D/E_D = 10^{-15}(-2.05 \pm 0.16)$ deg^{-1} for atoms on the surface and $\delta E_D/E_D = 10^{-15}(-2.17 \pm 0.16)$ deg^{-1} for internal atoms, which confirms the decrease of $< v^2 >$ on the surface. On the other hand, analysis of the temperature variation of the probability of the Mössbauer effect $f(T)$ for cobalt-57 atoms on the surface of silicon and within the bulk of the crystal yielded the Debye temperatures $\theta_T = 555°K$ on the surface and $\theta_T = 588°K$ within the bulk of silicon.

Results contrary to the calculations[5-9], i.e. a decrease of $< r^2 >$ on the surface relative to the bulk phase of the solid, were obtained by Bowles and Cranshaw[12], who deposited electrolytically radioactive tin on platinum. They observed an increase in the probability of the effect (a decrease of $< r^2 >$) for tin monolayers compared with individual, even very small particles. However, one should bear in mind that this type of effect might have been caused by the diffusion of tin into the bulk of platinum.

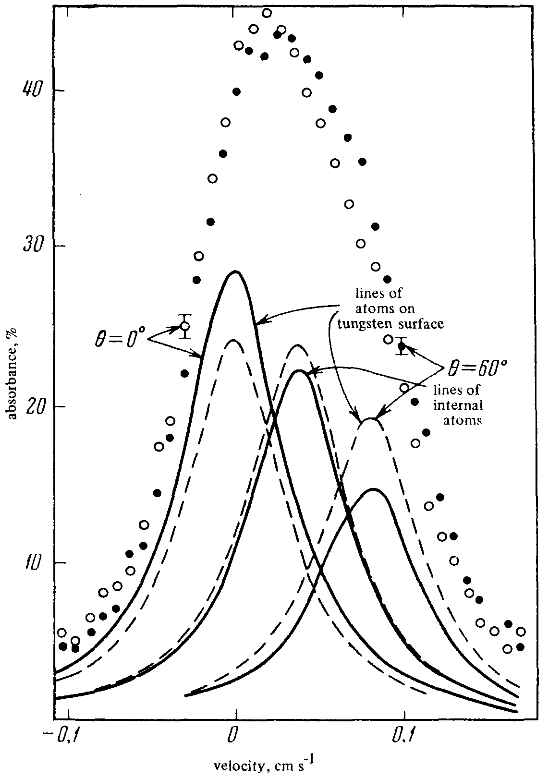


Figure 3. Spectrum of cobalt-57 on tungsten (300°K) with potassium hexacyanoferrate(II) as an absorber.

Burton and Godwin[8] investigated the cobalt-57 vibrations on single crystal and polycrystalline surfaces of tungsten and silver. Cobalt-57 was deposited on the metal by vacuum-evaporation (10^{-10} mmHg) in an amount corresponding to 0.1 of a monolayer (Fig. 3 shows the spectrum of cobalt-57 on tungsten). It is suggested that the spectrum consists of three lines—a doublet and a singlet—and that the asymmetric (due to the anisotropy of the thermal vibrations of cobalt-57 atoms) doublet is caused by cobalt-57 atoms on the surface of tungsten (as on silicon[11]), while the singlet corresponds to the cobalt which had diffused into the bulk of tungsten. Later it was found that $< r^2 >$ for atoms on the surface of tungsten increases relative to $< r^2 >$ for internal atoms and that the cobalt-57 vibrations on the surface are anisotropic:

$$\frac{\langle x^2\rangle_s}{\langle z^2\rangle_s} = 1.9 \pm 0.4 \quad \text{and} \quad \frac{\langle x^2\rangle_s}{\langle z^2\rangle_i} = 2.5 \pm 0.5.$$

Since $< x^2 > \; > \; < z^2 >$, here the cobalt atoms are located on the tungsten surface and not *within* the surface. For cobalt-57 atoms on the surface of silver, it was found[8] that $< r^2 >_s \; < \; < r^2 >_i$. The result is contrary to the usual increase of $< r^2 >$ on the surface. It is also contrary to the measurements of the Debye temperatures of the surface and internal silver atoms by diffraction of slow electrons[13] with the electron energy varied from 40 to 240 eV. Jones et al. obtained a value for $< z^2 >$ on the surface of silver twice as high as for internal atoms. Therefore the results of Burton and Godwin[8] are probably associated with the formation on the surface of silver of highly dispersed cobalt-57 and the effect of its intrinsic properties and not that of the surface of silver.

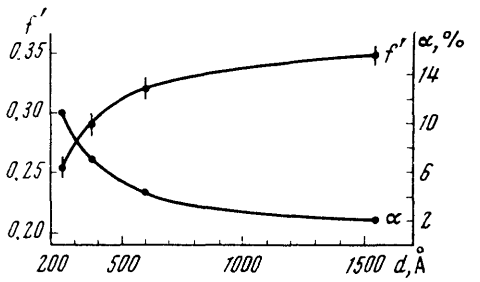


Figure 4. Variation with particle size of the probability of the Mössbauer effect f' and the specific surface α of particles of highly dispersed β-tin (77°K).

The use of large surface areas permits the study of atomic vibrations on the surface also with the aid of the bulk-phase emitter–surface absorber method. Thus the vibrations of atoms in tin dioxide on the surface of highly dispersed tin with a particle size of 300 Å were investigated[14] and a marked decrease of the probability of the Mössbauer effect compared with the probability for the usual tin dioxide was observed. The probability f' approached the normal value when the particles were fully oxidised. In another experiment[15] a study was made of the variation of f' and correspondingly of $< r^2 >$ for non-oxidised β-tin particles with $d = 250$ and 370 Å and $d = 650$ and 1550 Å. A decrease of f' with decrease of particle size was observed. Fig. 4 presents the function $f' = f'(d)$ and the variation of the specific surface $\alpha = f(d)$. The Debye temperature θ_D decreases from 140°K for $d = 1550$ and massive specimens to 120°K for $d = 250$ Å. For five surface layers, estimates yield $\theta_D = 100°K$. A decrease of f' was also observed for small tungsten particles by Roth and Hörl[16], although it was much smaller than might have been expected: $f' = 0.57$ for particles with a diameter of 30 Å and $f' = 0.61$ for particles with a diameter of 1 μm.

Van-Wieringen[17] noted that the vibrations of surface atoms are influenced by the matrix in which the dispersed particles are distributed. Thus, depending on the matrix,

f' ranging from 0.43 after incorporation in a matrix to 0.31 after preparation of a suspension in acetone and compression between two plates was obtained for Fe_2O_3 with a particle size of 30 Å.

In experiments with particles dispersed to an even greater extent, the nature of the vibrations of atoms on the surface is of course obscured by the vibrations of atoms within the particles.

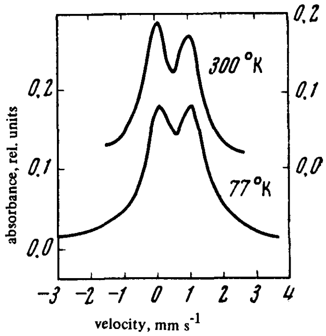


Figure 5. Spectrum of iron on the surface of η-Al_2O_3 at different temperatures.

A number of studies on the dynamics of the motion of surface atoms have been made under conditions where the Mössbauer atoms were sorbed on a large surface area. Such investigations were begun by Flinn et al.[18] with iron atoms on the surface of η-alumina and were followed by the present authors' experiments with tin on the surface of silica gel[19].

Spectra of iron, which is probably present in the form of Fe_2O_3 on the surface of alumina, are presented in Fig. 5. A striking feature is the asymmetry of the quadrupolar spectrum of Fe^{3+} on alumina, which is particularly pronounced at 300°K: $A = 0.94 = I_{3/2}/I_{1/2}$, where A is the ratio of the intensity of the doublet lines. This asymmetry, as well as the asymmetry observed in the study by Burton and Godwin[8] already noted above, is due to the anisotropy of the atomic vibrations on the surface. Assuming that the asymmetry of the components of the quadrupolar splitting is caused by the anisotropy of the probability of the Mössbauer effect (the Gol'danskii–Karyagin effect), Suzdalev et al.[18] found that $< z^2 > - < x^2 > = 10^{-18}$ cm². It was suggested that the electric field gradient is positive, i.e. the iron atoms are incorporated in the surface layer of the alumina lattice ($< z^2 > > < x^2 >$), in contrast to cobalt-57 on the surface of tungsten[8]. Generally speaking, in order to determine the sign of the electric field gradient, it is necessary to employ a single-crystal surface. Then, knowing the angle between the crystal field gradient (perpendicular to the surface) and the direction of the γ-beam, it is possible to determine unambiguously the sign of the crystal field gradient from the quadrupolar spectrum and hence the nature of the asymmetric vibrations.

The quadrupolar spectrum observed in studies[19,20] on tin (in the form of SnO) on the surface of a zeolite or silica gel with a pore diameter of 120 Å was also found to be asymmetric (Fig. 6). The asymmetry increased with temperature. Since in these experiments absolute values of f' were obtained, it proved possible to determine not only the difference $< z^{-2} > - < x^2 >$ but also each component separately: $< x^2 > = 0.46 \times 10^{-18}$ cm² and $< z^2 > = 1.76 \times 10^{-18}$ cm² at 210°K. Thus tin atoms are located within the surface layer of silica gel and the mean square of the displacement in a direction perpendicular to the surface of the globule exceeds by a factor of four the mean square of the displacement along the surface of the globule.

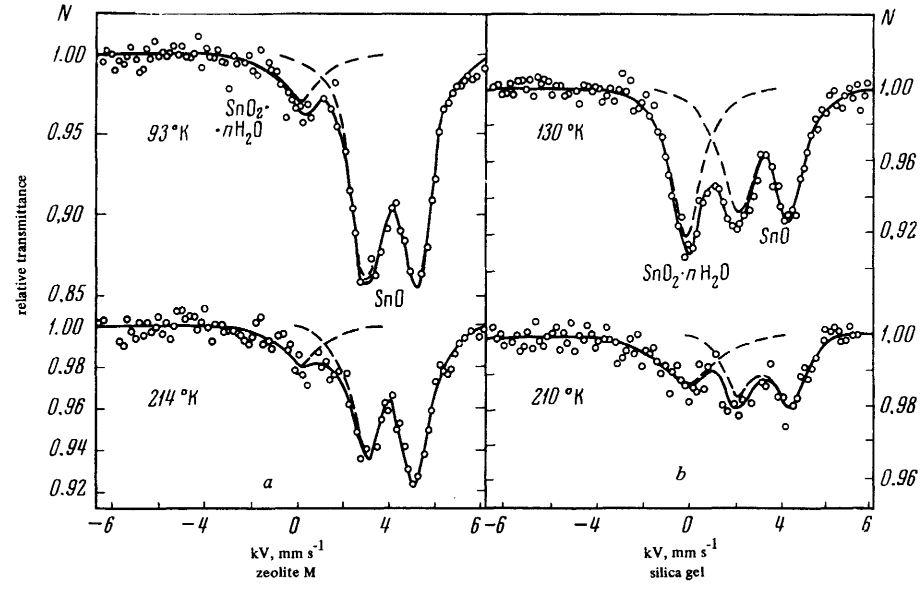


Figure 6. Spectrum of tin on the surface of a type M zeolite (mordenite) (*a*) and coarsely porous silica gel (*b*) at different temperatures. The left-hand line corresponds to $SnO_2.nH_2O$ and the two right-hand lines to SnO.

The temperature variation of the anisotropy of the atomic vibrations on the surface has been investigated theoretically and experimentally[20]. Silica gel and a zeolite with tin atoms on the surface were studied. When the Sn^{2+} ion on the surface was treated as a harmonic oscillator, a relation $A = f(T, \gamma)$ (γ is a parameter associated with the difference between the squares of the vibration frequencies of tin atoms in two directions at right angles) suitable for calculations was obtained:

$$A(T) = \frac{\int_0^1 (1+u^2)\exp(-\gamma T u^2)\,du}{\int_0^1 (^5/_3 - u^2)\exp(-\gamma T u^2)\,du}\,(u^2 = \cos^2\theta);\quad \gamma = \frac{\varkappa^2 k}{M}\left(\frac{1}{\omega_1^2} - \frac{1}{\omega_2^2}\right),$$

where κ is the wave number, M the mass of the particle, and θ the angle between the normal to the surface and the direction of the γ-ray beam. Fig. 7 presents the calculated values of $A = f(T)$ for different γ and shows satisfactory agreement between the experimental points and the calculated curve corresponding to $\gamma = 0.0045$ and $1/\omega_1^2$ and $1/\omega_2^2 = 4.5 \times 10^{-27}$ s^{-2}. This shows that the Sn^{2+} ion vibrates "along" the surface as a harmonic oscillator weakly interacting with its neighbours.

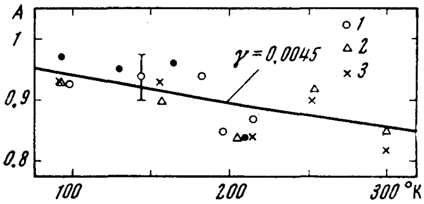


Figure 7. Temperature variation of the asymmetry of the quadrupole splitting lines of SnO on the surface of coarsely porous silica gels (*1*), a silica gel with fine pores (*2*), and a zeolite (*3*).

An important problem is also the elucidation of the effect of pore dimensions on the type of atomic vibrations, i.e. whether there are differences within the type of atomic vibrations on a surface close to the usual planar type and on a surface with an appreciable curvature. The vibrations of tin atoms on the surface of coarsely porous silica gel with pore dimensions of 120 and 250 Å, which is almost planar a relation to the tin atom and in silica gels with fine pores and a zeolite with nearly molecular pore dimensions were compared in the present authors' investigation[20].

Experiments on the temperature variation of the asymmetry of the vibrations showed that this kind of difference in pore dimensions does not affect the nature of the anisotropy of the vibrations but does influence the absolute values of $< r^2 >$. Probably $< r^2 >$ increases uniformly in all directions in the coarsely porous silica gels. In systems with pores having molecular radii, smaller values of $< r^2 >$ were observed for tin atoms on the surface than in coarsely porous systems, particularly at high temperatures.

However, the principal differences between the coarsely porous specimens and those having fine pores are shown in the diffusion pattern of tin atoms along the surface.

In conclusion and summarising the results obtained in this section, we may note that all the theoretical calculations associated with the increase of $< r^2 >$ and the anisotropy of the vibrations of atoms on the surface are largely consistent with the experimental data. An exception is the decrease of $< r^2 >$ and the corresponding increase of the probability of the Mössbauer effect for tin atoms on the surface of platinum[12] and for cobalt atoms on the surface of silver[8] (see in addition the remarks on pp. 610–611). We shall return to the discussion of this anomaly in the section dealing with the effect of the surface on the phonon spectrum of small particles.

2. Surface Diffusion

The diffusion of Mössbauer atoms may lead to an appreciable broadening of the observed lines in the γ-resonance spectra compared with their natural width. In solids the diffusion coefficients of atoms do not exceed 10^{-12} cm^2 s^{-1}, which gives rise to a widening significantly smaller than the natural line width. At the same time in liquids the diffusion coefficient is of the order of 10^{-5} cm^2 s^{-1} and therefore the experimental width exceeds by many powers of ten the natural width. However, in liquids there is no Mössbauer effect and therefore the widening of the experimental line cannot be observed. On the surface cases probably occur where the diffusion coefficients are in the intermediate range and therefore diffusion has a marked effect on line width in the Mössbauer spectra. The most probable mechanism of surface diffusion involves abrupt transition of atoms from one position to another. Then the widening of the line is determined by the Singwi–Sjolonder formula[21]: $\Delta\Gamma = 2h/\tau$ (h is the Planck constant, $\tau = l^2/6D_1$ the localisation time, l the distance between the localisation centres, and D_1 the coefficient of diffusion by "jumps"). For example in the case of iron τ must be less than 10^{-7} s^{-1} (for $l = 3 \times 10^{-8}$ cm) and D_1 must be greater than 10^{-9} cm^2 s^{-1} for appreciable widening to be observed. There exists yet another mechanism which operates, for example, in polymolecular adsorption, mainly continuous diffusion which leads to a widening

$$\Delta\Gamma = \frac{2E_\gamma^2 D_2}{\hbar c^2},$$

where E_γ is energy of the nuclear order of magnitude and D_2 the coefficient of continuous diffusion. The widening of the Mössbauer line is more sensitive to this type of diffusion; here it is sufficient for D_2 to exceed 10^{-11} cm^2 s^{-1}.

In a number of studies the surface diffusion of tin and iron atoms on the surfaces of silica gel[19,20], zeolites[22], and ion-exchange resins[23] was investigated. Tin was physically sorbed on the surface of silica gels and zeolites in the form of $SnO_2.nH_2O$. The temperature variation of line half-width was investigated. It was shown that in coarsely porous silica gels there is a phase transition in the adsorption layer at 200°K involving "jumps" by $SnO_2.nH_2O$ groups from one localised position to another, which leads to a marked line widening and a decrease of the probability of the Mössbauer effect. In silica gels with fine pores and in zeolites a phenomenon of this kind was not observed (with the exception of a slight widening at a higher temperature) probably because of the stronger bonds formed by $SnO_2.nH_2O$ with the surface in pores of molecular dimensions (Fig. 8). It was of interest to estimate the activation energy for the diffusion of the $SnO_2.nH_2O$ groups. Using the expression $\tau = \tau_0 \exp(Q/RT)$, the activation energies were found to be $Q \simeq 3.5$ kcal $mole^{-1}$ for coarsely porous silica gel and 7.5 kcal mole^{-1} for silica gels with fine pores[19]. A study was also made of the diffusion of Fe^{2+} ions in the pores of zeolites of type Y and M and in KU-2 ion-exchange resin[22-24]. An increase of temperature resulted in a widening of the Fe^{2+} line, which led to the estimates $\tau = 3.9 \times 10^{-8}$ s and $D = 0.7 \times 10^{-8}$ cm^2 s^{-1} at 213°K and $\tau = 2.2 \times 10^{-8}$ s and $D = 10^{-8}$ cm^2 s^{-1} at 300°K for the diffusion of Fe^{2+} in the channels of zeolite M (mordenite) in the presence of n-hexane molecules. The numerical values of τ and D are consistent with the data of Barrer et al.[25]

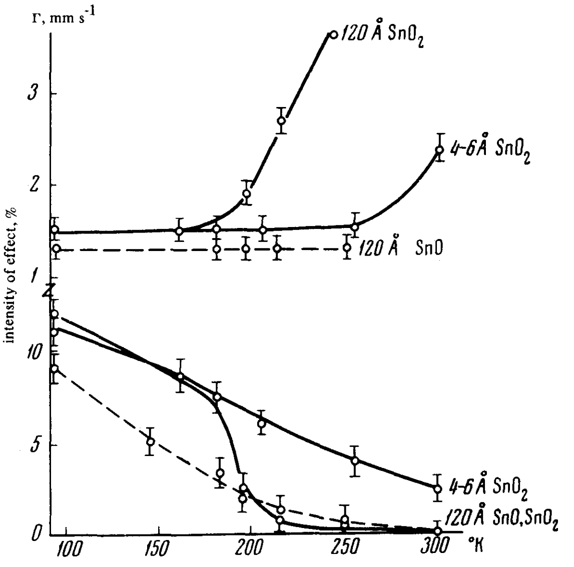


Figure 8. Temperature variation of the effect (%) and line width (Γ, mm s^{-1}) for tin on the surface of silica gels with pore diameters of 120 and 4–6 Å.

The diffusion of Fe^{2+} cations in the ion-exchange resin with sorbed hexane and water was investigated in greater detail (Fig. 9). The activation energy for diffusion in hexane was found to be 5 kcal mole^{-1} and for diffusion in water only about 1 kcal mole^{-1}, the diffusion of hexane occurring after its fusion (190°K). The lower activation energy for the diffusion of Fe^{2+} in KU-2 resin when water is present in the pores is probably due to the polarity of water molecules, which weakens the bond between the iron(II) cation and the resin lattice.

3. Electronic State of Atoms on the Surface

In this section we shall consider the problems of the type of electronic bonds involving the atoms on the surface compared with the bonds for atoms within the solid. It is difficult to expect that the valence of atoms will change on transfer to the surface. However, one may expect changes in the ionic character of the bond or in the mutual screening of the *s*, *p*, and *d* electrons. This might lead to a change of the isomer shift in the Mössbauer spectra of surface atoms. Such changes have not, however, been observed so far. Zeolites, where the pore dimensions are nearly molecular, appear to be an exception. Thus the isomer shift δE_I for Sn^{2+} in the type M zeolite[20] relative to SnO_2 increased from 2.7 mm s^{-1} (a value characteristic of the usual polycrystalline SnO) to 3.2 mm s^{-1} [henceforth the isomer shifts (IS) for tin will be reckoned relative to IS for tin dioxide and for iron relative to IS for sodium nitroprusside]. The above increase in isomer shift may be attributed, according to Donaldson and Senior[26], to a decrease of the contribution of the crystal field, which is very powerful in the normal compound SnO and leads to the mixing of the *s* and *p* electronic orbitals, thereby diminishing the isomer shift [i.e. the signal $|\Psi(0)|^2$]. Moreover, the atoms on the surface should be subject to the crystal field of lower symmetry compared with atoms within the bulk of the solid. This must lead to high electric field gradients the direction of which may be reasonably assumed to be perpendicular to the surface.

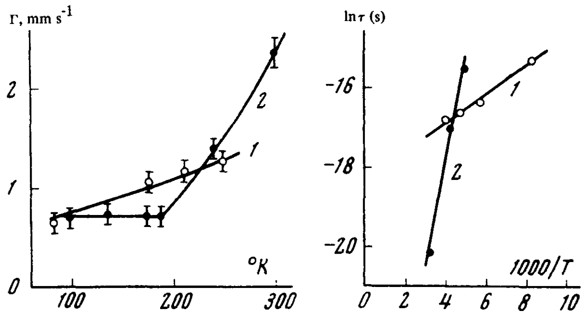


Figure 9. Increase in line width Γ for Fe^{3+} in an ion-exchange resin with increasing rate of diffusion of iron and the variation of the logarithm of the ion localisation time (ln τ) with temperature: *1*) water; *2*) n-hexane.

This may result in an increased quadrupole splitting in the Mössbauer spectra in the vicinity of the surface. Indeed in all the experiments the quadrupole splitting (QS) for surface atoms ΔE_Q increased and sometimes appeared even when the atoms within the bulk of the solid gave rise to no splitting at all. Thus Burton and Godwin[8] obtained $\Delta E_Q = 0$ for cobalt-57 atoms within a tungsten support and $\Delta E_Q = 0.78$ mm s^{-1} for cobalt-57 atoms on the surface of tungsten. For iron on the surface of η-alumina in the form of Fe_2O_3, Flinn et al.[18] observed an increase of QS from 0.3 mm s^{-1}, characteristic of the normal state of Fe_2O_3, to 1.06 mm s^{-1}. A similar increase of QS in consequence of the more important role of the surface was observed by Rumbic et al.[27] for highly dispersed Fe_2O_3 particles with dimensions of about 100 Å. Fig. 10 shows an increase of ΔE_Q as the particle size diminishes. Similar calibrations may be employed to estimate the particle size. An increase of QS for SnO on the surface to 2.1 mm s^{-1} compared with the normal value $\Delta E_Q = 1.3$ mm s^{-1} has been observed[19,20]. Finally the most striking feature is the occurrence of quadrupole splitting (ΔE_Q = 0.6 mm s^{-1}) in the Mössbauer spectrum of a metallic iron film 4.6 Å thick[28].

Continuing the discussion of the electronic state of atoms on the surface, we shall now deal with the magnetic properties.

4. Magnetic Properties of Atoms on the Surface

According to classical concepts, ferromagnetism is essentially a three-dimensional effect associated with the finite volume of matter[29]. Therefore magnetic ordering should not be expected for surface atoms. It is now known, however, that a hyperfine structure in Mössbauer spectra may arise not only in magnetically ordered systems but also in paramagnetic materials, provided that the relaxation time of electron spin is comparable to the precession time of the nuclear spin of the resonating atom[30,31]. Both spin–spin and spin–lattice relaxation is involved. At low concentrations of paramagnetic ions it is possible to ensure that the relaxation is wholly of the spin–lattice type. Since the paramagnetic ion on the surface is linked to the lattice less strongly than within the bulk of the solid, an increase in the spin–lattice relaxation time may be expected for surface atoms together with the appearance of a hyperfine structure in the Mössbauer spectra for such atoms, while those in the bulk phase do not give rise to a hyperfine structure.

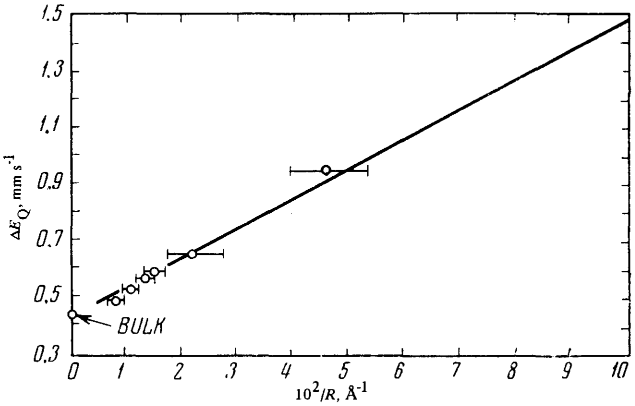


Figure 10. Variation of ΔE_Q with the reciprocal of the radius of highly dispersed Fe_2O_3.

The first result of this kind was obtained in the study of the relaxation of electron spin in ion-exchange resins[32]. The concentration of iron was extremely low (1.6 wt.%). A sharp increase in spin–lattice relaxation time was observed after the adsorption of water by this type of system. Fig. 11 presents the spectra of Fe^{3+} in a sulphonated ion-exchange resin before and after the adsorption of water. Water weakens the bond between Fe^{3+} and the resin lattice and increases the spin–lattice relaxation time τ. It was also noted that the increase of τ is accompanied by a decrease of the electric field gradient whenever it is caused by the withdrawal of the ion from the resin lattice and an increase in the symmetry in charge distribution occurring when the Fe^{3+} ion is surrounded by water molecules. We may note that, although the bond between the surface ion and the lattice is weakened, which leads to an increase of τ, the presence of high gradients may lower it (for two-phonon processes, which are responsible for relaxation in the case under discussion[32], the probability of spin–lattice relaxation is proportional to the square of the distance between the Stark levels, i.e. as a result of the increase of the electric field gradient and of the distance between the Stark doublets, the probability of relaxation increases and the relaxation time falls). Therefore Fe^{3+} ions in an ion-exchange resin exist under conditions more favourable for high relaxation times than in the case where Fe^{3+} is located on the usual type of surface, because the bond with the lattice is weak as on a normal surface but the electric field gradient is much weaker.

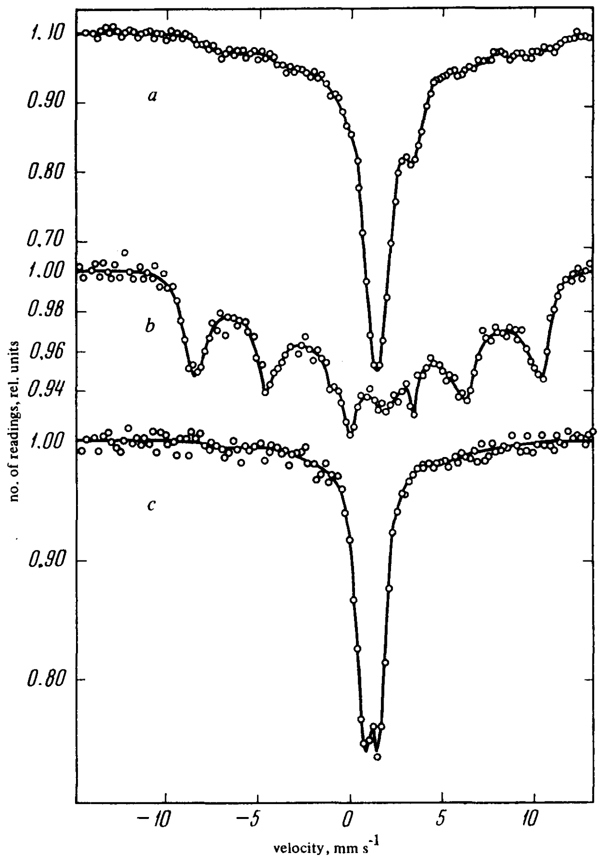


Figure 11. Spectra of a sulphonated resin with Fe^{3+} before (*a*) and after the adsorption of water (*b*) and of a phosphorylated resin after the adsorption of water (*c*) at 80°K.

Fig. 12 shows the temperature variation of the spin–lattice relaxation time for the Stark doublet $S_Z = \pm 5/2$ obtained experimentally and calculated using the Debye and Einstein approximations for $\theta_F = 325$°K and $\theta_D = 400$°K respectively[32]. θ_D determined in the usual way from the temperature variation of the probability of the Mössbauer effect is approximately the same. The vibration frequencies ($k\theta/\hbar$) of the lattice with Fe^{3+} obtained in this way are very high. Probably such high-frequency vibrations tend to average out the electric field at the Fe^{3+} ions and thereby retard the relaxation.

The effect of the immediate environment of the paramagnetic ion on the nature of spin–lattice relaxation has been investigated[33]. By sorbing different amounts of water molecules in an ion-exchange resin, it has been shown that the hyperfine structure is fully formed and the maximum relaxation time $\tau = 2.4 \times 10^{-8}$ s is observed when there are six molecules of water for each iron ion. Then each spectrum corresponding to an intermediate average number of water molecules (n_{av}) per Fe^{3+} ion does not arise by a simple superposition of spectra with different values of n (for example the hyperfine structure due to four water molecules is not a result of the superposition of spectra with zero, 1, 2, 3, 4, 5, and 6 water molecules for each Fe^{3+} ion). This is evidence that the spectra of partly hydrated resin are observed. It was found that under certain conditions it is possible to observe the hyperfine structure due to Fe^{2+} in the ice lattice, for example in a strongly acid medium with an excess of chlorine atoms relative to iron (0.02 M $FeCl_3$ in 4.5 M hydrochloric acid). Since in the presence of between one and six water molecules per Fe^{2+} ion the ice lattice is not as yet observed in the ion-exchange resin (the distance between the ion-exchange centres is about 20–30 Å), one may conclude that the spin–lattice relaxation time is determined by the nearest environment of Fe^{3+}, i.e. the water molecules and not the entire ice lattice. Thus ion-exchange resins are very suitable for the investigation of the effect of various ligands on the relaxation of electron spin of the Fe^{2+} ion.

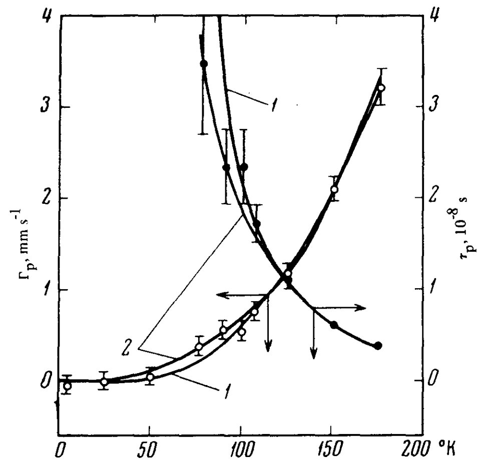


Figure 12. Temperature variation of the spin–lattice relaxation time of the Fe^{3+} ion and the width of the extreme spectral lines. The continuous curves were calculated using the Einstein (curve *1*) and Debye (curve *2*) approximations.

Widely occurring phenomena, such as adsorption and catalysis, are directly associated with the electronic and magnetic properties of atoms on the surface.

5. Elementary Steps in Adsorption. The Chemistry of Surface Compounds

The interaction of atoms or molecules with the surface of a solid leads, on the one hand, to a change in the state of the adsorbent atoms on the surface and, on the other hand, also in the properties of the sorbed groups themselves, i.e. the properties of the adsorbate. This entails a change in both the dynamic and electronic properties of atoms, which should be reflected in the Mössbauer spectra. The method employed in such experiments involves the use of an absorber of resonance γ-quanta as the adsorbate or the adsorbent. In order to obtain the Mössbauer spectra, it is necessary to have an adsorbent or adsorbate with atoms containing resonating nuclei and to follow the changes in the state of either the surface of the solid or of the sorbed substances. In some cases it is possible to follow both provided that the adsorbent and the adsorbate contain resonating nuclei. The application of Mössbauer spectroscopy makes it possible to distinguish physical sorption and chemisorption.

Since the bond between the surface atoms and the adsorbate is weaker in physical sorption than in chemisorption, the probability of the Mössbauer effect should be lower in physical sorption and the temperature variation more pronounced than in chemisorption, particularly at high temperatures. A distinction of this type was made[19] for $SnO_2.nH_2O$ physically sorbed on the surface of silica gel and Sn^{2+} chemisorbed as SnO. For physical sorption (Fig. 8), a more pronounced temperature variation of the probability of the effect was observed than in the case of chemisorption.

Moreover, since chemisorption entails a change in the electronic structure of both the adsorbent and the adsorbate, a radical rearrangement of the Mössbauer spectrum can be observed—with a change in the isomeric shift and quadrupole splitting, which is not a characteristic feature of physical sorption.

Physical sorption was investigated as a function of the number of monolayers of sorbed tin tetrachloride molecules on silica gel and a study was made of systems with pores whose size ranged from several hundred of angstroms to nearly molecular dimensions[20].

After the adsorption of $SnCl_4$ on silica gel, the form of the spectra hardly changed; the smallest decrease of the isomeric shift was observed in sorption on silica gel with nearly molecular pore dimensions.

A significantly different temperature variation of f' was observed on silica gels with fine pores for $SnCl_4$ sorbed in amounts less than one monolayer and in amounts corresponding to about five layers. The temperature variation of f' was much more pronounced for a large number of $SnCl_4$ layers than for a small amount, which is evidence that in physical sorption the $SnCl_4$ molecules are much more strongly bound to the surface of silica gel than to one another. For systems with fine pores, such a difference between the characteristics of the spectra with different numbers of sorbed layers is less marked.

The adsorption of water in ion-exchange resins was also investigated on the basis of changes in the probability of the Mössbauer effect[23]. The adsorption of water is known to lead to swelling of the resins and to a change in the state of the ion. KU-2 and KB-4 cation-exchange resins with the cations Fe^{3+} and Fe^{2+} and AV-16 and AV-17 anion-exchange resins with the anions $[Fe(CN)_6]^{3-}$ and $[Fe(CN)_6]^{4-}$ were investigated. All the ion-exchange resins were organic polymers or copolymers with functional groups capable of ion exchange. In KU-2 and KB-4 cation exchangers these are $R{-}SO_3^-$ and $R{-}COO^-$ groups respectively, in AV-16 anion exchangers these are the R_2NH, R_3N, and R_4N^+ groups, while AV-17 anion-exchange resins contain R_4N^+ groups. Whereas in KU-2 sulphonated resin the Mössbauer effect disappeared as a result of the adsorption of water, in KB-4 resin it persisted after such adsorption. This result is associated with the dissociation of water molecules and Fe^{3+} ions from the lattice of KU-2 sulphonated resin. Analysis shows that[24] (Fig. 13) three water molecules for each Fe^{2+} ion are required for complete dissociation of the iron cation from the SO_3 group in the resin and the disappearance of the Mössbauer effect. It has also been shown that the Mössbauer effect does not decrease because part of the ions are dissociated while others are not. For small amounts of water (up to three molecules per ion), $\langle r^2 \rangle$ increases and f' falls but Fe^{3+} ions remain localised (undissociated), while in the presence of a large amount of water Fe^{3+} ions cease to be localised, which leads to their diffusion by abrupt transitions ("jumps") from one localised position to another and the complete disappearance of the Mössbauer effect with simultaneous widening of the line due to diffusion. On the basis of the literature data[24,33] and the finding that the lines in the Mössbauer spectrum do not become wider when the average amount of water increases up to three molecules per Fe^{3+} ion while in the case of more pronounced hydration the lines do widen with increase of temperature owing to diffusion, one may conclude that the variance of the number of water molecules per metal ion is small.

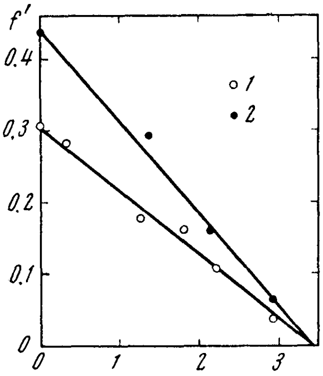


Figure 13. Decrease of the probability f for Fe^{3+} in a sulphonated ion-exchange resin after the adsorption of different numbers of water molecules per sulpho-group (300°K): *1*) resin with 12% of divinylbenzene as a cross-linking agent; *2*) non-swelling resin.

The effect of the degree of cross-linking of the sulphonated resin on the melting point of ice in the resin, at which the Mössbauer effect disappears, has been investigated[24]. It was found that an increase in the degree of cross-linking entails a shift of the point of disappearance of f' towards higher temperatures, probably due to the concentration of Fe^{3+} ions in the vicinity of the exchange centres. In the carboxylic acid KB-4 resin and in a phosphonic acid resin[32] there is probably an increase of $\langle r^2 \rangle$ for Fe^{3+} ions and a decrease of f' but not complete dissociation of Fe^{3+} from the COO^- and CO_2^- groups.

Krizhanskii and coworkers[34] and Mackey and Collins[35] studied ion-exchange resins with the anions $[SnCl_6]^{2-}$ and iron cations respectively. Mackey and Collins found that in sulphonated cation exchangers there are two types of Fe^{3+} cations, with normal and anomalously high values of ΔE_Q ($\Delta E_Q = 1.6$ mm s^{-1}). They suggested that lines with high quadrupole splitting arise as a result of the hydrolysis of Fe^{3+} and the formation of hydrated dimers with an excess electron. However, one should bear in mind that the adsorption of water results in the appearance of a magnetic hyperfine structure in the spectrum[32], which covers a wider range of velocities than was examined by Mackey and Collins[35] and therefore the lines attributed to anomalous quadrupole splitting might have been simply part of a magnetic hyperfine structure, which had not been detected. Delgass and Boudart[36] observed a change in the probability of the Mössbauer effect in a type Y zeolite after the adsorption of water. Probably the decrease of f' is associated in this case with the increase of $\langle r^2 \rangle$ for Fe^{3+} ions, as in ion-exchange resins[24], and not with the fact that part of the ions are dissociated and others are not, as suggested by Delgass and Boudart[36]. The adsorption of water can lead to an increase in the spin–lattice relaxation time too, as noted earlier[32,33] for Fe^{3+} in a sulphonated ion-exchange resin. An increase in spin–lattice relaxation time for Fe^{3+} ions was also observed after the adsorption of water, methanol, n-hexane, and tetramethyltin in zeolites of types Y and M containing Fe^{3+}, with a consequent asymmetry in quadrupole splitting of the Blume type[22,37], associated with the effect of electron spin relaxation on the Mössbauer spectra. Moreover, the adsorption of the substances enumerated above also led to the appearance of new lines in the spectrum, corresponding to divalent ions[22]. Since it is difficult to suppose that the adsorption of substances such as, for example, n-hexane leads to the reduction of iron in the zeolite, the appearance of the new lines may be attributed to the localisation in the zeolite channels of divalent iron ions which had been non-localised before adsorption and which had not given rise to a Mössbauer spectrum. The hypothesis of the presence of two types of cations in zeolites has been put forward previously by Dubinin[38] and Neimark[39]. The weak bond between Fe^{2+} and zeolite is characterised by the diffusion of the cation along the zeolite channel, which is reflected in a strong temperature-induced widening of the Fe^{2+} line.

All the previous experiments were related in one way or another to physical sorption, i.e. did not lead to a radical change in the spectrum. It is extremely interesting to investigate chemisorption by following the changes in Mössbauer spectra. When iron-containing zeolites were studied[22], the spectra of the $(CH_3)_4^{119}Sn$ adsorbate were also obtained and the presence of a bond between tetramethyltin molecules and $[AlO_4]^-$ was demonstrated. Similar spectra were obtained by Karasev et al.[40] in a study of the chemisorption of $(CH_3)_4Sn$ on alumina.

Morice and Rees[41] studied the adsorption of water and methanol on zeolites of types Y and M evacuated at 360°C. The adsorption of water or methanol resulted in a marked change in the spectra, the disappearance of certain forms of iron from the zeolite, and the appearance of others. It is at present difficult to identify all the forms of iron in the zeolites in experiments of this kind before and after adsorption.

The adsorption of polar solvents in zeolites alters the quadrupole splitting, the change being different for the Fe^{3+} and Fe^{2+} ions (see, for example, Refs. 22–24)—the quadrupole splitting increases for Fe^{2+} and decreases for Fe^{3+}. The results for Fe^{2+} probably indicate the formation of new chemical bonds, i.e. refer to chemisorption, while those for Fe^{3+} are related to water molecules surrounding the hydrated Fe^{3+} ion and diminishing the electric field gradient.

The experimental results for the chemisorption of iron(III) oxide on SiO_2 or Al_2O_3 carriers are easier to interpret. In this connection, we shall consider the studies of the oxidation and reduction of surface atoms. Hobson et al.[42,43] investigated the reduction of iron(III) oxide (Fe_2O_3) with different particle sizes on alumina and silica. The initial spectrum corresponds to highly dispersed Fe_2O_3 and reveals the very high value $\Delta E_Q = 1.87$ mm s^{-1}, which constitutes a record. Using the variation of the quadrupole splitting with particle size (Fig. 10) and extrapolating it to smaller particle sizes, Hobson and coworkers[42,43] estimated the dimensions of their own particles (about 20 Å). After the chemisorption of hydrogen, the spectra changed sharply. The authors postulate the presence of two forms of iron—the reduced, divalent iron with $\delta E_I = 1.35$ mm s^{-1} and $\Delta E_Q = 1.65$ mm s^{-1} corresponding to the usual ionic iron compounds and trivalent iron with $\delta E_I = 1.02$ mm s^{-1} and $\Delta E_Q = 0.98$ mm s^{-1}. For these particle sizes, reduction to metallic iron does not take place. The reduction of larger Fe_2O_3 particles on alumina[43] gave a mixture of metallic and divalent iron. The authors conclude that the smaller particles of silica gel cannot be reduced to metallic iron at all.

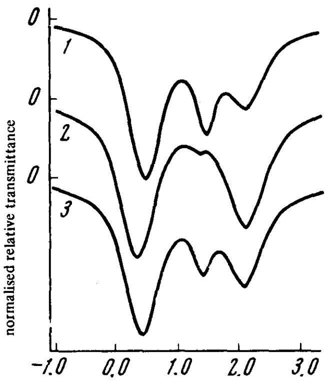


Figure 14. Spectra of iron on silica before (curve *1*) and after (curve *2*) chemisorption of ammonia.

Hobson studied the chemisorption of ammonia on iron(III) oxide obtained by preliminary heat treatment of silica gel impregnated with iron(III) nitrate[44]. Fig. 14 shows the spectra before chemisorption (curve *1*), after chemisorption (curve *2*), and after repeated degassing (curve *3*). The kinetic data indicate dissociative adsorption of ammonia in this system. Spectrum *3* shows the reduction of trivalent iron by ammonia, since the amine radical formed can supply electrons to the iron *d* orbital and thereby facilitate the formation of a high-spin iron(II) complex.

After the desorption of ammonia, the initial spectrum is restored[3]. These experiments characterise the change in the state of the adsorbents after chemisorption.

A series of experiments on the chemisorption of $(CH_3)_4Sn$ on silica gel and alumina were made by Karasev and coworkers[40,45], who showed that the form of the spectrum depends significantly on adsorption temperature. The spectra of freshly prepared specimens at 30°C differed sharply from those of specimens kept for 24 hours and longer in air. Fig. 15 shows the spectra of the initial $(CH_3)_4Sn$ adsorbed at 30°C on alumina and kept in air for 20 and 35 h. At an adsorption temperature of 30°C two additional peaks (curve *2*), which were attributed to the doublet of chemisorbed $(CH_3)_4Sn$, were observed in addition to the initial spectrum of tetramethyltin. The chemisorption centres are either oxygen or hydroxy-groups.

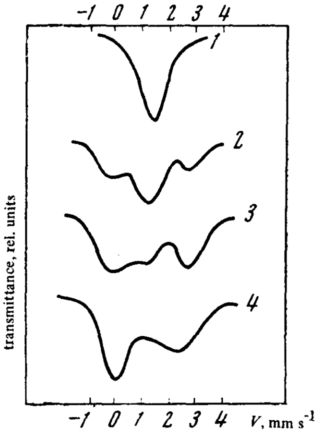


Figure 15. Spectra of $(CH_3)_4Sn$ chemisorbed on γ-Al_2O_3: *1*) initial spectrum of $(CH_3)_4Sn$ before chemisorption; *2*) after chemisorption; *3*) and *4*) after exposure to air.

The authors attribute the presence of the initial substance to physically sorbed $(CH_3)_4Sn$. When the specimen is kept for 20 h at room temperature (curve *3*), the intensity of the doublet increases. Further exposure to air leads to a radical alteration to the spectrum. Two lines appear, one of them (with $\delta E_I = 0$) is assigned to the chemisorption of $(CH_3)_4Sn$ involving the dissociation of tin–methyl bonds and the formation of a bond between the tin and oxygen atoms at the site of the aluminium vacancies; the second line is due to the bond between tin and aluminium and the surface dissociation of $(CH_3)_4Sn$. Chromatographic analysis of the gas phase over γ-alumina with adsorbed $(CH_3)_4Sn$ reveals the presence of ethane and methane, which may be attributed to the dissociative chemisorption of $(CH_3)_4Sn$.

To conclude this section, we emphasise yet again the principal results obtained in the study of the elementary adsorption steps. For physical sorption, these are (a) the observation of a more pronounced interaction of sorbed $SnCl_4$ molecules with the adsorbent than with one another; (b) the determination of the type of interaction between water molecules and iron cations in ion-exchange resins (the weakening of the bond between the cation and the lattice, dissociation in two stages, the presence of a definite number of water molecules per metal ion in the dissociation process, an increase in the spin–lattice relaxation time); (c) localisation of cations after the adsorption of molecules in the zeolite.

For chemisorption the following results were obtained: (a) the demonstration of the presence of two types of iron ions on the surface of silica gel after the chemisorption of hydrogen and the presence of a variety of forms of iron in zeolites; (b) demonstration of the adsorption of ammonia with formation of an iron(II) complex; (c) the existence of two types of active centres for the chemisorption of tetramethyltin.

6. Heterogeneous Catalysis

Two aspects of the application of Mössbauer spectroscopy in this field must be distinguished: (1) the determination of the relation between the rate and selectivity of catalytic reactions on the one hand and the electronic state of the catalyst atoms on the other; (2) the observation of intermediate complexes in catalysis.

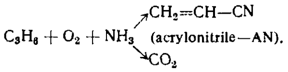
For the first aspect, it is sufficient to obtain the Mössbauer spectra of the catalysts before or after the catalytic reaction and to compare the parameters of these spectra with catalytic activity.

In order to investigate the second range of problems, it is necessary to have at one's disposal a Mössbauer proton spectrometer in which the reaction takes place directly in the zone where the spectra are recorded. Experiments of the second type have not as yet been achieved.

It is of considerable interest to investigate the relation between catalytic activity in any one reaction with parameters such as the isomeric shift and the quadrupole splitting in the Mössbauer spectrum. Probably catalytic activity should be related to both parameters and therefore in order to investigate correlations of this kind separately, it is necessary to have catalysts with variable catalytic activities and variable isomeric shifts for constant quadrupole splitting or conversely. It is simpler to vary the quadrupole splitting in a series of solid solutions for a constant isomeric shift.

The catalytic activities and selectivities of a number of iron- and tin-containing mixed oxide catalysts of the type of $X_aO_bM_cO_d$ solid solutions, where M is a Mössbauer atom and X a non-Mössbauer atom, have been compared[46]. For Fe^{3+} or Sn^{4+}, which have the symmetrical configurations $3d^5$ and $4d^{10}$, it is possible to alter the quadrupole splitting by varying X without changing the isomeric shift. The quadrupole splittings for these configurations are associated solely with the effect of the crystal field on these ions.

The oxidative ammonolysis of propene on catalysts of this kind has been investigated in this way. The reaction may take place via two pathways:



$$C_3H_6 + O_2 + NH_3 \begin{cases} \nearrow CH_2{=}CH{-}CN \text{ (acrylonitrile—AN).} \\ \searrow CO_2 \end{cases}$$

The curves relating the rate of formation of acrylonitrile to quadrupole splitting for a constant isomeric shift have a maximum. Similar "bell-shaped" curves are observed for the relation between the rate of reaction and the heat of formation Q of the surface compounds. An increase in the crystal field gradient and in the distortion of the lattice leads to an increase of Q and therefore at a certain value of the quadrupole splitting the rate of formation of acrylonitrile should be a maximum.

In order to investigate the possible mechanism of the catalysis, it is, however, necessary to choose simpler reactions involving one pathway only, such as for example, the classical catalytic oxidation of carbon monoxide to carbon dioxide on iron(III) oxide. An investigation of this kind was made[47] on a highly dispersed iron(III) oxide, the results of the Mössbauer experiment being compared with the kinetic data. In order to increase the fraction of surface ions, a highly dispersed iron(III) oxide with a particle size of about 80 Å and less was employed. The Mössbauer spectrum of such particles consisted of a paramagnetic component and a component with a magnetic hyperfine structure (Fig. 16). Several modifications of this experiment have been performed: (a) catalytic oxidation of carbon monoxide to carbon dioxide with and without freezing out the reaction product (carbon dioxide); (b) chemisorption of carbon monoxide on the specimen; (c) interaction of carbon monoxide with the specimen in the absence of oxygen with carbon dioxide frozen out; (d) heat treatment of the specimen with carbon monoxide and subsequent chemisorption of oxygen. The experiments were carried out at 100°C. The spectra and the kinetic measurements lead to definite conclusions concerning the mechanism of the catalytic oxidation of carbon monoxide to carbon dioxide, in agreement with Hauffe's data[48]. After the reaction of carbon monoxide with the catalyst surface, iron(II) cations bound firmly to the surface of Fe_2O_3 appear, the state of the iron remaining unchanged after heating to 100°C. The kinetic results show that there is a complete correspondence between the amount of carbon monoxide which has reacted with Fe_2O_3 and the amount of carbon dioxide frozen out.

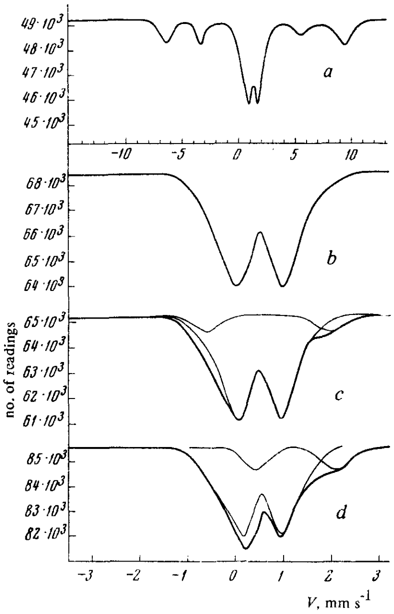


Figure 16. Spectra of iron(III) oxide in the catalytic oxidation of carbon monoxide to carbon dioxide: *a*) before oxidation; *b*) before oxidation at relatively low velocities of the source and absorber (the "paramagnetic" component of the spectrum is shown); *c*) after chemisorption of carbon dioxide; *d*) after chemisorption of carbon monoxide for measurements at room temperature.

This finding shows that the role of carbon monoxide involves in this case simply the reduction of Fe^{3+} to Fe^{2+} on the surface of the Fe_2O_3 particles without the formation of any surface compounds of carbon monoxide with iron(III) oxide. As a result, divalent iron ions appear on the surface of the particles and form a compound of the type of FeO. Indeed, the value $\delta E_I = 1.29 \pm 0.08$ mm s^{-1}, determined from the spectra, agrees with the value $\delta E = 1.32 \pm 0.06$ mm s^{-1} for the usual polycrystalline state of FeO.

However, the value $\Delta E_Q = 1.67 \pm 0.08$ mm s^{-1}, obtained for the surface compound FeO, greatly exceeds $\Delta E_Q = 0.77 \pm 0.03$ mm s^{-1} for the usual polycrystalline state of FeO. The observed increase of quadrupole splitting on the surface of iron(III) oxide may be attributed to the breakdown of symmetry in the distribution of atoms on the surface of the solid. The carbon monoxide molecules chemisorbed on the surface of Fe_2O_3 bind the oxygen of the catalyst and are desorbed in the form of CO_2 from the surface, leaving behind the Fe^{2+} ions. After the chemisorption of oxygen, the initial state of Fe_2O_3 is restored. A somewhat different process takes place after the adsorption of carbon monoxide on Fe_2O_3 (Fig. 16)—a surface compound with a fairly asymmetric configuration is formed. A similar surface compound arises when the catalytic oxidation of carbon monoxide is carried out without freezing out the carbon dioxide. When carbon dioxide is frozen out, the spectrum does not change. Probably the catalytic oxidation of carbon monoxide on Fe_2O_3 involves alternate reduction and oxidation of the catalyst. In the chemisorption of carbon monoxide the active part of the Fe_2O_3 surface is reduced to FeO, as a result of which carbon dioxide is formed. Oxygen in the gaseous mixture reoxidises FeO to Fe_2O_3.

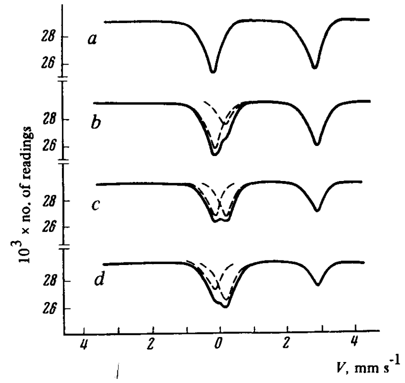


Figure 17. Spectra of Fe^{2+} on the surface of quartz before the pyrolysis of acetylene (*a*) and 0.5, 2, and 5 min (*c*, *b*, and *d*) after the start of the reaction (T_{exp} = 300°K).

In another study dealing with the pyrolysis of acetylene over an iron-containing quartz surface[49] an anomalous transparency of a film of pyrocarbon produced in the course of the reaction of acetylene with the iron atoms on the surface was observed. By evaporating Fe_2O_3 enriched with the iron-57 isotope to the extent of 91%, iron was deposited on the surface of quartz in the form of a divalent compound, probably iron(II) silicate ($FeSiO_3$) and also in the form of metallic iron and Fe_2O_3. After the pyrolysis of acetylene over this type of catalyst, there appears in the spectrum a line corresponding to a symmetrical surface compound, the amount of which increases with the duration of pyrolysis to a definite value, which is probably associated with the attainment of equilibrium between the complex formed in the reaction and the amount of iron(II) silicate present on the surface (Fig. 17). A layer of pyrocarbon with a thickness of several hundred angstroms, which is permeable in further penetration by acetylene to the quartz surface, is formed in the pyrolytic process on quartz. A control experiment was performed in which quartz with pyrocarbon on its surface was placed in a reactor with an argon atmosphere; under these conditions, iron was not bound in a surface complex, i.e. acetylene is essential for the formation of the complex. When the pyrocarbon was burnt off, the complex did not disappear either, which shows that the complex is located on the surface and is not bound to the bulk phase of the pyrocarbon. A similar conversion of metallic iron into the same complex has been observed.

In conclusion of the discussion of this class of phenomena, mention must be made of a new field in the chemistry of the solid state—the application of Mössbauer spectroscopy to surface phenomena, which permits the study of elementary processes on the surface taking into account the electronic and vibrational states of the atoms.

III. PHENOMENA ASSOCIATED WITH THE EFFECT OF THE BOUNDARIES OF THE SOLID ON THE PROPERTIES OF INTERNAL ATOMS

1. The Change in the Phonon Spectrum of a Substance in a Highly Dispersed State

In this section we shall consider the characteristic vibrations of atoms in small particles of a substance obtained by observing the changes in the probability of the Mössbauer effect. The changes in f for highly dispersed particles are associated with two effects: the first is the influence of the surface already mentioned above, which should lead to an increase of $\langle r^2 \rangle$. Since a decrease of particle size entails an increase in specific surface, f falls for this reason alone.

The second effect is associated with the change in the nature of the phonon spectrum itself for such particles and may act in the opposite sense, i.e. lead to an increase of f as the particle size is reduced. Marshall and Wilenzik[50], who assumed that for small particles the Debye approximation is applicable, concluded that the phonon spectrum must be displaced towards shorter wavelengths, which leads to an increase of f as the particle size is reduced. In fact, there is an upper limit to the wavelengths of phonons due to the dimensions of the particles themselves and therefore the phonon spectrum for small particles shows a more marked "cut off" on the long wavelength side (low frequency side) and, since the probability of the Mössbauer effect increases very markedly as the ratio $R/\hbar\omega$ falls (R is the recoil energy and ω the effective average vibration frequency), the low-frequency "cut off", which increases $\overline{\omega}$, results in a marked increase of f. Marshall and Wilenzik's reasoning is based, however, on the assumption that the Debye approximation is applicable to small particles. Actually, the phonon spectrum of small particles differs sharply from the usual spectrum by a set of discrete frequencies due to the presence of a finite number of atoms in such particles, which may lead to a change in $\overline{\omega}$ such that f will fall as the particle size is reduced. When account is taken of the decrease of the wavelength of the real phonon spectrum as a result of the effect of the surface, it is possible to predict the changes of f for particles of different kinds. The following in many ways contradictory results have been obtained experimentally. For β-tin particles, f falls with particle size (from 1550 to 250 Å)[15], while for gold particles it actually increases[50]. For small tungsten particles, f is also smaller than for foil[16].

For platinum[36], the probability of the effect hardly changes with particle size. Apart from these experiments, we investigated the changes in f for particles of FeNi (31% Ni) and FeCo (49% Co) alloys (particle size 800, 500, 300, and 160 Å), for which the probability of the effect fell with decreasing particle size, and for SnO_2 with a particle size of about 60 Å, for which f was also smaller than in macroscopic SnO_2. The literature data[15-17,36,50] and also our latest measurements are given in the Table.

Mössbauer effects in different substances

Substance	References	Size, Å	T, °K	f'_{exp}	Method of preparation
β-Sn	15	250	80	0.25	aerosol
		250	300	0.022	
		foil	80	0.35	
		foil	300	0.06	
FeNi (31% Ni)		160	80	0.7 rel. units	aerosol
		160	300	0.5 rel. units	
		800	80	1.4 rel. units	
		800	300	1.1 rel. units	
FeCo (49% Co)		160	80	0.7	aerosol
		160	300	0.5 rel. units	
		800	80	1.4 rel. units	
		800	300	1.3 rel. units	
W	16	30	4	0.57	hydrolysis of tungsten hexacarbonate
		1 μm	4	0.61	
Au	50	60	25	0.16	hydrosol
		60	60	0.07	
		200	25	0.14	
		200	60	0.05	
SnO_2		60	80	0.45	aerosol
		60	300	0.11	
		powder	80	0.9	
		powder	300	0.6	
Fe_2O_3	17	20—30	300	0.31—0.43	hydrosol
			100	0.37—0.51	
Pt	37	100	4	2-8 rel. units	platinum in silica gel pores
		foil	4	2-8 rel. units	

It follows from the Table that in almost all cases, with the exception of gold and platinum, the probability of the effect falls with decrease of particle size. However, the absolute values of f may oscillate somewhat, depending on the method of preparation of the particles[17] and therefore it is desirable to perform experiments of this kind for particles of 3-4 different dimensions, prepared by the same method (the aerosol method is apparently preferable, since under these conditions more nearly spherical particles are obtained). The increase of f for individual tin-119 atoms on the surface of platinum compared with polyatomic tin particles on platinum[12] and also the constancy of f for platinum in the pores of silica gel compared with platinum foil[34] can be included among the effects related to the increase of f with decreasing particle size. The results obtained for tin on the surface of platinum may, however, be attributed to the diffusion of tin into the bulk of platinum.

The most probable explanation of the increase of f with decreasing particle size is that the effect of the "compacting" of the phonon spectrum (as a result of the long wavelength cut off) predominates over surface effects. Unfortunately the influence of the surface can diminish f in different ways, depending on the method of preparation of the specimen. This makes it difficult to assess quantitatively the decrease of f taking into account the increase caused by the "compacting" of the phonon spectrum. Nevertheless experiments show that for gold and platinum the effect of the low-frequency component of the phonon spectrum on f is more significant than for the other substances investigated. This makes it possible to characterise the contribution of the long-wavelength part of the spectrum to the overall phonon spectrum by investigating very small particles of the substance.

2. Magnetic Properties of Small Particles. Superparamagnetic Phenomena

Thermal fluctuations of magnetisation do not occur in massive specimens which remain magnetically ordered up to the Curie (T_C) and Néel (T_N) points. As a result, whenever $T < T_C$, T_N, magnetic fields are found at the nuclei and the specimen shows macroscopic magnetisation. However, as the dimensions of the specimens decrease, thermal fluctuations in the magnetisation of the entire particle begin to occur, which leads to an averaging of the macroscopic magnetisation to values characteristic of the paramagnetic state of matter and the disappearance of magnetic fields at the nuclei, although the substance is still in the magnetically ordered state. Such behaviour of matter in a highly dispersed state in fact characterises the phenomenon of superparamagnetism. Indeed, for finite volumes of the substance, the frequency of the fluctuations in magnetisation may be described by the formula

$$\nu = \nu_0 \exp\left(-\frac{Kv}{kT}\right),$$

where ν_0 is usually of the order of 10^{10} s^{-1}, K(erg cm^{-3}) is the constant of anisotropy characterising the energy necessary to "overturn" the magnetisation vector and v is the volume of the particle. With increase of temperature, the fluctuation frequency ν increases, and, depending on the method used to investigate small particles of this kind, the latter will exhibit at a given temperature the properties either of magnetically ordered or magnetically disordered substances. This leads to an effective lowering of the Curie and Néel points as the particle size is reduced. By superimposing an external magnetic field of several kilo-oersteds, it is possible to increase artificially the constant of anisotropy by an amount μH:

$$\nu = \nu_0 \exp[(-Kv + \mu Hv)/kT],$$

where μ is the magnetic moment of the atom and H the external magnetic field. This provides an additional equation for the determination of the unknown volume of the particles. Mössbauer spectroscopy is the only method available for the investigation of superparamagnetism, since, in contrast to usual procedures, it permits the investigation of the relaxation of magnetisation during a period of 10^{-8} s. The frequency of thermal fluctuations and the relaxation time of magnetisation τ are determined from the widening of the Mössbauer line[32]:

$$\tau = \frac{\hbar}{\Delta\Gamma}.$$

A second feature of small particles is the absence of phase transition points associated with the change in the direction of the magnetisation of the spin relative to the axis of the crystal field, for example the absence of the Morin point in haematite.

The first experiment on superparamagnetism by the γ-resonance method was performed by Nakamura et al.[51], who found that, for Fe_2O_3 particles 50 Å in diameter, the Néel point is markedly reduced compared with large particles and lies between 120° and 300°K ($T_N \simeq 1000$°K for the usual Fe_2O_3). At 120°K there is the usual six-line hyperfine structure characteristic of an antiferromagnetic material and at 300°K the spectrum consists of a doublet corresponding to the superparamagnetic state of Fe_2O_3. Subsequently similar experiments were performed to investigate the effective changes in the behaviour of the Curie and Néel points and to determine the constants of anisotropy. Two methods may be employed to determine the constants. Kündig et al.[27] suggested that the frequency of the precession of the nuclear spin in the magnetic field acting upon the nucleus be used as a characteristic for which the contribution by the hyperfine structure amounts to approximately 50% of the entire spectrum under conditions where the frequency of the thermal fluctuations of the magnetisation is equal to the frequency of the precession of the nuclear spin. By determining the average volume of the particles at a specified temperature or the temperature for a specified column, for which the above condition holds, and by substituting these values in the exponential equation, the constant of anisotropy is found. The volume of the particles is determined by some other procedure, for example from X-ray diffraction data.

It is possible to suggest another method, associated with the possibility of the determination of τ from Mössbauer spectra, as was done by Suzdalev et al.[32] or by Wickman et al.[52] In this case one observes the experimental relation between $\ln\tau = \ln\tau_0 - Kv/kT$ and $1/T$, from which it is possible to determine the values of $\ln\tau_0$ and Kv/k. Kündig et al.[27] investigated highly dispersed Fe_2O_3 with a particle size of about 100 Å prepared by impregnating silica gel with a solution of $FeCl_3$ and subsequent thermal decomposition to iron(III) oxide. They also observed a decrease of the Curie point below 300°K. By analysing the change in the spacings between the hyperfine lines, the authors showed that in such Fe_2O_3 particles there is no Morin transition in which the magnetisation becomes parallel to the crystal field gradient when the temperature is reduced. The constant of anisotropy for Fe_2O_3 is $K = 4 \times 10^4$ erg cm^{-3} according to experimental data.

Shinjo[53] and Van der Kraan and van Loef[54] investigated the highly dispersed state of the antiferromagnetic material hetite (α-FeOOH) with a particle size between 60 and 500 Å. Here $K = 1 \times 10^4$ erg cm^{-2} and therefore the lowering of the Néel point and the appearance of superparamagnetism are already appreciable for larger particles than in the case of Fe_2O_3. When the particle size is reduced, the anisotropy constant may diminish somewhat[27]. Ando et al.[55] investigated the antiferromagnetic material NiO by introducing cobalt-57 into this oxide. The Néel point for NiO is 523°K. For 100 Å particles, obtained by impregnating with a mixture of $Ni(NO_3)_3$ and cobalt-57 with subsequent heat treatment at 500°C in air, the Néel point fell to 200°K. The investigators were able to demonstrate, using the characteristics of the structure of the highly dispersed initial oxide (with an excess of oxygen relative to the stoichiometric composition), that the Fe^{2+} spectrum observed previously by Bhide and Shenoy[56] and Triftshäuser and Craig[57], disappears for small particles and only the Fe^{3+} spectrum remains, owing to the presence of oxygen in excess of stoichiometry.

Schuele et al.[58] investigated highly dispersed ferrites ($NiFe_2O_4$ and $CoFe_2O_4$) with a particle size between 100 and 200 Å. Since the anisotropy constant for cobalt compounds is higher, superparamagnetism appears for smaller particles than in the case of nickel.

Another branch of studies of this kind involves the determination of particle distribution with respect to dimensions by comparing two parts of a complex spectrum: (1) component corresponding at a given temperature to the non-magnetic state without a magnetic hyperfine structure which arises from small particles; (2) component corresponding to the magnetic state with a hyperfine structure which arises for larger particles.

A study of this kind was made by Gonser et al.[59] for particles of the $MgFe_2O_4$ ferrite deposited on MgO. The particle size varied both with temperature and with the duration of heat treatment of the $MgO-Fe^{3+}$ system in which the ferrite particles were deposited. The form of the spectra suggested that particles with a volume $v = 0.5 \times 10^{-18}$ cm^3 (deposition temperature 700°C, time 15 min), 1.4×10^{-18} cm^3 (800°C, 20 min), and 9.7×10^{-18} cm^3 (800°C, 90 min) were obtained, the relaxation times of the magnetisation being respectively $\tau = 0.18 \times 10^{-9}$, 0.31×10^{-9}, and 14×10^{-9} s. The authors used the following expressions for the calculation:

$$\tau = \frac{a}{\omega}\exp\left(\frac{|K_1|\,v}{12\,kT}\right), \quad \omega = \frac{4}{3}\gamma\frac{|K_1|}{M_s},$$

where $a \simeq 1$, γ is the gyromagnetic ratio, K_1 the constant of anisotropy along the light magnetisation axis, M_S the spontaneous magnetisation, and v the volume of the particle. Cobalt-57 particles were deposited in copper and investigated by the same procedure[60].

Assuming that the magnetic structure of the spectrum disappears when $\tau = 3 \times 10^{-9}$ s[52] and that $K = 2 \times 10^5$ erg cm^{-3} for the face-centred cobalt lattice, Masu et al.[60] found the critical volume of the particles at different temperatures. The average particle size was 100 Å and at 335°K a paramagnetic spectrum was already observed ($T_C \simeq 1000$°K for cobalt).

Lindquist et al.[61] investigated highly dispersed nickel with a small admixture of cobalt-57 obtained in silica gel pores. The particle size was about 30 Å. The relaxation time at 300°K was found to be $\tau = 2 \times 10^{-9}$ s by comparing with the calculations of Wickman et al.[52] the form of the hyperfine structure for the paramagnetic Fe^{3+} ions in the Ferrichrome A lattice. Lindquist et al.[61] observed that, when an external magnetic field is applied, the hyperfine structure of the spectrum of the paramagnetic component of the superparamagnetic material appears.

Gen et al.[62] studied the magnetic properties of the FeNi (13% Ni) alloy and found that in particles 100 and 500 Å in diameter a magnetic α-phase and a non-magnetic γ-phase are present, while macroscopic specimens contain only the α-phase. The α-phase is magnetically ordered for particles with diameters < 100 and 500 Å. The study of the oxidation of such highly dispersed particles showed that, depending on the size, the relative proportions of the FeO, Fe_2O_3, and Fe_3O_4 phases change; the α-Fe_2O_3 and Fe_3O_4 phases are present in a highly dispersed state and have a reduced Néel point. The oxidation of the highly dispersed particles begins at 150°C, while that of macroscopic specimens takes place only at 500°C.

The study of the oxidation of highly dispersed systems permits the observation of the early stages in the oxidation, as was shown in the oxidation of highly dispersed β-tin[13]. The lowering of the Curie point to 600°K for the highly dispersed FeCo alloy (49% Co) with a particle size of 160 Å was observed. These particles were obtained by the aerosol method, which probably yields the purest specimens for the investigation of the magnetic properties of particles, since the effect of another phase (metal, oxide, silica gel), which probably operated in all other investigations, is excluded. Despite the fact that for ferromagnetic materials superparamagnetism begins to have an effect for particle sizes of about 200 Å, the critical thickness of the film for which the hyperfine structure of the spectrum vanishes at a given temperature is much smaller. Lee et al.[28] investigated ultrathin iron films with a thickness of 1.2–15 Å deposited on a silicon support. The magnetic field had the usual value for 15 Å and thicker films but began to diminish as the thickness was reduced further. The results show that T_C and K vary sharply when the dimensions of the film become equal to twice the lattice constant.

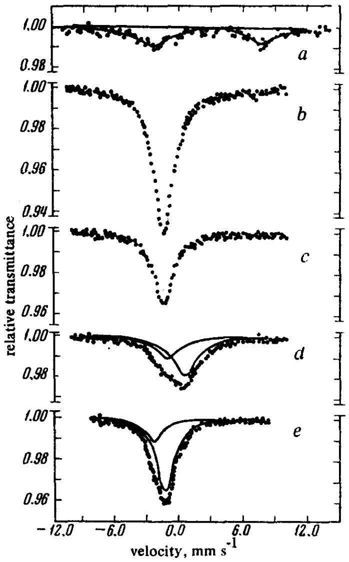


Figure 18. Spectra of gold-197 in the thermal decomposition of gold salts on η-Al_2O_3: *a*) $KAu(CN)_2$; *b*) and *c*) after high-temperature heat treatment; *d*) spectrum of $HAuCl_4$ after heat treatment at 140°K; *e*) spectrum after high-temperature heat treatment of $HAuCl_4$.

3. Topochemical Reactions

In the thermal or radiation-induced decomposition of a solid, the various phases interact and new substances are formed in a highly dispersed state and particles grow and become sintered. All these phenomena can be investigated very effectively by Mössbauer spectroscopy. Naturally, the results which we shall now discuss are directly related to the two fields dealt with previously, particularly to the preceding section. We shall divide topochemical reactions into two classes: (1) reactions in which the surface of the solid, which behaves as a carrier (for example silica gel or alumina), is involved and (2) reactions without a carrier.

Interesting studies of reactions of the first type were made by Delgass et al.[36] using the gold salts $KAu(CN)_2$ and $HAuCl_2$ on η-Al_2O_3 and MgO. The results of these investigations are presented in Fig. 18. The initial spectrum (*a*) of $KAu(CN)_2$ shows that, on drying at 140°C, the gold compound is not decomposed and spectra (*b*) and (*c*) demonstrate that, when the system is heat-treated in air, it is reduced to metallic gold. The spectra (*d*) for $HAuCl_4$ and η-Al_2O_3 at 140°C reveal the presence of metallic gold and a symmetrical gold complex and the spectrum (*e*) reveals, after heat treatment, yet another line, in addition to the line due to metallic gold.

An even more significant role of the carrier was noted in the studies of Hobson[42], Dunken et al.[63], and Arnold and Hobert[64]. Hobson[42] obtained iron(III) oxide by thermal decomposition of iron(III) nitrate and silica gel and alumina and the oxide was then reduced to hydrogen. He found that the distribution of Fe_2O_3 in η-Al_2O_3 with respect to particle size is wider than in the case of silica gel. Dunken et al.[63] observed that, after the thermal decomposition of $FeCl_3$ in alumina pores, only the superparamagnetic Fe_2O_3 phase is obtained when the percentage content of iron in alumina is varied from 0.125 to 9%, while Fe_2O_3 consisting of various phases (superparamagnetic and antiferromagnetic) was obtained in silica gel pores.

Among investigations of the second type, we may mention the studies on iron oxalates and hexacyanoferrates(III). Gallagher and Kurkijan[65] studied the thermal decomposition of the oxalates $Fe_2(C_2O_4)_3.5H_2O$, $Ba_3[Fe(C_2O_4)_3]_2.8H_2O$, and $Sr_3[Fe(C_2O_4)_3]_2.2H_2O$. With increase of temperature, divalent iron appears in all three compounds. The authors[65] found that at 300°C the highly dispersed Fe_2O_3 phase appears. Further increase of temperature leads to the appearance of the usual Fe_2O_3 phase. Heat treatment of strontium oxalate at 700°C and above resulted in the formation of an iron(IV) complex, while barium oxalate did not form such a complex.

Suzdalev and coworkers[66,67] investigated by Mössbauer spectroscopy and derivative plot analysis the thermal decomposition of iron(II) and iron(III) oxalates in an atmosphere of nitrogen. Fig. 19 shows differential plots and Mössbauer spectra for the decomposition of these oxalates. Iron(III) oxalate has three phase transitions at 200°, 280°, and 400°C, while iron(II) oxalate has only two: at 200° and 400°C. The first phase transition corresponds to the appearance of iron(II) oxalate with simultaneous dehydration. The third transition of iron(III) oxalate and the second transition of iron(II) oxalate correspond to the appearance of the Fe_3O_4 phase in the usual polycrystalline phase. The second phase transition in iron(III) oxalate corresponds to the formation of highly dispersed Fe_2O_4 with a particle size of about 100 Å.

The radiolysis of iron(III) oxalates[68] also indicates the formation of iron(II) oxalate. The spectrum of the latter does not alter on radiolysis. Probably the energy of the bond between iron and the lattice is higher in the divalent iron oxalate than in the trivalent iron salt. At a dose of 200 Mrad equilibrium is established between iron(II) and iron(III) oxalates. The growth of Fe_2O_3 particles in the second phase transition in the thermal decomposition of iron(III) oxalate was also investigated as a function of temperature as well as the kinetics of particle growth at a constant temperature[69].

The change in particle size was estimated from the change of the ratio of the area under the hyperfine structure to the area under the paramagnetic component corresponding to smaller particles. It was shown that, with increase of temperature from 240 to 280°C, the particle size increases and the contribution by the hyperfine structure rises also.

The results of the kinetic experiments show that at 240°C there is a slight increase in the contribution by the hyperfine structure over a period of 2–3 h and then no further changes are observed.

Probably heat treatment of the test substance at the same temperature leads to the establishment of a quasiequilibrium state, since equilibrium is established only as a result of the coalescence of smaller particles. At 240°C the growth of Fe_2O_3 particles begins, which, however, differ markedly in their dimensions and initially their system is not in equilibrium. In a study of the kinetics of particle growth, measurements were made of the relaxation times associated with the establishment of an average particle size. At higher temperatures equilibrium is established faster. As a result, the quasiequilibrium average particle size is related to a definite temperature and the actual particle size depends on the duration of the heat treatment.

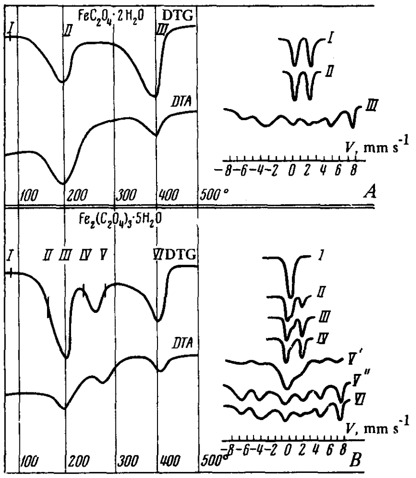


Figure 19. Differential plots (left-hand figure) and Mössbauer spectra (right-hand figure) obtained for the specimens at different temperatures: *A*) iron(II) oxalate; *B*) iron(III) oxalate.

The thermal decomposition of hexacyanoferrates was studied by Borshchagovskii et al.[70] using the compounds $LiY_8[Fe(CN)_6]_7.34H_2O$, $Sc_4[Fe(CN)_6]_3.xH_2O$, $Mn_2[Fe(CN)_6].6H_2O$, and $Sr_2[Fe(CN)_6].6H_2O$. All these compounds decompose by the same mechanism. At 160°C they are dehydrated and their spectra become somewhat wider, at 360°C iron atoms pass to the outer sphere, and at 760°C iron carbide (Fe_3C) is formed. By studying the kinetics, Borshchagovskii et al.[70] found that, after heat treatment for 2 h, metallic iron is formed from iron carbide.

In conclusion we shall consider the oxidation of highly dispersed tin (with particle sizes of 300 and 1000 Å).[14] It was shown that, up to the melting point of highly dispersed tin, its oxidation is hindered by the SnO_2 formed on the surface, but above the melting point the nature of the oxidation alters sharply. There is rapid formation of SnO, the proportion of which in material with a particle size of 300 Å becomes much greater than that of β-tin. However, up to 400 Å the spectra show the presence of unoxidised tin and for 1000 Å particles the amount of β-tin at an oxidation temperature of 300°C is greater than that of SnO.

These results show that up to 400°C the oxidation probably involves the reactions

$$2\,Sn + O_2 \rightarrow 2\,SnO,$$
$$2\,SnO \rightarrow SnO_2 + Sn,$$

and the reaction $2SnO + O_2 \rightarrow 2SnO_2$, a characteristic feature of which is the disappearance of SnO without the formation of β-tin, plays a very small role. About 400°C, this reaction begins to take place at a high rate and the entire tin is oxidised to SnO_2.

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Institute of Chemical Physics,
USSR Academy of Sciences,
Moscow

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Electrophilic Substitution in the Series of Six-membered Nitrogen-containing Heteroaromatic Compounds and Their *N*-Oxides

Zh.I.Aksel'rod and V.M.Berezovskii

This review deals with the present state of the problem of electrophilic substitution in the series of six-membered nitrogen-containing heterocycles using as an example simple derivatives of neutral monoazines and diazines, their *N*-oxides, and certain condensed structures containing not more than 2 nitrogen atoms in one ring. Much attention has been devoted to problems of the comparison of the reactivities of heteroaromatic compounds with the results of theoretical calculations by the molecular orbital method and also the application of kinetic methods to the determination of the nature of the reactants. The bibliography includes 199 references.

CONTENTS

1. INTRODUCTION

The extensive data on the reactivities of various nitrogen-containing heterocycles have been comprehensively described in the literature. The problems of the chemistry and in particular the electrophilic substitution of heterocyclic compounds which are extremely important both theoretically and in practice, such as mono- and diazines (pyridine, pyrazine, pyrimidine, etc.), their benzo-derivatives (quinoline, quinoxaline, etc.), and also more complex condensed structures, containing together with nitrogen atoms also other heteroatoms (phenoxazine, phenothiazine, and others), have been discussed in detail in reviews edited by Elderfield[1], Weissberger[2], and Katritzky[3] and in a number of monographs[4-6].

Studies by Soviet scientists have made a valuable contribution to the development of the chemistry of nitrogen-containing heterocyclic compounds. In this connection, mention should be made of the work of Yur'ev[7,8], Rubtsov[9], Nesmeyanov and Kochetkov[10,11], Postovskii[12], and many others[13,14]. In recent years, considerable advances, associated primarily with the study of the mechanism of heteroaromatic substitution, have been made in research on the reactivities of nitrogen-containing heterocyclic compounds. These advances have been reviewed recently by Katritzky[15] and Ridd[16,17] and also in monographs by Schofield[18] and Palmer[19] based on data from both experimental and theoretical studies of the mechanisms of these reactions.

In the present review an attempt is made to examine in detail the results of investigations of electrophilic substitution in the series of six-membered aromatic nitrogen-containing heterocycles from the standpoint of modern concepts of reaction mechanisms and also to compare these results with the calculated indices of the reactivity of the compounds. Neutral model systems are chosen for discussion: pyridine and also pyridazine, pyrimidine, and pyrazine (i.e. heterocycles containing not more than two nitrogen atoms in the ring) and some of their condensed systems and *N*-oxides.

The electrophilic substitution reaction in the series of nitrogen-containing six-membered heteroaromatic compounds takes place under much more severe conditions than those involving the corresponding hydrocarbons, i.e. the replacement of a =CH group by the more electronegative nitrogen atoms leads to a decrease of reactivity in both the heterocyclic and the fused aromatic ring. Thus the ring nitrogen atom plays the role of an electron-accepting *meta*-directing substituent.

On the whole, electrophilic substitution in the heterocyclic series has much in common with substitution in the series of aromatic-hydrocarbons. The directive influence of substituents on electrophilic attack in the series of six-membered nitrogen-containing heteroaromatic compounds is qualitatively the same as for aromatic hydrocarbons. Thus powerful electron-accepting groups (NO_2, SO_3H, COOH) hinder electrophilic substitution of pyridine derivatives, while powerful electron-donating groups (OH, NH_2, OR, NR_2) greatly facilitate such reactions.

Quantitatively the effect of substituents is different for heterocyclic and aromatic systems. For example, comparison of the rates of nitration of chloro- and methoxypyridines and the corresponding substituted benzene derivatives shows that the same substituents exhibit greater conjugative effects in pyridine than in benzene[15].

The principal characteristic of electrophilic substitution reactions in the heteroaromatic series is that the attack by electrophilic agents may be directed to the nitrogen atom, by virtue of its *p*-electron pair (an analogous situation is encountered in the series of amino-derivatives of aromatic compounds). The ease of this reaction depends on the electron density at the nitrogen atom and also on steric factors.

As a result of electrophilic attack, the nitrogen atom acquires a positive charge, which strongly deactivates the carbon atoms in the ring. Calculation of the partial rate factors for the nitration and hydrogen isotope exchange reactions of substituted pyridine derivatives in neutral and protonated forms shows that the replacement of a =CH group in benzene by the $=\overset{+}{N}H-$ group deactivates the ring in the *meta*-position much more than the replacement by =N– (the rate constants for these reactions in the case of the protonated and neutral forms are reduced relative to the rate constants for the reactions of benzene by a factor of 10^{12}–10^{18} and 10^6–10^7 respectively)[20,21].

The effect of the nitrogen atom and the $=\overset{+}{N}H-$ group in pyridine on the reactivity of the ring carbon atoms can also be estimated quantitatively with the aid of Hammett's σ constants, with =N– and $=\overset{+}{N}H-$ regarded as ring substituents introduced into the benzene molecule[22].

	α	β	γ
$\sigma_{=N-}$	0.8	0.6	0.9
$\sigma_{=\overset{+}{N}H-}$	—	2.1	2.3

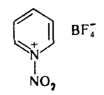
The constants quoted are smallest for the β-position, which is consistent with the *meta*-directing effect of the substituting groups in electrophilic substitution reactions. Moreover, all the $\sigma_{=N-}$ are smaller than $\sigma_{=\overset{+}{H}-}$, which is evidence of the greater reactivity of the neutral pyridine molecule compared with its cations. This is consistent with the conclusion based on the calculation of the partial rate factors for substitution in the pyridine series.

Experimental studies of the mechanism of electrophilic substitution in the heteroaromatic series permits solution of the problem of the nature of the reactive species—whether it is the free base or the species resulting from preliminary addition of a proton or the attacking agent to the nitrogen atom. These processes are frequently reversible and therefore even in weakly acid solutions there is a low equilibrium concentration of the free base. Furthermore, the predominant species present in solution is not always active, so that the nature of the reactive form of the compound may be established only by kinetic methods.

Since the mode of electrophilic substitution reactions in heterocyclic compounds, as well as in aromatic compounds, is determined by the state of the electron cloud in the molecule, the application of the molecular orbital theory permits the prediction of the preferred location of the substituent. For this purpose, one uses as the indices of reactivity the π-electron density, boundary π-electron density, localisation energy, etc.

2. SUBSTITUTION IN THE PYRIDINE SERIES

Electrophilic attack on unsubstituted pyridine is directed to the carbon atom in the 3-position. Pyridine is nitrated under very severe conditions—in oleum at 300°C—with a low yield (4.5%).[23] The kinetics of this process cannot be studied, since it has still not been established whether the result of this type of nitration is a consequence of the low reactivity of the positively charged pyridinium ion or whether the reaction involves the very small amount of the free base in the highly acid medium. The nitration of pyridine in a homogeneous aprotic medium at 30°C, using a solution of nitronium tetrafluoroborate (NO_2BF_4) in sulpholane (tetrahydrothiophen 1,1-dioxide), results in the formation of an *N*-nitropyridinium ion, as shown by ultraviolet and NMR spectroscopy[24]:



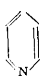
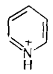
The sulphonation of pyridine also takes place in the 3-position under severe conditions (H_2SO_4–SO_3, 350°C).[25] Many electrophilic substitution reactions of pyridine derivatives are catalysed by salts of di- and ter-valent metals [$Hg(CH_3COO)_2$, $AlCl_3$, etc.], which can probably be accounted for by partial transfer of electron density from the coordinated metal atom to the nitrogen atom. This tends to decrease the formal positive charge of the nitrogen atom and consequently of the ring as a whole[26]. The use of optimum conditions for the sulphonation of pyridine—heating for 24 h in 20% oleum at 220–230°C in the presence of catalytic amounts of mercury(II) sulphate—leads to the formation of pyridine-3-sulphonic acid in 71% yield[27].

Gas-phase halogenation of pyridine at 300°C leads to the formation of 3-mono- and 3,5-di-halogeno-derivatives, while at 500°C 2-mono- and 2,6-di-halogeno-substituted compounds are formed[28]; probably in the latter case the reaction takes place not by an electrophilic but by a radical mechanism. Recently a method was described for the direct halogenation of pyridine in sulphuryl chloride or phosphorus oxychloride[29]. Thus bromination in the presence of one equivalent of sulphuryl chloride at 160–170°C gives a 45% yield of 3,5-dibromopyridine, while in phosphorus oxychloride the yield is about 20%. It is interesting to note that sulphuryl chloride is itself an electrophilic agent as a result of ionisation of the type $\overset{\delta+}{Cl}-\overset{\delta-}{SO_2Cl}$.[30]

Pyridine readily combines with mercury(II) acetate at 155°C, giving a 35% yield of 3-pyridylmercury acetate[31].

According to the LCAO-MO calculation[32,33], the electron densities q_r at the C_3 atom of pyridine and its cation is greater and the localisation energy for electrophilic substitution A_e smaller than the corresponding values for C_2 and C_4 (Table 1). Consequently electrophilic substitution of pyridine, both as a neutral molecule and in the protonated form, should be directed to the 3-position, in agreement with experiment.

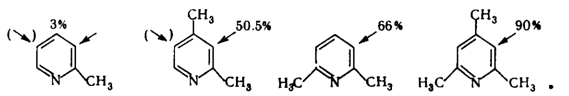
Table 1. Indices of the reactivity of pyridine[32,33].

Structure	q_r, charge units	A_e $(-\beta)$	position of carbon atoms	A_e $(-\beta)$	q_r, charge units	Structure
	0.923 1.004 0.950	2.672 2.538 2.701	2- 3- 4-	2.709 2.560 3.071	0.759 1.012 0.835	

Note. This and other Tables present the results obtained by the simple Hückel method without taking into account adjacent orbital overlap, using the parameters $h = 0.5$ and $h' = 0$ for the tertiary nitrogen atom and $h = 2$ and $h' = 0.2$ for the secondary nitrogen atom[34]. It should be noted that the predicted positions of highest reactivity for a given heterocyclic compound obtained by this method and also by the more accurate self-consistent field calculations agree[33].

On the other hand, the correlation between the calculated data and the observed relative reactivities in the series benzene–pyridine–pyridinium cation is unsatisfactory. While the capacity for electrophilic substitution decreases on going from benzene to pyridine, the electron density at the C_3 carbon atom of pyridine is higher than for benzene ($q_r = 1$) and the localisation energy for the pyridine C_3 atom is lower than for benzene ($A_e = 2.540$); moreover, the electron density at the carbon atom in the 3-position increases on transition from pyridine to its cation.

Depending on the position of the activating group, substituted pyridine derivatives can undergo electrophilic attack in the $\alpha\alpha'$- or $\beta\beta'$-positions. The nitration of alkylpyridines takes place more readily than that of unsubstituted pyridine. Thus 2-mono-, 2,4-, and 2,6-di- and 2,4,6-tri-methylpyridines interact with potassium nitrate or nitric acid in sulphuric acid at 100–160°C with formation of 3-mononitro-derivatives (in the case of 2-picoline and 2,4-lutidine, as a result of the concerted directing effects of the CH_3 groups and the nitrogen atom, an equimolar mixture of 3- and 5-mono-nitrocompounds is obtained), the yield in these reactions increasing with the number of methyl groups in the pyridine molecule[35–37]:

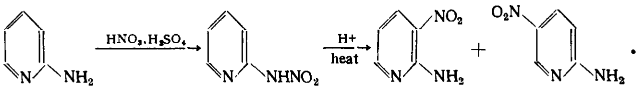


Nitration of the cation of 1,2,4,6-tetramethylpyridine in the 3-position takes place under the same conditions as the nitration of 2,4,6-trimethylpyridine and therefore the latter compound reacts in the protonated form[38]. This conclusion has also been confirmed by kinetic investigations.

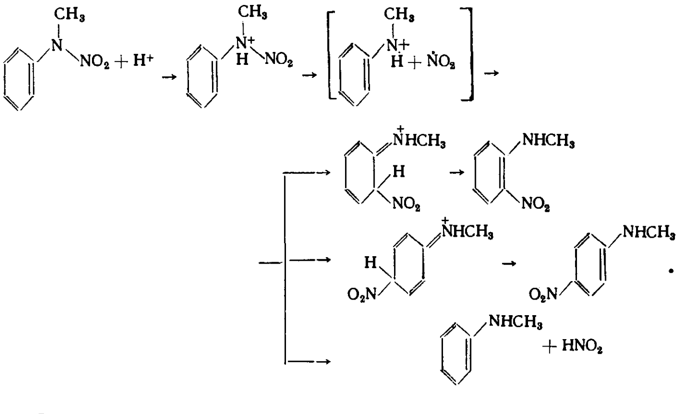
Katritzky and coworkers[21] established that the variation of the nitration rate constant with the acidity of the medium is similar for collidine and its N-methyl cation; the maximum possible rate constant for the reaction with participation of the free base, calculated on the basis of the transition state theory (2.26×10^9 litre $mole^{-1}$ s^{-1}), is much less than the experimental rate constant (1.6×10^{11} litre $mole^{-1}$ s^{-1}); finally, the entropy of activation for this reaction is −26.7 e.u. The theoretical entropy of activation should be higher for a reaction between two charged species (about −20 e.u.) than between a neutral molecule and a monocation[39]. All these data show that 2,4,6-trimethylpyridine enters into the nitration reaction in the protonated form.

Nitration of 3-bromopyridine as well as nitration of unsubstituted pyridine takes place under very severe conditions—with potassium nitrate in 10% oleum at 270°C in the presence of iron as a catalyst—and leads to the formation of 3-bromo-5-nitropyridine in 7% yield[40]. Thus the *ortho-para*-directing effect of the halogen atom in the pyridine series is less than the *meta*-directing effect of the ring nitrogen (or the $=\overset{+}{N}H$ group).

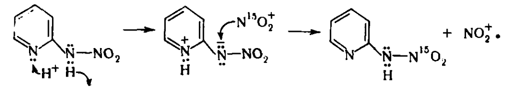
The presence in pyridine of the powerful electron-donating amino-group greatly facilitates electrophilic attack on the ring of the molecule. Nitration of 2-aminopyridine with nitric acid and sulphuric acid takes place in two stages: at 20°C and below 2-aminonitropyridine is formed initially and then at 40°C it undergoes endothermic rearrangement to a mixture of 2-amino-3-nitro- and 2-amino-5-nitropyridines in proportions of 1 : 8[41,42]:



The preferential substitution in the *para*-position relative to the amino-group in this reaction is evidence of an intermolecular or a partially intermolecular nature of the rearrangement. On the basis of a spectrophotometric determination of the amount of nitrous acid formed in the rearrangement of N-methyl-N-nitroaniline, it has been suggested[43] that the acid-catalysed rearrangement of the nitroamines takes place with dissociation of the $N{-}NO_2$ bond and the intermediate formation of two free radicals and therefore further reaction takes place not by an electrophilic but by a radical mechanism:

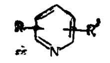


On the other hand, there are data supporting an intramolecular mechanism of the rearrangement. In a study of the rearrangement of α-nitroaminopyridine in sulphuric acid in the presence of sodium nitrate containing nitrogen-15, it was found that the labelled nitrogen enters into α-amino-β-nitro- and α-amino-β′-nitro-pyridines in a smaller amount than that remaining in the nitrate. The exchange of nitro-groups under these conditions probably involves a mechanism with electrophilic substitution at the amino-nitrogen, where a negative charge appears in consequence of the removal of a proton under the influence of two strongly electron-accepting groups[44]:



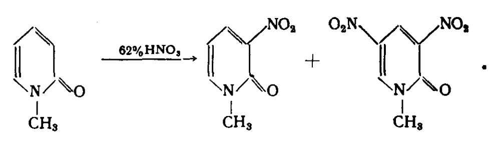
4-Aminopyridine is nitrated in the 3-position; the reaction also proceeds via a stage with rearrangement of the *N*-nitroamine but at a higher temperature (160°C). It is interesting to note that 3-nitroaminopyridine does not rearrange to the aminonitro-compound, while 3-(*N*-methyl-*N*-nitroamino)pyridine is readily converted into 3-methylamino-2-nitropyridine[45].

Table 2. Nitration of alkoxy- and hydroxy-pyridines with nitric acid.

		Reaction conditions		Position of entry of NO_2 group	Yield, %	Refs.
R	R′	medium	temp., °C			
2-CH_3O (C_2H_5O)	H	H_2SO_4	100	5-	—	46. 47
3-CH_3O (C_2H_5O)	H	H_2SO_4	60—80	2-	44.5 (80)	48. 49
3-CH_3O	H	H_2SO_4	120	2,6-	—	50
3-C_2H_5O	2-Br	H_2SO_4	55	6-	75	49
2-OH	H	H_2SO_4	0	3-; 3,5-	—	51
2-OH	6-CH_3	CH_3COOH	100	3-	—	52
2-OH	3-NO_2	H_2SO_4	80	5-	50.5	53
2-OH	5-NO_2 (COOH)	HNO_3(*d* 1.52),	50—80	3-	38 (46.5)	51
3-OH	H	H_2SO_4	0	2-	—	54
3-OH	2-NO_2	CH_3COOH	30	6-	68	55
3-OH	2-CH_3 (Cl)	H_2SO_4	0—5	4-; 6-	26.6	56
3-OH	2-CH_3	H_2SO_4	20	4,6-	52	57
3-OH	2.6-$(CH_3)_2$	H_2SO_4	20	4-	80	57
4-OH	H	H_2SO_4	100	3-	31	58
4-OH	2-OH 2-Cl	HNO_3(*d* 1,4),	100	3-	87	59
4-OH	3-CH_2CH_2Cl 6-OH	HNO_3(33%)	20	5-	48	60

For alkoxy- and hydroxy-pyridines, as for aminopyridines, the mode of the electrophilic substitution reaction is determined by the *ortho*-*para*-directing effect of the substituents present in the molecule. Table 2 presents data on the nitration of various alkoxy- and hydroxypyridines.

It is striking that in the nitration of 2-alkoxypyridines *para*-substitution takes place, while in the analogous reaction of 2-hydroxypyridines *ortho*-substitution is preferred. This difference in the mode of the nitration reactions of alkoxy- and hydroxy-derivatives of pyridine may be attributed to the tautomeric equilibrium of the hydroxy-compounds. Since 2-hydroxypyridine is present in solutions mainly in the oxo-form[61], it may also participate in the reaction in this form. This conclusion is confirmed by the preferred *ortho*-substitution in *N*-methyl-2-pyridone, which has a fixed lactam structure[51]:



Moreover, it has been established by kinetic methods that 4-hydroxypyridine, which like 2-hydroxypyridine is present in solutions in the pyridone form[61], enters into hydrogen isotope exchange in an acid medium in the oxo-form[62].

Another explanation of the *ortho*-nitration of 2-hydroxypyridine, namely that the substance reacts in the hydroxy-form and in the transition complex the NO_2 and OH groups are coordinated[63], appears to be unlikely.

The possibility in principle of the nitration of substituted pyridine in the γ-position relative to the heteroatom when the α-position is blocked was recently demonstrated by Dyumaev and coworkers[57] for 2-mono- and 2,6-di-alkyl-3-hydroxypyridines and then independently by De Selms[58] for 3-hydroxy-2-methylpyridine and 2-chloro-3-hydroxypyridine.

A systematic study of the kinetics of the nitration of a number of substituted pyridines in sulphuric acid enabled Katritzky and coworkers[64] to establish the following facts. In the nitration of more basic pyridines ($pK_a > +1$) containing electron-donating groups, the compounds react in the protonated form. Weakly basic pyridines ($pK_a < -2.5$) are nitrated as free bases. The behaviour of compounds with intermediate pK_a values has not as yet been investigated. The ring position occupied by nitro-groups is consistent with the general dependence on the type of substituents in the molecule.

Thus 2,6-dichloropyridine ($pK_a = -2.86$) is smoothly nitrated in the 3-position at 100°C.[21] At first sight this result is unexpected, since the chlorine atom in the benzene ring has a deactivating effect, but in the case of 2,6-dichloropyridine the reaction takes place via the free base, which is more reactive than the corresponding pyridinium cation[21]. In the case of 2,6- and 3,5-dimethoxypyridines, which are nitrated in the protonated form ($pK_a = 1.60$ and 4.44 respectively), the introduction of the first nitro-group reduces the basicity of substituted pyridines to such an extent that the mononitro-compounds formed ($pK_a = -3.86$ and -2.52) react further as free bases[21,64]:

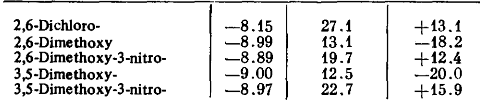


Table 3. Activation parameters for the nitration of substituted pyridine derivatives[21,64].

Substituted pyridine	H_0	E_a, kcal mole^{-1}	$\Delta S^{\neq}$, e.u.
2,6-Dichloro-	—8.15	27.1	+13.1
2,6-Dimethoxy	—8.99	13.1	—18.2
2,6-Dimethoxy-3-nitro-	—8.89	19.7	+12.4
3,5-Dimethoxy-	—9.00	12.5	—20.0
3,5-Dimethoxy-3-nitro-	—8.97	22.7	+15.9

The conclusions concerning the form in which chloro- and methoxy-pyridines are nitrated were based on a study of the kinetics of the processes, and in particular on the estimation of the activation parameters of these reactions (Table 3).

It follows from the data in Table 3 that all the above compounds may be divided into two groups with $\Delta S^{\neq}$ from +12 to +16 e.u. and from −18 to −20 e.u. This difference in activation entropy is evidence that they react by different mechanisms[39], namely that the compounds of the first group react as free bases and those of the second group in the protonated form.

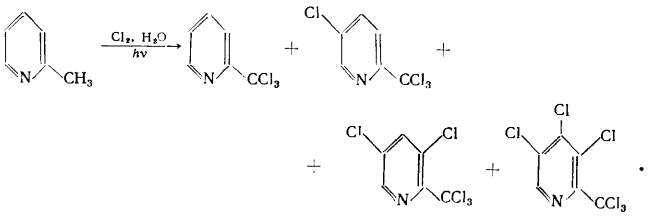
Comparison of the dependence of the nitration rate constants of substituted pyridines on the acidity of the medium with the theoretical dependence calculated for each of the possible reacting species on the basis that substituted pyridines are Hammett bases leads to the same conclusion[65].

The determination by kinetic methods of the form in which unsubstituted pyridine is nitrated is impossible. Most probably the reaction takes place as for methylpyridines, with participation of the pyridinium cation, since the pyridine nitrogen is fairly basic (for pyridine, pK_a = 5.23).[64]

A kinetic study of the mechanism of electrophilic substitution in the series of substituted pyridines has also been made in acid-catalysed hydrogen isotope exchange.

On heating, the tritilation of 2,6-lutidine and 2,4,6-collidine in a sulphuric acid–trityl ether mixture takes place in the 3- and 5-positions[20]. The study of the kinetics of these reactions showed that the protonated species are subjected to electrophilic attack; the reaction was shown to be pseudomonomolecular and to have an AS_E2 mechanism[20].

The halogenation of alkylpyridines as well as their nitration takes place under milder conditions than the halogenation of unsubstituted pyridine. Thus 2- and 4-picolines are readily brominated in the 3- and 5-positions at 80°C in the presence of aluminium chloride[26]. The chlorination of 2-picoline with chlorine water in the light involves homolytic substitution of the side chain and subsequent electrophilic substitution of the ring; under the same conditions, 3- and 4-picolines do not react[66]:



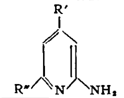
Bromination of monohalogenopyridines as well as their nitration requires more severe conditions. 2-Bromopyridine reacts with bromine in the gas phase at 300°C in the presence of an iron salt with formation of a mixture of 2,5-dibromo- and 2,3,5-tribromo-derivatives[28].

Halogenation of 2-aminopyridines takes place readily under mild conditions in the 5-position with formation of aminomonohalogenopyridines. Halogenation under severe conditions leads to 3,5-dihalogeno-derivatives. Thus *para*-substitution relative to the amino-group is preferred for 2-aminopyridines both in halogenation and in nitration (Table 4). 4-Aminopyridines are also halogenated in the 3- and 5-positions[68] and 3-aminopyridines in the 2- and 6-positions[69].

Halogenation of hydroxypyridines takes place under mild conditions. 2- and 4-Hydroxypyridines are readily brominated with bromine water, forming 3,5-dibromo-derivatives[70]. Bromination of 2,4-dihydroxypyridines under the same conditions leads only to the 3-monobromo-substituted compound. Analogous results were obtained in a study of the bromination of 2-ethoxy-4-pyridone and 4-ethoxy-2-pyridone—in these compounds the carbon atom between the carbonyl and ether groups is most reactive[71]. On the other hand, 2,4-diethoxypyridine is brominated in the 5-position, which may be associated with the steric screening of the carbon atom in the 3-position by the two ethoxy-groups[71].

In contrast to nitration, bromination of 3-hydroxypyridine takes place readily in aqueous solution at 20°C in the 2-, 4-, and 6-positions with formation of a tribromo-derivative (yield 50%).[72]

Table 4. Bromination of 2-aminopyridines with free bromine[67].

		Reaction conditions		Position of entry of bromide
R′	R″	medium	temp., °C	
CH_3	H	—		5-
H	CH_3	20 % H_2SO_4	0	5-
H	CH_3	20 % H_2SO_4	35	3,5-
CH_3	CH_3	—		5-
Br	H	CH_3COOH	0	5-
Br	H	CH_3COOH	20	3,5-
H	Br	CH_3COOH	0	5-; 3,5-
Br	Br	CH_3COOH	0	5-; 3,5-
C_2H_5	H	H_2SO_4	100	3,5-

Sulphonation of alkylpyridines takes place under the same conditions (20% oleum, 220°C, $HgSO_4$ catalyst) as that of unsubstituted pyridine but with a lower yield (for example, the yields of monosulphonic acids for 2-, 3-, and 4-picolines are 60, 23, and 40% respectively[37]), owing to a side reaction involving the oxidation of the alkyl groups in concentrated sulphuric acid. The position of the sulpho-group is determined by the *meta*-directing effect of the ring nitrogen atom, since only the 5-sulphonic acid is obtained from 3-picoline on sulphonation. In contrast to nitration, sulphonation of 2-picoline also takes place only in the 5-position. In all probability, under the above sulphonation conditions, picoline reacts in the protonated form. If one excludes the possibility of protonation, then substitution of the hydrogen atom takes place under much milder conditions. Thus 2,6-di-t-butylpyridine with a sterically screened nitrogen atom is readily sulphonated with sulphur trioxide in the 3-position at −10°C.[73]

In the sulphonation of aminopyridines substituted in different positions the location of the sulpho-groups is the same as in halogenation, but only monosulphonic acids are formed[74].

3. SUBSTITUTION IN THE DIAZINE SERIES

Diazines are more inert in electrophilic substitution reactions than monoazines let alone benzene. In the pyrimidine molecule the 5-position is most aromatic, which is consistent with the calculations of electron densities q_r and localisation energy A_e for this compound in both neutral and protonated form. In pyrazine and pyridazine molecules, where the nitrogen atoms are in the *para*- and *ortho*-positions relative to one another, the electronegative effects of both are not concerted and their resultant effect is much weakened. According to calculations, the electron charge q_r at any carbon atom in pyrazine and pyridazine, in both the neutral molecule and the cation, is higher than in the 2- and 4-positions but lower than in the 5-position of pyrimidine (Table 5).

The reactivity of unsubstituted pyrimidine is extremely low; for successful nitration, nitrosation, and sulphonation, the pyrimidine molecule must contain at least two activating electron-donating groups[77]. Thus 2- or 4-hydroxypyridine is not nitrated. 2,4-Dihydroxypyrimidine (uracil) is nitrated in boiling fuming nitric acid in the 5-position[78]. 4,6-Dihydroxypyrimidine and its derivatives are also nitrated in the 5-position but under milder conditions—in acetic acid at 20°C. This difference may be associated with the state of tautomeric equilibrium involving these dihydroxypyrimidines—it has been established by numerous spectroscopic studies that, while 2,4-dihydroxypyrimidine exists preferentially in the diketo-form, 4,6-dihydroxypyrimidine has one phenolic and one oxo-group[79]:

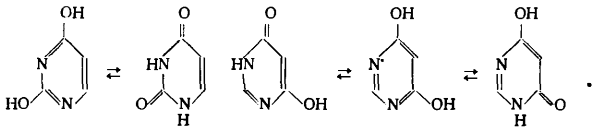
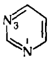
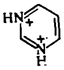
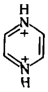
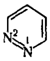
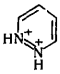


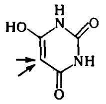
Table 5. Indices of the reactivities of pyrimidine, pyrazine, and pyridazine[32,33,75,76].

Neutral form	q_r, charge units	A_e (−β)	Position of carbon atom	A_e (−β)	q_r, charge units	Protonated form
	0.845 0.874 1.009	2.865 2.691 2.539	2- 4- 5-	3.456 3.146 2.579	0.467 0.632 1.029	
	0.926	2.664	2-	2.667	0.735	
	0.970 0.982	—	3- 4-	—	0.866 0.922	

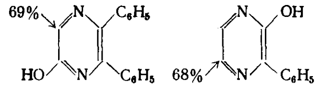
When the pyrimidine molecule contains together with the hydroxy-group also an amino- or alkylamino-group, nitration takes place in the 5-position at 50–60°C (nitric acid in sulphuric acid)[80,81].

For successful halogenation of pyrimidine derivatives, it is sufficient if one hydroxy or amino-group or two alkoxy-groups are present in the 2-, 4-, or 6-positions[82]. Halogenation takes place readily in the 5-position on heating with halogenosuccinimide in acetic acid or chloroform[82].

The halogenation of 2,4-dihydroxypyrimidine (uracil) and 2,4,6-dihydroxypyrimidine (barbituric acid) takes place in a more complex manner. On halogenation, barbituric acid gives rise initially to 5-mono- and then 5,5-di-halogeno-substituted compounds. The mechanism of this reaction has not been completely elucidated—it may involve the addition of HOHal to the double bond between the C_4 and C_5 atoms with subsequent dehydration[77]. Uracil usually yields monohalogeno-derivatives, but bromination in an aqueous medium yields 5,5-dibromo-2,4,6-trihydroxy-4,5-dihydropyrimidine[83], i.e. initially there is substitution in the 5-position accompanied by 4,5-addition[84]. This reaction differs fundamentally from the halogenation of barbituric acid:

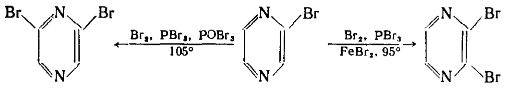


Electrophilic substitution in the pyrazine series, as in the pyrimidine series, usually requires the presence in the molecule of activating hydroxy- or amino-groups[85]. Thus arylpyrazines are nitrated in the benzene ring while the nitration of 2-hydroxy-5,6-diphenylpyrazine with fuming nitric acid in acetic acid at 25°C takes place in high yield in the 3-position of the pyrazine ring[86]. 2-Hydroxy-3-phenylpyrazine is nitrated under the same conditions in the *para*-position relative to the hydroxy-group[87]:



The halogenation of pyrazine can take place also in the absence of activating groups in the molecule, but under very severe conditions—in the vapour phase at 400°C.[88] Bromopyrazine is obtained also when pyrazine hydrobromide is treated with bromine in an inert solvent: the reaction results initially in the formation of a perbromide, which on heating to 200–250°C rearranges to 2-bromopyrazine[89].

Depending on the reaction conditions, the bromination of monobromopyrazine takes place in different positions in the molecule and leads to 2,3-[90] or 2,6-dibromo-derivatives[91]:



The mode of halogenation of hydroxypyrazines is determined by the *ortho–para*-directing effect of the hydroxy-group. Thus 2-hydroxy-3-methylpyrazine is brominated with bromine in chloroform in the 5-position (yield 20%); under the same conditions, 2-hydroxy-5,6-dimethylpyrazine gives the 3-bromo-derivatives (yield 61%), while 2-hydroxy-3,5-dimethylpyrazine is not brominated at all[87].

Substitution in the pyridazine series has been inadequately investigated. The pyridazine ring is very resistant to electrophilic substitution reactions. Powerful nitrating agents either have no effect at all on pyridazine or cause it to char[92]. 3-Pyridazinone also does not change under the action of the nitrating mixture, probably because of the low reactivity of the cation formed[93]. The introduction of a nitro-group into the pyridazine molecule takes place successfully only when amino-derivatives are employed and involves the rearrangement of the corresponding nitroamines. Thus nitration of 4-amino-3-methoxy-6-methylpyridazine with potassium nitrate in sulphuric acid at 20°C takes place in the 5-position[93], while 3,5-diaminopyridazine is nitrated in the 4-position[94].

Chlorination of 6-methyl-2-phenyl-3-pyridazinone with phosphorus pentachloride at 160°C leads mainly to the 4-chloro-derivative[95], while 3,6-dichloropyridazine forms with phosphorus pentachloride the 3,4,5,6-tetrachloro-derivative[96]. Under these conditions, 2,6-dimethyl-3-pyridazinone is not chlorinated and on reaction with chlorine at 100°C is substituted in the 5-position[97].

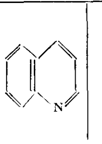
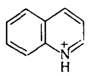
4. SUBSTITUTION IN THE BENZOMONOAZINE (QUINOLINE, ISOQUINOLINE, ACRIDINE) SERIES

In heteroatomic compounds containing a condensed benzene ring electrophilic substitution may take place both in the benzene and in the heterocyclic ring, depending on the reaction conditions.

In sulphuric acid quinoline is substituted in the 5- and 8-position. Nitration of quinoline with fuming nitric acid in concentrated sulphuric acid at 0°C yields a mixture of almost equal amounts of the 5- and 8-mononitro-derivatives[98].

Quinoline is nitrated faster than pyridine because of the presence of the condensed benzene ring; the rate of this process can be readily measured. The considerable rate of reaction (higher by a factor of 10^2 than expected for a diffusion-dependent process with participation of the free base) and the variation of the reaction rate constant with the acidity of the medium in the range 85–98% sulphuric acid are evidence that the nitronium cation reacts with the protonated species—the quinolinium cation[99]. The participation of quinoline in the nitration reaction as a protonated species is consistent also with the calculated entropy of activation for this reaction (−9.3 e.u; see p. 629) and is confirmed by a comparison of the rates of nitration of quinoline and the methylquinolinium ion[100].

Table 6. Indices of the reactivity of quinoline[98,101,102].

Neutral form	q_r, charge units	A_e * $(-\beta)$	Position of carbon atom	A_e ** $(-\beta)$	q_r, charge units	Protonated form
	0.896	2.725	2-	4.75	0.690	
	1.008	2.487	3-	1.97	1.267	
	0.932	2.500	4-	3.63	0.787	
	0.988	2.350	5-	1.82	0.967	
	1.003	2.475	6-	1.97	1.078	
	0.984	2.544	7-	2.26	0.950	
	1.012	2.306	8-	1.60	1.346	

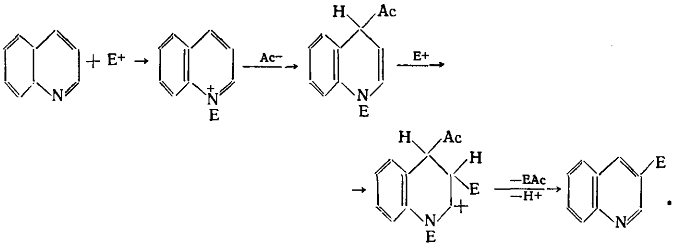
* Data presented in a graphical form.

** The energy data (in kcal mole^{-1}) have been expressed in units of $-\beta$, assuming that $\beta = 6$ kcal mole^{-1}.

It is noteworthy that the location of electrophilic substituents in the quinolinium cation is in good agreement with the calculated localisation energies for electrophilic substitution (A_e is a minimum for the 5- and 8-positions) but is in much worse agreement with the distribution of electron densities in this system (Table 6).

Calculation of the partial rates of nitration of quinoline and naphthalene in an acid medium shows that the 5- and 8-positions of the quinolinium ion are deactivated compared with the 1-position of naphthalene by a factor of 10^{10}. This result differs from the data obtained by the calculation of the localisation energy, which shows that the 5- and 8-positions of the quinolinium ion are less reactive than the 1-position of naphthalene by a factor of 5 and 100 respectively[99]. Probably the methods employed to calculate the localisation energy to a large extent underestimate the effects of the heteroatom of the aromatic system.

In the nitration of quinoline with nitric acid in acetic anhydride a low yield (about 6%) is obtained of 3-nitroquinoline and traces (0.7%) of the 6- and 8-isomers[103]. Probably under these conditions the non-protonated form mainly reacts; then the distribution of π-electron densities in the neutral quinoline molecule correctly indicates the location of the substituent in the 3-, 6-, and 8-positions but is inconsistent with the relative amounts of the isomers (3 > 6 and 8). This finding can be readily explained if one assumes that the reaction involves an addition–elimination mechanism, i.e. initially there is 1,2- or 1,4-addition of a weak nucleophilic agent (acetyl anion) and then substitution in the dihydroquinoline system[103]. Since this system does not have a positive charge, one may expect on substitution a correlation between the reactivity and the distribution of π-electron density. Calculations for 1,2-dihydroquinoline yields the following sequence of the decrease of π-electron density: 8 > 6 > 3, and for 1,4-dihydroquinoline: 3 > 6 > 8.[101] Thus the proposed mechanism for electrophilic substitution in the neutral quinoline molecule involves a preliminary 1,4-addition stage:



In the halogenation of quinoline the location of the substituent depends on the acidity of the medium, as happens in the nitration reaction. Thus, in the bromination of quinoline in sulphuric acid substitution takes place in the 5- and 8-positions[104] and in acetic acid in the 3-, 6-, and 8-positions[105]. Hence by varying the experimental conditions for the electrophilic substitution reaction, it is possible to obtain a number of quinoline derivatives differing in the positions of the substituents (Table 7).

Table 7. Bromination of quinoline[106].

Position of substituent	Yield, %	Reaction conditions
2-Bromo-	(50—60)	Br_2, 500°C, vapour phase
3-Bromo-	(91)	Br_2, CCl_4, pyridine, heat
6-Bromo-	(~2)	
4-Bromo-		heat treatment of 3-bromoquinoline hydrobromide, 300°C
5-Bromo-	(28)	Br_2, Ag_2SO_4, H_2SO_4
8-Bromo-	(29)	
1,1-Dibromo-	(~100)	Br_2, CCl_4, in the cold
3,6-Dibromo-	(35)	Br_2, glacial CH_3COOH
3,6,8-Tribromo-		
5,8-Dibromo	(43)	$2Br_2$, Ag_2SO_4, H_2SO_4
5,6,8-Tribromo-		$3Br_2$, Ag_2SO_4, H_2SO_4

Depending on temperature, the sulphonation of quinoline (200–300°C) yields quinoline-5-, quinoline-6-, quinoline-7-, and quinoline-8-sulphonic acids or their mixture[107], the formation of these derivatives being probably determined by the stability of the quinolinium ion.

Quinoline substituted in the benzene ring usually directs electrophilic agents to the 5- or 8-position in an acid medium regardless of the nature of the substituent already present. Thus, electrophilic substitution of 8-hydroxyquinoline—halogenation, sulphonation, nitrosation, and mercuration—takes place preferentially in the 5-position, while under more severe conditions 5,7-disubstitution takes place. It is interesting that in the direct nitration of 8-hydroxyquinoline with 37% nitric acid in sulphuric acid at 20°C it is impossible to isolate the mononitro-compound, only 8-hydroxy-5,7-dinitroquinoline being obtained in 57% yield[108].

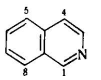
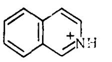
The presence of substituents in the pyridine ring of quinoline can alter significantly the position of the reaction centre relative to unsubstituted quinoline. Thus 4-hydroxyquinoline is nitrated in sulphuric acid as the protonated species, largely with formation of the 6-nitro-derivative[109].

Electrophilic substitution in two different positions has been observed for isoquinoline, as for quinoline. Nitration of isoquinoline by fuming nitric acid in concentrated sulphuric acid at 0°C gives a mixture of 5- and 8-mononitroisoquinolines, the 5-nitro-isomer predominating considerably (90.4%)[98], while under more severe conditions only the 5,7-dinitro-compound is formed. In the study of the kinetics of the nitration of isoquinoline it has been established that the reaction takes place with participation of the protonated form of isoquinoline, as in the nitration of quinoline. The simultaneous nitration of a quinoline–isoquinoline mixture shows that the ratio of the reactivities of these compounds is 1 : 24.5. [98]

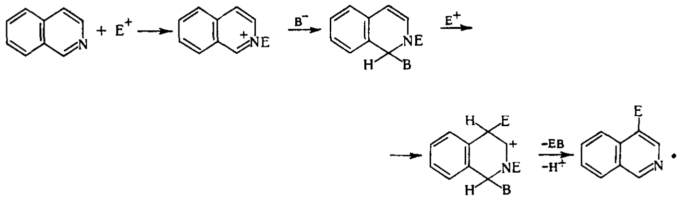
The fact that the reactivity of isoquinoline in electrophilic substitution reactions is higher than that of quinoline follows also from a comparison of the conditions for the sulphonation of these compounds. Isoquinoline is sulphonated under milder conditions (40% oleum, 180–200°C) than quinoline, and only isoquinoline-5-sulphonic acid is formed[110].

The location of the nitro- and sulpho-groups in the 5-position in the nitration and sulphonation of isoquinoline in a strong acid is in good agreement with the calculated localisation energies A_e for electrophilic substitution (Table 8).

Table 8. Indices of the reactivity of isoquinoline[98,111].

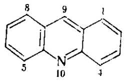
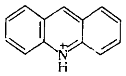
Position	 q_r, charge units	 A_e, kcal mole^{-1}
1-	0.844	—21.8
3-	0.943	—13.5
4-	0.973	—13.0
5-	1.001	—9.5
6-	0.968	—13.5
7-	0.992	—11.8
8-	0.971	—10.9

The mercuration of isoquinoline with mercury(II) acetate at 150–160°C takes place smoothly in the 4-position[112]; bromination takes place in the same position when isoquinolinium perbromide or its salts are heated[113]. Substitution in the 4-position is inconsistent with the distribution of electron densities q_r in the neutral isoquinoline molecule—calculation shows that the electron densities decrease in the sequence $5 > 7 > 4 \simeq 8$ (Table 8). The experimentally observed mode of reaction can be accounted for by a 1,2-addition mechanism:



Calculation of the distribution of π-electron density in the 1,2-dihydrocation yields a higher value for the 4-position[34].

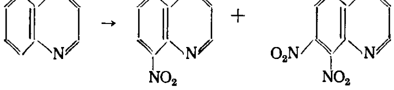
Table 9. Indices of the reactivity of acridine[98,115].

Position	 q_r, charge units	 A_e, kcal mole^{-1}
1-	0.984	—12.4
2-	1.005	—9.0
3-	0.979	—16.4
4-	1.016	—7.3
9-	0.915	—21.1

Substitution in the acridine series has been investigated in less detail. Nitration of acridine in sulphuric acid gives a mixture of 13% of the 4- and 68% of the 2-mononitro-derivative and a certain amount of 1- (3%) and 3-isomers (< 1%)[114]. This ratio of the 2- and 4-substituted compounds is unexpected, since it is inconsistent either with the distribution of π-electron density or with the localisation energies (Table 9). The reaction probably proceeds via the protonated form of the acridine molecule[98]. Evidently the above calculations fail to take adequate account of the inductive effect of the nitrogen atom in the α-position of the acridine molecule.

5. SUBSTITUTION IN THE BENZODIAZINE (QUINOXALINE, PHENAZINE, CINNOLINE, QUINAZOLINE) SERIES

Quinoxaline is resistant to nitration under mild conditions; when it is treated with fuming nitric acid in oleum at 90°C for 24 h, 1.5% of 5-mononitroquinoxaline and 24% of 5,6-dinitroquinoxaline are obtained[116]. The location of the electrophilic agent in the 5-position agrees well with calculated data (Table 10). It is interesting to note that the second nitro-group enters the *ortho*-position and not the *meta*-position relative to the first:



The presence of polar substituents in both the pyrazine and the benzene ring of quinoxaline favours electrophilic substitution. Nitration of 6-methoxyquinoxaline with potassium nitrate in sulphuric acid at 0°C takes place readily in the 5-position; 5-methoxyquinoxaline yields on nitration the 6,8-dinitro-derivative, and it is impossible to isolate the mononitro-compound[117].

The location of the substituent in the nitration of 2-hydroxyquinoxaline, which is a very weak base ($pK_a = 1.37$), depends on the acidity of the medium; in acetic acid the 7-nitro-derivative is obtained[117], while in sulphuric acid the product is the 6-isomer[118]. Possibly the neutral molecule is nitrated in acetic acid and the monocation in sulphuric acid:

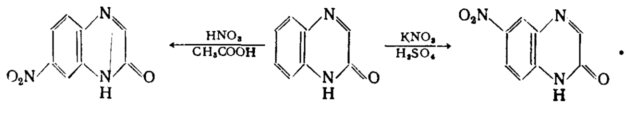
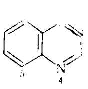
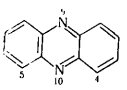


Table 10. Indices of the reactivities of quinoxaline and phenazine[98,102,111].

Structure	Neutral form q_r, charge units	Dication A_e, kcal mole^{-1}	Position of carbon atom	Dication A_e, kcal mole^{-1}	Neutral form q_r, charge units	Structure
			1-	—13.5	0.991	
	0.902	—31.8	2-	—17.9	0.955	
	1.002	—13.3	5-			
	0.987	—16.8	6-			

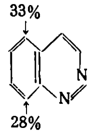
Substitution in the 6-position is observed also when quinoxaline-2,3-dione is treated with potassium nitrate in sulphuric acid; in the presence of an excess of the nitrate, the 6,7-dinitro-derivative is formed[119]. When quinoxaline is refluxed in aqueous nitric acid, the product is 6-nitroquinoxaline-2,3-dione, probably in consequence of the oxidation of quinoxaline and subsequent nitration of quinoxaline-2,3-dione[120].

Like quinoxaline, phenazine (Table 10) reacts with electrophilic agents only under very severe conditions. The α-carbon atoms are reactive in this case, in full agreement with calculation. Probably both quinoxaline and phenazine interact in the protonated form with electrophilic agents in an acid medium.

The nitration of phenazine with a mixture of nitric acid ($d = 1.42$) and sulphuric acid at 130°C gives 1-nitrophenazine in 1.5% yield. It is striking that in the nitration of phenazine under conditions corresponding to the synthesis of dinitro-derivatives, the nitro-groups enter into different benzene rings. Thus in the reaction with sulphuric acid with a tenfold excess of nitric acid ($d = 1.48$) at 70°C, a mixture of 1,5- and 1,8-dinitrophenazines is formed in 80% yield[121].

When phenazine derivatives with electron-donating substituents in the β-position are nitrated, the nitro-group enters the α-position adjacent to the substituent already present; in the nitration of substituted phenazines with electron-donating substituents in the α-position, the nitro-group enters the *para*-position relative to the substituent already present, with formation of 1,4-substituted phenazine derivatives[121].

Substitution reactions in the cinnoline and quinazoline series have been investigated much less than in the quinoxaline series and in the phthalazine series they are altogether unknown. Nitration of cinnoline with fuming nitric acid in concentrated sulphuric acid between −5° and 20°C yields a mixture of almost equal amounts of the 5- and 8-nitrocinnolines:

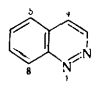
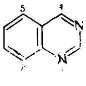


Under the same conditions, 4-methylcinnoline gives only the 8-nitro-derivative in 49% yield[122].

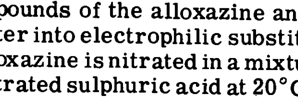
By comparing the rates of nitration of the 2-methylcinnolinium, 2-methylisoquinolinium, and isoquinolinium cations, it has been shown that in 76–83% sulphuric acid cinnoline is nitrated as the cation[123]. It is known that the cinnolinium monocation is formed with the positive charge in the 2-position[124]. The non-protonated nitrogen atom (N_1) deactivates the system of the cinnolinium cation to a greater extent than that of the isoquinolinium cation by a factor of 2×10^2 and the carbon atom in the 5-position is deactivated more than in the 8-position[123]. This leads to an increase in the amount of the 8-nitro-isomer in the nitration of cinnoline compared with the amount of the nitro-derivative formed in the nitration of isoquinoline.

The location of nitro-groups in the nitration of cinnoline agrees well with the distribution of π-electron density in the neutral molecule of this compound and the localisation energy of its cation (Table 11).

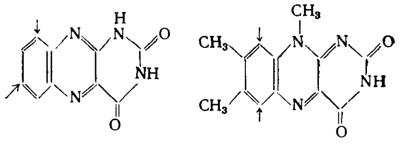
Table 11. Indices of the reactivities of cinnoline and quinazoline[98,102].

Structure	Neutral form q_r, charge units	Dication A_e, kcal mole^{-1}	Position of carbon atom	Dication A_e, kcal mole^{-1}	Neutral form q_r, charge units	Structure
			2-	—33.5	0.841	
	0.950	—16.8	3-			
	0.938	—31.5	4-	—36.8	0.830	
	0.991	—12.1	5-	—14.5	0.973	
	0.987	—15.1	6-	—13.5	1.003	
	0.983	—15.1	7-	—18.5	0.969	
	0.998	—12.1	8-	—10.9	1.016	

In contrast to the nitration of quinoline and isoquinoline, quinazoline is nitrated in an acid medium in the 6-position[125], which agrees poorly with theoretical calculations (Table 11). However, in a study of ultraviolet spectra of quinazoline solutions in sulphuric acid it has been established that the quinazolinium cation readily undergoes covalent hydration[126] and consequently electrophilic substitution in the hydrated cation takes place in the *para*-position relative to the NH group:



It is noteworthy that, among more complex condensed structures, compounds of the alloxazine and isoalloxazine series readily enter into electrophilic substitution reactions. Unsubstituted alloxazine is nitrated in a mixture of fuming nitric and concentrated sulphuric acid at 20°C with formation of the 6- and 8-mononitro-derivatives in proportions of 2 : 3, while in the nitration in oleum at 70°C 6,8-dinitroalloxazine is obtained[127]. This mode of the alloxazine nitration reaction corresponds to the distribution of π-electron density in the neutral alloxazine molecule[128]: there are no calculated data available in the literature for protonated structures of this series.

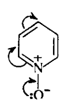


6,7-Dimethyl-substituted alloxazines and isoalloxazines are nitrated in the 5- and 8-positions under mild conditions[129].

6. ELECTROPHILIC SUBSTITUTION OF HETEROAROMATIC *N*-OXIDES

Substitution reactions in the series of *N*-oxides of nitrogen-containing heterocyclic bases, which are unusually reactive, are of particular interest. Linton[130], Jaffé[131], and Katritzky et al.[132] demonstrated the presence in heterocyclic *N*-oxides of two opposed electronic effects due to the electron-accepting properties of the positively charged nitrogen atom on the one hand and the conjugation of the free electron pair of the oxygen atom in the N→O group with the π-electrons of the ring on the other. By virtue of the dual effect of the *N*-oxide group on the electronic structure of the heteroaromatic ring, electrophilic and nucleophilic substitution in this series may involve the same position in the molecule[133,134].

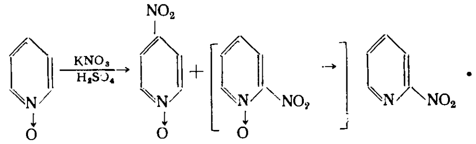
At the instant of the electrophilic substitution reaction, the *N*-oxide group in the neutral molecule is readily polarised and exhibits at the same time electron-donating properties and a *para*-orienting effect. An electrophilic agent may attack the ring of the *N*-oxide in the α- or γ-position, where, by virtue of the positive effect of conjugation, an enhanced electron density is created. However, the reaction in the γ-position should take place particularly readily, since the effect of conjugation in the α-position is partially compensated by the opposed inductive effect of the neighbouring nitrogen atom:



The presence of the N→O group in the molecule not only alters the mode of substitution in the initial heterocycle but also facilitates electrophilic substitution.

Tupitsyn and coworkers[135] investigated the kinetics of base-catalysed deuterium exchange involving methyl groups in isomeric picolines, quinaldines and their *N*-oxides, reactions which simulate electrophilic substitution in a side-chain of heterocycles, and showed that the *N*-oxides undergo exchange much faster than the non-oxidised bases. The authors discovered the main features of the mechanism of the transmission of the electronic effects of the heteroatoms on the reaction centre[136,137]. Similarly reactions involving substitution of the ring hydrogen atoms are faster with the *N*-oxides than with the initial heterocycles.

Indeed, in contrast to the nitration of pyridine, the nitration of pyridine *N*-oxide with potassium nitrate in sulphuric acid at 100°C takes place in the 4-position in 94% yield[138]. It is noteworthy that this involves the formation also of a small amount (1.5–4%) of 2-nitropyridine, probably in consequence of the reduction of its *N*-oxide[139]:

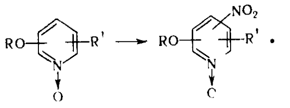


The *N*-oxides of alkyl- and halogeno-substituted pyridines are smoothly nitrated in the 4-position. Thus the *N*-oxides of 2-mono- and 2,6-di-methyl-[138], chloro[140,141], and bromo-pyridines[142,143] are nitrated with nitric acid in sulphuric acid at 90–100°C with formation of 4-nitro-derivatives as the sole reaction products. The same mode of substitution is noted also in the nitration of the *N*-oxides of 3-alkyl-, 3,5- or 2,5-dialkyl-[144–146], or 3-halogeno-pyridines[147,148] under identical conditions. Thus the strong *para*-directing effect of the *N*-oxide group is shown in these reactions.

The *N*-oxides of 2,4-lutidine and 2,4,6-collidine, where the 4-position is blocked by an alkyl group, are resistant to nitration under similar conditions[149].

It is interesting to note that, in the presence of the bulky t-butyl group in the 3-position of pyridine *N*-oxide, nitration takes place not in the γ-position but in the α-position and subsequent reduction leads to 3-t-butyl-2-nitro- or 3-t-butyl-6-nitro-pyridines; the isopropyl group does not show this type of effect[150].

Table 12. Nitration of the *N*-oxides of alkoxy- and hydroxy-pyridines with nitric acid



OR	R′	Reaction conditions		Position of entry of NO_2 group	Yield, %	Refs.
		medium	temp., °C			
2-OC_2H_5	H	H_2SO_4	85	4-	10—15	142
(OCH_3)	H	H_2SO_4	75	4-	55—60	151
3-OC_2H_5	H	H_2SO_4	85	4-	70—80	142
(OCH_3)	H	H_2SO_4	75	4-	70—75	151
3-OH	H	H_2SO_4	0—15	2-	60.5	152
2-OH	H	CH_3COOH	0	5-	67	153
2-OH	H	CH_3COOH	40	3,5-	—	154
4-OH	H	CH_3COOH	90—100	3,5-	80	155
4-OH	2-CH_3	CH_3COOH	65—75	3,5-	15	156
4-OH	3- or 5-NO_2	CH_3COOH	65—75	3,5-	—	156
3-OC_2H_5	5-OC_2H_5	H_2SO_4	0	2-	100	157
3-OC_2H_5	5-OC_2H_5	H_2SO_4	85	2,6-	90—95*	157
3-OCH_3	5-Br	H_2SO_4	30—35	2-	80	158
3-OCH_3	5-OCH_3	H_2SO_4	0°	2-	—	158

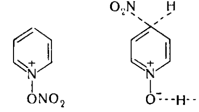
* With simultaneous de-oxidation of the *N*-oxide.

In electrophilic substitution reactions in the series of pyridine *N*-oxides the directing effect of the N→O group is greater than that of the alkoxy-group but smaller than the effect of the hydroxy-group. This is consistent with substitution in the 4-position in the *N*-oxides of alkoxy-pyridines and in the 2- or 3- and 5-positions of the *N*-oxides of hydroxy-derivatives of pyridine (Table 12).

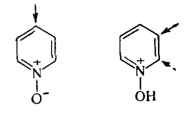
It is striking that in the presence of two alkoxy-groups in the 3- and 5-positions, substitution takes place at the C_2 and C_6 carbon atoms[157,158], the authors explaining this effect by the steric hindrance arising when the substitution reaction involves the 4-position. However, subsequently, using kinetic methods, it was shown that the difference in the location of the nitro-group in the *N*-oxides of 2- [2–6? (Ed. of Translation)] and 3,5-dialkoxypyridines is due to the fact that they undergo nitration in different forms[159].

It should, however, be noted that the mechanism of electrophilic substitution reactions in the series of pyridine *N*-oxides cannot be regarded as finally elucidated. The conclusions drawn from the study of the kinetics of the reactions may be contradictory when they are based on different kinetic criteria for the determination of the nature of the reactant. Thus Schofield and coworkers[160] showed that the *N*-methoxypyridinium cation does not react with nitric acid in 88% sulphuric acid at 95–125°C, i.e. under conditions where the *N*-oxide of pyridine is readily substituted in the γ-position. Probably the neutral molecule of the *N*-oxide participates in the latter reaction.

Subsequently, on the basis of a study of the dependence of the rate constant for the nitration of the *N*-oxide of 2,6-dimethylpyridine in the 4-position on the acidity of the medium, it was shown that the *N*-oxide of 2,6-lutidine is also nitrated as the neutral molecule[161]. The following activation parameters are quoted for these reactions: $E = 23.9$ kcal mole^{-1} and $\lg A = 10.7$ at 25°C in 81.4% sulphuric acid[161]. However, subsequently the same authors' calculations showed that the theoretical value is $\lg A = 4$ for this process and is even smaller when the *N*-oxide reacts in the protonated form[162]. Therefore it is possible that the reaction takes place either with formation of a pre-equilibrium *O*-nitro-complex, which then slowly rearranges to the 4-nitro-compound, or the nitronium cation is bound to the C_4 carbon atom of the pyridine ring and the proton is removed synchronously from the *N*-oxide group[162]:



On the other hand, in a study of the kinetics of the nitration of a number of substituted *N*-oxides of pyridine, Katritzky and coworkers[159] concluded that in the case of substitution in the 4-position *N*-oxides react as the free bases and in the case of 2- or 3-substitution as the protonated species:



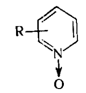
The conclusion that in the nitration in the 4-position the *N*-oxides of substituted pyridines react as the free bases is confirmed also by the finding that the entropy of activation for these compounds (Table 13) is much lower than −20 e.u., i.e. the theoretical entropy of activation for the reaction of two charged species[39]. The estimation of the absolute reaction rates leads to the same conclusion: the experimental rate of nitration of the above *N*-oxides (10^{-1}–10^{-5} litre mole s^{-1}) is much lower than the limiting rate of the diffusion process with participation of the free bases (8.5×10^8 litre mole s^{-1}).

The kinetics of the nitration of the *N*-oxides of substituted pyridines in the β-position have been investigated for the *N*-oxides of 2,4,6-trimethoxy-, 2,6-dimethoxy-, and 4-methoxy-2,6-dimethylpyridines and the kinetics of α-nitration have been studied for the *N*-oxides of 3,5-dimethoxy- and 3,5-dimethoxy-2-nitropyridines[159].

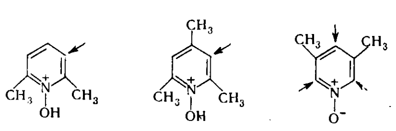
Examination of the dependence of the rate constants for α- and β-nitration on the acidity of the medium established that in all the examples quoted *N*-oxides react in the protonated form. For substitution in the α-position, this is also confirmed by a comparison of the rates of nitration of the *N*-oxides of 3,5-dimethoxypyridine and the 1,3,5-trimethoxypyridinium cation (this method has not been used for β-substitution).

The activation parameters have been determined for the nitration of substituted pyridine *N*-oxides in the α- or β-positions, as for γ-nitration (see above) (Table 13). The entropies of activation in the β-position ($\Delta S^{\neq}$ between −17 and −26 e.u.) agree well with the expected value of $\Delta S^{\neq}$ for a reaction with participation of the protonated form of the *N*-oxide. However, the entropy of activation for α-nitration (−12.3 e.u.) is lower than the expected value (−20 e.u.)[39].

Table 13. Activation parameters for the nitration of substituted pyridine *N*-oxides[159].

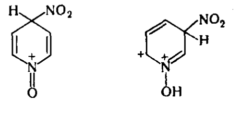
 Position of substituent	Position of entry of NO_2 group	H_2SO_4, %	E_a, kcal mole^{-1}	lg*A*	$\Delta S^{\neq}$
—	4-	87.9	23.5		
3.5-$(CH_3)_2$	4-	91.8	25.3	19.0	+26.3
2.6-Cl_2	4-	82.4	26.9	13.5	+1.5
3.5-Cl_2	4-	90.0	27.8	14.0	+15.1
2.4,6-$(OCH_3)_3$	3-	81.0	16.9	9.5	−17.2
2.6-$(OCH_3)_2$	3-	84.8	14.5	6.9	−26.1
2.6-$(CH_3)_2$-4-OCH_3	3-	90.3	16.6	9.1	−18.5
3.5-$(OCH_3)_2$	2-	82.3	20.3	10.5	−12.3
3.5-$(OCH_3)_2$-2-NO_2	6-	82.0	23.8	10.4	−13.0
1,3,5-Trimethoxypyridinium perchlorate	2-	82.3	14.5	6.9	−29.0

Conclusions analogous to those obtained as a result of the study of the kinetics of the nitration of substituted pyridine *N*-oxides were arrived at also in a study of the kinetics of acid-catalysed isotope exchange of hydrogen involving the same compounds. Katritzky and coworkers[163] established that the deuteration of 2,6-lutidine and 2,4,6-collidine *N*-oxides at 200–250°C and an acidity $H_0 = 8.7$ takes place in the 3-position in the protonated form, while the exchange of hydrogen in the *N*-oxide of 3,5-dimethylpyridine is observed in the 2-, 4-, and 6-positions with participation of the free base:



Under the same conditions, the rate of exchange of hydrogen in the β-position of pyridine *N*-oxide is only one-quarter of the rate of exchange in unoxidised pyridine, i.e. the $\overset{+}{N}$–OH group has a more deactivating effect than $\overset{+}{N}$H, in consequence of the negative inductive effect of the OH groups[164].

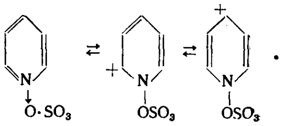
Comparison of the nitration and hydrogen isotope exchange reactions of the *N*-oxides of substituted pyridines reveals an interesting feature: the nitration takes place preferentially in the 4-position in the free base of the *N*-oxide, while the slower and consequently more selective hydrogen exchange reaction involves the 3-position of the cation of the *N*-oxide, which is present in excess but is less reactive (for example, in the case of the *N*-oxide of 2,6-lutidine). This result is unexpected because of the high reactivity of the nitronium cation. The proposed explanation of this difference in the location of electrophilic agents is associated with the difference in the stabilities of the transition states in 4- and 3-nitration; possibly the electron-accepting effect of the NO_2 group in the case of β-substitution leads to a marked destabilisation of the doubly charged intermediate structure[163]:



Nevertheless sulphonation of *N*-oxides takes place preferentially in the 3-position, which makes this explanation less convincing, since the sulpho-group is also a powerful electron acceptor.

The appreciable conjugation effect of the N→O group in the nitration of pyridine *N*-oxide becomes very slight in the sulphonation reaction. Pyridine *N*-oxide is sulphonated under severe conditions (in 20% oleum at 220°C in the presence of mercuric sulphate) with formation of the 3-sulphonic acid (yield 67%).[165] Probably the *N*-hydroxypyridinium cation is sulphonated; substitution in the 3-position of the cations is in good agreement with the calculated localisation energies for electrophilic substitution (the values of A_e for the 2-, 3-, and 4-positions are respectively 2.70, 2.58, and 2.67 – β units)[166].

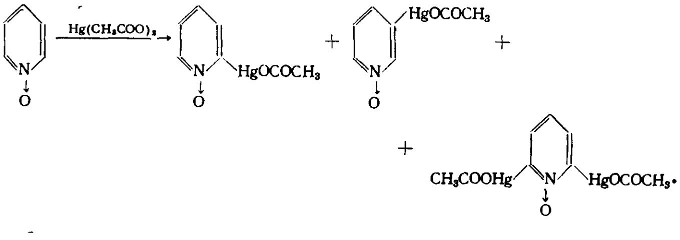
den Hertog et al. [167] showed that the bromination of pyridine *N*-oxide also takes place under severe conditions: with an excess of bromine in 90% sulphuric acid with heating to 200°C in the presence of catalytic amounts of silver sulphate—and leads to the formation of 2- and 4-monobromo-derivatives in proportions of 1 : 2 with an overall yield of about 10%. Bromination in 65% oleum at 120°C gives only the 3-bromo-compound and it is possible that an adduct of sulphur trioxide and pyridine *N*-oxide reacts[168]:



Nor can one exclude the possibility that in this case the reaction involves the protonated form of the *N*-oxide.

When the pyridine ring contains powerful electron-donating groups, the mode of halogenation of the *N*-oxide is determined by the conjugation effects of these groups and substitution takes place under milder conditions. Bromination of 2-hydroxypyridine *N*-oxide with bromine in acetic acid takes place in the 3-position[169], while iodination of 3-hydroxypyridine *N*-oxide gives the 4,6-di-iodo-derivative[170].

The mercuration of pyridine *N*-oxide with mercury(II) acetate in acetic acid at 100°C gives a mixture of 2-, 2,6-, and 3-substituted compounds in proportions of 8 : 1 : 2[171]:



The predominance of the α- and not the γ-derivative in this reaction may be attributed to a difference in the mechanism of the nitration and mercuration of *N*-oxides.

Mercuration with mercury(II) sulphate in sulphuric acid at 170°C yields only the 3-, and 2-monomercuri-derivatives in proportions of 2 : 1.[171] The higher amount of the β-isomer is probably associated with the protonation of the *N*-oxide.

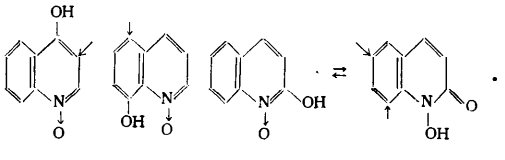
Quinoline *N*-oxide undergoes electrophilic substitution more readily than pyridine *N*-oxide. In the nitration of quinoline *N*-oxide in sulphuric acid, Ochiai[172] observed an interesting temperature variation: at 10°C a mixture of the 5- and 8-isomers is formed but on raising the temperature the formation of 4-nitroquinoline *N*-oxide becomes appreciable and this nitro-derivative constitutes the main reaction product at 70°C. Above 100°C reduction begins, and the amount of the 4-nitro-compound falls.

Later it was found for the *N*-oxides of 6-substituted quinoline derivatives that the directing effect of the N→O group in the nitration reaction depends to an even greater extent on the concentration of sulphuric acid than on temperature[173]. At the same temperature the amount of the 4-nitro-derivative diminishes and that of the 5- and 8-nitro-derivatives increases with the acidity of the medium. The use of the usual kinetic criteria enabled Schofield and coworkers[162] to establish that the 1-hydroxyquinolinium cation undergoes 5- and 8-nitration and the free base of quinoline *N*-oxide undergoes 4-nitration.

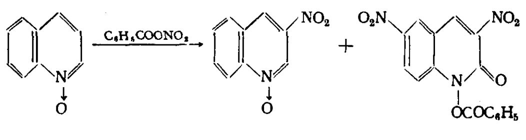
It is striking that the rate constant for the nitration of the 1-hydroxyquinolinium cation is lower than that for the quinolinium cation (0.78×10^4 and 1.67×10^4 litre $mole^{-1}$ s^{-1} respectively[162]); consequently in the protonated form the *N*-oxide group plays the role of a deactivating electron-accepting substituent. The same effect is shown also in the electrophilic deuteration of quinoline and quinoline *N*-oxide in an acid medium, where both compounds react in the protonated form. Substitution involves the same positions (the 3-position in the benzene ring) but in the case of the *N*-oxide the yield of the reaction is lower[174].

In the series of quinoline *N*-oxide derivatives the usual direction to the *para*-position relative to the N→O group occurs when methyl[175] and halogeno-derivatives[176] are nitrated in concentrated sulphuric acid at 40–70°C. At the same time the alkoxy-group, in contrast to alkoxypyridine *N*-oxides, is a more powerful directing agent in this series than the N→O group[177].

Hydroxyquinoline *N*-oxides are nitrated in the *ortho*- and *para*-positions relative to the hydroxy-group under milder conditions—with nitric acid in glacial acetic acid[178–180]:

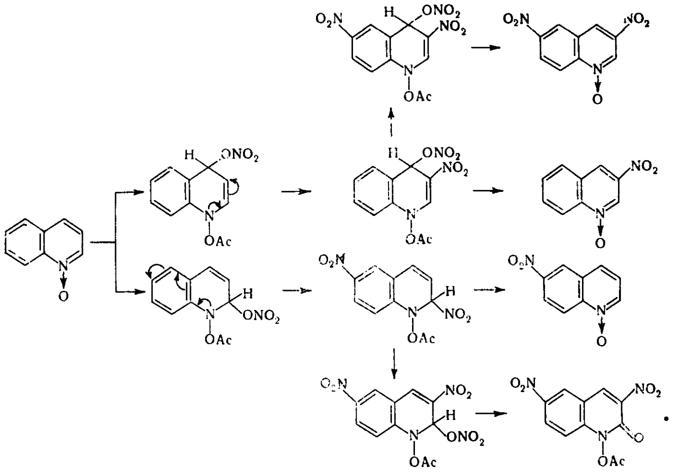


In the nitration of quinoline *N*-oxide with benzoyl nitrate in a neutral medium (in chloroform or dioxan) at 20°C, the *N*-oxide of 3-nitro-quinoline is formed in 40% yield together with some *N*-benzoyloxy-3,6-dinitro-2-oxoquinoline[181]:

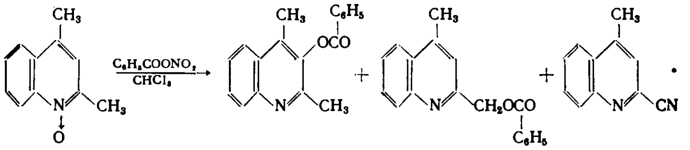


The use of a mixture of acetyl chloride with silver or potassium nitrate as a nitrating agent avoids the formation of 2-hydroxyquinoline and leads to the synthesis of 3- and 6-mono- and 3,6-di-nitro-compounds in yields of 32, 1.4, and 100% respectively[181].

Ochiai and Kaneko[181] suggested that in nitration with acyl nitrates in a neutral medium the reaction does not involve a simple electrophilic substitution mechanism but includes a stage with addition and subsequent elimination:

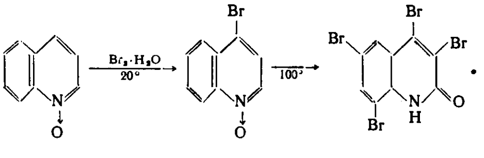


One may adduce in favour of this hypothesis data showing that 2- and (or) 4-substituted quinoline *N*-oxides do not give rise to nitration products on treatment with acyl nitrates, as shown for 2,4-dimethylquinoline *N*-oxide[182]:



Moreover, Ochiai and Ohta[183] showed that the *N*-methoxyquinolinium cation and also the adduct of quinoline *N*-oxide and boron trifluoride are nitrated with potassium nitrate in dimethyl sulphoxide at 140°C in the 3-position, which is likewise evidence of the validity of the above mechanism.

Hamana and Jamazaki[184] observed that, when quinoline *N*-oxide is brominated in a neutral medium, substitution also takes place in the 3-position: on refluxing quinoline *N*-oxide with bromine and chloroform in acetic anhydride, 3,6-dibromoquinoline *N*-oxide is formed in 60% yield (under the same conditions, pyridine *N*-oxide gives a 35% yield of the 3,5-dibromo-derivative). When quinoline *N*-oxide is brominated with bromine water at 20°C, initially normal substitution takes place in the *para*-position relative to the N→O group, but on heating to 100°C the *N*-oxide of 4-bromoquinoline formed may undergo further reaction, resulting in the formation of 3,4,6,8-tetrabromo-2-oxoquinoline[185]:

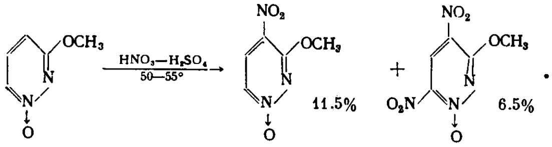


Electrophilic substitution of acridine *N*-oxide—nitration in sulphuric acid at 0°C and also bromination in glacial acetic acid at 100°C—takes place in the *para*-position relative to the N→O group and leads to the formation of 9-substituted acridine *N*-oxides[186].

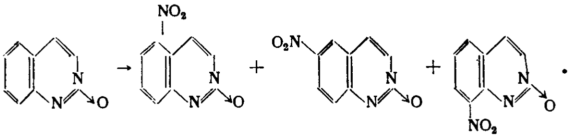
In isoquinoline *N*-oxide, where the *para*-position relative to the N→O group is occupied, the polar directing effect of the *N*-oxide group is not shown and, as in the case of isoquinoline, nitration takes place only in the 5-position (95%) and to a much lesser extent in the 8-position (1.5%)[187]. The study of the dependence of the rate of nitration of isoquinoline *N*-oxide and the *N*-methoxyisoquinolinium ion on the acidity of the medium by Schofield and coworkers[160] established that isoquinoline *N*-oxide reacts in the protonated form.

In the series of diazine *N*-oxides electrophilic substitution reactions have been studied only for the *N*-oxides of pyridazines, phthalazines, and cinnolines. While unsubstituted pyridazine is resistant to nitration under fairly severe conditions[92], the 1-*N*-oxide of pyridazine is nitrated in the *para*-position relative to the N→O group in a mixture of nitric and sulphuric acid at 130–140°C with a yield of 22%;[188] the same location of the new substituent is observed for the *N*-oxides of methylpyridazines[189].

In consequence of the competing directing effects of the substituents, nitration of 3-methoxypyridazine *N*-oxide results in the formation only of a mixture of 4-mono- and 4,6-dinitro-derivatives[190]:



When cinnoline 2-*N*-oxide is heated in a mixture of nitric and sulphuric acids at 90°C, 5-, 6-, and 8-mononitro-derivatives are formed in yields of 3, 15 and 23% respectively together with the unreacted initial *N*-oxide[193]:



The authors believe that these proportions of the isomers can be accounted for by the fact that the directing effect of the 2-N→O group favours substitution in the 6- and 8-positions, while the effect of the cinnoline ring favours 5- and 8-substitution, so that both effects reinforce one another in the 8-position. However, this explanation cannot be regarded as satisfactory, since isoquinoline *N*-oxide is substituted only in the 5-position[187]. The study of the kinetics of the nitration of cinnoline 2-*N*-oxide in 64.4–90.0% sulphuric acid suggests that 5- and 8-nitro-derivatives are formed entirely or largely in the nitration of the cation, while 6-substitution takes place in the free base of cinnoline 2-*N*-oxide[162].

Nitration of cinnoline 1-*N*-oxide with a mixture of nitric and sulphuric acids leads only to the 4-substituted compound[194], i.e. in this case the usual *para*-directing effect of the N→O group is shown.

Quinoxaline *N*-oxide is resistant to nitration with fuming nitric acid in concentrated sulphuric acid even at 100°C[117].

Phenazine 10-*N*-oxide behaves differently—it is readily nitrated even at 0°C with formation largely of 3- and small amounts of 1-nitro-compounds[191]; when the reaction is carried out at 100°C, the 10-*N*-oxides of 3,6- and 1,6-dinitrophenazines are formed[192]:

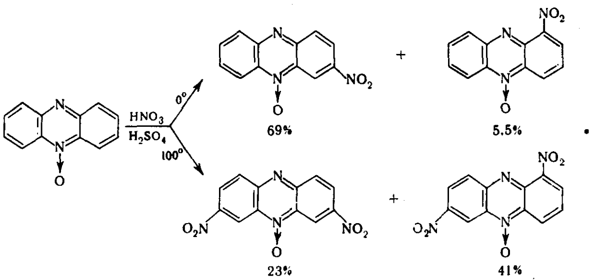


Table 14. Indices of the reactivities of pyridine and pyridazine *N*-oxides[131,166,195].

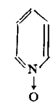
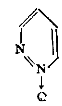
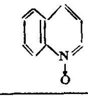
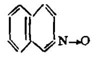
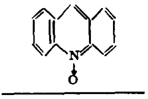
Structure	q_r, charge units	$A_e(-\beta)$	Position of carbon atom	q_r, charge units	Structure
	0.976	2.36	2-		
	1.003	2.58	3-	0.922	
	0.994	2.44	4-	1.001	
			5-	0.955	
			6-	0.978	

Table 15. Indices of the reactivities of quinoline, isoquinoline, and acridine *N*-oxides[196–199].

Position of carbon atom				
	q_r, charge units	A_e $(-\beta)$	q_r, charge units	q_r, charge units
1-	—	—	1.184	0.992
2-	0.975	2.30	—	0.959
3-	1.003	2.50	1.139	0.984
4-	0.994	2.21	0.896	1.012
5-	1.000	2.29	0.968	—
6-	1.000	2.48	0.990	—
7-	0.998	2.45	0.958	—
8-	1.004	2.32	1.022	—
9-				1.004

Note. The application of computational methods to the *N*-oxides requires the introduction of additional parameters for the Coulombic integral of the oxygen atom and the resonance integral of the N–O bond; usually the required values are found to be within the ranges $\alpha_{O^-} + (0.8 - 1.2)\beta$ and $\beta_{N^+-O^-} = (0.5 - 1)\beta$.

According to preliminary kinetic data, the monocation of the *N*-oxide formed by the addition of a proton to the unoxidised nitrogen atom is nitrated[15].

In the series of phenazine *N*-oxides the N→O group is a more powerful directing agent than halogens but weaker than alkoxy-groups and therefore the nitration of the 10-*N*-oxides of 1-, 2-, and 3-chlorophenazines takes place in the 6-position[193] and the nitration of the 10-*N*-oxide of 1-methoxyphenazine involves the *para*-position relative to the methoxy-group[121].

It is at present impossible to make a far-reaching analysis of the correlation between the experimental reactivities of the *N*-oxides of heteroaromatic compounds in electrophilic substitution reactions and the theoretical values obtained by the LCAO-MO method, because of the limited amount of calculated data. In particular, a calculation for the cationic form of the *N*-oxides has been made only in the case of pyridine *N*-oxide[166]. Tables 14 and 15 list the indices of the reactivities of certain *N*-oxides calculated by the simple LCAO-MO method. Comparison of these values with the experimental data shows that more successful correlations with the reactivities of the *N*-oxides are observed by considering the localisation energies A_e rather than the distribution of electron density q_r.

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All-Union Vitamins Research Institute,
Moscow

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Influence of Steric Factors on the Structure and Physicochemical Properties of Monohydric Phenols

G.A.Nikiforov and V.V.Ershov

The specificity of a series of chemical properties of sterically hindered phenols depends greatly on their structure. In the series of 2,6-di-t-alkylphenols in which conjugation of the aromatic ring and hydroxyl group is retained (insignificant departure from coplanarity) the C–O–H bond system is subjected to some deformation due to the bulky *o*-alkyl groups (a steric effect), which is reflected in the energy of homolytic breaking of the O–H bond and the physicochemical parameters of these phenols. The unusual nature of the spectral characteristics (ultraviolet, infrared, and NMR) of sterically hindered phenols is due to the steric effect of the ortho-substituent. For the same reason these compounds do not form self-associates; the hydrogen bond is somewhat stretched and weaker. Steric effects also play a decisive part in the reduction of acidity of sterically hindered phenols, preventing the solvation of the anion formed. For all the examples considered data are given on the effect of a para-substituent on the physicochemical parameters of the phenols. 98 references.

CONTENTS

I. INTRODUCTION

Sterically hindered phenols have found wide application as additives to prevent the oxidation of fats, oils, fuels, and various polymeric materials. The ability of sterically hindered phenols to retard (inhibit) radical-chain processes of oxidation of organic substances led to a very intense study of various practical and theoretical aspects of the chemistry of these compounds. The large number of studies in this field show distinctly that in many instances sterically hindered phenols show specific properties due to peculiarities in their structure. The physicochemical properties of sterically hindered phenols are largely responsible for their behaviour as oxidation inhibitors. In this connection the effect of the steric factor on the change in one or another property of phenolic compounds has frequently been investigated and a large body of experimental results on this problem has now accumulated, allowing certain generalisations to be made. In both the Russian and foreign literature there have been reviews dealing solely with the oxidation of sterically hindered phenols[1,2], their participiation in inhibited oxidation[3-6] and the properties of the phenoxyl radicals formed from them[7-10].

2,6-Dialkyl substituted phenols and their numerous derivatives are usually associated with the idea of sterically hindered (screened) phenols in the Soviet and foreign literature. Even in the first stages (1945–1950) of the intensive study of the 2,6-dialkylphenols it was observed that their properties depend on the effective volumes of the alkyl substituents. In this connection it was proposed[11,12] to classify such phenols in a separate group, termed sterically hindered phenols. To this period belong also the first attempts to evaluate the steric influence exerted by alkyl groups on the properties of the phenols. Thus Coggenshall[13,14], who used ultraviolet and infrared spectroscopy to study the ability of phenols to form hydrogen bonds (self-association), divided the phenols into three groups: non-screened, semiscreened, and screened. Naturally, the most pronounced steric influence is shown by phenols containing tertiary alkyl groups in the ortho-positions, and therefore specific properties of sterically hindered phenols were studied mainly for examples of compounds of this type.

II. STRUCTURE AND ENERGY OF THE O–H BOND OF STERICALLY HINDERED PHENOLS

The problem of the structure of sterically hindered phenols mainly reduces to a consideration of the relative arrangement in space of the aromatic ring, and the hydroxyl and alkyl groups. It is well known[15], that many physical and chemical properties of ordinary phenols are determined by the electron-withdrawing properties of the aromatic ring. Hence their enhanced acidity (in comparison with aliphatic alcohols), corresponding position of the signal of the hydroxyl proton in the NMR spectra, tendency to participate in radical processes, peculiarities of the mechanism of electrophilic substitution, etc. Evidently, the most characteristic properties of a phenol correspond to a structure in which the hydroxyl group (the C–O bond) is coplanar with the aromatic ring. The departure of the hydroxyl group from the plane of the ring will decrease the conjugation of the lone pair of electrons of the oxygen atom with the π-electrons of the aromatic ring, and consequently the properties of the phenol will approximate on the one hand to the properties of benzene, and on the other to the properties of aliphatic alcohols. Such a departure of the hydroxyl group most probably occurs in sterically hindered phenols containing t-alkyl groups, since it should be facilitated by the effect of bulky alkyl groups in the ortho-positions relative to the phenolic hydroxyl. Even a simple comparison of the effective radii of the hydroxyl and t-butyl groups shows the possibility of the destruction of the coplanarity of the hydroxyl group and aromatic ring in compounds of the series of sterically hindered phenols. Many investigators working in this field were primarily interested in this very question. And since a breakdown in the conjugation of the *p*-electrons of the oxygen atom with the aromatic system in sterically hindered phenols should lead to a marked change in the physicochemical properties of the phenol, that possibility and the nature of the departure of the hydroxyl group from the plane of the ring were usually investigated with the aid of various physical methods[16-27]. The first studies in this field were made by Ingold, using infrared spectroscopy[22-25]. He showed[22] that the increase in the hydroxyl group frequency in the infrared spectra observalbe in 2,6-di-t-butyl-4-substituted phenols in comparison with the corresponding 4-substituted phenols is too great to be the result of only electronic effects of the t-butyl groups. Evidently, in this instance the steric effect of the alkyl groups is considerable. However, the changes in the frequencies of the O–H bond vibrations in a series of 4-substituted phenols and in a series of 4-substituted 2,6-di-t-butylphenols with change in substituent obey the same law. Fig. 1 shows the variation of ν_{OH} with σ_p for 4-substituted phenols and their sterically hindered analogues. The parallelism of the straight lines on the graph shows that both groups of phenols have similar spatial structure.

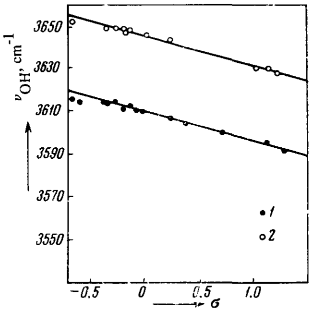


Figure 1. Variation of ν_{OH} with σ_p of para-substituents in the series of 4-X-phenol (*1*) and 4-X-2,6-di-t-butylphenol (*2*).

A similar conclusion can also be reached on the basis of the following discussion. The displacement of the hydroxyl group from the plane of the ring should sharply reduce its resonance interaction with strongly accepting substituents in the para-position, that is, σ_p, for example, for the nitro-group should have a value intermediate between the maximal (1.27, characteristic for *p*-nitrophenol) and the minimal (0.78, characteristic for other nitroderivatives of benzene in which direct conjugation of the substituents is absent). However, the best correlation in the series of sterically hindered phenols in coordinates ν_{OH} against σ_p is observed on using the maximal values of σ_p. The picture is analogous when maximal values of σ_p for the formyl and nitrile groups are used.

The coplanarity of the aromatic ring and hydroxyl group is also shown by the following calculation, given by Ingold[22,25]. It is known that the fundamental frequency of the carbonyl group in various substituted benzaldehydes is linearly dependent on σ_p for the *p*-substituent. If the hydroxyl group is coplanar with the aromatic ring for 2,6-di-t-butyl-4-formylphenol, then:

$$\sigma_{eth} = \sigma_p^{OH} + 2\sigma_m\text{-t-butyl} = -0.36 + 2\cdot(-0{,}12) = -0.60.$$

When there is a linear relation between ν_{CHO} and σ_p, the shift in frequencies on going from 4-formylphenol to 2,6-di-t-butyl-4-formylphenol should be in the ratio 0.36 : 0.60 (3 : 5), which agrees with the experimental results.

On the basis of the above facts it could have been suggested that in 2,6-di-t-butylphenols the hydroxyl group lies in the plane of the aromatic ring or close to this position. However, it must be borne in mind that the infrared spectroscopic results do not permit the electronic influence of the substituents on the nature of the absorption by the hydroxyl group to be evaluated with sufficient accuracy, and consequently the above discussion is approximate, since at small angles of departure from coplanarity the resonance energy and electron density hardly change because these quantities are approximately proportional to the square of the cosine of the dihedral angle[28].

The electronic spectra can be a more sensitive characteristic of the electronic interaction of the hydroxyl group and the aromatic ring. Ultraviolet spectroscopy is interesting because the position of the absorption bands of the benzenoid system is determined mainly by the resonance effect of the substituent and therefore is more sensitive to a change in coplanarity than ν_{OH} in the infrared region.

For example, having obtained a series of resonance parameters for para-substituents ($\sigma_{R'} = \sigma_{\bar{p}} - \frac{2}{3}\sigma_m$), Cohen and Jones[18] showed that in a plot of $\sigma_{R'}$ against $\Delta\bar{\nu}$ there is satisfactory correlation for any substituents. It is characteristic that the straight lines for 4-X-phenols and 4-X-2,6-di-t-butylphenols are only approximately parallel. The presence of two t-butyl groups increases the value of ρ both for phenols and for the phenolate ions by 11%. This shows the insignificant departure of the C–O bond from the plane of the aromatic ring.

Finally, data on the molecular polarisability of phenols have been used to find the coplanarity of the hydroxyl group and the aromatic ring[21]. Unlike dipole moments, which depend weakly on the volume of the replacing groups[19], the molar polarisability of the compounds allows the spatial position of the individual fragments of the molecule to be calculated rather precisely. A comparison of the observed Kerr constants with the values calculated theoretically for various conformations of 2,4,6-tri-t-butylphenol showed that here the hydroxyl group is displaced ~ 14° out of the plane of the aromatic ring.

It is noteworthy that the observed departure from coplanarity is increased significantly when the hydroxyl group in 2,6-di-t-butylphenyl is replaced by methoxyl. In this instance, as spectroscopic investigations have shown[26,29,30] the angle made by the C–O bond at the ring plane approaches 90°.

The departure (although insignificant) of the hydroxyl group from coplanarity in 2,6-di-t-butylphenol is due to the interaction of the electron clouds of the hydroxyl and t-butyl groups. As an investigation of molecular models showed[31], the overlap of the effective radii of the phenol hydrogen and each of the equivalent hydrogen atoms of the neighbouring t-butyl groups found in the most convenient conformation is approximately 0.25 Å. This suggests that the total bond strain energy is within the range 0.1–0.2 kcal mole^{-1}, appreciably less than the energy of conjugation which is gained by the hydroxyl group being in the plane of the ring (~ 7.0 kcal mole^{-1}).

The steric hindrances created by the t-butyl groups also prevents the normal rotation of the hydroxyl group around the C–O bond, increasing the rotational barrier. This barrier calculated on the basis of dielectric measurements is 2.2–2.8 kcal mole^{-1} for 2,4,6-tri-t-butylphenol[32,33]. It is interesting to note that this value is lower than for the unsubstituted phenol (4.4 kcal mole^{-1}). The high value of the rotational barrier in unsubstituted phenol is due to its self-association, whereas in 2,6-di-t-butylphenol this is completely absent and consequently, the presence in it of a rotational barrier is due solely to the existence of steric hindrances created by the bulky *o*-alkyl groups.

Hence, the general features of the structure of the sterically hindered phenols are that when the conjugation of the aromatic ring with the hydroxyl group is retained (insignificant departure from coplanarity) the system of C–O–H bonds is subjected to certain deformations, in addition to which there is a rather high rotation barrier (restricted rotation) of the hydroxyl group around the C–O bond. All this leads to the specificity of certain physicochemical properties in a series of sterically hindered phenols.

The strains which arise in a system of C–O–H bonds of a phenol on the introduction in the ortho-position of t-butyl groups should evidently cause some change in the bond energy in this system, particularly the dissociation energy of the O–H bond. However, the direct determination of the dissociation energy of the O–H bond is extemely difficult and has been done only in the simplest instances.

To the first approximation the dissociation energy of the O–H bond in phenol ($D_{O...H}$) is proportional to the energy of the highest filled molecular orbital (E_{hfmo}),[34-36] and in this connection quantum-mechanical investigations of the activity of the phenolic compounds in oxidations yield a satisfactory correlation between the inhibiting activity of phenols and E_{hfmo}.[37] An extremely successful version of the estimation of the strength of the O–H bond is a combination of Fiesser's experimental method[38] used for the determination of the redox potential of unstable systems (E_C) and quantum-mechanical calculations of the dissociation energy of the O–H bond ($D_{O...H}$).[34] By combining these methods the dissociation energies of the O–H bond were calculated for a series of the simplest phenols, particularly unsubstituted phenol $D_{O...H}$ = 84 kcal mole^{-1}.

In the series of sterically hindered phenols the strength of the O–H bond was calculated on the basis of results obtained in investigating the equilibrium reactions of substituted 2,6-t-butylphenols with one of the nitrogenous radicals (2,2,6,6-tetramethyl-4-ketopiperidyl-1-oxyl) with the aid of the EPR method[39]. It has been shown that the strength of the O–H bond of certain sterically hindered phenols varies within the limits 76 ± 3 kcal mole^{-1}.

As the data show, the introduction of two t-butyl substituents into the ortho-positions to the hydroxyl group causes some weakening of the O–H bond, which agrees with results on the structure of sterically hindered phenols.

III. SPECTROSCOPIC CHARACTERISTICS OF STERICALLY HINDERED PHENOLS

1. Electronic Spectra

The first spectroscopic investigations of sterically hindered phenols were in 1948, when Coggenshall[14], on the basis of shifts in the absorption maxima of these phenols in the range 265–275 mμm, produced on replacing octane by alcohol as solvent, attempted to estimate the steric effect of *o*-alkyl substituents. However, the more detailed ultraviolet characteristics and their change with the structure of the phenol and medium were investigated much later[18,40-43].

Like their unscreened analogues, sterically hindered phenols exhibit two characteristic absorption bands in the ultraviolet range: 210–220 mμm (the B-band with high absorptivity) and 260–280 mμm (the C-band with low absorptivity). Table 1 gives the ultraviolet spectra of ortho-substituted phenols with gradual increase in the volume of the ortho-alkyl substituents. As Table 1 shows, the change in the size of the alkyl groups does not affect the characteristics of the ultraviolet spectra strongly, but the following two facts must be considered. The first is the low sensitivity of the position of the B-band to increase in the volume of the ortho-substituent. Dearden[40] considers that this anomaly is explained by the considerable contribution to the ground state of the phenol of the bipolar structure of the type:

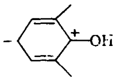


Table 1. The ultraviolet spectra of *o*-alkylphenols[40].

Compound	Cyclohexane				Ethanol			
	B-band		C-band		B-band		C-band	
	λ_{max}, mμm	E_{max}	λ_{max}, mμm	E_{max}	λ_{max}, mμm	E_{max}	λ_{max}, mμm	E_{max}
Phenol	210	6000	269	2200	218	6000	271	1900
o-Cresol	213	7000	270	1850	213	7100	272	2050
o-Isopropylphenol	211	7500	270	2100	215	6200	271	2250
o-t-Butylphenol	213	5900	268	2050	216	5100	271	2300
2,6-Dimethylphenol	211	7900	275	1600	214	8500	271	1550
2,6-Di-isopropylphenol	211	9200	275	1950	214	8000	270	1850
2,6-Di-t-butylphenol	211	7500	275	1800	212	7600	268	1550

The second fact is the shift of the B-band to longer wavelengths on going from a non-polar solvent to a polar one. It is suggested[14,40] that this effect is connected with steric hindrances which arise during the formation of associates with the solvent. The most pronounced change in form and position of the maxima in the spectrum are observed on increasing the pH of the medium. Thus, when an alcoholic solution of phenols is made alkaline there is a displacement of both bands to longer wavelengths and simultaneously there is an increase in the absorptivity. These facts are evidently due to an increase in the fraction of quinonoidal structure in the ground state of the ionised form of the phenol, which in the reactivity scheme leads to an increase in the ambidentate properties of the phenoxide anion.

The introduction of various substituents into the para-position of sterically hindered phenols also has a considerable effect on the parameters of the ultraviolet spectra. As might be expected, the presence of electron-withdrawing substituents brings about a shift of B- and C-bands to longer wavelengths, the shift increasing with the electronegativity of the substituent (Table 2). Since the parameters of the ultraviolet spectrum are extremely sensitive to changes in the effects of conjugation of the hydroxyl group with the para-substituents[44,45], they should be correlated with the constants of the para-substituent. Such a relation is observed sufficiently well in using σ_R' constants[18], which reflect the resonance constituent in the total value of σ_p^- on allowing for the regular change in the inductive effect with distance, that is,

$$\sigma_{R'} = \sigma_p^- - {}^2/_3\sigma_m.$$

Table 2. Ultraviolet spectra of 4-X-2,6-di-t-butylphenols in 50% ethanol[43].

X	Neutral media				Alkaline media			
	B-band		C-band		B-band		C-band	
	λ_{max}, mμm	E_{max}	λ_{max}, mμm	E_{max}	λ_{max}, mμm	E_{max}	λ_{max}, mμm	E_{max}
H	214	6250	271	1600	244	11000	295	3630
CH_3	222	6900	278	1800	250	10600	303	3780
$C(CH_3)_3$	223	9500	272	1700	251	10200	300	3450
OCH_3	229	8200	285	3400	—	—	—	—
$(CH_3)_3N^+$	224	6350	270	1025	261	8800	298	4200
Br	226	11500	280	1275	257	16000	305	3580
SO_3^-	233	12300	272	1150	270	18400	300	3000
COO^-	250	13700	—	—	302	20400	—	—
COOH	260	13300	—	—	—	—	—	—
$CONH_2$	258	12000	—	—	321	22200	—	—
$COOC_2H_5$	261	14800	—	—	324	29600	—	—
CN	252	16900	—	—	307	31200	—	—
$COCH_3$	284	13300	—	—	363	32500	—	—
CHO	293	15000	—	—	370	38400	—	—
NO_2	325	10000	—	—	450	30500	—	—
NO	305	13250	—	—	382	18500	—	—

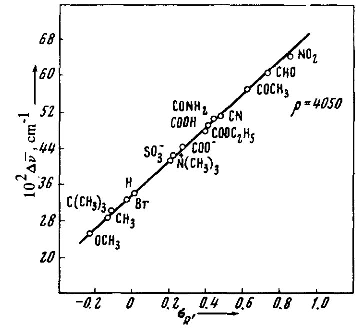


Figure 2. Correlation of $\Delta\bar{\nu}$ and $\sigma_{R'}$ in the 4-X-2,6-di-t-butylphenol series.

This correlation is made in the coordinates $\Delta\bar{\nu}$ against $\sigma_{R'}$ (Fig. 2). The shift in frequencies is calculated from the equation

$$\Delta\bar{\nu} = \bar{\nu}_a - \bar{\nu}_b,$$

where $\bar{\nu}_a$ is the frequency of the B-band of 4-X-2,6-di-t-butylphenol, and $\bar{\nu}_b$ that of the band for the corresponding substituted benzene. Table 2 gives the results for the ultraviolet spectra of 4-X-2,6-di-t-butylphenols in neutral and alkaline solutions. The shift in the bands observable on going from a neutral medium to an alkaline one increases with the electronegativity of the substituent and also depends linearly on $\sigma_{R'}$. The marked shift of the B-band in an alkaline medium in comparison with a neutral one with strongly electron-withdrawing substituents (CHO, CN, COOR, $COCH_3$, NO, and NO_2) is due to the considerable contribution of the quinonoid structure to the ground state of the ionised form[18,46].

2. Infrared Spectroscopy of 2,4-Dialkylphenols

The infrared spectra of sterically hindered phenols has been investigated in considerable detail[13,16,20,22-26,47-59]. The studies made in this field deal mainly with two problems: finding the spatial structure of the phenols of this series and their ability to form a hydrogen bond.

Table 3. Frequencies (ν_{OH}, cm^{-1}) of the hydroxyl group in the alkylphenol series (CCl_4).

Alkylphenol	ν_{OH}	Reference
Phenol	3612	16, 23, 25, 50, 51, 61, 62
2,6-Dimethylphenol	3622	20, 61, 62
2,6-Diethylphenol	3623	20, 53
2,6-Di-isopropylphenol	3623	20, 50, 53, 61, 62
2,6-Di-t-butylphenol	3651	20, 23, 25, 50, 51, 53, 61, 62
2,6-Di-t-pentylphenol	3646	59
p-Cresol	3617	51
2,4,6-Trimethylphenol	3626	51
2,6-Di-isopropyl-4-methylphenol	3628	23, 25, 51
2,6-Di-t-butyl-4-methylphenol	3650	16, 20, 23, 25, 51, 53, 54
4-Methyl-2,6-di-t-pentylphenol	3642.5	23, 25
4-Methyl-2,6-bis(triethylmethyl)phenol	3635	23, 25

In examing the infrared spectra of sterically hindered phenols the most noteworthy effect is that the band of the hydroxyl group is a narrow signal strongly displaced to shorter wavelengths in comparison with unsubstituted phenol (in KBr and CCl_4). The observed increase in the frequency of the hydroxyl group is evidently due to the interaction of the electron clouds of the hydroxyl and *o*-t-butyl groups[22,25]. Such an explanation was given in the interpretation of the results of an investigation of the chemical shifts in the PMR signal from the hydrogen atom of the hydroxyl group for a series of di-*o*-alkylphenols[60]. Table 3 gives results on the change in frequency of the hydroxyl group with the effective volume of the ortho-substituent for certain di-*o*-alkylphenols. It can be seen that the frequency of the hydroxyl group reaches maximal value when t-butyl groups are present.

Table 4. Frequencies (ν_{OH}, cm^{-1}) of the hydroxyl group in a series of 4-X-2,6-di-t-butylphenols in CCl_4.[18,22]

X	ν_{OH}	σ_p	X	ν_{OH}	σ_p
NO_2	3626.5	1.24	Cl	3643.5	0.23
CHO	3630.0	1.04	H	3647.0	0.00
CN	3632.5	0.88	OCH_3	3649.0	−0.13
$COCH_3$	3633.0	0.84	CH_3	3649.0	−0.15
COOH	3634.0	0.77	$C(CH_3)_3$	3649.0	−0.14
$COOC_2H_5$	3636.5	0.64	OH	3649.0	−0.37
Br	3643.0	0.25	NH_2	3650.5	−0.66

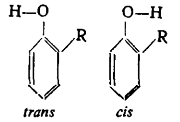
An increase in the lengths of the alkyl chains at the tertiary carbon atom in the ortho-substituents leads to a decrease in the frequency, which is evidently due to a decrease in the steric hindrances resulting from the breakdown of spherical symmetry of the substituents as a whole owing to the large number of possible conformations.

The results of an investigation of the variation of the frequency of the hydroxyl group with the electronegativity of the para-substituent in the 4-X-2,6-di-t-butylphenols is given in Table 4, from which clearly the frequency of the hydroxyl group decreases as the electronegativity of the para-substituent, which affects the polarisation of the O–H bond, is increased. There is good correlation of the data in Table 4 with one another (Fig. 1).

It is noteworthy that the hydroxyl group band for sterically hindered phenols in CCl_4, which is a narrow isolated signal, does not change when the solution is diluted. This is possible only if self-association is absent[47,51,53,57]. A rise in temperature decreases the intensity of the absorption band of the hydroxyl group of sterically hindered phenols[55,56].

There is another interesting, but not completely strict, correlation based on the infrared spectra of sterically hindered phenols, which can yield additional information about the structure of this series of compounds. This is the correlation of the difference in free energy (ΔG) between the *cis*- and *trans*-isomers of mono-*o*-t-alkylphenols with $\Delta\nu_M$ and the change in the band intensity (ΔA) for 2,6-di-t-alkylphenols[24,25].

Careful study of the infrared spectra of *o*-alkylphenols in the range of absorption of the hydroxyl group led to the observation of a group of bands consisting of a band of high intensity with approximately the same frequency as for the unsubstituted phenol, and an incompletely resolved band with intensity and position close to the band of 2,6-di-t-alkylphenols[16,23,24]. The more intense band at the lower frequency was assigned to the so-called *trans*-isomer of the *o*-t-alkylphenol, and the second band to the *cis*-isomer:



The properties of these isomers are different. When the polarity of the medium is varied, the *trans*-isomer behaves like phenol (ν_{OH} decreases as the polarity is raised) but the *cis*-isomer exhibits all the spectroscopic properties of 2,6-di-t-alkylphenols. It is characteristic that for *o*-t-alkylphenols the *trans*-form is more stable than the *cis* form. This again shows the existence of a steric repulsion between the hydroxyl group and the alkyl residues. As Ingold has shown[24,25], the ratio of the intensities of the bands of the isomers can be used to calculate the difference in free energy (ΔG) between these isomers. When from these results ν_{OH} and ΔA are plotted against ΔG for the corresponding 2,6-dialkyl phenols, curves with a maximum or minimum are obtained, showing a sharp difference between the 2,6-dialkylphenols. However, it is noteworthy that the increase in ΔG with the effective volume of the *o*-alkyl substituents is slower than expected. This is evidently because of the decrease in energy as the angle C–H–O is increased.

3. Nuclear Magnetic Resonance Spectra

With the development of the NMR method a more detailed study of the electronic interaction in sterically hindered phenols arising as a result of the steric effect of the alkyl groups became possible. Measurement of the chemical shift of the hydroxyl group proton signal for a series of mono- and di-*o*-alkylphenols showed that as the volume of the substituent is increased there is a successive displacement of the signal to weaker fields, owing to the decrease in the magnetic screening of the hydroxyl group. This behaviour could be due solely to the steric influence of the *o*-alkyl groups, since the other possible factors affecting the position of the signal (appreciable departure from coplanarity, influence of the inductive effect, dipole moment, and magnetic anisotropy) should here result in a displacement to stronger fields. Table 5 shows the values of the chemical signals (τ_{OH} and $\Delta\tau_{OH}$) of the hydroxyl group proton in *o*-alkylated phenols. Clearly, from these results[31,60] the magnetic screening of the hydroxyl group proton decreases in the following order of substituents:

$$H > CH_3 > CH(CH_3)_2 > C(CH_3)_3 \ .$$

In addition, there is a decrease in screening on going from monoalkylphenols to dialkylphenols.

Table 5. Chemical shifts of the signal of the proton of the hydroxyl group in *o*-alkylphenols[31].

Compound	τ_{OH}	$\Delta\tau_{OH}$	ν_{OH}
Phenol	5.77	—	3612
o-Cresol	5.62	—0.15	3615
o-Isopropylphenol	5.54	—0.23	3614.5
o-t-Butylphenol	5.36	—0.41	3607; 3647
2,6-Dimethylphenol	5.56	—0.21	3622
2,6-Di-isopropylphenol	5.48	—0.29	3623
2,6-Di-t-butylphenol	5.13	—0.64	3648

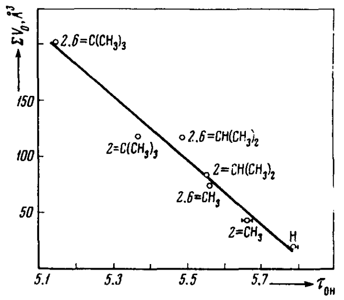


Figure 3. Correlation of the chemical shift of the hydroxyl-group proton and the total volume of the *o*-alkyl substituents in a series of alkylphenols.

It is characteristic that the values of ν_{OH}, also given in Table 5, follow the same relation but in the reverse order. Evidently the reason for this change in the two parameters is the same. In the examples considered the mutual repulsion of the electron clouds of the hydroxyl-group hydrogen and *o*-alkyl substituents leads to a decrease in the electron density at the hydroxyl proton, and consequently to a decrease in its diamagnetic screening. Furthermore, in this there is a definite decrease in the symmetry of the cloud of *S*-electrons of the hydroxyl-group hydrogen, which should lead to an increase in the paramagnetic contribution in the screening and a shift of the signal to weaker fields. The facts examined are illustrated well by the linear dependence of the chemical shift of the hydroxyl proton on the total volume of the *o*-alkyl substituent (Fig. 3). The screening of the hydroxyl proton is also altered by the introduction of a para-substituent into the 2,6-dialkylphenol[19,60]. With increase in the electronegativity of the para-substituent there is a shift of the signal from the hydroxyl-group proton to weaker fields and this shift is correlated with the $\sigma\bar{p}$-values of the substituents. This once again agrees with Ingold's results[22,23,25] on the investigation of the vibrations of the O–H bond in a series of 2,6-di-t-butylphenols. Direct confirmation of the correctness of the conclusions drawn is given by the linear dependence of τ_{OH} on ν_{OH}.

The above results suggest that the para-substituent brings about a redistribution of the electron density not only in the benzene ring but also at the oxygen atom of the hydroxyl group. In this connection, there is also a linear relation between the chemical shift of the signal of the hydroxyl proton and the charge on the oxygen atom (q_0).[31]

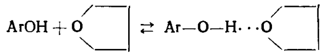
IV. THE HYDROGEN BOND OF 2,6-DIALKYLPHENOLS

Usually, hydroxyaromatic compounds are capable of forming a hydrogen bond and for many of them the formation of self-associates is also characteristic. It is noteworthy that all the spectroscopic methods considered above allow us to estimate in some measure the ability of alkylphenols to form associates with the solvent or self-associates. And since the hydrogen bond is especially sensitive to steric hindrances, the observable spectroscopic effects are often criteria of the steric hindrances created by the *o*-alkyl substituents. Most of the information on the influence of steric factors on the formation and strength of the hydrogen bond in a series of sterically-hindered phenols has been given by use of infrared[13,47–51,53,57,63,64] and NMR[31,65–69] spectroscopy.

It is known that many *o*-alkylphenols form self-associates in inert solvents at appreciable concentrations, whereas at a sufficiently great dilution they exist as monomers. In this connection, during the dilution of the solution with an inert solvent (for example, CCl_4) there is a displacement, the stronger the tendency of the phenol to form a hydrogen bond and consequently the hydroxyl group is less sterically screened. This change in the frequency of the hydroxyl group during the dilution of the solutions ($\Delta\lambda = \lambda^{OH}_{conc} - \lambda^{OH}_{dil}$) was also suggested by Coggenshall[13] for use in evaluating the steric effect of alkyl substituents in the formation of a hydrogen bond in the alkylphenol series. By using this parameter, which characterises the strength of the hydrogen bond, he divided the phenols into three groups: $\Delta\lambda > 0.15$ mμm, unscreened phenols; 0.04 mμm $< \Delta\lambda < 0.15$ mμm, semiscreened phenols; $\Delta\lambda < 0.04$ mμm, screened phenols. However, later[47] an empirical index of the hydrogen bond was introduced, which correlated with the screening effect of the alkyl substituents, and it was shown[51] that 2,6-di-t-butyl-4-methylphenol generally does not form self-associates.

More rigorous results can be obtained by investigating the association of 2,6-dialkylphenols with various substituents. Thus Bellamy[57] found that the relative strength of the hydrogen bond formed between solvents and di-*o*-alkylphenols is independent of the effective volume of the ortho-substituent. An exception is 2,6-di-t-butylphenol for which the steric hindrance is so great that during the formation of its associates with the solvent the volume of the solvent molecules (acceptor) starts to play a decisive role. Careful analysis of the frequencies[63] of the hydroxyl group of 2,6-di-t-butyl-4-methylphenol showed that the associates of this phenol with the solvent can exist in two forms: in the first the hydroxyl-group proton lies in the plane of the ring (or close to it), and in the second it is perpendicular to the plane. In the second form resonance stabilisation of the hydrogen bond is assumed to be absent but there is also a decrease in the steric hindrances of solvation.

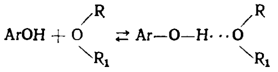
The existence of two forms of associates is confirmed by the results of Borod'ko's work[65], who observed, in an investigation of complex formation between 2,6-di-t-butylphenol and tetrahydrofuran, two bands from an associated hydroxyl group (3560–3390 cm^{-1}). On the basis of the thermodynamic parameters of the equilibrium:



he calculated the length of the hydrogen bond for each form: 2.85 and 3.05 Å. It is noteworthy that the length of the hydrogen bond for the unsubstituted phenol is ~ 2.7 Å. There is also a noticeable difference in the energy of the hydrogen bond. Thus for the unsubstituted phenol it is 6 kcal $mole^{-1}$, but for 2,6-di-t-butylphenol it is only 2 kcal $mole^{-1}$.

Spectroscopic results[63] have also been used to calculate the fraction of non-bonded hydroxyl groups of sterically hindered phenols in various solvents. However, the correlation between the basicity of the solvent and the fraction of non-bonded hydroxyl groups could not be deduced. Evidently, the reason for this lies in the geometry of the solvent molecules.

The change in the frequency of the hydroxyl group during association and the equilibrium constants of the reaction



$$ArOH + O\begin{matrix}R\\ R_1\end{matrix} \rightleftarrows Ar{-}O{-}H\cdots O\begin{matrix}R\\ R_1\end{matrix}$$

have been used for a quantitative estimation of the steric factor in the series of sterically hindered phenols[53].

Table 6. Equilibrium constants and shift of the frequencies of the hydroxyl group in the formation of associates of alkylphenols with ethers[51].

Phenol	Ethers											
	di-t-butyl		di-iso-propyl		tetra-hydrofuran		di-n-butyl		diethyl		$[(CH_3)_3Si]_2O$	
	K_{equil}	Δν	K_{equil}	Δν	K_{equil}	Δν	K_{equil}	Δν	K_{equil}	Δν	K_{equil}	Δν
Phenol	3.90	325	7.20	308	10.4	301	4.90	292	6.00	288	0.40	168
o-Cresol	1.70	309	3.20	301	5.5	294	2.60	288	3.40	283	0.00	159
o-Isopropylphenol	2.00	300	3.90	300	6.7	296	3.00	289	3.90	285	0.06	163
o-t-Butylphenol	2.30	280	4.10	291	5.7	284	2.90	280	3.70	278	0.00	169
2,6-Dimethylphenol	0.22	205	0.62	234	2.0	229	0.63	228	0.67	220	0.03	—
2,6-Di-isopropyl-phenol	0.19	197	0.48	215	1.7	201	0.23	201	0.51	191	0.06	—
2,6-Di-t-butylphenol	0.00	—	0.00	—	0.0	—	0.00	—	0.00	—	0.00	—

It was assumed here that the equilibrium constants are a measure of the overall effect and the frequency shift reflects the change in the strength of the hydrogen bond since it is determined by the changes in the force constant of the O–H bond. Table 6 gives the results obtained in this work.

As Table 6 shows, the value of $\Delta\nu$ changes symbathically with the basicity of the ether and increase in the steric effect of the alkyl substituents. An exception is 2,6-di-t-butylphenol, for which the steric hindrances during solvation are too great. On the other hand, the equilibrium constants for the association are not correlated with the basicity of the ether but are arranged in the order of an increase in the steric effects of the ethers. The small difference in the value of $\Delta\nu$ shows that the contributions of the hydrogen bond to the free energy of the system are approximately the same and the significant differences in the equilibrium constants are evidently due to the entropy factor, which is especially sensitive to steric effects. Similar results were obtained by Singh and Rao[50]. They noted that despite the decrease in the equilibrium constant for the association as the volume of the substituent is increased there is an increase in the enthalpy of the reaction. The decrease in $\Delta\nu$ accompanying the increase in the enthalpy of the reaction is evidently the result of an increase in the activation energy during the change of a proton into a hydrogen bond. If the conclusions drawn are correct then a direct relation between $\Delta\nu$ and the change in free energy of the system (ΔF_0) is to be expected. Actually, such a correlation between $\Delta\nu$ and ΔF_0 was observed. Subsequently Singh and Rao investigated the structure of the associate formed. They obtained equilibrium constants in the association of 4-X-2,6-di-t-butylphenols with tetrahydrofuran and the absence of a correlation of these constants with σ_p for the X substituent.

The observed behaviour is explained by certain breakdowns in coplanarity of the hydroxyl group, which leads to a non-planar hydrogen complex. The latter brings about a hindrance to the transfer of electronic effects of the para-substituent to the reaction centre and consequently to the destruction of the linearity between σ_p and K_{equil}. It should be noted that the relief of steric hindrances created by alkyl groups leads to a linear relation between these quantities, which occurs with an unsubstituted phenol[70].

The NMR method played a great part in the investigation of the hydrogen bond of sterically hindered phenols. The main parameter in studying a hydrogen bond by this method is the chemical shift of the proton participating in the formation of the hydrogen bond and also the dependence of this quantity on the concentration of the test substance in various solvents. The change in the position of the signal is due to the fact that with dilution or rise in temperature there is breaking of hydrogen bonds and the signal is shifted to higher fields. The existence of a hydrogen bond, on the other hand, shifts the signal to weaker fields, that is, there is a decrease in the magnetic screening of the proton. Theoretical analysis[71] of the causes of the change in the magnetic screening of the proton showed that the principal ones are the change in polarity of the O–H bond (displacement of the centre of gravity of the electron cloud to the side of oxygen) and the formation of a donor–acceptor bond ArO–H...X (shift of the lone pair of electrons of atom X to the side of the hydrogen atom).

In investigating the hydrogen bond arising in the self-association of alkylphenols and the nature of the complexes formed there have been several studies[31,67,68,72] of the concentration dependence of the parameters of the PMR spectra. In these studies it was found that the position of the signals for the protons of the alkyl groups and benzene ring are almost independent of the concentration of the substance whereas the signal from the proton of the hydroxyl group is usually shifted to higher fields on dilution. Consequently, the change in position of the signal of the hydroxyl proton is the result of the formation of self-associates. With increase in the volume of the alkyl substituents the chemical shift corresponding to the undiluted solution increases; the difference in the chemical shifts also changes on going from a dilute solution to a concentrated one. Both these facts are due to the increase in the length of the hydrogen bond during self-association owing to the increase in the volume of the substituents, that is, with decrease in the possibility of self-association. Table 7 gives the parameters of the self-association process:

$$n \cdot \text{ArOH}_{\text{monomer}} \rightleftarrows n\text{—ArOH}$$

showing the effect of the volumes of the *o*-alkyl substituents. Evidently the equilibrium constants (K_n) and chemical shift (δ_n) in the associated state gradually drop as the steric hindrances increase. The nature of the associate also changes. 2,6-Di-t-butylphenol does not give self-associates ($n = 1$), 2,6-dimethylphenol and 2,6-di-isopropylphenol form cyclic tetrameric associates ($n = 4$), and in the self-association of unsubstituted phenol a cyclic trimer is formed ($n = 3$).

Table 7. Comparison of the self-association parameters with the effective volume of the ortho-substituents[31].

Compound	Total volume, A^3	δ_n	K_n	n
Phenol	14.4	—3.11	4.78	3
2,6-Dimethylphenol	67.0	—0.82	$5.7 \cdot 10^{-2}$	4
2,6-Di-isopropylphenol	131.0	—0.44	$1.25 \cdot 10^{-2}$	4
2,6-Di-t-butylphenol	226.2	0.00	0.00	1

Interesting results were obtained in investigating the associates of phenols with proton-withdrawing solvents[31,72]. The ease of formation of such associates and their stability are determined not only by steric hindrances in the phenol molecule, but also by the volume and proton-acceptor properties of the solvent molecule. These investigations were made with the following solvents: acetone[31], diethyl-ether[31], triethylamine[31], dioxan[72], and ethanol[72]. With decrease in the concentration of phenols in ether, acetone, ethanol, and dioxan the chemical shift of the signal of the hydroxyl proton decreases. This shows that associates with these solvents are more stable that self-associates. When solutions of dialkylphenols in triethylamine are diluted the concentration dependence observed has a characteristic minimum. This anomaly can evidently be explained by the existence of two processes:

$$\text{ArOH} + \text{N}(\text{C}_2\text{H}_5)_3 \rightleftarrows \text{ArOH}\cdots\text{N}(\text{C}_2\text{H}_6);\ \text{ArOH} + \text{N}(\text{C}_2\text{H}_5)_3 \rightleftarrows \text{ArO}^{\ominus} + \text{H}\overset{+}{\text{N}}(\text{C}_2\text{H}_5)_3\,.$$

The concentration dependences of phenols in proton-withdrawing solvents usually reflect the competition of two processes: the dissociation of the self-associates and complex formation with the solvent. With 2,6-di-iso-propyl-, 6-t-butyl-2-methyl-, and 2,6-di-t-butyl-phenols the first process can be neglected, which allows the equilibrium constant of the reaction

$$\text{ArOH} + \text{X} \rightleftarrows \text{ArOH}\cdots\text{X}$$

to be estimated.

The results in Table 8 show that with increase in the steric factor in the phenol the stability of the complexes decreases. An increase in the volumes of the solvent molecules also affects their stability in the same direction.

Investigation of the association of 4-X-2,6-di-t-butyl-phenols with t-butyl alcohol showed that the nature of a para-substituent in the nucleus of the phenol has an effect on the nature of the association[69]. Unlike the results of Singh and Rao[50], obtained by infrared spectroscopy, the value of the chemical shift (τ_{OH}) of the phenol in the presence of t-butyl alcohol is correlated with the σ constants of substituent X (see Fig. 4, straight line *3*). The parallelism of straight lines *2* (in the absence of an alcohol) and *3* (in the presence of an alcohol) shows that the hydroxyl group of the 4-substituted 2,6-di-t-butylphenol in a complex with t-butyl alcohol is subjected to the same effect of the para-substituent as it is for a phenol unsubstituted in the ortho-positions.

Table 8. Equilibrium constants for the complex formation by alkylphenols[31,72].

Compound	Solvent and K_{equil}		
	ether	acetone	dioxan
2,6-Di-isopropylphenol	—	—	7.1
6-t-Butyl-2-methylphenol	3.0	4.2	5.6
2,6-Di-t-butylphenol	0.6	1.9	0.7

It is interesting to note the effect of substituent X in the phenol nucleus on τ_{OH} for t-butyl alcohol (see Fig. 4, straight line *1*). It can be seen that the increase in the degree of association of the phenol with the alcohol brings about the destruction of the alcohol–alcohol associates (shift of the signal of the proton of the hydroxyl group of the alcohol to a stronger field). The shift increases with increase in the electronegativity of the substituent. The latter is evidently due to the polarisation of the O–H bond of the phenol, which brings about an increase in the acidity of the phenol, that is, its proton-donating properties.

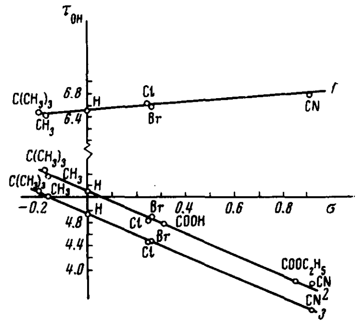


Figure 4. Correlation of τ_{OH} for 4-X-2,6-di-t-butylphenols (*2*, in the presence of t-butyl alcohol; *3*, in its absence) and τ_{OH} of t-butyl alcohol (*1*) with the σ^--factors of the para-substituent.

Bearing in mind the symbathic nature of the strength and bond order, an increase in the order ($P_{O...O}$) and polarisability ($\pi_{O...O}$) of the hydrogen bond with increase in the electronegativity of the para-substituent in the series of phenols must be expected. Such relations are actually observed[69]. They confirm the conclusion that the hydrogen bond in the associate is influenced by the nature of the para-substituent.

Generalising the above results, the following conclusions can be drawn: (*a*) all the 2,6-dialkylphenols are capable of forming hydrogen bonds; (*b*) the increase in the volume of the ortho-substituent reduces the capability of phenols for self-association; (*c*) 2,6-di-t-butylphenols do not give self-associates but can form a hydrogen bond with proton-withdrawing solvents, the nature of which depends on the nature of the substituent in the para-position of the phenol and the geometry of the solvent molecule.

V. ACIDITY OF STERICALLY HINDERED PHENOLS

The increased acidity of phenols in comparison with aliphatic alcohols is a characteristic feature of hydroxyaromatic compounds. This is due to the electron-withdrawing properties of the aromatic ring. Naturally, the change in the conjugation of the π-electrons of the nucleus with the p-electrons of the oxygen atom of the hydroxyl group should be reflected in the ease of heterolytic splitting of the O–H bond.

The introduction into the ortho-position to the hydroxyl group of alkyl substituents usually brings about a marked drop in the acidity of the phenol[73-85]. The reasons for the drop in acidity can be as follows: a positive inductive effect of the alkyl substituents, leading to electronic saturation of the O–H bond (however, as Table 9 shows, its contribution is small), the breakdown of the coplanarity of the aromatic ring and hydroxyl group, which decreases the effect of the electron-withdrawing properties of the ring, and finally the steric hindrances of the solvation of the anion formed.

Table 9. Dissociation constants of alkylphenols[43,73,82].

Compound	pK, 25°	pK, 25°
	water	methanol
Phenol	10.02	14.20
o-Cresol	10.33	14.80
o-Propylphenol	10.55	15.07
o-t-Butylphenol	11.35	16.25
2,6-Dimethylphenol	10.63	15.27
2,6-Di-isopropylphenol	11.08	15.11
2,6-Di-t-butylphenol	11.70	17.08
p-Cresol	10.27	14.55
2,4,6-Tri-t-butylphenol	12.19	—
2,6-t-Butyl-4-methylphenol	12.23	17.51

It has already been shown above that the introduction of even two t-butyl groups into ortho-positions displaces the OH group from the plane of the aromatic ring by ⊁ 14°, which is almost without effect on the conjugation of the p-electrons of the oxygen atom with the aromatic ring. This shows that the contribution of this effect to the decrease in acidity of the derivatives of 2,6-di-t-butylphenols is very small. Therefore the main reason for the drop in acidity is the steric hindrances of the solvation which is clear from Table 9, which gives the dissociation constants of the phenols in water and methanol for the three groups of compounds. It is suggested[42,43,80,81,86,87] that voluminous alkyl groups hinder the solvation of the anion formed as a result of dissociation and decrease its stability. Furthermore, the alkyl groups in the phenol molecule decrease the effective dielectric constant around the hydroxyl group, which increases the electrostatic energy of the anion and leads to a decrease in the dissociation constant. This conclusion is confirmed also by an investigation of the electrical conductivity of solutions of alkylphenols[88], which drops sharply with increase in the volume of the *o*-alkyl substituents.

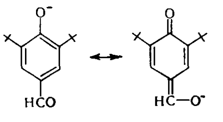
In considering the effect of the nature of the para-substituent on the acidity of the phenol it must be borne in mind that for some para-substituted phenols there is the possibility of tautomeric conversions (for example, quinoxime ⇌ nitrosophenol). This leads to rather complex dependences, especially for sterically hindered phenols, which generally tend to be converted into compounds with quinolide or quinonoid system of bonds. Problems of the tautomerism of phenols have been discussed in detail in a review[85].

From the example of unsubstituted phenol[43,89] and 2,6-dichlorophenol[74,90], it was repeatedly noted that the introduction of electron-withdrawing substituents into the para-position markedly increases the acidity of the phenol and it increases with the electronegativity of the substituent. A similar picture is observed for sterically hindered phenols[42,46,79,84,91,92]. Table 10 gives results on acidities for two series of 4-substituted phenols, which are correlated well with the σ_p constants of the para-substituents.

Table 10. Dissociation constants of 4-X-phenols at 25°C (water).[43]

X	pK_a		σ_p	X	pK_a		σ_p
	unsubstituted phenol	2,6-di-t-butyl phenol			unsubstituted phenol	2,6-di-t-butyl phenol	
CH_3	10.26	12.23	—0.15	$COOC_2H_5$	8.50	9.50	0.64
$C(CH_3)_3$	10.23	12.19	—0.14	$(CH_3)_3N^+$	8.21	9.84	0.77
OCH_3	10.21	12.15	—0.13	$COCH_3$	8.05	8.68	0.84
H	9.99	11.70	0.00	CN	7.97	8.70	0.88
COO^-	9.39	10.80	0.24	CHO	7.60	8.05	1.04
Br	9.36	10.83	0.25	NO_2	7.15	6.65	1.24
SO_3^-	9.03	10.40	0.40	NO	6.36	8.18	1.60
$CONH_2$	8.56	9.53	0.61				

It should be noted that for some 4-X-2,6-di-t-butylphenols with strongly electron-withdrawing substituents, (for example, CHO) the changes in p*K*a on going from the corresponding 4-X-phenol is not so great and can be satisfactorily explained by the inductive effect of the *o*-t-butyl groups without allowance for their steric factor. Values of p*K*a for a series of sterically hindered phenols in various solvents were found experimentally and calculated with allowance only for electronic effects of the two t-butyl groups; these values of p*K*a agreed satisfactorily for 2,6-di-t-butyl-4-formylphenol. When X is an alkyl residue, there is no such agreement, that is, in addition to the inductive effect of the para-substituent there is also the steric effect of the *o*-t-butyl groups. The observed anomaly can be explained by assuming delocalisation of the negative charge in the phenoxide ion with participation of the para-substituent.



If the requirements for solvation of both oxygen atoms in the anion formed are the same, then the total solvation of the 4-formylphenoxide and 2,6-di-t-butyl-4-formylphenoxide anions should be approximately the same. This suggests that although the steric effect of t-butyl groups greatly reduces the solvation of the phenol oxygen, it simultaneously facilitates the redistribution of the electron density at the oxygen atom of the formyl group and increases its degree of solvation, that is, the total change in the solvation of the anions as a whole is probably extremely small.

Hence the steric hindrances created by bulky alkyl groups show the twofold action on the ionisation of sterically hindered phenols. On the one hand, the strain in the O—H bond produced in the screening of the hydroxyl group facilitates the heterolytic breaking of the O—H bond, and on the other hand the phenoxide anion formed loses its stability due to the hindered solvation. The introduction of a para-substituent changes the value of some effect and leads to a marked change in the acidity of sterically hindered phenols.

VI. DIPOLE MOMENTS AND SORPTION PROPERTIES OF STERICALLY HINDERED PHENOLS

The steric effect of *o*-alkyl substituents is also decisive for certain other physicochemical parameters of sterically hindered phenols. First of all there are the dipole moments and the related sorption properties of phenols. These aspects have been discussed in a series of studies, in which the importance of steric hindrances is stressed to some extent. Thus, it was noted[19,93,94] that the introduction of t-butyl groups brings about a change in conjugation. This is expressed in an increase in the moment of the C—O bond from 0.66 D in phenol to 1.53 D in 2,4,6-tri-t-butylphenol. However, it must be remembered that the dipole moment is less sensitive to different steric effects than the physicochemical characteristics discussed above.

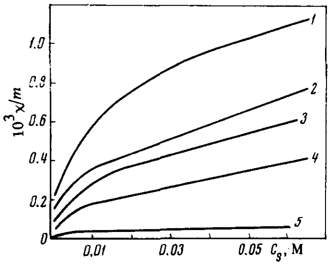


Figure 5. Freundlich isotherms in the adsorption of alkylphenols from cyclohexane on carbon: *1*) H; *2*) CH_3; *3*) *p*-t-C_4H_9 phenol; *4*) $CH(CH_3)_2$; *5*) $C(CH_3)_3$.

The more pronouned dependences on the values for the *o*-alkyl substituents were obtained in investigating the sorption properties of phenols[95-98]. The study of the sorption on carbon[97] and aluminium oxide[96] shows a decrease in the degree of sorption with increase in the volume of the *o*-alkyl substituents. Fig. 5 shows the Freundlich isotherms for several di-*o*-alkylphenols, where X is the amount of working adsorbent, *m* the total amount of adsorbent, and *C* the equilibrium concentration of adsorbent.

Fig. 5 shows there is a sharp difference in the sorption properties of phenols. Similar results were obtained in studying the chromatographic behaviour of phenols[95] (Table 11).

Table 11. Sorption of alkylphenols on silicic acid[95].

Alkyl	R_f		
	o-alkyl-phenol	*p*-alkyl-phenol	2,6-dialkyl-phenol
H	0.26	0.26	0.26
CH_3	0.37	0.28	0.55
C_2H_5	0.43	0.30	—
$CH(CH_3)_2$	0.52	0.30	0.95
$C(CH_3)_3$	0.74	0.31	1.00

Table 11 gives the R_f values obtained in the adsorption of phenols on silicic acid. A comparison of the change in frequency of the adsorption of the hydroxyl group of the phenol in the infrared range with the K_a values, where $K_a = 1/(R_f - 1)$, depending on the value of the *o*-alkyl substituents, obeys a first-order equation[98]. Evidently, the observed increase in the value of R_f with increase in the volume of the *o*-alkyl substituents also shows the decisive role of the steric screening of the hydroxyl group.

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The above features of the structure and certain physicochemical properties of sterically hindered phenols greatly determine the behaviour of compounds of similar type in various chemical changes. Thus a very characteristic property of these phenols is the ease with which they lose the hydrogen atom of the hydroxyl group as a proton or radical in ionic or radical processes. At the same time the considerable steric hindrances ensure that this oxygen is a not very accessible reaction centre of the molecule. These very properties agree well with the structure of sterically hindered phenols and are responsible for many interesting features of their behaviour: the inhibition of radical reactions, the formation of stable phenoxide radicals, the change into cyclohexadienones and methylenequinones, etc.

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Institute of Chemical Physics,
Academy of Sciences of the USSR,
Moscow

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Nuclear Magnetic Resonance Spectroscopy of Organometallic Allyl Compounds

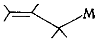
L.A.Fedorov

The NMR spectroscopic data for organometallic allyl and related derivatives have been examined. It is suggested that allyl compounds of transition metals be classified solely as σ- and π-derivatives and NMR spectroscopic criteria for the assignment of the test compounds to one of these types have been formulated. The effects of the structural non-equivalence of allyl ligands in a series of compounds, certain types of isomerism of allyl derivatives and also their possible lack of stereochemical rigidity have been considered. The validity, from the standpoint of NMR experiments, of the hypothesis of the σ-π transformations of allyl derivatives of transition metals in the presence of bases has been discussed. Hypotheses have been put forward concerning the geometry of the allyl compounds of certain non-transition metals.
The bibliography includes 171 references.

CONTENTS

I. INTRODUCTION

Depending on the geometry of the allyl−metal (a transition or non-transition metal) bond, allyl derivatives can be divided into two basic types: (1) compounds with the usual localised σ-bond [structure (I)]; (2) compounds with a non-classical delocalised bond [structure (II)].



(I)

σ-Bond

(II)

Delocalised bond

Allyl derivatives of the σ-type (I) are more characteristic of the chemistry of non-transition metals, while compounds with a delocalised bond (II), usually referred to as the π-bond[1], are typical with transition metals. There is no rigorous correspondence between the nature of the metal (transition or non-transition) and the bond type [(I) and (II)]. A fair number of transition metal derivatives with an allyl−metal σ-bond have been synthesised. On the other hand, structures with a delocalised bond (II) are known for non-transition metals, but, in order to regard them as π-complexes, a group-theoretical justification is necessary. Together with organometallic compounds containing an unsubstituted or substituted allyl group, it is natural to consider also compounds of certain other classes in which the allyl fragment is part of an open or closed carbon chain. In the discussion on derivatives with a delocalised bond, such grouping permits the consideration from one standpoint of all compounds where this bond is formally formed by three electrons from the three carbon atoms of the ligands.

Nuclear magnetic resonance (NMR) spectroscopy has proved to be the most important physicochemical instrument for the discovery and comprehensive investigation of complexes of the π-allyl type. For example, the non-classical structure of certain allyl (and also π-benzyl and trimethylenemethane) transition metal derivatives was initially proposed on the basis of NMR studies[2-4] and only subsequently confirmed by diffraction methods[5-7]. The isomerism in the series of allyl derivatives, various rearrangements, and many other structural and chemical problems have been successfully investigated by NMR spectroscopy. During the last decade, numerous spectroscopic data have accumulated and probably in the immediate future the NMR method will provide much information about compounds of this type.

However, for a number of reasons the data obtained are not always interpreted with sufficient rigour. As a result, certain conclusions which "follow from NMR data" and which have been widely adopted in the literature, actually proved to be incorrect. Apart from other reasons, this was because in studies of organometallic allyl compounds the entire "arsenal" of the NMR method was not employed. For example, until now no studies have been made of such important characteristics as $^{13}C-^{1}H$ spin−spin coupling, although the constants $J_{^{13}C-^{1}H}$ provide information about the valence state of the carbon atoms in the allyl ligand. Moreover, in the discussion of the screening of the proton in the π-allyl ligand the effect of the magnetic anisotropy of other ligands, for example triphenylphosphine, is as yet rarely taken into account.

All these considerations led us to undertake the present review. We must stipulate that the method chosen for the treatment of the subject, namely the use of data based on only one physicochemical procedure, dictated both the principles governing the selection of facts and the manner of their presentation. As a result, we have to concentrate attention only on the conclusions which follow unambiguously from NMR spectroscopic data. Clearly, the final answer to the majority of the problems considered can be obtained only by considering together results obtained by several physicochemical methods.

II. COMPOUNDS WITH A LOCALISED σ-BOND

NMR spectroscopic studies have been made on a number of organometallic σ-allyl derivatives[1, 8–17] and related compounds containing the σ-allyl fragment—cyclopentadienyl[18–24], benzyl[3, 25–28], and indenyl[19, 29–32] derivatives. In almost all cases NMR spectroscopy permits fairly reliable identification of the σ-allyl type. The relevant spectroscopic characteristics are presented in Table 1. For comparison, data for certain other organometallic allyl compounds are also included.

The ^{1}H NMR (PMR) spectra of σ-allyl derivatives (Fig. 1) show at least three groups of signals (intensity ratios 1 : 2 : 2) characteristic of the normal allyl system ($AKLX_2$, in the limiting case $ABCX_2$):

=CH—	CH_2=	—CH_2M
δ 6.0—6.6 p.p.m.	δ 3.5—5.0 p.p.m.	δ 1.5—2.8 p.p.m.

The lines due to the most screened aliphatic CH_2 protons (X_2) are split by CH vinyl protons, which to a first approximation gives rise to a doublet in the spectrum. The vinyl protons of the =CH_2 (KL) group are non-equivalent and therefore produce a poorly resolved multiplet in the spectrum. As a result of splitting by all the remaining protons in the allyl fragment, the vinyl =CH proton (A) gives rise in the spectrum to a distinct asymmetric multiplet, typical for vinyl compounds, located in the region of the weakest fields.

It follows from the data in Table 1 that the screening of individual groups of protons in each compound differs somewhat from the corresponding values in propene.

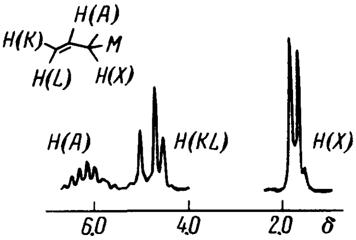
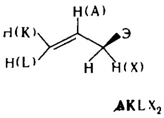
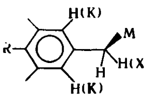
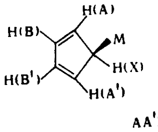
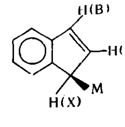


Figure 1. NMR spectrum of the compound σ-$C_3H_5Mn(CO)_5$ ($AKLX_2$ spin system)[1].

Table 1. Parameters of the PMR spectra of σ-allyl derivatives of the elements.

Type of molecule and type of spectral system of allyl component of spectrum	Compound	δ_H, p.p.m. rel. to TMS*			$J_{HH'}$, Hz		Conditions of measurement (solvent, temp., °C)	References
		H(A)	H(K, L) H(B)	H(X)	AK (*cis*)	AL (*trans*)		
 $AKLX_2$	$C_3H_5Mn(CO)_5$	6.15	4.77	1.85	10	17		1
	$C_3H_5Fe(CO)_2$-π-C_5H_5	6.16	4.59	2.07	9.2	17.1		8
	$C_3H_5Mo(CO)_3$-π-C_5H_5	6.0	3.5	2.27				9
	$C_3H_5W(CO)_3$-π-C_5H_5	~6.0	4.53	2.32			C_6H_{12}	10
	$C_3H_5Rh(CO)Cl_2[P(C_6H_5)_3]_2$	6.58	4.82	2.8			$CDCl_3$	12
	$C_3H_5IrCl_2[P(CH_3)_2C_6H_5]_3$	6.2	4.90	2.70			$CDCl_3$	11
	$(C_3H_5)_4Si$	5.62	4.70	1.50			<165	14
	$(C_3H_5)_3B$	5.65	4.70	2.05			<—40°	14
	$(C_3H_5)_4Sn$	5.88	4.83 (K) 4.72 (L)	1.88	9.39	16.90		15
	$C_3H_5Ge(CH_3)_3$	5.94	4.79 (K) 4.92 (L)	1.74				16
	$(C_3H_5)_2Hg$	5.98		1.86	9.52	16.75	[$^2H_8$] THF	17
	C_3H_6	5.73	4.88 (K) 4.97 (L)	1.72	10.02	16.81	CCl_4	33
	$C_6H_5CH_2Mo(CO)_3$-π-C_5H_5		7.13	2.88			CS_2	3
	4-$CH_3C_6H_4CH_2Mo(CO)_3$-π-C_5H_5		7.04	2.92				25
	4-$CH_3C_6H_4CH_2W(CO)_3$-π-C_5H_5		7.07	2.99			$CDCl_3$	25
	$(C_6H_5CH_2)_4Ti$		6.42	2.57			[$^2H_8$] toluene	27
	$(C_6H_5CH_2)_4Zr$		6.38	1.53			C_6D_6	28
	$(C_6H_5CH_2)_4Sn$			2.22			$CHCl_3$	26
	$C_6H_5CH_3$			2.34			CCl_4	34
 AA'BB X	σ-$C_5H_5Fe(CO)_2$-π-C_5H_5	~6.0	~6.3	3.5			CS_2, —80	18
	σ-$C_5H_5Cr(NO)_2$-π-C_5H_5	6.28	6.5				CS_2, —110	19
	σ-$C_5H_5Si(CH_3)_3$	6.48		3.23				22
	(σ-$C_5H_5)_2Ge(CH_3)_2$	6.63		3.51				22
	C_5H_6	6.42		2.90				34
 ABX	$C_9H_7Fe(CO)_2$-π-C_5H_5	6.72	6.53	3.97			$CDCl_3$, 25	19
	$(C_9H_7)_2Hg$	6.76		3.81	~5.7		<—41	29
	$C_9H_7Sn(CH_3)_3$	6.80	6.58	3.87			CS_2, —37	30
	$C_9H_7Ge(CH_3)_3$	6.65		3.50			<134	30
	$C_9H_7Si(CH_3)_3$	6.73	6.41	3.29			<180	30
	C_9H_{10}	6.14	6.67	2.99	5.88			35

* Tetramethylsilane (Ed. of Translation)

However, these differences do not make it necessary to take into account additional factors apart from those already known: the electronegativity of the metal, the magnetic anisotropy of the C – M bond, and the anisotropies of the individual fragments of the molecule. The coupling constants J_{HH} (*cis*) and J_{HH} (*trans*) of the compounds under considerations, including transition metal derivatives, in fact agree with the corresponding constants for propene. Nor are any other spectroscopic differences observed between σ-allyl derivatives of transition and non-transition metals. Furthermore, one may conclude that, under the conditions (temperature, solvent) where NMR spectroscopy indicates a σ-allyl structure of the compounds considered, no signs of coordination of the double bond of the allyl fragment to the metal atom are observed.

The available data permit the formulation of the principal spectroscopic characteristics of organometallic allyl compounds with a localised σ-bond: (1) the non-equivalence of the CH_2 groups; (2) the equivalence of the protons in the aliphatic CH_2 group and their non-equivalence in the olefin group; (3) the agreement of the vicinal coupling constants J_{HH} (*cis*) $\simeq$ 9 – 10 Hz and J_{HH} (*trans*) = 17 Hz with the corresponding constants for propene and other allyl derivatives.

The PMR spectra of σ-benzyl, σ-indenyl, and σ-cyclopentadienyl derivatives of transition and non-transition metals are also very similar to the spectra of the corresponding hydrocarbons (toluene, indene, and cyclopentadiene). In all cases the aliphatic protons are the most screened and the observed spectrum fully agrees with expectation for a spin system with a C – M σ-bond. It should also be noted that the signals due to aliphatic protons, geminal relative to the metal atoms, are located in a fairly narrow region of the spectrum for each of the above classes of compounds:

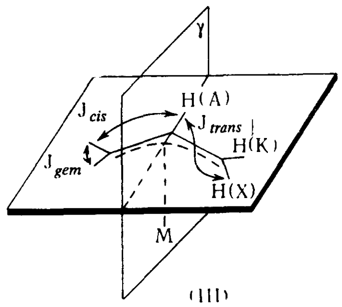
$CH_2{=}CH{-}CH_2M$	$C_6H_5CH_2M$	C_5H_5M	C_9H_7M
δ 1.5—2.8 p.p.m.	δ 2.2—3.0 p.p.m.	δ 3.2—3.5 p.p.m.	δ 2.9—4.0 p.p.m.

This evidently can be used as a test for the formation of a localised bond.

III. DERIVATIVES WITH A DELOCALISED BOND

The PMR spectra of the compound π-$C_3H_5Co(CO)_3$ with a delocalised bond were investigated for the first time in 1960 by Heck and Breslow[2]. The PMR spectra of allyl derivatives of transition metals with a delocalised C_3H_5 – M bond were investigated in greater detail by McClellan et al[1]. The number of studies which in one form or another relate to the NMR spectroscopy of π-allyl compounds increases steadily. Spectroscopic data are now available both for compounds containing allyl groups only [$(C_3H_5)_nM$, M = Ni, Pd, Zr, Hf, Th, Rh, Ir, Pt, U, etc.)] [36–44] and for mixed compounds containing, apart from the π-allyl ligands, one or several other groups: a halogen[1,45–47], carbonyl[1,2,48–50], π-cyclopentadienyl[1,47,54,55], a halogen and carbonyl[56–60], a halogen and π-cyclopentadienyl[54,61], carbonyl and π-cyclopentadienyl [8–10,51–53], etc. Spectroscopic data are also being quoted for π-allyl complexes in which the transition metal atom is coordinated to phosphines, pyridine, dimethyl sulphoxide, the acetylacetonate ion, and similar basic ligands [11,12,46,62–73,82].

Historically the NMR spectra of non-transition metal derivatives with a postulated delocalised bone [structure (II)] were investigated earlier than those of the π-allyl complexes of transition metals. Thus, as early as 1959, Nordlander and Roberts[74] observed in the PMR spectrum of C_3H_5MgBr characteristics the interpretation of which did not exclude the possible existence in this compound of one of the forms of the delocalised C_3H_5 – Mg bond:



(III)

Table 2 lists certain spectroscopic characteristics of the π-allyl derivatives of transition metals. In the PMR spectra of compounds with an unsubstituted ligand, as in the case of σ-complexes, there are as a rule three groups of signals with intensity ratios of 1 : 2 : 2 (Fig. 2). However, the spin system of the AK_2X_2 spectrum indicates a greater symmetry of the allyl – M group in compounds of the π-type. In particular, it follows from the spectrum that each of the two signals in a strong field (K_2X_2) no longer refers to an individual CH_2 group, as in the σ-structure, but to an individual type of proton from each CH_2 group—*cis* or *trans*†.

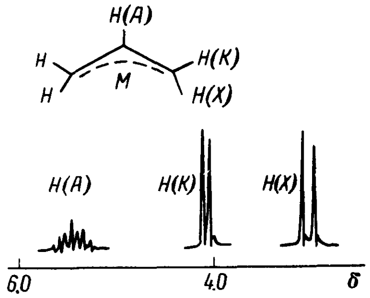


Figure 2. NMR spectrum of the compound $(\pi\text{-}C_3H_5PdCl)_2$ (AK_2X_2 spin system)[66].

The results led to the conclusion that in derivatives of π-type [structure (III)] a delocalised bond is formed and all the carbon atoms of the allyl fragment are in a state of sp^2-hybridisation (strictly speaking, in order to assess the valence state of the carbon atoms of the π-allyl ligand, it is also necessary to have data on $^{13}C-{}^1H$ spin – spin coupling). Then both C – C bonds of the ligands prove to

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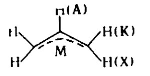
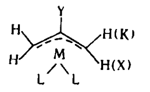
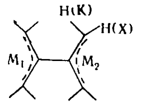
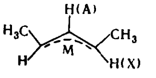
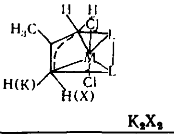
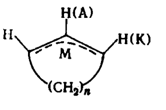
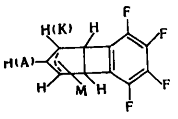
† Here and subsequently we are considering the position of the terminal protons relative to the central proton or the group replacing it [structure (III)]. The terms *"cis"* and *"trans"* were introduced for these compounds in 1959 by Nordlander and Roberts[74] and are used in the discussion of both allyl and π-olefin, π-butadiene, π-pentadienyl, and similar complexes. Two years later[1] the terms *"syn"* and *"anti"* were introduced, but have not been widely adopted by investigators of π-complexes (with the exception of allyl complexes).

Table 2. Parameters of the PMR spectra of transition metal derivatives with a symmetrical π-allyl–M bond.

Type of molecule and type of spectral system of allyl component of spectrum	Compound	δ_H, p.p.m.rel. to TMS			J_{HH}, Hz		Conditions of measurement (solvent, temp., °C)	References
		H (A)	H(K) (*cis*)	H(X) (*trans*)	*cis*	*trans*		
1	3	3	4	5	6	7	8	9
 AK₂X₂	$(C_3H_5PdCl)_2$	5.45	4.02	2.95	7.1	12.1	$CHCl_3$	47
	$(C_3H_5PdI)_2$	5.40	4.35	3.05	6.3	11.8	$CHCl_3$	47
	$C_3H_5PdC_5H_5$	5.68	4.37	3.19	5.0	10.0	$CDCl_3$	1
	$(C_3H_5)_2Pd$, two types of symmetrical	5.06	4.14	2.40	7.6	13.0	$CDCl_3$	36
	π-allyl groups	4.93	3.90	2.56	7.6	13.0	—20°	
	$(C_3H_5NiBr)_2$	4.3	2.3	1.2	7.0	13.3	C_6H_6	75
	$C_3H_5NiC_5H_5$	3.70	3.09	1.88	3.0	11.0		1
	$C_3H_5NiCH_3$	5.33	2.76	2.25			TMS, —60	76
	$(C_3H_5)_2Ni$, two types of symmetrical	5.03	3.79	1.67	7.0	14.0	$CDCl_3$	36
	π-allyl groups	4.55	3.58	2.20	7.0	14.0	—40°	
	$C_3H_5Mn\ (CO)_4$	4.7	2.8	1.8	7.0	12.0	C_6H_6, 160	48
	$C_3H_5Co(Co)_3$	4.91	3.07	2.15	6	10		1
	$C_3H_5Mo(CO)_2(CH_3CN)_2Cl$	4.44	3.59	1.01	6.0	9.0	C_6H_5Cl	77
	$C_3H_5FeC_5H_5(CO)$	4.16	2.67	1.68	8.0	11.0	C_6H_6	8
	$(C_3H_5)_3Rh$, three types of symmetrical	5.26	2.87	2.53	7.0	14.0	$CFCl_3$	38
	π-allyl groups	4.17	2.68 or 2.62	1.33	6.5	11.0	—74	
		3.50	2.62 or 2.68	1.71	6.5	11.0		
	$(2\text{-}CH_3C_3H_4PdCl)_2$	—	3.83	2.83	—	—	$CHCl_3$	47
	$2\text{-}CH_3C_3H_4$Pdacac	—	3.52	2.66	—	—	CCl_4	46
	$2\text{-}CH_3C_3H_4Rh[P(C_6H_5)_3]_2$	—	2.46	2.27	—	—	C_6H_5Cl	78
	$(2\text{-}ClC_3H_4PdCl)_2$	—	4.27	3.26	—	—	$CDCl_3$, 34	68
	$2\text{-}ClC_3H_4$Pdacac	—	4.55	3.12	—	—	$CDCl_3$, 34	68
	$2\text{-}ClC_3H_4Co(CO)_3$	—	3.83	2.92	—	—		1
 K₂X₂	$(C_5H_5NiC_3H_4)_2$	—	3.05	1.3			C_6D_6, 30	79
	$C_5H_5NiC_3H_4—C_3H_4PdC_5H_5$	—Ni	2.75	1.15			C_6D_6, 30	79
		Pd	3.65	2.15				
	$(C_5H_5PdC_3H_4)_2$		3.65	2.24			$CDCl_3$	72
	$(acacPdC_3H_4)_2$		4.01	2.81			$CDCl_3$	72
 AX₂	$(C_5H_9PdCl)_2$	5.14	—	3.62	—	10.7		80
	$C_5H_9Co(CO)_3$					9.8	CDCl, 33	81
 K₂X₂	$2\text{-}CH_3C_3H_4IrCl_2[P(C_2H_5)_3]_2$		4.10	3.20	—	—	$CDCl_3$, 34	11
	$2\text{-}CH_3C_3H_4RhCl_2[As(C_6H_5)_3]_2$		4.15	3.74	—	—	$CDCl_3$, —60	82
	$2\text{-}CH_3C_3H_4RhCl_2[Sb(C_6H_5)_3]_2$		4.39	3.15	—	—	$CDCl_3$, —50	82
 AK₂	n=2, $C_5H_7NiC_5H_5$	5.13	3.96	—			C_6H_6	83
	n=2, $C_5H_7Cr(CO)_2C_5H_5$	5.10	4.00	—			C_6H_6	51
	n=3, $(C_6H_9PdCl)_2$	5.51	5.22	—				84
	n=3, $C_6H_9Rh[P(C_6H_5)_3]_2$	5.25	3.60	—	6.6	—	C_6H_5Cl	78
	n=5, C_8H_{13}*Co-cyclo-octa-1,5-diene*	5.5	3.3		8	—	C_6D_6	85
	n=5, $C_8H_{13}Rh[P(C_6H_5)_3]_2$	5.25	3.47		8.0	—	C_6H_5Cl	78
	$C_{11}H_5F_4NiC_5H_5$	5.02	3.85					86

be equivalent and the metal is located symmetrically relative to the terminal carbon atoms. Subsequently these conclusions were confirmed by diffraction data (see, for example, Refs. 5, 80, 87, and 88).

The H(A) proton bound to the central carbon atom proves to be least screened in all cases. Its signal consists of a complex symmetrical multiplet due to splitting by the two pairs of terminal protons. Two other signals are due to the *cis*-protons H(K) and *trans*-protons H(X). To a first approximation, each of them consists of a doublet due to splitting by the central atom. In a more detailed investigation of these "doublets" it is possible to observe a fine structure due to the interaction of the non-equivalent geminal protons H(K) and H(X). The corresponding coupling constant J_{HH} (*gem*) usually does not exceed 1.5 Hz [36,41,62,66] but in the case of substituted compounds of the allyl type higher splittings for geminal protons are also known: 2 Hz for $2\text{-}ClC_3H_4$Pdacac[68] and

3 Hz for π-$C_6H_5CH_2Mo(CO)_2C_5H_5$.[3] We may note that for the compound $(CH_2)_3CFe(CO)_3$ this value reaches up to 5 Hz.[4]

As in π-complexes of other types, the proton spin–spin coupling constants for π-allyl complexes J_{HH} (*cis*) = 3–8 Hz and J_{HH} (*trans*) = 10–15 Hz (Table 2) are much lower than for the initial olefins [for example in the case of ethylene J_{HH} (*cis*) = 11.5 Hz and J_{HH} (*trans*) = 19.1 Hz[89]] and the corresponding σ-allyl derivatives. Complex formation is the evident explanation of this effect.

However, it should be emphasised that, despite the lowering of the absolute values of the constants J_{HH} of all three types, the sequence of their relative values established previously[34,90] in the olefin series is strictly maintained:

$$J_{HH}\,(trans) > J_{HH}\,(cis) > J_{HH}\,(gem).$$

This finding permits an unambiguous assignment of the signals due to *cis*- and *trans*-protons in the spectroscopic study of each new π-complex.

The experimental data so far accumulated (Table 2) show that in π-allyl complexes the *cis*-protons H(K) are less screened than the *trans*-protons H(X). The range of variation of the screening of the individual groups of protons in π-complexes is much wider than in derivatives of the σ-type.

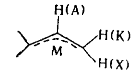
$$\begin{array}{ccc} \mathrm{H(A)} & \mathrm{H(K)} & \mathrm{H(X)} \\ 5.68 \geqslant \delta \geqslant 3.5 & 4.4 \geqslant \delta \geqslant 2.7 & 3.2 \geqslant \delta \geqslant 1.3 \end{array}$$

This can probably be accounted for by the greater sensitivity of the π-allyl ligand to the characteristics of the complex-forming metal. Differences in experimental conditions can also play a decisive role: Table 2 includes for certain compounds data for screening in benzene solutions, although the use of this solvent can seriously distort the results. Evidently, as information accumulates on the spectra of the π-allyl derivatives of an increasing number of metals, the range of variation of the screening of protons of each type may become extended. At the same time, there is also a possibility that the range of variation will be found to be narrower in repeated NMR measurements under standard conditions, particularly when NMR spectroscopic data for the compounds in solvents such as benzene, toluene, etc. are excluded. We may also note that, although the ranges of variation of the chemical shifts of the individual groups of protons overlap to a considerable degree, for each specific π-complex the sequence of increasing screening is as a rule maintained: H(A) < H(K) < H(X).

Thus, using as an example compounds containing an unsubstituted π-allyl group, it is possible to formulate a number of criteria for the π-coordination of the transition metal atom to the ligand: (1) the equivalence of both CH_2 groups and the non-equivalence of the protons in each; (2) the shift of the signals of all the protons towards stronger fields compared with the σ-allyl complexes, particularly for *trans*-protons; (3) a sharp reduction of the J_{HH} (*cis*) and J_{HH} (*trans*) constants.

At a fairly low temperature, the PMR spectrum[91] of C_3H_5Li resembles the spectra of the π-allyl complexes of transition metals (Table 3). It consists of three signals and corresponds to the AK_2X_2 spin system. All the necessary spectroscopic criteria of the delocalised bonds were observed: the equivalence of the CH_2 groups, the non-equivalence of the *cis*- and *trans*-protons, and the lowering of the constants J_{HH} (*cis*) and J_{HH} (*trans*). The only difference between the spectra of C_3H_5Li and the π-allyl complexes, for example $(C_3H_5)_4Zr$, consists in the reversal of the positions in the spectrum of the signals due to the *cis*- and *trans*-protons: in contrast to transition metal π-complexes, the *cis*-protons in allyl-lithium are the most screened. Thus one may conclude that, under conditions where the spectrum of allyl-lithium was measured (Table 3), a delocalised bond of type II and not a σ-bond is formed, the metal atom being located symmetrically relative to both CH_2 groups.

Table 3. Comparison of the spectroscopic parameters of zirconium and lithium derivatives with a delocalised allyl–M bond.



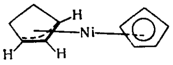
Spectrocopic parameters, conditions of measurement		Compound	
		$(C_3H_5)_4Zr^{36}$	$C_3H_5Li^{91}$
δ_H, p.p.m. rel. to TMS	H (A)	5.18	6.38
	H (K)	3.28	1.78
	H (X)	1.90	2.24
J_{HH}, Hz	*cis*	8.5	8.6
	trans	15.5	15.2
Solvent		$CFCl_3$	$[^2H_8]$THF
Temperature		—74°	—87°

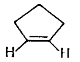
The NMR spectrum of the π-allyl complex becomes significantly simplified after symmetrical substitution in the ligand: substitution of the central proton[1,11,46,47,68,82], substitution of both *cis*-protons by identical groups[80,81,92,93], and substitution of both *trans*-protons with formation of a π-enyl ring[47,51,78,83,84,94-96]. The chemical shifts and the spin–spin coupling constants of the remaining protons in general differ little from the corresponding values for π-complexes with an unsubstituted ligand.

Table 4. Chemical shifts of cycloheptatrienyl protons.

Compound	Solvent	Temp., °C	δ_H, p.p.m.rel. to TMS				References
			H_1	H_2	H_3	H_4	
$C_5H_5Fe(CO)C_7H_7$	$[^2H_8]$toluene	—50	2.44	4.32	6.05	5.20	100
	$CDCl_3$		3.08	4.75	6.10	5.15	100
$C_5H_5Mo(CO)_2C_7H_7$	CCl_2F_2—$[^2H_8]$toluene	—107	1.13	3.76	6.20	5.19	101
	$CHCl_2F$	—118	2.32	4.59	6.50	5.40	101
	$CHCl_2F$ $[^2H_8]$toluene	—118	2.00	4.37	6.36	5.36	101
	$CFCl_3$—CS_2	—110	2.10	4.27	6.0	5.0	102
$Co(CO)_3C_7H_7$	CF_2Cl_2	—140	3.50	4.95	~6.5	~5.8	102
C_7H_8			2.19	5.27	6.09	6.51	103

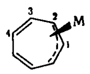
We may note a characteristic feature of the π-enyl complexes associated with the sensitivity of the spin–spin coupling constants to ring size[97-99]. The J_{HH} (*cis*) constants for π-enyl rings are lower than those for the non-complex molecules, as can be seen from a comparison of the corresponding values, for example, for compounds (IV) and (V). However, the absolute values of these constants are significantly lower for both types of compounds than in the case of open-chain systems—π-allyl complexes and olefins[78,96]. Thus the J_{HH} (*cis*) constants for the π-enyl complexes may not fall in the range of values found for the π-allyl compounds:

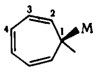

(IV)


(V)

$J_{HH}(cis)$ = 2.7 Hz (Ref.96) $J_{HH}(cis)$ = 5.4 Hz (Ref.97)

For certain stereochemically non-rigid cycloheptatrienyl molybdenum and cobalt compounds (Table 4), the existence of a π-allyl bond has been postulated [structure (VI)] [104-106]:


(VI)


(VII)

However, recent studies[101,102], including one on the corresponding iron derivative[100], show that at fairly low temperatures the NMR spectra of these compounds agree better with the instantaneous formation of a C_7H_7-M σ-bond [structure (VII)]: the aliphatic proton proves to be most highly screened and the chemical shifts of each of the three pairs of olefinic protons are similar to the corresponding values for cycloheptatriene. To resolve this contradiction, it is evidently necessary to carry out structural studies. However, it should be emphasised that discrepancies between the actual structures of organometallic compounds and those expected on the basis of the effective atomic number rule are being increasingly observed. This can be illustrated, for example, by the structure of the indenyl compound of samarium for which NMR data indicate a localised C–Sm σ-bond[31], although a delocalised π-bond had been suggested, by analogy with the corresponding cyclopentadienyl derivatives of the lanthanides.

IV. PROTON SCREENING IN π-ALLYL COMPLEXES

A shift of the PMR signals to the "aliphatic" region of the spectrum is observed on formation of π-complexes by aromatic and olefinic ligands of a wide variety of types[107]. Since the effect itself has not so far been fully interpreted quantitatively, its discussion for π-allyl compounds must be restricted to certain qualitative considerations. As usual[34,90], it is natural to assume that the magnetic screening of protons is determined mainly by the relation between two factors: the simultaneous effect of the anisotropy of the magnetic susceptibility of the adjacent atoms and bonds and the changes in electron density at the given hydrogen atom.

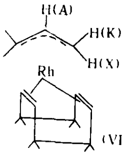
The effect of the anisotropy of the magnetic susceptibility on the screening of protons in the π-allyl ligand may include both the effect of the magnetic anisotropy of the ligand itself and the effect of the transition metal atom and other groups bound to it. One of the main causes of the shift towards stronger fields of the signals due to the protons in olefinic derivatives on formation of π-allyl compounds is the change in the magnetic anisotropy of the multiple bonds on complex formation[108].

The magnetic anisotropy of the double bond, which leads to a shift of the proton signal towards weaker fields compared with its "true" position (i.e. when only local screening is taken into account), is known[34,90] to make a considerable contribution to the screening of olefin protons. On formation of the π-allyl complex the contribution of this effect diminishes, which is shown in the spectra by a shift of the signals of the protons investigated towards stronger fields, although their screening then merely approaches the "true" value.

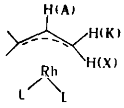
The magnetic anisotropy of the transition metal, particularly the presence in the latter of filled *d* levels, can have a significant effect on the screening of the protons of the coordinated ligand. This effect is clearly revealed by the fact that in all π-allyl complexes the *trans*-protons located close to the transition metal atom are screened more than the *cis*-protons. This type of feature is not characteristic only of allyl-lithium (Table 3), where a non-transition metal is involved in the formation of a delocalised bond[91].

The magnetic anisotropy of other ligands bound to the transition metal atom can also influence the screening of the protons. For example, when the chemical shifts of the protons in two allylrhodium derivatives [(VIII) and (IX), Table 5] are compared, it is evident that the replacement of cyclo-octa-1,5-diene by two triphenylphosphine groups alters the screening of the allyl protons in different ways. Then the central proton is screened to a greater extent, while the terminal protons are in fact descreened, a particularly pronounced effect being observed for *trans*-protons located closest to the source of perturbation. One cause of this behaviour is probably the fact that the effect of the magnetic anisotropy of the triphenylphosphine groups is greater than the effect of cyclo-octa-1,5-diene.

Table 5. Changes in the screening of the protons in the π-allyl derivatives of rhodium as a function of the structure of the compound.



(VIII)



(IX)

$L = P(C_6H_5)_3$

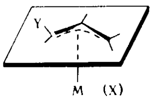
Type of proton	δ_H, p.p.m.rel. to TMS		Δδ
	(VIII)(Ref.109)	(IX)(Ref.78)	
H (A)	5.17	4.95	0.22
H (K)	2.65	2.74	–0.09
H (X)	1.67	2.19	–0.42

It follows from the data in Table 2 that in certain cases a shift of the signal due to the protons in the π-allyl ligand towards strong fields, relative to that of the protons of the non-coordinated olefin, reaches 3–4 p.p.m. Such a shift cannot be explained without postulating that, apart from the influence of the magnetic anisotropy of neighbouring atoms and bonds, the change in the local screening of the ligand protons, caused by the partial transfer of electron density from the metal atom to the ligand (M → L), also has a definite effect. This is evidently a reflection of the electropositive nature of the metal compared with carbon atoms. Unfortunately, it is very difficult to isolate this factor against the background of the experimentally observed overall effect.

It is quite likely that the displacement of electron density from the metal to the ligand is accompanied by its non-uniform distribution in the π-allyl group. Possibly this is why in the complexes examined the central proton proves to be least screened compared with others. A more pronounced screening of the terminal protons may be evidence of an enhanced electron density at the corresponding carbon atoms. Consequently, if electrophilic substitution reactions involving a π-allyl ligand are discovered, the point of attack in such reactions will be primarily the terminal carbon atoms. However, in choosing model systems for such reactions, it is necessary to observe certain conditions. Such models must evidently be characterised not only by the presence of an excess electron density in the ligand but also by a fairly pronounced inertness of the molecule towards possible competing reactions (a strong allyl–M bond, the absence of labile M–halogen bonds, etc.). It may be that in fact an unsuitable choice of models is the reason why all known attempts to achieve electrophilic substitution in a π-allyl ligand (see, for example, Rubezhov[110]) have so far proved unsuccessful.

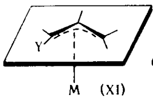
V. ASYMMETRIC ALLYL COMPOUNDS WITH A DELOCALISED BOND

Like any other symmetrical system, a π-allyl complex may lose, as a result of some perturbation, the plane of symmetry γ passing through the metal and the central carbon atom [structure (III)]. As a result, the two "arms" of the π-allyl ligand may become non-equivalent. One may point to several sources of perturbation, which lead to a non-uniform distribution of electron density in a π-allyl ligand. In the simplest case this is a substituent Y joined to one of the terminal carbon atoms [structures (X) and (XI)].



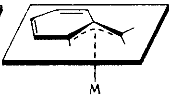
(X)

cis-isomer



(XI)

trans-isomer



(XII)

An asymmetric π-complex of this type, crotylcobalt tricarbonyl, was investigated by the NMR method earlier than others[111]. Subsequently many other asymmetric π-allyl complexes were described[41,55,66,76,112-116]. Some of them are listed in Table 6. Lithium derivatives with asymmetric allyl ligands are also known[117].

It follows from the data in Table 6 that in the complexes under consideration the *trans*- (and *cis*-) protons of the same ligands can have different chemical shifts and somewhat different constants for spin–spin coupling to the central proton (Fig. 3).

The π-benzyl and π-thienyl derivatives of a number of transition metals constitute an interesting class of asymmetric π-allyl complexes[3,25,118,119]. In these compounds asymmetry is an inseparable property of the molecules: three carbon atoms of the ligand form with the metal a delocalised π-allyl bond in such a way that one of its "arms" belongs to the ring [structure (XII)]. At a low temperature, when the geometry of these compounds is fixed, the protons of the CH_2 group are non-equivalent. In particular in $\pi\text{-}C_6H_5CH_2Mo(CO)_2\text{-}\pi\text{-}C_5H_5$ the chemical shifts of these protons at −30°C differ approximately by 1 p.p.m. The proton on the part of the ring involved in the π-allyl bond becomes much more screened than the others and acquires a chemical shift uncharacteristic of aromatic protons [$\delta = 5.2$ p.p.m. for $\pi\text{-}C_6H_5CH_2Mo(CO)_2C_5H_5$]. Because of the structural characteristics of molecules of this class, there is only one piece of spectroscopic evidence for the asymmetry—the difference between the screening of the two *trans*-protons.

Groups external to the allyl ligand and also the low symmetry of the entire molecule can also give rise to the asymmetry of the π-allyl ligand. However, in compounds where these factors may operate, the possibility or impossibility of asymmetry is not evident in all cases. We shall examine two examples of the occurrence of asymmetry of this type in π-allyl complexes of two classes—planar square and octahedral complexes.

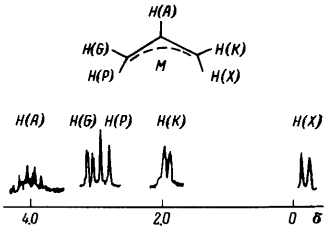
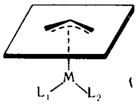


Figure 3. NMR spectrum of the compound $(\pi\text{-}C_3H_5)_4Mo$; four equivalent asymmetric π-allyl ligands (AGKPX spin system)[41].

Complexes of the platinum group metals (XIII) have been investigated fairly comprehensively. When $L_1 = L_2$ [for example, $(C_3H_5PdCl)_2$, [46,47,66,93] $(C_3H_5NiBr)_2$, [75] etc.], they have a spectrum of the AK_2X_2 type, characteristic of a symmetrical π-allyl ligand. Evidently asymmetry may arise only when the substituents are non-equivalent ($L_1 \neq L_2$), which leads to the corresponding non-equivalence of the *cis* and *trans*-protons and the appearance in the spectrum of five signals of equal intensity (AGKPX spin system).



(XIII)

However, the possibility of asymmetry is not realised in all cases (Table 6). For example, when the groups L_1 and L_2 do not differ very much in their electronic effects, the spectrum characteristic of symmetrical complexes is maintained. As already stated, the chemical shifts of protons may be influenced not only by changes in electron density but also by the magnetic anisotropy of adjacent groups. In many cases the asymmetry of the allyl group is due precisely to this factor. For example, the spectra of compounds C_3H_5PdClL correspond to the symmetrical allyl group (AK_2X_2) [66] when L = dimethyl sulphoxide (DMSO) and to an asymmetric ligand (AGKPX, Table 6) when $L = E(C_6H_5)_3$ (E = P, As, or Sb), whose basicity is close to that of dimethyl sulphoxide. Probably in this case the magnetic anisotropy of the aromatic rings of the substituents is in fact of decisive importance.

When the π-complexes have an octahedral structure, the number of situations favouring asymmetry is much greater.

For example, we shall consider the conditions under which the π-ligand in derivatives of the type $(\pi\text{-}C_3H_5)_2ML_1L_2$ (Table 7) may become asymmetric.

If the compound has the *trans*-configuration and the ligands L_1 and L_2 are identical or different, then both allyl groups must be symmetrical and equivalent. Correspondingly the NMR spectrum should show only one set of signals associated with the spin system AK_2X_2. For the *cis*-configuration of the molecule and identical ligands L_1 and L_2, the terminal CH_2 groups of both equivalent allyl ligands become non-equivalent. In consequence, the NMR spectrum should show a group of signals of the system AGKPX, characteristic of an asymmetric π-allyl ligand. Such a spectrum was observed, for example, in the study

Table 6. Parameters of the NMR spectra of metal derivatives with an asymmetric π-allyl–M bond.

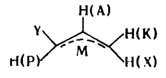
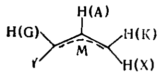
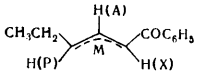
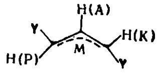
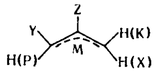
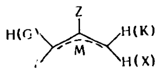
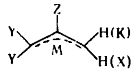
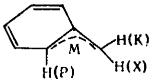
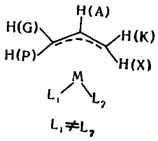
Type of molecule and type of spectral system of allyl component of spectrum	Compound	δ_{HH}, p.p.m. rel. to TMS			J_{HH}, Hz		Conditions of measurement (solvent, temp., °C)	References
		H(A)	H(G,K) (*cis*)	H(P, X) (*trans*)	*cis*	*trans*		
	Source of perturbation in allyl group							
 AKPX	$(1\text{-}ClCH_2C_3H_4PdCl)_2$	5.45	4.02	3.03(X)	6.9	12.0	$CHCl_3$	46
	$1\text{-}CH_3C_3H_4Co(CO)_2P(n\text{-}C_4H_9)_3$	4.42	2.17	2.60(P) 1.35(X)	6.2	10.4 9.0	C_6D_6	115
 AGKX	$1\text{-}CH_3C_3H_4Co(CO)_3$				7.1 6.8	12.3		81
	$1\text{-}CH_3C_3H_4Rh[P(C_6H_5)_3]_2$	~4.9	3.35(G) 2.47(K)	2.01	6 6.9	14.0	C_6H_5Cl 30	78
	$1\text{-}ClC_3H_4Co(CO)_3$	5.99	4.68 3.35	2.38	8	11		1
 APX	$1\text{-}C_2H_5\text{-}3\text{-}COC_6H_5C_3H_3Mn(CO)_4$	5.77		3.59(P) 3.13(X)		10.1 10.0	$CDCl_3$	120
 AKP	$1,3\text{-}(CH_3)_2\text{-}C_3H_3Co(CO)_3$				7.2	11.3		81
 KPX	$(1\text{-}CH_3\text{-}2\text{-}Cl\text{-}C_3H_3PdCl)_2$	—	4.04	3.05	—	—	$CDCl_3$	68
	$(1\text{-}t\text{-}C_4H_9\text{-}2\text{-}CH_3C_3H_3PdCl)_2$		3.62	2.67(P) 3.48(X)	—	—		121
 GKX	$(1\text{-}t\text{-}C_4H_9\text{-}2\text{-}CH_3C_3H_3PCl)_2$	—	4.44	3.87(P) 3.47(X)	—	—		121
 KX	$[1,1(CH_3)_2\text{-}2\text{-}ClC_3H_2PdCl]_2$	—	4.18	3.44				68
	$\pi\text{-}C_6H_5CH_2Mo(CO)_2C_5H_5$	—	2.82	1.81(X) 5.2(P)			$CFCl_3$, —30	3
	Source of perturbation outside allyl group							
 AK_2X_2	$C_3H_5PdCl\cdot DMCO$	5.81	4.29	3.43	6.7	11.6	$CDCl_3$ —20	66
	$C_3H_5NiBr\cdot P(C_6H_5)_3$	5.1	3.38	2.45	6.5	14.5	C_6H_5Cl 30	62

Table 6 (contd.).

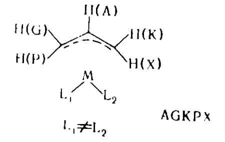
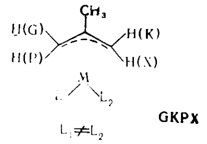
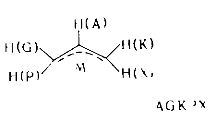
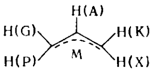
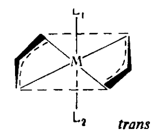
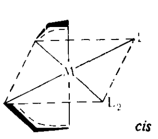
Type of molecule and type of spectral system of allyl component of spectrum	Compound	δ_{HH}, p.p.m.rel. to TMS			J_{HH}, Hz		Conditions of measurement (solvent, temp., °C)	References
		H(A)	H(G,K) (*cis*)	H(P,X) (*trans*)	*cis*	*trans*		
	$C_3H_5PdCl \cdot P(C_6H_5)_3$	5.58	4.69 3.07	3.70 2.82	6.0 7.0	12.0 13.5	$CDCl_3$, —30	66
	$C_3H_5PdCl \cdot As(C_6H_5)_3$	5.50	4.70 3.25	3.65 2.83	6.0	13.5 11.5	$CDCl_3$, —50	66
	$C_3H_5NiCH_3 \cdot P(C_6H_5)_3$	5.00	3.61 2.88	2.71 1.91				76
	$2\text{-}CH_3C_3H_4PdCl \cdot As(C_6H_5)_3$	—	4.54 3.82	3.57 2.78	—	—	$CDCl_3$, —72	122
	$2\text{-}CH_3C_3H_4PdCl \cdot P(C_6H_5)_3$	—	4.52 2.85	3.59 2.79	—	—	—20	112
	$2\text{-}CH_3C_3H_4PdSnCl_3 \cdot P(C_6H_5)_3$		4.48	3.32				116
	$(C_3H_5)_4Mo$	4.08	3.11 1.93	2.88 —0.20	8.5 9.1	11.5 13.3	$CDCl_3$, 30	41
	$[(C_3H_5)_2RhCl]_2$	4.76	5.08 2.50	4.02 1.82	6.0 6.8	10.8 12.0	$CDCl_3$. —20	113
	$(C_3H_5)_2Fe(CO)_2$	4.16	2.04 3.13	1.01 1.90	6.5	12.3	$[(CH_3)_3Si]_2O$, —67	49
	$(C_3H_5)_2Ru(C_8H_{12})$	~4.2	4.79 1.70	3.65 —0.03	6	12.0 10.5	$CDCl_3$, 34	123
	$(C_3H_5)_2RhCl \cdot As(C_6H_5)_3$,	5.02	4.50 1.88	3.13 0.71	6.0 7.0	10.3 11.5	$CDCl_3$, 30	41
	Two types of asymmetric π-allyl groups	4.46	4.27 3.54	3.22 2.91	5.8 7.2	11.0 11.6		

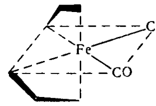
Table 7. Structure and suggested NMR spectra of the compounds $(\pi\text{-}C_3H_5)_2ML_1L_2$.



Structure of compound		Characteristics of π-allyl groups	Suggested type of NMR spectrum
geometrical configuration	characteristics of L$_1$ and L$_2$		
 *trans*	$L_1 = L_2$	two equivalent symmetrical allyl ligands: H(G) = H(K) H(P) = H(X)	AK$_2$X$_2$
	$L_1 \neq L_2$	ditto	AK$_2$X$_2$
 *cis*	$L_1 = L_2$	two equivalent asymmetric allyl ligands: H(G) ≠ H(K) H(P) ≠ H(X)	AGKPX
	$L_1 \neq L_2$	two non-equivalent asymmetric allyl ligands: H(A) ≠ H (A') H(G) ≠ H (G') H(K) ≠ H (K') H(P) ≠ H (P') H(X) ≠ H (X')	AGKPX + +A'G'K'P'X'

of $(\pi\text{-}C_3H_5)_2Ru\text{-}\pi\text{-}$cyclo-octa-1,5-diene[123] and $[(\pi\text{-}C_3H_5)_2RhCl]_2$ at a temperature below −20°C.[113]

In turn the observation of the spin system AGKPX in the spectrum of the compound $(\pi\text{-}C_3H_5)_2ML_1L_2$ with $L_1 = L_2$ may be regarded as evidence for the *cis*-arrangement of the allyl group. Such a case probably occurs in the $(\pi\text{-}C_3H_5)_2Fe(CO)_2$ molecule[49]: at −67°C the spectrum corresponds to the system AGKPX (the alternative description of the spectrum by two AK$_2$X$_2$ sets in which the screening of the central protons of two types of allyl groups is fortuitously identical is less likely) which permits the assignment to the compound of the *cis*-structure (XIV):



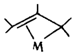
(XIV)

The spectrum is most complex for the *cis*-configuration with $L_1 \neq L_2$, since in this structure both asymmetric π-allyl groups become non-equivalent. In the spectra of such compounds two sets of signals of the AGKPX system should be observed. This type of situation has indeed been observed in a spectroscopic study of $(\pi\text{-}C_3H_5)_2RhClAs(C_6H_5)_3$ and similar compounds[41].

The number of examples may be increased. Thus the application of the double resonance technique makes it possible to establish[41] that in $(C_3H_5)_4Mo$ there are four asymmetric and equivalent π-allyl ligands (Fig. 3). However, it is much more difficult to arrive at a conclusion concerning the structure of this compound.

Examination of the spectroscopic data for allyl derivatives with asymmetric ligands shows that, despite the appreciable differences in screening, these complexes retain all the spectroscopic features of the π-structure: the screening of the central proton does not alter significantly; the signals of the *trans*-protons are as a rule located in the region of stronger fields than those of *cis*-protons; the constants J_{HH} (*cis*) and J_{HH} (*trans*) differ significantly from one another and are of the same order of magnitude as for asymmetric π-complexes.

The idea of the possible formation of asymmetric π-allyl compounds has been most clearly formulated only in the last two or three years[41,66,67,76,62,113,124,125]. At one time these derivatives were classified as compounds with a mixed bond type – the so called π, σ-complexes [structure (XV)] [58,68,112,126]. However, subsequently this view met certain objections[48,113,125].



(XV)

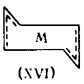
In this connection, it is necessary to emphasise that the available NMR spectroscopic data indicate only a certain asymmetry in the distribution of electron density in a delocalised allyl – M bond, while the π-structure is retained. There are no data indicating a more far-reaching rearrangement of these compounds, including the formation of complexes of the π, σ-type.

VI. ISOMERISM OF π-ALLYL COMPLEXES

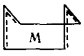
The characteristics of the π-allyl bonds, the considerable coordinating capacity of transition metals, and finally the retention under certain conditions of a stable steric orientation of the π-allyl ligand relative to the coordination centre are all factors which give rise to a great variety of π-allyl complexes. In recent years quite a number of examples of different types of isomerism and non-equivalence of allyl ligands have been found with the aid of NMR spectroscopy.

The simplest type is the *cis – trans* isomerism in complexes with asymmetric π-allyl ligands [structures (X) and (XI)]. Isomers of this kind are known for many metals and may be successfully identified by NMR methods even in mixtures[78,81,111,114,121].

An interesting type of isomerism was observed in the study of the derivatives (π-allyl)$_2$M (M = Pd, Ni, or Pt, i.e. metals capable of forming planar square complexes). Two sets of signals (due to the AK_2X_2 spin system for the unsubstituted ligand and K_2X_2 for the ligand substituted at the central carbon atom) have been found in the NMR spectra of these compounds in proportions depending on the metal, temperature, the nature of the medium, and the substituent at the central carbon atom[36,42,53,127–130]. This phenomenon was explained by the fact that such compounds may exist in solution not only in form (XVI), characteristic of the solid state[88], but also in the isomeric form (XVII)[127]:



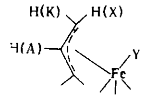
(XVI)



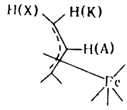
(XVII)

The rotational isomers of the compounds $C_3H_5Fe(CO)_3Y$ (Y = Cl, Br, I, or NO_2) have been investigated[59]. In the crystal such molecules have the structure (XVIII)[131]. Therefore the NMR study of their solutions shows, with increasing electronegativity of Y (I < Br < Cl < NO_2), a shift towards weaker fields of the signals due to the H(A) and H(K) protons most remote from the substituent (Table 8). This behaviour is not shown solely in the case of *trans*-protons H(X), the screening of which is determined not only by the electron density at the terminal carbon atoms but also by the influence of the magnetic anisotropy of the nearest substituent. In the spectra of compounds with Y = halogen, less intense signals of another isomer, which according to the authors has the structure (XIX), were found in addition to the signals due to the isomer (XVIII). In the spectra of these isomers a shift towards weaker fields with increasing electronegativity of Y is observed for signals of the *cis*- and *trans*-protons and corresponds, in accordance with structure (XIX), to signals of the central proton H(A). The content of the isomer in the mixture depends appreciably on the steric hindrance due to the substituent Y: for Y = NO_2, the isomer does not exist.

Table 8. Chemical shifts of protons of different types in the compounds $C_3H_5Fe(CO)_3Y$ (according to data of Nesmeyanov et al.[59]).



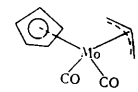
(XVIII)



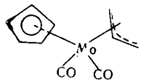
(XIX)

Y	δ_H p.p.m. rel. to HMDSO*						Solvent
	H (A)	H(K) (*cis*)	H(X) (*trans*)	H (A)	H(K) (*cis*)	H(X) (*trans*)	
	XVIII			XIX			
I	4.55	4.13	3.77	5.90	3.75	2.24	CCl_4
Br	4.85	4.28	3.41	5.7	3.94	2.58	CS_2
Cl	5.11	4.48	3.21	5.80	4.22	2.63	$CDCl_3$
NO_2	5.31	4.70	2.63	—	—	—	$CDCl_3$

An analogous situation was observed in the NMR spectra of the compounds π-allyl – Mo(CO)$_2$ – π-C_5H_5.[13,52] It was found that the relative amounts of the isomers (XX) and (XXI) depend on steric factors determined by the substituent at the central carbon atom of the allyl ligand:



(XX)



(XXI)

An interesting example of the non-equivalence of allyl ligands was observed in the study of triallylrhodium. It was found that at a low temperature (–74°C) the three symmetrical allyl ligands are non-equivalent (in the spectrum there are three groups of AK_2X_2 signals in proportions of 1 : 1 : 1).[38] It was suggested (following Green and Nagy[132]) that each ligand occupies two coordination sites and thus the triallylrhodium molecule may have the form of a trigonal prism or an octahedron[38,40].

VII. STEREOCHEMICAL NON-RIGIDITY OF ORGANOMETALLIC ALLYL COMPOUNDS.

The advances of organometallic chemistry in the last decade led to the synthesis of a multiplicity of compounds of most varied and sometimes unexpected types. Among these, there are quite a few systems where stereochemical non-rigidity was observed or is possible in principle. The terminological aspect of this problem has not yet been clearly resolved. Therefore we shall adopt the convention that the concept "stereochemical non-rigidity" will be applied to two basic types of intramolecular rotation (recognising, of course, the non-rigorous nature of such subdivision in many cases): intramolecular rotation and metallotropy.

For organometallic compounds, including allyl derivatives, it is possible to indicate several types of intramolecular motion, which are analogous to those in the usual organic derivatives, for example rotation about the C–M σ-bond in σ-allyl compounds. However, there is a possibility in principle also of processes specific to organometallic compounds, the nature of which is fairly difficult to predict and the study of which provides much information about the structure and properties of such compounds. In the classification of intramolecular dynamic processes in organometallic allyl compounds it is most natural to use as a basis the spin system of the allyl component of the NMR spectrum.

1. INTRAMOLECULAR ROTATION.

a. Processes with Retention of the AK_2X_2 Spin System.

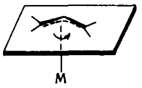
We shall isolate in a separate group those cases where in a certain temperature range the spin system of the allyl part of the spectrum is not simpler than AK_2X_2. One should evidently include here both asymmetric derivatives where the asymmetry of the allyl ligands disappears with increasing temperature (in the sense AGKPX → AK_2X_2) and compounds with a symmetrical C_3H_5-M bond in which the dynamic process is accompanied by the retention of the formal AK_2X_2 spin system.

For example, it is possible to assign to this group the asymmetric complex $[(C_3H_5)_2RhCl]_2$ in the spectrum of which the four separate signals due to each of the four terminal protons merge into two pairs of signals as the temperature is raised from −20° to 90°C. Under these conditions, there is hardly any change either in the position in the spectrum or the form of the signal due to the proton attached to the central carbon atom of the allyl ligand[41]. Apparently an analogous phenomenon is observed in the NMR spectrum of the compound $(C_3H_5)_2Fe(CO)_2$: on raising the temperature from −67° to 20°C, the set of signals of the AGKPX spin system is transformed into the set of signals of the AK_2X_2 system[49].

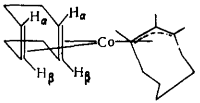
Compounds of the type $2\text{-}RC_3H_5Mo(CO)_2C_5H_5$ (R = H, CH_3, etc.) constitute stereochemically non-rigid systems where the temperature-dependent spectroscopic changes are accompanied by the retention of the spin system. Probably at temperatures exceeding 80–90°C the rate of mutual transformations of the isomers (XX) and (XXI) increases so much that each can no longer be observed spectroscopically as a separate entity. As a result the spectrum contains no longer two but only one set of signals of the AK_2X_2 system[52,53]. Allyl compounds of molybdenum with a more complex structure were examined by Trofimenko[133].

An analogous phenomenon was observed[31] in the study of the spectra of triallylrhodium. The signals of the protons in two of the three nonequivalent π-allyl groups merged into a common system of lines on raising the temperature from −67° to 10°C. In the case of diallylnickel a change in temperature affected the NMR spectrum in such a way that, on transition from −40°C (in $CDCl_3$) to 60°C (in benzene), the ratio of the intensities of the two groups of AK_2X_2 signals associated with the isomers (XVI) and (XVII) gradually changed from 3 : 1 to 2.2 : 1.[36]

The stereochemically non-rigid systems considered have a common characteristic. Neither the removal of the asymmetry of the π-allyl ligand in one isomeric form {in $[(C_3H_5)_2RhCl]_2$ and $(C_3H_5)_2Fe(CO)_2$, etc.} nor the mutual transformation of the isomers [(XX) and (XXI), (XVI) and (XVII), etc.] is accompanied by the equalisation of the chemical shifts of the *cis*- and *trans*-protons. The dynamic process satisfying this condition may be only the rotation of the π-allyl group about the axis joining the metal atom to the central carbon atom of the ligand [structure (XXII)]. This type of process was observed for the first time by Becconsall and O'Brien[38] in a study of the temperature variation of the triallylrhodium spectrum:



(XXII)



(XXIII)

It must be emphasised that this type of dynamic process was observed for derivatives of significantly different transition metals: rhodium, iron, molybdenum, and nickel. It is quite possible that it occurs also in many other π-allyl compounds, but is observed only in those few systems where there are structural factors which retard it and make possible its spectroscopic study. The compounds investigated exhibit in this sense a similarity with complexes where there is a C_nH_n-M π-bond (C_nH_n is a cyclic ligand with n = 4, 5, 6, or 7) and in which the rotation of the ligand about the n-fold axis has been reliably established.

We may quote an opposite example. In the spectrum of π-cyclo-octenyl-π-cyclo-octa-1,5-diene derivative of cobalt (XXIII) the α- and β-protons of the diene ligand are magnetically non-equivalent in the temperature range between −88° and 60°C.[85] The most acceptable explanation of this finding is that there is no rotation about the π-enyl–cobalt bond. However, we may note that in the spectrum of π-C_3H_5–Rh–π-cyclo-octa-1,5-diene the signals of all the diene protons are equivalent[109].

b. Processes with Degeneration of the Spin System to AX_4.

All the compounds in which the allyl component of the NMR spectrum is simplified on raising the temperature to such an extent that the *cis*- and *trans*-protons become indistinguishable ($AK_2X_2 \rightarrow AX_4$) will be assigned to this group of stereochemically non-rigid allyl systems. This type of phenomenon was observed[36,37,44,124], for example, in the NMR spectrum of tetra-allylzirconium. While at a low temperature (−74°C) the spectrum has a form characteristic of a π-allyl complex with symmetrical ligands (AK_2X_2 spin system), on raising the temperature the doublets due to the *cis*- and *trans*-protons initially broaden, then approach one another, and finally merge at −40°C, the width of the signal in the transition region being independent of the concentration of the compound[124]. When the temperature is raised further to −10°C, the signal, which is now associated with all four terminal protons, consists of a distinct doublet, while the signal due to the central proton consists of a quintet (at a low temperature this is a nonet) (Fig. 4). Thus at −10°C the spectrum already belongs to the AX_4 spin system. This shows that under such conditions the terminal protons of all the allyl groups of tetra-allylzirconium are equivalent. The following factors are important for the understanding of the mechanism of this process: (1) when the spectrum changes from AK_2X_2 to AX_4, the screening of the central proton remains unchanged; (2) at −10°C the doublet due to the terminal protons occupies a position in the spectrum intermediate between those of the doublets of the *cis*- and *trans*-protons in the low-temperature spectrum; (3) the

$J_{H(A)-H(X)}$ coupling constant for the AX_4 spectrum is equal to half the sum of the constants J_{HH} (*cis*) and J_{HH} (*trans*) for the AK_2X_2 spectrum.

An analogous spectral pattern was observed in the study of certain other symmetrical allyl derivatives with a delocalised C_3H_5-M bond: tetra-allylthorium (AK_2X_2 at 10°C and AX_4 at 80°C) [37], tetra-allylhafnium (the AX_4 spin system is already observed at −72°C) [36], and allyllithium (the $AK_2X_2 \rightarrow AX_4$ transition occurs at about −87°C) [91]. Above 90°C the $AK_2X_2 \rightarrow AX_4$ transition is also observed in the spectrum of the compound $[(C_3H_5)_2RhCl]_2$ but this is probably a not altogether apt example, since the pattern may be complicated by the dissociation of the Rh−Cl bond[41].

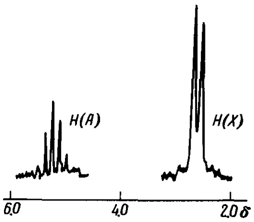
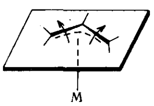
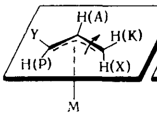


Figure 4. NMR spectrum of the compound $(\pi\text{-}C_3H_5)_4Zr$ at −20°C (AX_4 spin system)[36].

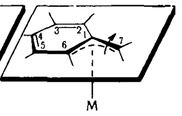
The averaging out of the chemical shifts of the *cis*- and *trans*-protons and of the spin−spin coupling constants has been frequently observed also in the NMR study of asymmetric derivatives with a delocalised allyl−M bond, in particular in the study of the phenylallyl compounds of alkali metals[117]. Thus on raising the temperature the distinct signals associated with the two H(K) and H(X) protons, non-equivalent at 5°C in the $1\text{-}C_6H_5C_3H_4Li$ spectrum, begin to broaden and gradually approach one another and at 90°C become spectroscopically indistinguishable, the process being reversible [structure (XXV)]:



(XXIV)



(XXV)



(XXVI)

Probably the temperature-dependent averaging out of the chemical shifts of the *cis*- and *trans*-protons is determined to some extent by the 1.5 bond order of the delocalised allyl−M bond. It may be supposed that the degree of its double-bond character will be variable and will depend on the nature of the substituent in the ligand and at the metal, on the electron-donating capacity of the metal, and many other factors. Thus under certain conditions the 1.5 order of the delocalised bond can apparently only hinder internal rotation about the $C \overset{...}{-} C$ bonds but cannot prevent it altogether.

Thus the temperature-dependent effects observed in the study of the NMR spectra of the allyl compounds under consideration may be caused entirely by changes in the rate of internal rotation of the CH_2 groups about bonds joining them to the central carbon atom [structures (XXIV) and (XXV)] [36,37,124]. It is useful to note that such effects have so far been observed in compounds of both transition (zirconium and thorium) and non-transition (lithium) metals, where on formation of a delocalised bond the *d* electrons of the metal cannot participate in the formation of dative bonds with the ligand[37], which would favour the fixation of its position in space relative to the metal atom. In the spectra of the derivatives of many other metals, for which the formation of dative bonds is not excluded, the temperature-dependent changes were not observed {the spectra of $C_3H_5Mo(CO)_4$ at 160°C [48], $(C_3H_5PdCl)_2$ at 150°C [48], $(C_3H_5)_4Mo$ at 170°C [41], and $C_3H_5Rh[P(C_6H_5)_3]_2$ at 130°C [78] have been investigated}.

A reversible change in the allyl component of the spectrum was observed in the study of the π-benzyl derivatives of molybdenum, tungsten, and palladium, [3,25,119]. For example, in $\pi\text{-}C_6H_5CH_2Mo(CO)_2\text{-}\pi\text{-}C_5H_5$ the screening of the CH_2 protons is averaged out when the temperature is raised from −30° to 64°C. There are also corresponding changes in the signals of the phenyl protons. Under these conditions, the average chemical shift of each pair of protons [CH_2-, 2−6, and 3−5; structure (XXVI)] is exactly equal to half the sum of the initial shifts[3]. King and Fronzaglia[3] suggested that this effect is caused by the rotation of the benzyl ligand about the 1−7 axis. They did not exclude also alternative mechanisms, in particular a mechanism with a postulated intermediate formation of a σ-type compound. The latter mechanism has been supported by Cotton and Marks[25]. We may note that in the spectra of certain π-thienyl derivatives of molybdenum no changes were observed in the temperature range between −60°C and 105°C [118].

VIII. SPECTRA OF π-ALLYL COMPOUNDS IN THE PRESENCE OF BASES

In 1961 Chien and Dehm[134] observed that, when the solvent is changed (chloroform replaced by dimethyl sulphoxide), the NMR spectrum of $(C_3H_5PdCl)_2$ alters sharply. In the case of an unsubstituted π-allyl ligand this transformation consists of a change of the spin system of the allyl components of the spectrum from AK_2X_2 to AX_4; corresponding changes have also been observed for 1- and 2-substituted allyl groups. Subsequently quite a few papers have been published on these changes, which were observed in the NMR spectra of the π-allyl derivatives of palladium, platinum, rhodium, and other transition metals under the influence of bases (sulphoxides, phosphines, arsines, stibines, etc.)[13,48,62,66,67,69,78,82,112,114,122,124-126,135-139].

Formally these are the same changes which occur in the spectrum of tetra-allylzirconium on raising the temperature, i.e. the equalisation of the screening of the *cis*- and *trans*-protons is accompanied by a simplification of the spin system of the spectrum ($AK_2X_2 \rightarrow AX_4$ for symmetrical π-allyl derivatives and $AGKPX \rightarrow AK_2X_2 \rightarrow AX_4$ for asymmetric derivatives). In fact the situation is much more complex‡.

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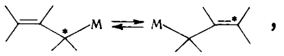
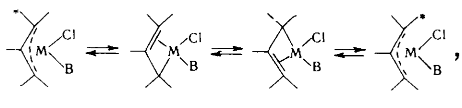
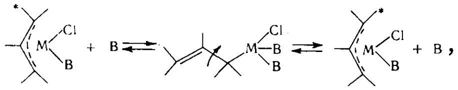
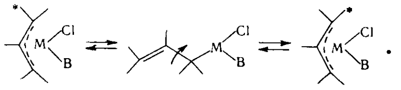
‡ In recent years the term "dynamic allyl"[37] has been frequently used in the literature to designate a new (apart from the σ- and π-allyl derivatives) type of allyl compound. Usually this term designates any situation (associated with the solvent, temperature, etc.) which leads to the appearance in the NMR spectrum of an AX_4 spin system. However, examination of the corresponding data shows that a new "dynamic" type of allyl compound does not exist, just as compounds of the π, σ-type apparently do not exist. In fact there is only a group of phenomena, frequently of a different nature, which have the same spectroscopic effect. Therefore further use of the concept "dynamic allyl" does not appear to be justified.

Chien and Dehm[134] suggested that the π-allyl derivatives of palladium are wholly converted into the σ-form on dissolution in a solvating medium and in this form can in fact undergo the rearrangement (1) put forward by Nordlander and Roberts[74] in the discussion of the spectra of the allyl derivatives of magnesium. However, subsequently it was found that mixed compounds of (π-allyl$-$PdCl)$_2$ with dimethyl sulphoxide and other bases (phosphines, etc.), i.e. compounds of the type C_3H_5PdClB, are, in fact not σ- but π-allyl complexes—symmetrical or asymmetric[48,66,112,137]. Therefore the observed effects were explained not by complete transformation of the compound into the σ-form but by the formation of σ- or π, σ-complexes at a very low concentration, which is, however, sufficient to promote the interchange of the *cis*- and *trans*-protons [Eqns. (2)$-$(4), M = Pd or Ni][48,69,112,125,126]. Moreover, Becconsal and O'Brien[154] pointed out that these effects can be accounted for by rotation about the C$-$C bond.

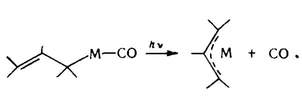

74, 134 (1)


66, 112, 113 (2)


48, 69 (3)


67, 82 (4)

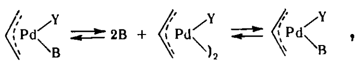
Among the various mechanisms of the rearrangement of the π-allyl derivatives of transition metals to σ- or π, σ-complexes, proposed to account for their spectroscopic behaviour in the presence of bases [Eqns. (1)$-$(4)], the mechanism of type (3) is particularly successful. Essentially this mechanism represents the π-σ transformation of the molecules investigated with retention of the coordination number of the transition metal owing to the simultaneous formation of an M$-$B bond and constitutes a special process, the converse of the transformation of the σ-allyl derivatives of iron, manganese, molybdenum, and tungsten into π-allyl derivatives[1,8-10]:

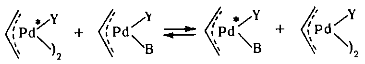

(5)

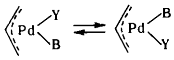
Therefore it might have been expected that the allyl compounds of "pentacoordinate palladium" or nickel isolated in a pure form are in fact σ-complexes. For nickel, such $C_3H_5NiClB_2$ complexes were obtained (B = phosphine or phosphite), but their investigation did not confirm the above hypothesis. It was found that the spectra of derivatives with ligands such as $P(OC_6H_5)_3$ and $P(C_6H_5)_3$ do not differ from those of the corresponding π-allyl derivatives of tetracoordinate nickel: the AK_2X_2 spin system was transformed into AX_4 only in the case where B = $P(C_2H_5)_3$. [62] An analogous conclusion follows from the spectroscopic data for and the structural investigation of other allyl compounds of pentacoordinate nickel[140,141].

Strictly speaking, the spectral spin system AX_4 is too symmetrical to indicate unambiguously any one dynamic process. In principle, several such processes are compatible with a spectrum of type AX_4. Moreover, in solutions of π-allyl derivatives of palladium, nickel, rhodium, and certain other metals in the presence of bases, the exchange reactions (6)$-$(11) occur or can occur (here M = Pd; X = halogen, SCN, etc.; B = DMSO, phosphine, amine, etc.).

These reactions do not relate directly to π-σ rearrangements and in any case can occur without the participation of allyl$-$M bonds. However, they can also cause the merging of the signals due to the *cis*- and *trans*-protons in the NMR spectrum[41,66,69,137,143].


137 (6)


66, 138, 139 (7)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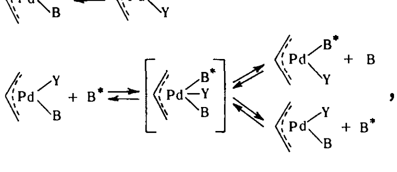
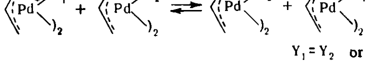
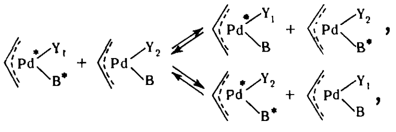

69, 125, 142 (9)


139, 143, 144 (10)

$Y_1 = Y_2$ or $Y_1 \neq Y_2$


125, 139 (11)

$Y_1 = Y_2$ or $Y_1 \neq Y_2$; etc.

It must be emphasised that the structure of the transition state in reactions (6)$-$(11), their stereochemical results, and similar problems associated with their mechanism have only now begun to be seriously investigated by various procedures including the NMR method[143]. For example, it has been found that the rate of exchange depends on temperature, the concentrations of the π-allyl compound and the base, and other factors. A clear similarity of these compounds (lability of the M$-$X bonds, their capacity for exchange reactions, etc.) to organic derivatives of non-transition metals, for which exchange reactions have been investigated fairly thoroughly by the NMR method (see, for example, Brown[145]) has also been observed.

Thus the problem of the causes responsible for the changes observed in the NMR spectra of certain π-allyl derivatives of transition metals under the influence of bases remains at present unresolved. Such a cause may be the internal rotation of the allyl ligand about the C$\overset{\dots}{-}$C bond, which is facilitated by the donor$-$acceptor interaction between the metal and the base. Another cause may be exchange reactions of types (6)$-$(11). Finally the changes may arise also as a result of $\pi$$-$$\sigma$ rearrangement, but so far no evidence has been obtained by the NMR method indicating the formation of a σ-complex under the action of bases which would not be susceptible to some other interpretation.

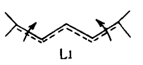
IX. THE NATURE OF THE ALLYL–METAL BOND IN CERTAIN NON-TRANSITION METAL (LITHIUM, MAGNESIUM, ZINC, AND CADMIUM) DERIVATIVES.

According to NMR spectroscopic data, an allyl–Hg σ-bond is formed in allyl derivatives of mercury[17,91,146,147]. Triallylboron below –65°C [14,148] and other allyl compounds of boron[149,150] have similar structures. However, the spectroscopic behaviour of allyl-lithium suggests the formation of a delocalised bond in this compound[91]. In the study of the derivatives of certain other non-transition metals with an allyl–M bond (M = Li, [117,151–153] Mg, [74,154–157] Zn, [158,159] or Cd [160]) it was found that, as in the case of allyl-lithium, close to room temperature the NMR spectrum has an AX_4 spin system for compounds with an unsubstituted ligand and the corresponding spectral pattern for substituted ligands.

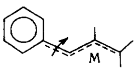
To explain the spectrum of allylmagnesium bromide, Nordlander and Roberts[74] examined three possibilities: (1) the establishment of rapid equilibrium between two σ-structures [Eqn. (1)]; (2) the formation of a structure with a delocalised allyl–M bond in which there is rapid rotation about C–C bonds [structure (XXIV)]; (3) the formation of an ionic bond.

In principle, neither Roberts[161] nor other investigators (see, for example, Lanpher[162]) excluded the possibility of the formation of a delocalised bond of type (II) by non-transition metals. However, since the bond order in such compounds should be greater than unity, Nordlander and Roberts[74] disregarded the second and third possibilities and subsequently interpreted their experimental data only from the standpoint of the formation of a σ-structure undergoing rapid 1,3-transformations [Eqn. (1)]. This view was also adopted by many other investigators[151,153], although in recent years it encountered objections from supporters of the formation of an ionic bond[91,117,158,160].

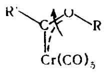
During the last decade extensive data have accumulated in the literature on the NMR spectra of allyl derivatives of transition and non-transition metals. The hypotheses concerning the structures of these compounds have also undergone a definite change. Moreover, experimental spectroscopic studies on organic and organometallic compounds showed that, when the order of the bond under consideration is greater than unity and less than 2, rotation about it is not precluded, for example in the compounds (XXVII), [163] (XXVIII, M = Li), [117] (XXIX) [164], and even in classical olefinic derivatives[165]:



(XXVII)



(XXVIII)



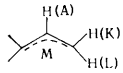
(XXIX)

Therefore it appears necessary to reconsider the possibilities proposed by Nordlander and Roberts[74] and to determine which of them is most acceptable in the light of the available facts.

It has been suggested[91] that in C_3H_5Li the delocalised bond is ionic. Probably this involves some exaggeration. It is known that organic derivatives of lithium do not dissociate into ions. For example, the C_5H_5Li molecule, like C_5H_5Na, has the C_{5v} symmetry and not D_{5h} as might have been expected if it dissociated into ions (a D_{5h} symmetry has been established for C_5H_5M with M = K, Rb, or Cs) [166]. An analogous result was obtained in a study of the Li-NMR spectra of fluorenyl-lithium[167]. In certain organolithium derivatives the metal–carbon bond may be significantly covalent [for example, in a study of the tetramer $(CH_3Li)_4$ it proved possible to observe $^{13}C-^{7}Li$ spin–spin coupling [168,169]. Thus it is probably more justifiable to speak not of an ionic but of a fairly polarised bond (in the sense allyl$^{\delta-}$–M$^{\delta+}$). Then the allyl derivatives of the metals considered may be discussed from a single standpoint. We shall assume that magnesium, zinc, cadmium, and similar metals, as well as lithium, are capable of forming a delocalised allyl–M bond. We shall also postulate that the delocalised bond in any real compound is always polar to some extent and the degree of its polarity depends on the electropositivity of the metal, the nature of the substituents in the ligand and the metal, the nature of the medium, and other factors.

Apart from the effect of other factors, the steric stability of the allyl–M fragment in transition metal derivatives can be achieved also as a result of the participation of the metal *d* electrons in a dative interaction. For allyl compounds of non-transition metals, such a stabilising factor may be the amount of double-bond character of the C⩦C bonds of the ligand, which in turn is a function of the electropositive properties of the metal.

Table 9. Chemical shifts of the methylene protons in certain allyl compounds of non-transition metals.



Compound	Solvent	$\delta_{H(K, L)}$	Electronegativity of metal E_M [170]
C_3H_5Li	THF	2.17[91]	1.0
$(C_3H_5)_2Mg$	THF	2.45[157]	1.2
$(C_3H_5)_2Zn$	C_6D_6	2.96[158]	1.6
$(C_3H_5)_2Cd$	THF	2.86[160]	1.7

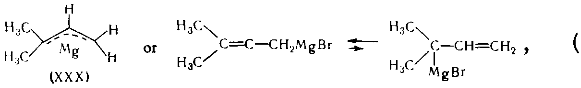
Table 9 shows that the screening of the terminal protons in non-transition metal derivatives varies in parallel with their electropositivity:

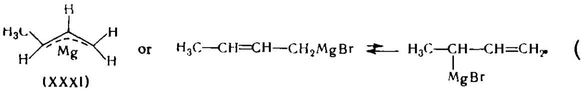
$$\xleftarrow[\text{enhancement of screening and the electropositivity of the metal}]{\text{Li} > \text{Mg} > \text{Zn} \sim \text{Cd}}$$

Consequently, the amount of double-bond character in the allyl group should decrease from lithium to zinc and cadmium with a corresponding increase in the rate of internal rotation. The experimental data do not contradict this conclusion. On lowering the temperature to –87°C, "freezing" of internal rotation [structure (XXIV)] is observed in the spectrum of allyl-lithium. Spectroscopically this is shown by a separation of the signals due to the *cis*- and *trans*-protons and in a change of the spin system of the spectrum ($AX_4 \rightarrow AK_2X_2$) [91]. For cadmium and magnesium derivatives, such "freezing" has not so far been achieved even at a lower temperature (diallylmagnesium at –120°C in tetrahydrofuran[157], allylmagnesium bromide at –80°C in ethyl ether[156], and diallylcadmium at –100°C in tetrahydrofuran[160] have been investigated).

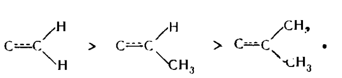
Over a wider range of variation of the amount of double-bond character, observations are also consistent with predictions. Thus, while for allyl derivatives of lithium, including asymmetric derivatives[117], internal rotation may be "frozen" by varying the temperature, in studies on asymmetric allyl derivatives of more electropositive metals [potassium and sodium—structure (XXV)] internal rotation was not observed even at a fairly high temperature[117].

We may note that for allyl compounds of magnesium and cadmium it is possible to raise the "freezing temperature" of the spectral pattern, for example by introducing into the ligand electron-donating substituents capable of increasing the amount of double-bond character of the C⋯C bonds. This phenomenon was observed, in particular, by Roberts and coworkers[155] in a spectroscopic study of 1,1-dimethylallylmagnesium bromide (XXX): when the temperature is reduced to only −26°C, the splitting of the signal due to the methyl protons into two components, associated with the *cis*- and *trans*-groups, is already observed:


(XXX) (12)


(XXXI) (13)

The molecular structures of 1-$CH_3C_3H_4MgBr$ and 1,1-$(CH_3)_2C_3H_3MgBr$ merit special examination. The spectra, investigated by Roberts and coworkers[154,155], are fully consistent with the structures (XXXI) and (XXX) with a delocalised allyl−M bond if it is assumed that the rate of rotation about the bond of order 1.5 varies in the sequence



Roberts and coworkers interpreted the spectra obtained in a different way. They suggested that each of the compounds considered constitutes one of two possible non-equivalent σ-structures, which are interconverted at a high rate. To reconcile this possibility with the observed spectral patterns, it was suggested that equilibria (12) and (13) are almost entirely displaced to the left.

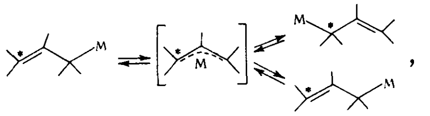
However, whereas previously both possibilities [delocalised structures (XXX) and (XXXI) or equilibria (12) and (13)] might have been regarded as at least equally probable, although only one of them had been considered, further investigations[91,117,163-165] show that there is no justification for rejecting the very possibility of rotation about a C⋯C bond of order 1.5. There are no other objections to the formation of a delocalised bond. On the other hand, equilibria (12) and (13) are not altogether consistent with the spectroscopic and chemical features of the compounds examined. For example, the NMR spectra undergo hardly any changes when the temperature is reduced [if one disregards the splitting of the signal due to the methyl groups in the spectrum of 1,1-$(CH_3)_2C_3H_3MgBr$], although the screening of the CH_2 protons cannot fail to change under these conditions. The assumption that equilibria (12) and (13) are almost completely displaced to the left over the entire temperature range investigated is inconsistent with the results of the analysis of the decomposition products, for example, butenylmagnesium bromide[161].

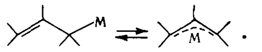
Investigations in the next few years, in particular structural studies by diffraction methods, will show which view is closer to the truth. However, even if the hypothesis of the formation of a delocalised bond in the allyl compounds of lithium, magnesium, zinc, and cadmium is confirmed, there will remain many other problems the solution of which is at present not evident: association of the compounds considered, the role of the solvent in the formation of a σ- or delocalised structure, the relation between the intramolecular and intermolecular bonds, etc.

X. METALLOTROPY IN ALLYL DERIVATIVES OF NON-TRANSITION METALS

It is not claimed that the view put forward in the preceding section is of completely general validity. It merely shows how the possibility of two interpretations (on the basis of the published NMR data) of the structures of the allyl derivatives of magnesium, zinc, and cadmium—with a localised or a delocalised bond—gives rise as a consequence to two interpretations of the dynamic behaviour of these compounds—a metallotropic 1,3-transition [Eqn. (1)] or rotation about the C⋯C bond of order 1.5 [structures (XXIV) and (XXV)].

Continuing this analysis, we also find it necessary to conclude that the mechanism of metallotropic transformations of those derivatives for which a σ-structure could be reliably demonstrated§ is not also not unambiguous. There are at least two possibilities;


(14)


(15)

The only difference between them is in fact that in one case the formation of a delocalised bond is suggested in the transition state and in the other in the ground state [Eqns. (14) and (15)].

As a rule the mechanism represented by Eqn. (14) is considered, in particular in the discussion of the NMR spectra of the allyl derivatives of boron[14,150]. It was found that below −65°C the spectrum of triallylboron has an $AKLX_2$ spin system corresponding to the allyl−boron σ-bond. On raising the temperature to room temperature, the signals of both methylene groups become broader and on further increase to 135°C two symmetrical signals of the AX_4 spin system appear. In the high-temperature spectrum the chemical shift of the methylidyne proton H(A) remains virtually unchanged but the form of the signal becomes simplified. The chemical shift of the protons H(X) amounts to approximately half the sum of the shifts of the methylene protons of both types in the low-temperature spectrum ($KLX_2 \rightarrow X_4$). In the study of other allyl derivatives of boron similar changes in the NMR spectrum were found.

Certain characteristics of the rearrangement of the allyl compounds of boron have been elucidated[14,150]. In particular, it has been found that the rate of rearrangement of triallylboron in carbon tetrachloride or cyclohexane is independent of concentration, which indicates that the

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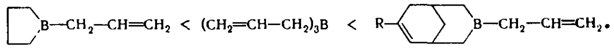
§ For example the allyl derivatives of boron[14,148-150], diallylzinc in solvating media at a low temperature[37,171], indenyl derivatives of mercury at −41°C [29] and of tin(IV) at −37°C [30], etc.

rearrangement is intramolecular. Solvating solvents (tetrahydrofuran and in particular pyridine), which are capable of being coordinated to a vacant orbital of boron, appreciably retard the rearrangement. The rate of the process depends also on the structural characteristics of the compound:



These data lead to the suggestion[14] that the 1,3-transition (it can hardly be called metallotropic because boron is not a metal) in allyl derivatives of boron takes place via a transition state with a delocalised allyl–boron bond [Eqn. (14)]. However, it must be emphasised that the available NMR spectroscopic data do not yet allow a distinction to be drawn between a rearrangement of this type and the interconversions of the two forms of the compound considered in which there is a localised or a delocalised bond [Eqn. (15)]. This applies also to the rearrangement of the indenyl derivatives of tin[30], mercury[29], and similar systems. Probably future spectroscopic investigations will demonstrate the reality of both processes or it will be possible to choose between them.

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Institute of Organic Derivatives of
the Elements, USSR Academy of
Sciences

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The Changes in the Luminescent Properties of the Lanthanides in Consequence of Their Interaction

L.I.Anikina and A.V.Karyakin

Information about the changes in the luminescent properties of the lanthanide elements in consequence of their interaction and as a function of their relative amounts in the test objects is reviewed together with data on the mechanism of this process in various systems.
The bibliography includes 93 references.

CONTENTS

I. INTRODUCTION

The luminescent properties of crystalline phosphors are determined by the activator. If there are several activators, then, apart from the additive properties due to each activator, there appear non-additive properties resulting from the interaction of the activators. Owing to rearrangement of the system of energy levels, the interaction may be reflected in a change in absorption and emission spectra, the duration of the excited state and the probability of energy transitions, the nature of local levels, and many other properties. Numerous examples of this phenomenon may be quoted. The sensitisation of one activator by another and also the quenching of luminescence by admixtures may be regarded as the most familiar examples of interaction between activators. The interaction between activators may be employed in some cases as a useful property, while in others one attempts to avoid it.

In practice one usually deals with crystals containing several impurities and it is of course very important to know the nature of their interactions in a particular case. Moreover, the problem of the interaction between activators is of theoretical importance, since it is associated with the problem of energy transfer in matter.

The lanthanide elements are widely used at present in engineering, particularly in laser engineering. In the manufacture of high-purity lanthanides, their luminescent properties are used for production quality control[1]. It is then often necessary to determine in one specimen several elements present simultaneously. To avoid errors in the analysis, it is necessary to know to what extent the luminescent properties of a given system may be non-additive.

II. INTERACTION OF LANTHANIDE ACTIVATORS AND SENSITISATION OF THE LUMINESCENCE OF LANTHANIDE IONS BY OTHER SUBSTANCES

The interaction between lanthanides in phosphors has been known for a long time. The sensitisation of one lanthanide by another was observed for the first time by Tomaschek[2] in the excitation of the SrS–Gd,Sm phosphor by cathode rays. The luminescence of samarium in the phosphor increased appreciably in the presence of gadolinium. It is noteworthy that in the very early studies errors might have been made owing to the lack of highly pure lanthanide preparations. Moreover, the majority of investigations dealing directly with the interaction of lanthanides have been published in the last few years. They deal with the behaviour of lanthanides mainly in crystals, both inorganic (crystalline phosphors) and organic (lanthanide complexes).

A comparatively small number of papers deal with the behaviour of lanthanides in solutions, most of them being concerned with the dependence of the luminescence of terbium and europium on other lanthanides present in solution.

Gallagher et al.[3] examined two-stage energy transfer in solutions and showed that only in the presence of terbium ions is the energy of exciting light transferred from 4,4′-di-*m*-hydroxybenzophenone (DMB) to europium. The authors concluded that terbium ions constitute an intermediate link in energy transfer from DMB to europium, sensitising europium. It has also been noted that other lanthanides (praseodymium, neodymium, samarium, holmium, erbium, and thulium) quench the luminescence of a mixture of DMB and terbium. It has been suggested that the quenching involves an exchange–resonance mechanism.

Ballard and Edwards[4] made a detailed study of energy transfer from an organic substance to a lanthanide ion as a function of the concentration of the latter and also the self-quenching by the lanthanide ion in solution. The transfer of the energy of exciting light from the organic substance to the lanthanide ion may be called sensitisation of the ion by the organic substance. This is also of interest for a wider understanding of the interaction between various components of luminescent systems.

Ballard and Edwards[4] studied the luminescence of certain lanthanide (samarium-, dysprosium, terbium, and europium) nitrates in acetophenone. The intense luminescence of certain lanthanide ions is due to intermolecular energy transfer from the triplet state of acetophenone, provided that there is no self-quenching by the lanthanide ions. It has been established that the self-quenching is excluded in those cases where the difference ΔE between the energies of the resonance and lowest levels is high. When ΔE is low, self-quenching is possible.

Since the investigation was carried out at low temperature (frozen solutions), it was essentially concerned with crystalline substances containing lanthanides.

Holloway and Kestigian[5] examined a case of the quenching of terbium by neodymium, holmium, and erbium ions. The experiments were performed on aqueous solutions of the lanthanide chlorides. The degree of quenching was determined from the change in the duration of the luminescence of terbium. It was found that the probability of the quenching of the fluorescence of terbium is proportional to the square of the concentration of the lanthanide or inversely proportional to the sixth power of the distance between the ions. Such a concentration dependence ($\propto 1/R^6$) characterises a dipole–dipole interaction. The authors conclude that the quenching of the luminescence of terbium takes place by resonance energy transfer.

Heller and Wasserman[6] examined intermolecular energy transfer from an excited organic substance (aldehydes and ketones) to lanthanides (europium or terbium) in dilute solutions. The excitation spectra show that the luminescence of europium and terbium appears when ultraviolet light is absorbed by the organic molecules. The constancy of the luminescence spectrum is evidence of the absence of complex formation. It has been suggested that the energy transfer is regulated by diffusion processes, since the intensity of the fluorescence of the lanthanide diminishes with increasing viscosity. As the temperature is reduced, the intensity of the fluorescence of the lanthanide falls and the phosphorescence of the organic substance appears.

Cabezas and De Shazer[7] investigated the possibility of the sensitisation of the lanthanide ion in the europium trihexafluoroacetylacetonate complex in a liquid medium with intermolecular excitation energy transfer from the organic donor to the organic complex. Benzophenone, excited by illumination with light at $\lambda = 3800$ Å, was employed as a donor. Under these conditions, the complex is not excited. The excitation energy transfer from the triplet state of benzophenone to the triplet state of the complex with subsequent intramolecular energy transfer to the Eu^{3+} ions takes place over a period shorter than 10^{-6} s.

A similar phenomenon was described by Charles et al.,[8] who observed the transfer of the energy absorbed by the *p*-benzoylbenzoate ion in solution to the ethylenediaminetetra-acetatoeuropium ion.

Kropp[9] reported the sensitisation of europium ions by the uranyl ion in solutions: aqueous (in particular in D_2O), alcoholic, in acetonitrile, etc. The luminescence of the UO_2^{2+} ions is then quenched and the intensity of the fluorescence of europium increases. The greatest effect is observed in D_2O. It has been noted that gadolinium does not quench the luminescence of the uranyl ion, since its excited level lies relatively higher and therefore there is no energy transfer.

Briskina et al.[10] observed the transfer of the energy of exciting light from organic dyes, in particular fluorescein, to lanthanide ions (europium and terbium). The energy is transferred from metastable levels of the dye.

McCarthy and Winefordner[11] showed how great is the extent of the intermolecular energy transfer in the determination of traces of lanthanides. The sensitivity of their determination in solution may be enhanced by employing an organic energy donor.

The mechanism of energy transfer from aromatic compounds such as ketones to lanthanide ions in solutions has been examined[12] and the hypothesis that the energy transfer takes place from the triplet level of aromatic molecules to the lanthanide ions was confirmed experimentally.

In a number of investigations published in 1964–1968, a study was made of the interaction between lanthanides in glasses (solid solutions). Cabezas and De Shazer[7] reported the occurrence of energy transfer in glasses activated simultaneously by terbium and dysprosium. At high concentrations of the activator (about 3 wt.%) the enhancement of the luminescence of terbium by about 70% is observed. The authors suggest that energy transfer from dysprosium to terbium takes place via the excitation of the resonance level of Tb^{3+} ($^5D_4$) by emission from Dy^{3+} with $\lambda = 485$ nm ($^4F_{9/2} \rightarrow {}^6H_{15/2}$).

The authors also reported a sensitising effect of terbium or europium on the luminescence of neodymium in glasses (the intensity of the luminescence of neodymium increases by about 10%). They suggest that in this case the energy transfer (accompanied by emission) occurs in the region of $\lambda \simeq 580$ nm (the region of absorption by neodymium and of emission by terbium or europium).

The interaction between terbium and neodymium in a glass was studied in detail by Nakazawa and Shionoya[13]. On the basis of experimental data and theoretical calculations, they concluded that the energy transfer from terbium to neodymium takes place preferentially by a resonance mechanism and is of a dipole–quadrupole type.

In a paper by Karapetyan and Mokeeva[14] on energy transfer in glasses activated by terbium and dysprosium, the existence of two energy transfer mechanisms is indicated: with emission (from dysprosium to terbium) and without emission (resonance) (from terbium to dysprosium).

The studies by a number of investigators[15–18] dealing with the sensitisation of the luminescence of ytterbium by neodymium and praseodymium in a glass are of interest. The luminescence of ytterbium in the infrared part of the spectrum arises both on excitation with light at $\lambda = 0.93$ μm and in the ultraviolet region (the $^2F_{5/2} \rightarrow {}^2F_{7/2}$ transition). The intensity and duration of the luminescence of neodymium and praseodymium then diminish. The authors conclude that the quenching takes place in the excited state and that the energy is transferred to the terbium ions by a non-radiative pathway in an inductive interaction. The probability of excited transfer per unit time depends on the degree of overlapping of the spectra, the degree of prohibition of the interacting transitions, and the donor–acceptor distance. It has been shown[16] that praseodymium can also behave as a quenching agent for the luminescence of ytterbium. It has been stated[17] that praseodymium can quench the luminescence not only of ytterbium but also of neodymium, samarium, and dysprosium.

Shionoya and Nakazawa[19] reported the sensitising effect of cerium ions on the emission by terbium or neodymium in glasses. They suggest that the energy transfer takes place via a non-radiative pathway. Gandy et al.[20] observed the sensitisation of ytterbium by cerium in a glass. Pearson and coworkers[21,22] present experimental data confirming the occurrence of non-radiative energy transfer from gadolinium to terbium in a borate glass. In another study dealing with the concentration-dependent quenching of the luminescence of gadolinium and ytterbium in glasses, Pearson and coworkers[23] concluded that the quenching occurs not only as a result of the quenching interaction in the corresponding activators, but that the process includes also quenching by an admixture of europium present in gadolinium.

Woodcock and Smitzer[24,25] investigated the sensitisation of the luminescence of erbium in a silicate glass by ytterbium ions. The mechanism of the energy transfer is represented as follows. Energy from the $^2F_{5/2}$ level of ytterbium is transferred to the $^4I_{11/2}$ level of erbium; then the erbium ion undergoes a non-radiative transition to the $^4I_{13/2}$ state, from which there is a transition accompanied by emission at $\lambda = 1.5$ μm. Under these conditions, the duration of the fluorescence of ytterbium ($\lambda \simeq 1$ μm) and the fluorescence intensity diminish.

Artamonova et al.,[26] who reported the sensitising effect of UO$_2^{2+}$ on the luminescence of lanthanide ions, note that in a glass the transfer of excitation energy takes place via the following chain of ions: $UO_2^{2+} \rightarrow Nd^{3+} \rightarrow Yb^{3+} \rightarrow Er^{3+} \rightarrow Tm^{3+}$. The greatest energy transfer effect is observed in the following links of the system: $UO_2^{2+} \rightarrow Nd^{3+}$ and $Nd^{3+} \rightarrow Yb^{3+}$.

The sensitisation of the luminescence of erbium in glasses by ytterbium ions was investigated in detail by Kudryashov and coworkers[27]. According to their data, in the presence of ytterbium the intensity of the luminescence of erbium ($^4I_{13/2} \rightarrow {}^4I_{15/2}$ transition) increases by a factor greater than 3 and this occurs on excitation of the luminescence by light in the range 0.75–1.1 μm, which includes the absorption bands of both ytterbium and erbium.

It is noteworthy that in the above investigations the concentrations of the lanthanides in the liquid solutions and glasses were in most cases relatively high (several tenths per cent and above). At low lanthanide concentrations in solutions, interaction was hardly observed.

The effect of the interaction of lanthanide activators is shown most distinctly in crystals. This is probably why the number of studies on the interaction of lanthanides in crystalline specimens is much greater.

A series of studies have been made on the interaction between lanthanides in organic crystals (lanthanide complexes). Soden[28] investigated the effect of substitution of certain lanthanides on the fluorescence of hexa-antipyrine-terbium tri-iodide in crystals of the following series: $TR_{1-x}Tb_x(AP)_6I_3$ (TR = Gd, Er, Dy, Y); AP = antipyrine ($C_{11}H_{12}ON_2$), and $x = 1.0$, 0.5, 0.2, 0.1, 10^{-2}, 10^{-3}, or 10^{-6}. He noted that the presence of dysprosium does not influence the fluorescence of terbium; the intensity of the luminescence of terbium ($\lambda = 549$ nm) falls in proportion to the decrease of x. In the presence of gadolinium or yttrium the intensity diminishes more slowly than x, which is attributed to excitation energy transfer from the antipyrine complexes of these elements to the terbium complex. On introduction of erbium, a more rapid decrease of the intensity of the fluorescence of terbium is observed, which is accounted for by energy transfer from the terbium complex to the erbium complex, where non-radiative transitions take place. Thus, the sensitising effect of gadolinium and yttrium and the quenching effect of erbium on the fluorescence of terbium were demonstrated.

Van Uitert and Soden[29] present the results of a more complete investigation of the effect of substitution by other lanthanides on the fluorescence of hexa-antipyrineterbium tri-iodide and sodium–europium tungstate. A study was made of the luminescence of crystals with the composition $Tb_xM_{1-x}(AP)_3I_3$, where M = Y, La, Ce, Pr, Nd, Sm, Eu, Gd, Tb, Dy, Ho, Er, Tm, or Yb and $x = 1.0$, 0.5, 0.25, and 0.1 and also the series $Na_{0.5}M_{0.5-x}Eu_xWO_4$, where x varies from 3×10^{-3} to 0.5. The luminescence was excited by the emission of a mercury lamp at $\lambda = 2537$ and 3660 Å.

Van Uitert and Soden[29] believe that the distribution of excitation energy absorbed by the antipyrine molecule between terbium and M^{3+} ions in the first series of crystals is determined by the ground energy level of the M^{3+} ions. The ease of energy exchange between the antipyrine molecule and lanthanide ions increases with the total orbital angular momentum of the $4f$ electron. If the ground state of these ions is S (Ga, La, Y), a large proportion of the energy absorbed by the antipyrine molecules bound to the above ions is transferred to terbium; for the H- and F-states, the effect of M^{3+} is slight and M^{3+} ions with the ground state I (Nd, Ho, Er) cause pronounced quenching of the luminescence of terbium.

In the case of ions with the same ground state (F) the exchange of excitation energy takes place preferentially for ions with the normal positions of the multiplets (Eu and Ce—ground states $^7F_0$ and $^2F_{5/2}$) than in the case of reverse multiplets (Tb and Yb—ground states $^7F_6$ and $^2F_{7/2}$).

The quenching of the luminescence of europium in sodium tungstates obeys the same rule as in substitution by other lanthanides according to the authors' data. As an exception, cerium in a tungstate environment causes pronounced quenching of the luminescence of europium. The authors believe that this may be caused by the relatively weak attachment of its uncombined electrons to the $4f$ levels ($4d$–$5d$ transitions). It has been shown that terbium slightly sensitises europium.

Peterson and Bridenbaugh[30] observed a change in the duration of the fluorescence of terbium in the antipyrine–terbium complex on substitution by other lanthanides. They note that both the intensity and duration of the luminescence diminish when favourable conditions are created for the resonance transfer of excitation energy to another, neighbouring lanthanide. The presence of erbium, holmium, and neodymium ions greatly diminishes the duration and intensity of the luminescence of terbium.

Poluektov et al.[31] investigated the luminescence of europium in crystals of ternary phenanthroline–acetophane and phenthroline–thenoyltrifluoroacetone complexes in the presence of other lanthanides. According to the data, the intensity of the luminescence of europium depends on the composition of the deposit. They compared the logarithms of the luminescence intensity of europium and the energy difference ΔE between the triplet state of the molecule and the nearest lower energy level of an extraneous lanthanide. There is a parallelism in the form of the $\lg I_{Eu}$ and ΔE curves as a function of the element. The higher the value of ΔE, the higher is I_{Eu} (Gd, Y, La). For low values of ΔE, the luminescence of europium is quenched (Pr, Nd, Ho, Er, Tm)†.

Despite the high value of ΔE, cerium strongly quenches the luminescence of europium. The authors explain this by the characteristics of the $4f$–$5d$ transitions in cerium and also note that the quenching of the luminescence of europium by other lanthanides is observed only in crystalline complexes. In solutions, for example in benzene, the quenching of the luminescence of europium is not observed.

The same investigators[32] made a detailed study of the sensitisation of the luminescence of europium by terbium in complexes with salol, anthranilic acid, and ternary antipyrine–salicylate complexes.

The excitation of the luminescence of lanthanide ions in complexes takes place[33–36] in consequence of the transfer of the energy of the exciting light from the organic base of the complex to the lanthanide ion and energy may be transferred from both triplet and singlet levels. For this, it is necessary that the energy of the triplet or singlet level of the complex should be equal or should exceed that of the resonance level of the lanthanide ions. The redistribution of energy within the molecule takes place very rapidly, over a period less than the duration of the excited state. When the complex contains several lanthanides interacting with one another, during the excitation period there is

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† It is noteworthy that the upper energy levels of praseodymium, neodymium, erbium, and thulium ions are located below the $^5D_0$ level of europium, which in fact gives rise to energy transfer.

probably a two-stage energy transfer: from the organic substance to the lanthanide ion and then from the latter to another lanthanide ion interacting with it.

The majority of the literature data on the interaction of lanthanides refer to inorganic crystals (crystalline phosphors). As early as the late 1940's, detailed investigations were made in the luminescence laboratory FIAN [Physical Institute of the USSR Academy of Sciences? (Ed. of Translation)] of the mutual effects of activator lanthanides (cerium, samarium, and europium) in crystalline alkaline earth phosphors[37,38]. A study was made of the absorption and luminescence spectra, the temperature-induced glow, the spectral sensitivity of the flash, etc. On the basis of the considerable changes in the luminescence spectra of one activator in the presence of another, the authors[37,38] suggested that the activators are located side by side and that they tend to form "complicated compounds", which constitute the luminescence centres. The probability of a random distribution of activators close to one another is insignificant when the concentrations are low (about 10^{-3}%).

During recent years a number of studies on the interaction of activator lanthanides by Soviet investigators have been published. Levshin et al.,[39] who studied the determination of small amounts of gadolinium, samarium, and europium in thorium by luminescence methods, paid some attention to this problem. They established that the luminescence of gadolinium is strongly quenched by admixtures of samarium, cerium, and neodymium when their concentrations in the specimen are about 10^{-3}% and above. The luminescence of samarium is strongly quenched by admixtures of neodymium and dysprosium. In another study by Levshin et al.,[40] energy transfer from silver to samarium ions in ZnS phosphors was considered. It was emphasised that the interaction of the activators is observed at very low concentrations (about 10^{-3}%), where the relevant species may not be close neighbours. The authors believe that the pronounced temperature dependence of the interaction is related to a change in the transfer of charge carriers through different bands. However, they do not reject the possibility of resonance energy transfer between activators as well.

Voronov and Levshin[41] investigated the interaction of the silver, samarium, thulium, and europium activators in the cathodoluminescence of ZnS-based phosphors. Samarium was chosen as the principal activator, since it is most sensitive to changes in the immediate environment. The effect of a second activator reduces to a marked redistribution of energy in the spectrum and to a change in the overall luminescence yield. At a low temperature the integral luminescence of samarium in the presence of a second activator hardly changes. Partial quenching of the luminescence of samarium is observed at room temperature. The authors believe that the quenching of the luminescence of samarium involves an electron–hole mechanism. The necessity to compensate charges, suggests a great likelihood of the formation of lanthanide ion pairs, occupying adjacent lattice sites and replacing three Zn^{2+} ions. This is indicated by the formation of deep localisation levels (about 0.5 eV) and a redistribution of energy in the spectrum.

Cherepnev and Pakhomycheva[42] and Leonov[43] investigated the sensitising effect of cerium on the luminescence of samarium in the $SrSO_4$ [42] and $3MgO.B_2O_3$ phosphors[43]. Bozhevol'nov and Fakeeva[44] used the sensitising effect of cerium on the luminescence of samarium in the $PbSO_4$–Ce,Sm phosphor to increase the sensitivity of the determination of samarium by a luminescence method.

O'Connor and Hargreaves[45] reported the excitation energy transfer from cerium to neodymium in CeF_3. Blasse and Bril[46] studied the energy transfer from cerium to samarium, europium, terbium, and dysprosium.

A number of non-Soviet and Soviet investigators studied the luminescence of crystalline phosphors activated by europium in the presence of other lanthanides[47-61]. Van Uitert and coworkers published a series of papers[47-49,55] on the interaction between lanthanide activators, attention being concentrated on the luminescence of europium. In one of their papers[47] they present data on the sensitising effect of terbium on the luminescence of europium. The experiments were performed with tungstates having the composition $M_{0.5}Tb_{0.5-x}Eu_xWO_4$ and $M_{0.5}Y_{0.5-x}Eu_xWO_4$, where M = Na, K, Rb, or Cs and $x = 10^{-4}$, 10^{-3}, 10^{-2}, 10^{-1}, or 0.5. It was shown that the intensity of the luminescence of europium in alkaline earth metal tungstates increases in the presence of terbium in proportion to its concentration. Up to 90% of the energy absorbed by terbium ions is transmitted to europium ions. When terbium is replaced by yttrium, the intensity of the luminescence of europium diminishes. It was also established that the relative intensity of the luminescence of terbium and europium diminishes with increasing radius of the alkali metal ions in the crystal lattice.

In other studies[48], the authors investigated the mechanism of energy transfer from terbium to samarium in the $Na_{0.5}Y_{0.5(x+y)}Tb_ySm_xWO_4$ system, from europium to neodymium in $Na_{0.5}(Y, Eu, Nd)_{0.5}WO_4$ and $(Y, Eu, Nd)_2O_3$, and from dysprosium to terbium in $Na_{0.5}(Y, Tb, Dy)_{0.5}WO_4$.

The quenching of the luminescence of terbium by samarium is characterised by a dipole–quadrupole interaction, but the luminescence of samarium was not observed under these conditions. Energy transfer from europium to neodymium takes place mainly via a dipole–dipole interaction. Energy may be transferred from the $^4F_{9/2}$ level of dysprosium to the $^5D_4$ level of terbium in the above system at 295.77° and 4.2°K. At 295°K the reverse transfer may occur.

In the next study by Van Uitert and coworkers[49], the problem of energy transfer from the main component of the crystal to lanthanide ions and also the concentration-dependent quenching of the luminescence of lanthanide is considered. The authors conclude that the energy of the exciting light is transmitted to the activator more effectively when it is close to the absorption limit of the main component. At frequencies below the absorption limit but not in the region of absorption by the lanthanide ions, excitation via the main lattice is relatively ineffective. At frequencies in excess of the absorption limit the energy is strongly absorbed and is distributed in the lattice. Energy transfer from the main component of the crystal to the lanthanide ions may be regarded as an independent problem.

Levshin and coworkers[50] studied the energy transfer from ZnS to a lanthanide activator and concluded that in this system, following excitation via the main component, the lanthanides receive energy predominantly by an electron–hole mechanism. The process depends markedly on the nature of the activators and the relative positions of their levels.

Two studies[51,52] on the luminescence of lanthanide ions in $Cs_2(NO_2Cl_4)$ crystals also demonstrate the sensitisation of the luminescence of lanthanide ions by the main component of the crystal. It has been shown that the migration of excitation energy of uranyl ions in the crystal lattice plays a significant role in energy transfer.

Mooney and Toma[53], who studied the system YVO_4–Eu suggest a mechanism for energy transfer from VO^{3-} to Eu^{3+} in which the colinearity of the positions of the V–O–Eu ions is not obligatory, as suggested by Blasse[54]. On the basis of structural data, it is concluded that in YVO_4 the π-bonding orbitals of the VO_4^{3-} ions have a maximum electron density in the direction of Y^{3+}. Therefore, in the substitution of yttrium by europium there is maximum overlapping of these π bonding orbitals with the f orbitals of the lanthanide ions. The authors explain in this way the high effectiveness of the luminescence of europium in YVO_4. The vanadium, oxygen, and europium ions do not lie on a single straight line under these conditions.

Blasse and Bril[54] investigated the energy transfer from the main component to lanthanide ions in Ln_2WO_6, Ln_2MoO_6, and $Y_2W_{1-x}Mo_xO_6$ ($0 \leq x \leq 0.1$) activated by europium. The authors suggest that the following conditions are necessary for the effective luminescence of europium: (1) the absorbing group must be a nearest neighbour; (2) the emission and absorption spectra of these groups must overlap; (3) the centre of the absorbing group, the intermediate oxygen ion, and the europium ion must be colinear; (4) the oxygen ions surrounding europium must respond to a high-potential field.

Bril and Wanmaker[56] observed the luminescent properties of phosphors activated by europium with a base incorporating lanthanides: Gd_2O_3, Y_2O_3, La_2O_3, $GdPO_4$, $LaPO_4$, etc. The phosphors exhibited the luminescence of europium. On the basis of the excitation spectra, the authors concluded that the energy absorbed by the main lanthanide ions is transferred to the impurity europium ions.

The study by Van Uitert and Jida[55] on the interaction of lanthanide ions in crystals of different compositions is of great interest. They investigated the single crystals of sodium and potassium tungstates and aluminates containing lanthanides ranging from yttrium and cerium to ytterbium. The cases of identical (concentration-dependent quenching) and different lanthanides (their mutual influence) were examined. Identical ions in immediate proximity quench each other's luminescence. The authors believe that the interactions between the lanthanides may be direct or via oxygen (in the presence of oxygen the quenching is more pronounced). Attention was concentrated on the luminescence of europium and terbium.

When europium and terbium ions interact with those of other lanthanides, the intensity of their luminescence diminishes exponentially with decrease of the spacing between the "fluoresceing" levels of the europium and terbium ions and the nearest lower levels of other lanthanide ions.

Holloway et al.[57] obtained direct proof of energy transfer from terbium to europium. They studied compounds with the composition $(Tb_{1-x}Eu_x)_2(WO_4)_3$. The luminescence of europium (λ = 6150 Å) and terbium (5460 Å) was observed.

The luminescence of europium in the presence of terbium appears both on excitation with ultraviolet light and on excitation with light at λ = 4950 Å (λ corresponding to the excitation of the terbium ion). On the other hand, if the phosphor does not contain terbium $[(Gd, Eu)_2(WO_4)_3]$, then, on excitation with light at λ = 4950 Å, the luminescence of europium is not observed. According to the authors, energy transfer from terbium to europium ions takes place by a non-radiative pathway (sensitisation of europium by terbium). The authors regard the process mechanism as obscure.

In another paper Holloway and Kestigian[58] quote data on the sensitisation of the luminescence of europium by terbium in the $Y_{3-x}Tb_xAl_5O_{12}$ system. The same study dealt with the concentration-dependent quenching of the fluorescence of terbium at 300° and 77°K. It was shown that the probability of quenching varies exponentially with the concentration of terbium.

Ropp[59] studied energy transfer from terbium to europium in Y_2O_3. Holloway and Kestigian[60] made an interesting study on energy transfer between samarium, europium, terbium, and dysprosium in sodium tungstate. They compared the experimental energy transfer data with the relative compositions of the energy levels in the interacting ions. There should be energy transfer of ions with higher excited levels to those with lower fluorescence levels (possibly via an excited state intermediate between the fluorescence levels of the acceptor ion).

Axe and Weller[61] presented experimental data on energy transfer between europium and other lanthanide ions in Y_2O_3. They reported that the addition of lanthanides such as holmium, erbium, thulium, and particularly neodymium strongly quenches the fluorescence of europium. It is suggested that the quenching is caused mainly by non-radiative resonance energy transfer from one lanthanide ion to another. The authors assert that the overlapping of adjacent zones in quadrupolar fields is of great importance in this process.

The interaction between lanthanide ions has been demonstrated also in a number of studies by other investigators. For example, Margolis et al.[62] note that the luminescence of praseodymium in $CeCl_3$ is readily excited by light at $\lambda \simeq 350$ nm (cerium absorption band). The authors wished to demonstrate experimentally that collective absorption of photons, when the energy of the exciting quantum is consumed in the simultaneous excitation of two ions‡, may be observed not only for identical ions, as shown by Varsanyi and Dieke[64], but also for different ions. Possibly in this case there is the usual transfer of energy absorbed by cerium ions to praseodymium ions.

The sensitisation of the luminescence of lanthanides by cerium has been frequently noted[42-44]. Linares[65] investigated the luminescence and excitation spectra and fluorescence lifetimes τ of europium and other lanthanide ions in CeO_2 and ThO_2. Regions corresponding to energy transfer from CeO_2 to europium, samarium, and erbium were observed in the excitation spectrum.

Scott et al.[66] considered the problem of energy transfer from praseodymium to neodymium. They made a theoretical calculation of the width of the spectral lines on the basis of a dipole interaction modulated by phonons.

Rast et al.[67] and Ewanizky et al.[68] investigated the interaction of neodymium and ytterbium in LaF_3 and CaF_2 crystals. In consequence of the transfer of excitation energy from neodymium to ytterbium, the intensity of the luminescence of ytterbium in the region of 0.97 μm increases by two powers of 10 according to Ewanizky et al.[68] In the case of divalent ytterbium, energy transfer from Yb^{2+} and Nd^{3+} is observed.

Brown[69] studied the energy transfer from thulium to holmium in Y_2O_3. The luminescence of holmium was observed on excitation with light corresponding to the absorption bands of thulium ($\lambda \simeq 590$–820 nm). A non-radiative energy transfer is suggested.

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‡ Collective or cooperative absorption may occur also in the excitation of an acceptor ion as a result of the summation of the energies of two donor ions[63]. For example, the excitation of Tm^{3+} (470 nm) by two quanta capable of exciting Yb^{3+} (960 nm).

Brown and Whiting[70] studied the interaction of lanthanides in LaF_3 and determined the quantum yield and duration of the visible fluorescence of praseodymium in an LaF_3 single crystal in the presence of other lanthanide admixtures: cerium, neodymium, europium, gadolinium, terbium, dysprosium, holmium, erbium, thulium, and ytterbium. The system with praseodymium and cerium was studied in detail. The concentration-dependent quenching of the luminescence of praseodymium in LaF_3 and CeF_2 was examined as a function of temperature. To interpret the experimental data, calculations were made for two simple models; (1) isolated praseodymium; (2) praseodymium adjoining another ion. It was found that the sphere of interaction extends from nearest neighbours up to about 300 atomic distances. It was shown that quadrupole interaction predominates.

In a later study by Van Uitert[71] on the concentration-dependent quenching of the fluorescence of samarium, europium, terbium, erbium, and neodymium in solid matrices, it was established that the quenching of the luminescence of samarium, terbium, and erbium ions occurs as a result of dipole–dipole interaction. The authors believe that the quenching of the fluorescence of europium is influenced by the crystal structure of the matrix.

Blasse's study[72] dealt with the concentration-dependent quenching of the luminescence of europium in $Ba_2Gd_{1-x}Eu_xM^{5+}O_6$ (M = Nd or Ta) and $Gd_{1-x}Eu_xAl_3B_4O_{12}$ with different crystal structures. The extent of the influence of the crystal structure on the concentration-dependent quenching was demonstrated.

Peterson and Bridenbaugh[73] analysed the duration of the luminescence of terbium in the presence of other lanthanide ions to investigate the interaction between pairs of lanthanides. A study was made of the duration of the excited state $(\tau)/{}^5D_4$ of terbium ions in a series of mixed crystals $Tb_{0.9}TR_{0.1}Cl_3.6H_2O$. It was established that the lanthanide ions which absorb light in the region corresponding to emission by terbium (europium, thulium, praseodymium, samarium, neodymium, erbium, and holmium) reduce τ, while lanthanum, gadolinium, ytterbium, yttrium, lutetium, dysprosium, and cerium, which do not absorb in the range 4875–6800 Å, hardly change τ. Erbium, holmium, and neodymium ions have the greatest effect. The intensity of luminescence varies approximately in parallel with τ. This phenomenon is explained by the resonance transfer of excitation energy from terbium to other lanthanide ions, which leads to quenching and decrease of τ.

In another study by the same investigators[73], the problem of self-quenching by neodymium in $Na_{0.5}Gd_{0.5-c}Nd_cWO_4$ was examined and it was shown that the probability of quenching is proportional to $1/r^6$, where r is the distance between the interacting ions.

Osiko and Voron'ko[74], who investigated the concentration-dependent quenching of the luminescence of neodymium in CaF_2, concluded that the resonance Nd–Nd interaction accompanied by quenching takes place only at distances of about 4 Å, corresponding to the distance between the neodymium ions in an ion pair centre (3.8 Å). On the other hand, the probability of a non-radiative energy transfer between single centres at a distance greater than 4 Å is low, as shown by the weak dependence of τ for single centres on the concentration of neodymium. Thus, according to the authors, the concentration-dependence of the quenching of the luminescence of neodymium is due to the association of neodymium ions. In consequence of the increase in the number of ion pair centres, an increase of concentration entails an increase of inactive absorption, which lowers the overall luminescence yield.

In another paper by the same investigators[75] experimental data are quoted for excitation energy transfer from erbium to holmium and thulium in CaF_2 crystals.

Porter and Moos[76] reported ion pair interaction in the $LaCl_3$–holmium system. On the basis of the relative luminescence intensities in transitions from the ${}^5S_2$, ${}^5I_4$, and ${}^5I_7$ levels, it was concluded that the ${}^5S_2 \rightarrow {}^5I_4$ transition takes place via the interaction between a pair of holmium ions. The variation of the probability of the pair interaction with concentration is linear. The effective region of interaction for the ion pair is about 7.5 Å (third nearest neighbour).

Bril and Wanmaker[77] observed energy transfer from gadolinium to terbium in $CaNaBO_3$. On excitation of the phosphor in the region 256–280 nm, both gadolinium and terbium luminesce, the fluorescence of gadolinium being weaker than in the absence of terbium. The excitation of the terbium fluorescence by emission from gadolinium (in the region of 311 nm) can be virtually excluded, since the fluorescence of terbium on excitation with light at λ = 311 nm is very weak. Consequently there is a non-radiative energy transfer from gadolinium to terbium. The quantum yield of the fluorescence of terbium sensitised by gadolinium is 60% according to the authors.

Jonson et al.[78] reported energy transfer from erbium ions to thulium and holmium ions in $CaMoO_4$ crystals. The transition takes place from the ${}^4I_{13/2}$ state of erbium to the ${}^3H_4$ state of thulium and the ${}^5I_7$ state of holmium. As a result of the energy transfer, it is possible to achieve an increase in the infrared emission by thulium and holmium ions. The sensitisation of the emission from thulium and holmium by erbium is used in lasers. The sensitisation of the luminescence of holmium and thulium by erbium in CaF_2 crystals was investigated by Osiko and coworkers[79].

In a study designed to elucidate the role of the effect of lanthanide admixtures in the determination of small amounts of any one lanthanide in yttrium oxide, we found[80] that, in the presence of terbium in an amount of 5×10^{-3}% and above, the luminescence of dysprosium is quenched.

Later Taylor[81] reported the observation in CaF_2 crystals at 300°K not only of the quenching of the luminescence of dysprosium by terbium at their concentrations of about 0.1 at.% but also an increase in the intensity of the fluorescence of terbium (by a factor of about 5). The study of the luminescence kinetics showed that the mechanism of energy transfer from dysprosium to terbium is non-radiative and takes place from the ${}^4F_{9/2}$ level of dysprosium to the ${}^5D_4$ level of terbium.

In connection with the development of methods for the luminescence analysis of lanthanide impurities in pure substances, Poluektov et al.[82] investigated also the effect of extraneous lanthanides on the intensity of the fluorescence of the sought lanthanide ion. The luminescence of samarium, europium, terbium, and dysprosium in different matrices was observed. The greatest luminescence yield was found in compounds of lanthanum, gadolinium, lutetium, and yttrium, which is evidence of their sensitising effect. Elements such as praseodymium, neodymium, holmium, erbium, and thulium quench fluorescence.

III. MECHANISM OF THE INTERACTION OF LANTHANIDE ACTIVATORS

There is a fairly large amount of data on the changes in the luminescence properties of lanthanides in consequence of their interaction. At comparatively low concentrations the interaction is reflected mainly in energy transfer from one lanthanide to another, which leads to the observation of the quenching of the luminescence of one or both interacting ions, in particular concentration-dependent quenching, the quenching of the luminescence of one ion and the sensitisation by it of that of another or only the sensitisation of the fluorescence of the other ion, and as a rule a change in the duration of luminescence.

At high concentrations or in the case of a deviation from the random distribution of lanthanide ions in the crystal lattice, it is possible to observe also other signs of the interaction: a change in the absorption and luminescence spectra—displacement of the lines and redistribution of their intensities, appearance of new lines and disappearance of old lines[74,83,84], and certain other properties.

In this review we are considering mainly processes involving the sensitisation and quenching of the luminescence of lanthanides. The experimental data on the mutual effects of lanthanides are presented in the Table below, where, together with each lanthanide, are indicated others which have a sensitising or quenching effect on its luminescence. The data are presented for liquid solutions, glasses, and organic and inorganic crystals.

Many authors have put forward hypotheses concerning the mechanism of the interaction. Most of them conclude that there is a resonance energy transfer from one ion to another (exchange-resonance or inductive-resonance)[3,5,15,19,30,34,40,48,57,66–71,73,77,87]. Only in isolated cases are other hypotheses put forward: energy transfer via emission[7,14] and energy transfer via energy bands by charge carriers[40,41,50]. Depending on the structure of the system investigated and on the specific conditions of the excitation of the luminescence, any of the mechanisms proposed is possible. When the crystalline phosphor exhibits photoconduction, energy transfer via energy bands by charge carriers is quite possible (Mott–Gurney theory[88]). When the emission spectrum of one lanthanide overlaps the absorption spectrum of another, there is a possibility of energy transfer via emission. However, it appears that most often there is an inductive resonance energy transfer process.

The theory of resonance energy transfer was described in detail by Dexter[89], who concentrated attention on the problem of the sensitised luminescence of solids. At the same time he reviewed critically other theoretical studies on the mechanism of the interaction.

In the presence of sensitised luminescence in inorganic compounds there is usually energy transfer from an allowed level of the sensitiser to a forbidden level of the activator. Some investigators (Botden[90], Kröger[91], and

Effect of lanthanide and other ionic impurities on the luminescent properties of the main lanthanide.

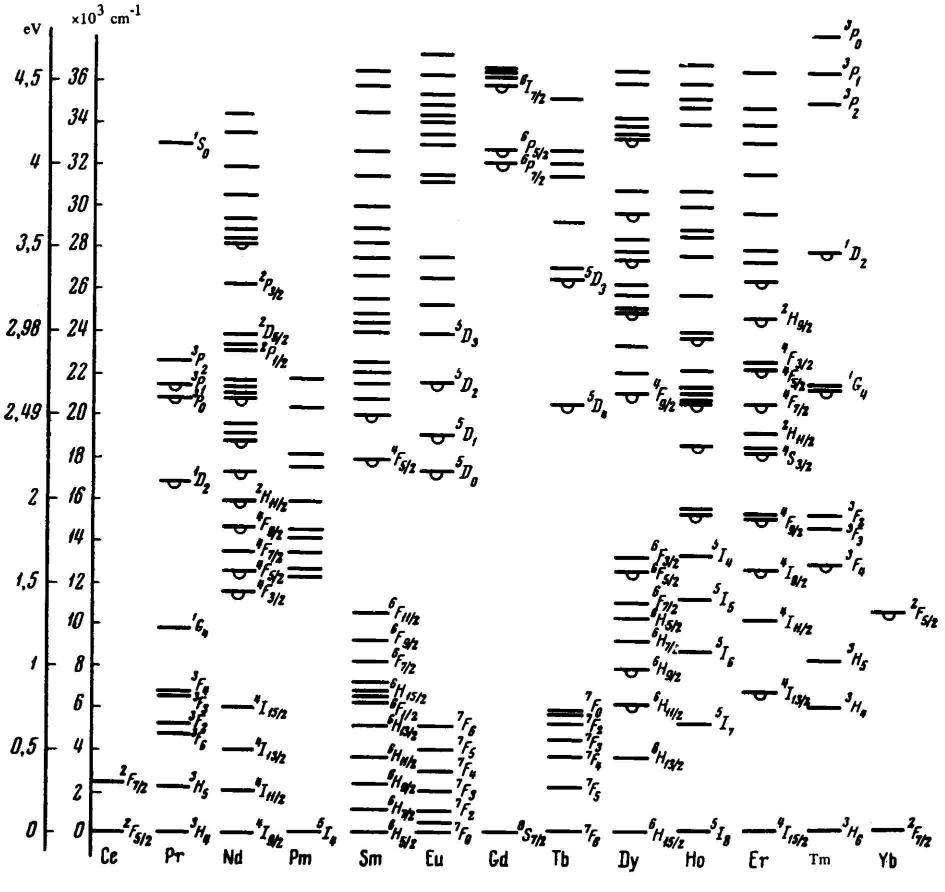
Main element	Effect of impurity	Medium			
		liquid solution	glass	organic crystal	inorganic crystal
Ce	sensitisation	4,4′-dimethoxybenzophenone[11]			
	quenching				Er[65]
Pr	sensitisation	4,4′-dimethoxybenophenone[11]			Ce[62], Cd, La[70]
	quenching		Yb[16.17]		
Nd	sensitisation	4,4′-dimethoxybenzophenone[11]	Eu[7], Tb[7.13], Ce[19], UO_2[26]		Ce[45], Pr[66]
	quenching		Pr[17]		
Sm	sensitisation	actophenone[4], 4,4′-dimethoxybenzophenone[11]			Gd[2.82], Ce[41—44.46,65], Tb[57], La, Lu, Y[82]
	quenching		Pr[17]		Nd, Dy[39], Nd, Pr, Ho, Er, Tm[82]
Eu	sensitisation	terbium[3], acetophenone[4], aldehydes, ketones[6,12], benzophenone[7], *p*-benzoylbenzoate[8], uranyl (UO_2),[9] fluorescein[10]		Tb[29,32], Gd, La, Y[31]	Tb[47.57—59], Ce[46.62,65], La, Gd, Y[56.82], Lu[82]
	quenching			Ce[29.31], Pr, Nd, Ho, Er, Tm[31]	Ho, Er, Tm, Nd[61.82], Nd[48], Pr[82]
Gd	sensitisation				
	quenching		Eu[23]		Sm, Ce, Nd[39], Tb[77], Eu[85]
Tb	sensitisation	acetophenone[4], aldehydes, ketones[6,12], fluorescein[10], 4,4′-dimethoxybenzophenone[11]	Dy[7.14], Ce[19], Gd[21.22]	Gd, Y[28.29], La[29]	Gd[73.77,82], Dy[81], La, Lu, Y[82]
	quenching	Pr, Sm, Tm[3], Ho, Er, Nd[3.5]		Er[28—30], Nd, Ho[29.30]	Ho, Er, Nd, Tm, Pr[73.82], Eu[73], Sm[48.60,73]
Dy	sensititsation	acetophenone[7]			La, Gd, Lu, Y[82]
	quenching		Pr[17]		Tb[48.60,80], Eu, Sm[60], Pr, Nd, Ho, Er, Tm[82]
Ho	sensitisation	4,4′-dimethoxybenzophenone[11]			Er[75.78,79.86], Tm[69]
	quenching				
Er	sensitisation	4,4′-dimethoxybenzophenone[11]	Yb[24—26.27]		Ce[65]
	quenching				Tm, Ho[75.78,86]
Tu	sensitisation	4,4′-dimethoxybenophenone[11]	Er[26]		Er[75.78.86.79]
	quenching				
Yb	sensitisation	4,4′-dimethoxybenzophenone[11]	Nd[15.16,26]Pr[16], Ce[20]		Nd[67.68]
	quenching		Pr[16.17]		

others) believe that the probability of such a transition is determined by the overlapping of the wave functions of the sensitiser and the activator and that the transition is possible only when the activator and sensitiser occupy adjacent sites in the lattice[74]. Tests of this theory showed that this is not always so. Energy transfer can occur also in the case of a random distribution of sensitiser and activator ions in the crystal. When they are located close to one another (about 5 Å), there is a possibility of direct energy transfer from the sensitiser to the activator via quantum-mechanical resonance. If the excited sensitiser ion is remote from the activator ion (at a distance greater than 50 Å), the excitation energy may be transmitted by other sensitiser ions to the activator ion via resonance. Thus the formation of sensitiser–activator pairs is not obligatory. The role of the sensitiser may be fulfilled both by additional admixtures to the main component of the crystal and by the main component itself when the excitation energy is transmitted to the activator directly from the main component as the energy donor[49-54].

The hypothesis of the resonance energy transfer process is not inconsistent with the effect of various factors on energy transfer. According to the literature, these include the following:

1. The distance between lanthanide ions, which is determined mainly by their concentration[5,15,37,38,73]; the probability of dipole–dipole interaction is inversely proportional to the sixth power of the distance between the interacting ions, while the probability of dipole–quadrupole interaction is proportional to the eighth power.

2. The degree of overlapping of the bands[15,61,73] or the energy difference between interacting levels[31,55]; the energy of the excited sensitiser level should be approximately equal to, or should exceed, the energy of the resonance level of the activator, the probability of energy transfer decreasing with increase in the difference ΔE between



Comparison of schematic sets of electronic levels for triply charged lanthanide ions (the semicircles designate "fluoresceing" levels).

these levels. The transfer of excitation energy from one ion to another for large values of ΔE is accompanied by the emission of phonons with energies approximately equal to ΔE.[86]

Since the activator plays the role of a quenching agent in relation to the sensitiser, it is to be expected that the energy of the excited level of the quenching agent should be equal to or lower than that of the resonance level of the activator.

3. The degree of prohibition of the interacting transitions[15].
4. The energy of the principal level of the interacting lanthanide ions, determined by the total orbital moment[29]; the probability of energy transfer increases with increase in the total orbital angular momentum of the $4f$ electrons.
5. Temperature[6,17,40,41] and other factors; with decrease of temperature, in most cases the probability of energy transfer falls, which can be accounted for by a decrease of the overlapping of the energy levels.

Review of published data shows that the luminescence properties of lanthanides vary significantly in consequence of their interaction. The factors enumerated, which influence energy transfer, show that the interaction is intense at high concentrations. The change in luminescent properties under these conditions is greater the more complete is the overlapping of the energy levels of the interacting ions.

Only at very low lanthanide concentrations (about $1 \times 10^{-3}\%$ and below)[39,80,82] is there virtually no interaction and hence no changes in the optical properties. Thus in the determination of small amounts of lanthanide impurities in high-purity substances by the luminescence method the analytical errors owing to their interaction are virtually excluded in many cases. The present authors' recent studies[85,93] showed that the problem of the determination of lanthanide impurities by the luminescence method is not always simple. For example, the determination of small amounts of gadolinium (about $10^{-5}\%$) in europium oxide[85] by the luminescence method is impossible without preliminary enrichment and subsequent introduction of the concentrate into yttrium oxide—a donor of the excitation energy of gadolinium. The reason for this is the nature of the interaction between gadolinium and europium. The relative energy levels in the atoms of these elements (see Figure) is favourable for energy transfer from gadolinium to europium but not conversely. Thus europium behaves in this case as a quenching agent for the luminescence of gadolinium.

In relation to neodymium, holmium, erbium, and thulium, europium can behave as an energy donor and therefore the determination of these impurities in europium oxide by the luminescence method should not present difficulties, if one disregards the partial overlapping of the luminescence spectra.

In the determination of lanthanide impurities in metallic uranium[93] by the luminescence method, the overlapping of the luminescence spectra has been the chief obstacle, since uranium can also function as an effective activator of many compounds[94] and its luminescence spectrum consists of a group of broad bands in the visible region. In this case an important condition for the choice of a base for the crystalline phosphor is the absence from it of uranium luminescence, which is almost impossible, or at least the presence of luminescence with a reduced intensity only. Then it is also necessary to achieve a careful separation of the lanthanide impurity from the base element (uranium). The determination of lanthanides by the luminescence method is not interfered with by the presence of uranium only if the latter is present in an amount less than or equal to $1 \times 10^{-3}\%$.

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Vernadskii Institute of Geochemistry
and Analytical Chemistry,
USSR Academy of Sciences,
Moscow

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The Present State of the Problem of Lignin-Carbohydrate Bonds in Plant Tissues

O.P.Grushnikov and N.N.Shorygina

The studies of the last 10-15 years showed that chemical and hydrogen bonds between lignin and carbohydrates and also three-dimensional network structures of lignin immobilising the carbohydrate chains are involved in the formation of a single set of components of the plant cell wall. This review presents data demonstrating the presence of the most likely types of lignin-carbohydrate bonds: ester, ether, acetal, and phenol-glycoside. However, the problems concerning the type, nature, and number of lignin-carbohydrate bonds still remain open. The possible inhomogeneity of the lignin in plant tissues complicates further the solution of these problems.
The bibliography includes 143 references.

CONTENTS

I. INTRODUCTION

During the last 10–15 years considerable advances have been achieved in the chemistry of lignin. The Swedish chemist Björkman developed a method for the isolation of lignin, which consists in the mechanical milling of the lignified material in a ball vibromill and does not involve the use of acid or alkali, thereby yielding a product closest to the "natural" material, i.e. lignin not isolated from plant tissue. The German chemist Freudenberg achieved the laboratory synthesis of a "dehydropolymer" in many respects similar to natural lignin from conifer wood. This preparation was obtained by dehydrogenating *in vitro* a very dilute mixture of coniceryl, *p*-coumaryl, and sinapinic alcohols under the action of laccase (a dehydrogenase). The problems of the biosynthesis of lignin in plants have been elucidated to a considerable degree. There have been undoubted advances in the study of the structure of lignin, its functional groups, and the types of its intramolecular bonds, as well as in the study of processes associated with the modification of lignin in the sulphite and sulphate pulping of wood and in its chlorination for the bleaching of cellulose. Some progress in the industrial utilisation of lignin, which is a large-scale by-product of the cellulose, paper, and hydrolytic industries, may also be noted.

However, despite the appreciable and unquestionable advances in the chemistry of lignin, a number of problems still give rise to a lively controversy among investigators in this field, and these are some of the most important problems in both theory and practice. In the first place this applies to the problem of the lignin–carbohydrate bonds in plant tissues and the related problems of the quantitative content of lignin in lignified material.

Indeed, as regards lignin–carbohydrate bonds, not only the problem of the type, nature, and number of chemical bonds of this kind in plant tissues but the very fact of the presence of such bonds is controversial. Nevertheless, the problem of whether lignin is linked to the carbohydrate components of plant tissues by chemical bonds or whether it is present in a free state, i.e. in a mechanical mixture with polysaccharides, is not only of theoretical interest but is also important for the quantitative separation of plant components in order to analyse them and understand various delignification processes in wood. It is noteworthy that in the chemistry of lignin there is still no single standard method for the quantitative determination of the content of lignin in plant materials, which naturally results in an appreciable discrepancy between results obtained using different methods and between the conclusions based on the results.

The problem of the presence or absence of chemical bonds between lignin and carbohydrate components of plant tissues has been the subject of controversy for more than 100 years. At the beginning two opposed views on this problem were in fact put forward: in 1838 Payen put forward the so called "incrustation theory" on the basis of the fact that cellulose in cell walls does not give rise to characteristic reactions until the non-cellulose material has been removed, namely that wood is a physical mixture of components and that cellulose is subjected to mechanical incrustation by lignin, while in 1866 Erdmann [7,8] postulated the existence in plant tissues of "glycolignose" in which cellulose is linked by an ester or ether bond to a non-carbohydrate component (lignin). In the following period a considerable number of data supporting one or other theory were published. However, in the last decade the majority of investigators clearly tend to recognise the presence of a chemical lignin–carbohydrate bond in plant tissues. A comprehensive review of the literature on this problem was carried out by Merewether [9], who examined in detail data on the morphology of the cell wall and microbiological degradation of wood and also data obtained in various chemical reactions of woody tissues and lignin.

During the ten years which have elapsed since the publication of Merewether's review, a considerable number of interesting data concerning the bonds between the components of plant tissues have been obtained and are discussed below. However, although stress has been laid on studies published in the last decade, in some cases earlier publications have been referred to make the exposition more complete.

2. CHEMICAL BONDS BETWEEN LIGNIN AND CARBOHYDRATE COMPONENTS OF PLANT TISSUES

The existence of lignin–carbohydrate complexes (LCC), consisting of soluble fragments of wood containing both lignin and carbohydrates in a form not separable by physical methods, has now been firmly established.

Lignin–carbohydrate complexes have been isolated by heating wood with water[10,11], on chlorination[10,12], alcoholysis[10,13,14], acetylation[15,16] and ozonolysis[17] of wood, in the sulphite[18-21], sulphate[22], soda[23-25], and chlorite[26] pulping of wood, and also as a result of the enzymatic breakdown of wood[27-31] and its treatment with a neutral aqueous solvent[32]; however, the major advances in the isolation and investigation of these complexes are undoubtedly due to Björkman.

In 1954 Björkman[33] proposed a new method for the isolation of lignin from lignified materials. After preliminary extraction, fir wood sawdust was ground in a ball vibromill in toluene or another solvent which does not cause the swelling of the material. Extraction of the ground wood with moist dioxan permitted the isolation of up to 50% of its lignin content in the form of mechanically ground lignin (MGL).[34] Further extraction of the ground wood with dimethylformamide, dimethyl sulphoxide, and water gave an additional amount of material containing, together with lignin, also a considerable amount of carbohydrates, the components being separated only by acid hydrolysis[35]. Fractionation of the extracts yielded a series of lignin–carbohydrate complexes containing between 16 and 34% of lignin. The composition of the carbohydrate component was always the same and corresponded to the composition of wood hemicelluloses (Table 1).

Table 1. Carbohydrate composition (rel. %) of hemicelluloses and lignin–carbohydrate complexes extracted with dimethylformamide from various species of wood (according to the data of Björkman[35]).

Carbohydrates	Fir (*Picea abies*)		Pine (*Pinus silvestris*)	Birch (*Betula verrucosa*)	
	LCC	Hem.	LCC	LCC	Hem.
Galactan	10	8	15	9	4
Glucan	17	18	25		7
Mannan	50	46	32	3	7
Araban	4	4	13	2	7
Xylan	19	24	15	86	75

LCC = lignin–carbohydrate complex; Hem. = hemicellulose (Ed. of Translation).

Further grinding of the isolated lignin–carbohydrate complexes in the vibromill yielded 40% of their lignin content in the form of MGL, identical in elemental and functional group composition and also in molecular weight to the MGL isolated in the grinding of wood[36]. Moreover, Björkman[35] carried out special experiments to establish whether the complex is formed during the grinding process. After the usual treatment in the vibromill of a mixture of MGL and hemicelluloses from *Picea abies* in proportions of 1 : 3, about 85% of the initial lignin was isolated. On this basis, it was concluded that the lignin–carbohydrate complexes are present in the wood and are not formed during its grinding in the vibromill.

The latter finding was convincingly confirmed by the data of Lindgren[37], who investigated the electrophoretic mobility of MGL and the lignin–carbohydrate complexes isolated from fir wood by Björkman's method. In the electrophoresis of the fraction designated by Björkman as the lignin–carbohydrate complexes, two subfractions were obtained: a slower carbohydrate fraction and a faster fraction containing both lignin and carbohydrates. The latter give a positive response to the test for lignin and yielded on hydrolysis glucose, mannose, and xylose. The relative amounts of lignin and carbohydrates in the fraction were about 1 : 1. Moreover, Lindgren established that MGL obtained in a preliminary grinding of the lignin–carbohydrate complexes had an electrophoretic mobility approximately equal to that of the MGL isolated initially, which constitutes yet another confirmation of the formation of MGL as a result of the dissociation of the lignin–carbohydrate complexes.

Thus, as a result of grinding in the vibromill, it is possible to isolate up to 50% of the lignin content in the wood in the form of MGL. The difficulty of extracting large amounts of lignin by neutral solvents can be accounted for, according to Björkman[34], either by the existence of strong chemical bonds between the lignin and carbohydrates or by the high molecular weight of the lignin and the possibility of the formation of three-dimensional network structures. Björkman also pointed out the possibility of the effect of weaker forces, namely hydrogen bonds, since the solvents employed for the isolation of MGL and the lignin–carbohydrate complexes should exhibit a high capacity for the formation of hydrogen bonds, which is necessary for the dissociation of the lignin–carbohydrate hydrogen bonds.

Hayashi and Tachi[38] showed that dilute alkali can extract from wheat straw powder a lignin–xylose complex, the so called "xylolignin" which breaks down after prolonged treatment with alkali. A similar complex is extracted with butanol, acetone, or ethanol containing water and sodium hydroxide. It has been established that the carbohydrate component of the complex, consisting mainly of xylose, contains small amounts of glucose and arabinose. Acetylated xylolignin has been extracted from acetylated wheat straw powder with acetone and chloroform[39,40]. The carbohydrate part of this complex has a composition analogous to that of the carbohydrates of xylolignin. Hydrolysis of acetylated xylolignin with a methanol solution of sodium hydroxide results not only in deacetylation but also in the dissociation of the lignin–carbohydrate bonds[41]. In subsequent communications Hayashi and Tachi[42-45] showed that dioxan, 50% acetic acid, and dimethylformamide extract lignin–carbohydrate complexes from wheat straw powder without preliminary grinding in the vibromill. The composition of the carbohydrate component (xylose, glucose, arabinose, and galactose) of the lignin–carbohydrate complexes extracted by these solvents differed from that of xylolignin.

Thus glucose predominated in the lignin–carbohydrate complexes extracted with dimethylformamide and the complexes extracted with dioxan and aqueous acetic acid, in which xylose constituted the major part of the carbohydrates, were enriched in galactose and arabinose compared with xylolignin. On the basis of these investigations, the authors[44] suggest the presence in wheat straw of lignin–carbohydrate complexes of different types.

Brownell and West[46] proposed a comparatively mild procedure for the dissolution of both lignin and wood carbohydrates without the application of strong acids, alkalies, or oxidising agents. After preliminary extraction with an alcohol–benzene mixture, air-dry sawdust was ground for 21 days in the usual rotary ball mill. As a result of the grinding, the degree of polymerisation of carbohydrates fell to about 40†. Then the ground wood was dissolved by treatment with epoxyethane in dimethylformamide. The dissolved hydroxyethylated wood was subjected to fractional precipitation, separation by paper and column chromatography, electrophoresis, and partition between two immiscible liquids. The investigation established that the main part of lignin cannot be freed from carbohydrates under such conditions. In subsequent publications Brownell[47–50] reported a method for the separation into components of the wood ground in a ball mill. This method consists in the separation of ground wood into components in the system aqueous solution of sodium thiocyanate–benzyl alcohol–dimethylformamide. Lignin and a lignin–carbohydrate complex analogous to the preparations obtained by Björkman's method were obtained, and the stability of the lignin–carbohydrate complex under conditions of various physical and chemical treatments was investigated[47,48]. Although both Brownell[47,48] and Björkman[35] believed it to be established that the lignin–carbohydrate complex is not formed during the grinding by free-radical grafting, we believe that this conclusion requires additional experimental confirmation, since in the course of intense mechanical degradation (grinding in a vibromill or a rotary ball mill) chemical bonds of different types are broken and the resulting macroradicals are capable of recombination, which may lead to the formation of new chemical compounds differing in bond type and composition from the initial polymers.

The fact that the lignin–carbohydrate complexes can be isolated from wood by a wide variety of methods, which include many different types of chemical treatment, grinding in a vibromill or ball mill, and enzymatic breakdown of lignified materials undoubtedly indicates that at least part of the wood exists in the form of lignin–carbohydrate complexes. At the same time the impossibility of isolating the individual components of the lignin–carbohydrate complexes in a pure form without the use of powerful chemical reagents (acids and alkalies) or without the application of mechanical energy, light energy, irradiation, or ultrasonication constitutes one of the most convincing proofs of the existence of chemical bonds between lignin and carbohydrates in plant tissues.

Interesting data concerning the presence of lignin-carbohydrate bonds were obtained in recent years in studies on lignin by physical methods (ESR spectra, infrared spectroscopy, etc.). Rex[51] showed that lignin does not contain free radicals before isolation from plant tissues. At the same time in isolated lignins free radicals persist for a long time during humification and coal formation. Kleinert and Morton[52] observed that free radicals are present in wood subjected to grinding, ground wood giving an ESR signal approximately ten times more intense compared with ground cellulose. On this basis, the authors concluded that the presence of free radicals is due to the presence of lignin which has a more rigid structure than cellulose. It was suggested that during grinding both carbon–carbon and carbon–oxygen ester bonds are broken. Steelink et al.[53] showed that lignins isolated by treating plant tissues with acids, alkalies, and enzymes or as a result of mechanochemical degradation of plant materials give rise to fairly considerable ESR signals.

According to the view of Chudakov et al.[54], these data indicate that free radicals are formed in lignin as a result of the dissociation of the lignin–carbohydrate bonds. Chemical, enzymatic, or mechanochemical treatments of plant tissues can give rise to the formation in lignin of free radicals such as the aroxy-radicals, owing to the dissociation of β-phenyl glycoside bonds, which the authors believe to be the most probable type of bond between lignin and carbohydrates. Another possible explanation[53] is that, as a result of the above treatments, lignin is demethylated and the preparations obtained contain *ortho*-quinonoid and quinomethane structures, which may serve as sources of free radicals.

Hachihama and Takamuku[55] investigated the effects of γ-radiation on wood and lignin and established that irradiation of the powdered wood of the red pine with γ-rays (4×10^6–10^8 r.e.p.) appreciably reduces its content of holocellulose and α-cellulose but has only an insignificant effect on the lignin content. Sulphite pulping of wood subjected to the action of γ-radiation increases the yield of lignosulphonic acid by a factor of three compared with the control specimen (the digestion was carried out under the conditions adopted by the authors). At the same time lignin from irradiated wood has properties analogous to those of lignin from ordinary wood. Irradiation of wood results also in an increased yield of "Braun's lignin", which can be extracted with 95% ethanol, and also an increase in the yield of lignin–carbohydrate complexes[56]. The latter were extracted with dimethylformamide from irradiated wood after the removal of the Braun's lignin. The extraction was carried out over a period of 12 days at room temperature. The yield of lignin–carbohydrate complexes increased from 0.3% (relative to the initial wood) for the non-irradiated specimen to 1.7% (after irradiation with 8×10^7 r.e.p.) and 6.9% (after irradiation with 1.1×10^8 r.e.p.). It was established that the content of carbohydrates in the lignin–carbohydrate complexes varies appreciably in different fractions, while their composition is almost identical and corresponds to that of the wood hemicellulose. The results were interpreted by the authors on the basis that γ-radiation causes partial dissociation of the lignin–carbohydrate bonds.

Information about lignin–carbohydrate bonds was also obtained in a spectroscopic study of wood and its components. Bolker[57,58], who investigated the infrared spectra of different types of wood, wood celluloses containing different amounts of residual lignin, and also isolated lignin, established that all the isolated lignins give rise to an absorption band at 1710 cm^{-1} (±15 cm^{-1}) with a variable intensity, which depends on the method of their isolation, but the band is absent from all the spectra of various types of wood and celluloses. The value of Bolker's work consists primarily in the fact that, by applying differential spectroscopy (an equivalent amount of holocellulose isolated by a standard method was used as a reference), it proved possible to obtain the infrared spectra of lignin contained in wood without modifying it by a chemical reagent. The above band was assigned by Bolker to a non-conjugated β-keto-group formed in the course of the isolation of lignin as a result of the dissociation of lignin–carbohydrate bonds. Bolker's experimental data were confirmed by subsequent studies of Higgins and coworkers[59,60]. Pilipchuk et al.[61] studied the infrared spectra of fir wood, acetylated MGL, holocellulose, MGL, and a mixture of MGL and holocellulose (in proportions of 3 : 7) in the range 1735–1750 cm^{-1} and from the results obtained concluded that there is a chemical bond between lignin and the carbohydrate components of plant tissue.

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†The degree of polymerisation of wood cellulose is 2500–3000 (by ultracentrifugation).

3. HYDROGEN BONDS AND THE POSSIBILITY OF THE FORMATION OF THREE-DIMENSIONAL NETWORK STRUCTURES

Apart from the chemical bonds between lignin and carbohydrates (the presence of which is regarded as established, as shown in the preceding section), both Björkman[34] and Brownell[48] pointed out the considerable role of hydrogen bonds in the formation of a single complex of plant tissue components.

Lignin is known to contain a large amount of phenolic and alcoholic hydroxy-groups, ester and carbonyl groups, and also a certain amount of carboxy-groups, which may be involved in the formation of intramolecular hydrogen bonds and also hydrogen bonds between lignin and carbohydrates. In a special study of the intramolecular hydrogen bonds in the lignin macromolecule, Lindberg[62,63] noted their influence on important properties of lignin such as solubility and capacity for precipitation. Lindberg established the presence of lignin of hydrogen bonds with an average energy of 2–3 kcal mole^{-1}. In order to penetrate the lignin macromolecule and dissolve it, the solvent must overcome this barrier, i.e. must be capable of forming hydrogen bonds with the corresponding lignin group and the energy of these bonds must be equal to or greater than 2–3 kcal mole^{-1}. These data were confirmed by the infrared spectra of lignins and model lignin compounds in the region 3600–3000 cm^{-1}, i.e. in the region of absorption by hydroxy-groups, and also by thermodynamic studies on monomeric models.

As regards the hydrogen bonds between lignin and carbohydrates in plant tissues, to which Björkman attributed a great importance, Lindberg concluded that in the complex of bonds between the plant tissue components they play only a secondary role. Indeed, despite the great likelihood of the formation of hydrogen bonds between lignin and carbohydrates in wood, in consequence of the amorphous nature of lignin it is difficult to imagine that these bonds are oriented along the molecules, as happens in cellulose chains, and the effect of irregularly distributed hydrogen bonds is known to be small.

The fact that wood is only very slightly susceptible to the action of enzymes, while the carbohydrate components and lignin are separately readily broken down by microorganisms has been regarded by many investigators[27-31, 64,65] as proof of the presence of a bond between lignin and carbohydrates in plant tissues. The data on the microbiological degradation of wood were interpreted somewhat differently by Pew[66,67]. While noting the undoubted presence of hydrogen and chemical bonds between the plant cell components, Pew emphasised that the immobilisation of the carbohydrate chains by the three-dimensional network structure of lignin, in a manner resembling the "serpent in a cage" system, has a considerable influence on the properties of lignified material and contributes to the formation of a single complex of the components of the plant cell wall. In a study of wood ground in a vibromill and its digestion by cellolytic enzymes, Pew showed that, while ordinary wood is resistant to the action of enzymes, after grinding for 10 min in a vibromill it is possible to remove about two-thirds of the wood carbohydrates and more prolonged preliminary grinding leads to complete digestion of the wood carbohydrate by cellolytic enzymes, leaving lignin as the residue. It is remarkable that the treatment of fir powder with a 1% hydrochloric acid, which should hydrolyse the chemical bonds between lignin and carbohydrates, did not increase its susceptibility to the action of enzymes, while reagents causing the swelling of wood had a very pronounced effect. A similar behaviour in relation to fine grinding and enzymatic digestion was shown by fir holocellulose, which had been impregnated with a water-soluble phenolic resin and then hardened at 110°C. On the basis of the results, Pew concluded that lignification is the factor which prevents the action of cellolytic enzymes on wood carbohydrates. The three-dimensional network structure of lignin, which immobilises the carbohydrate chains, prevents the access of large enzyme molecules to the system. Delignification completely eliminates this barrier, while grinding of wood or its swelling facilitates the contact between enzymes and wood carbohydrates.

In the summing up remarks at the end of his review, Merewether[9] concluded that the problem of the existence of a chemical bond between lignin and carbohydrates in lignified cellulose materials still remains open. Many facts can be explained on the basis of the incrustation theory, while others may be accounted for only by postulating the presence of chemically bound lignin–carbohydrate complexes. The data obtained during the last decade and discussed above lead to the conclusion that the existence of the chemical bond between at least part of the lignin and the carbohydrate components of plant tissues (mainly hemicelluloses) is established. Hydrogen bonds play a decisive role. Finally, account must be taken of the presence of the three-dimensional network structure of lignin which immobilises the carbohydrate chains.

4. POSSIBLE TYPES OF CHEMICAL LIGNIN–CARBOHYDRATE BONDS

Despite the fact that the majority of studies published in the last ten years hardly cast any doubt on the existence of a chemical bond between carbohydrates and lignin in wood, the problem of the types of the lignin–carbohydrate bond and also the problem whether or not all the lignin macromolecules are chemically bound to carbohydrates remain open.

It is known that after the removal of extractable substances from wood, which are evidently not bound to lignin since they are removed by simple physical methods without the removal of appreciable amounts of lignin, three carbohydrate components remain: cellulose, hemicelluloses, and polyuronides. The reactive groups in the carbohydrate components of plant tissue, which may participate in the formation of lignin–carbohydrate bonds, include primary and secondary hydroxy-groups, carbonyl groups, and finally the carboxy-groups in polyuronic acids. At the same time the reactive groups of lignin include phenolic and alcoholic hydroxyls of various types and also carbonyl groups capable of enolisation. The types of chemical lignin–carbohydrate bonds examined above may in fact arise between these reactive groups of lignin and the carbohydrate components of plant tissue.

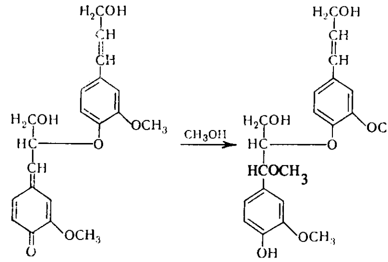
a. Ester and Ether Bonds

The presence of ester and ether bonds between lignin and carbohydrates, postulated at an early stage of Erdmann[7,8], is indicated by the results of a number of investigators. Thus Hoppe–Seyler[68] and Lange[69] concluded on the basis of the results of alkaline digestions of wood that there is an ester bond between the two components. Similar views on the nature of the lignin–carbohydrate bond were maintained by Czapek[70] and Grafe[71].

Klason[72,73] suggested that β-lignin contains a carboxy-group, which is not free in wood and should be bound to cellulose. In a study of the extraction of corn cobs under different conditions, Phillips[74] concluded that lignin is bound to carbohydrates in at least two ways: part of it is weakly bound, probably as ester groups of uronic acids, and the residue is combined via bonds of the ether type. Using the Cross and Beavan method for the determination of cellulose, Hawley and Norman[75] isolated two groups of hemicelluloses, one of which did not contain uronic acid and remained with the cellulose residue, and the other, usually containing uronic acid, was eliminated under the conditions of this determination. The authors believe that lignin is in fact bound to the latter group of hemicelluloses. The concept of an ether or ester bond between lignin and polysaccharides was supported by Lieser and Schwind[76] by experiments on the acetolysis of fir wood. Sarkar and coworkers[77,78] observed that, when jute is treated with 0.25% alkali, the acid number doubles. The authors believe that the additional free acid is formed in the hydrolysis of the ester bonds between lignin and polyuronides. Later Bhattacharjee and Callow[79] also observed an increase in the amount of free carboxyls in jute subjected to both acid (dilute hydrochloric acid) and alkaline (0.25% sodium hydroxide) treatment. Moreover, Sarkar[77] noted for jute and Tachi and Yamamori[80] for beech and elm wood a higher content of carboxy-groups in holocellulose, compared with the initial jute or wood. This observation was also accounted for on the basis of the hypothesis of the presence of an ester lignin–polyuronide bond. Foster et al.[81] believe that the ester bond between the carboxyl of uronic acid and the hydroxyl of lignin constitutes a likely explanation of the different rates of liberation of uronic acid from eucalyptus wood and from the holocellulose of this wood under identical conditions (1 *N* H_2SO_4; 91–92°C; 3 h).

In order to remove hemicelluloses, Harris[82] treated extracted wood powder with cold 17.5% sodium hydroxide and then extracted it four times with boiling methanol. Harris believed that the isolation of the methanol-soluble lignin (24% for fir wood and 70% for maple wood and aspen wood, in relation to Klason's lignin) constitutes proof of the cleavage of ester bonds between lignin and polyuronides. Stewart and coworkers[83,84] carried out a series of methanol extractions of eucalyptus wood at 150°C. The glucuronides found in the methanol extracts of holocellulose or wood pre-treated with alkali were absent from the extracts of the initial wood. The authors suggested that they are formed as a result of the hydrolysis of a lignin–polyuronide complex. Experiments on the pulping of aspen wood with a neutral butanol–water mixture at 158°C led Aaltio[85] to the conclusion that ester bonds are present between the acidic xylan chains and lignin. In a study of the infrared spectra of fir wood, acetylated MGL, holocellulose, MGL, and a mixture of MGL and holocellulose (in proportions of 3 : 7), Pilipchuk et al.[61] established that in the region 1735–1750 cm^{-1} in the infrared spectra of MGL, holocellulose, and their mixture, there are virtually no absorption bands or they are very weak. At the same time the infrared spectra of wood and acetylated MGL show very intense absorption bands in this region. Since it had been shown earlier[86] that the band in the region 1735–1750 cm^{-1} is due to the presence of ester groups, the authors concluded that an ester bond exists between lignin and other components of plant tissue (the amount of acetyl groups in fir wood is very insignificant and therefore their presence alone cannot account for the intense absorption in the above region, which is observed in the spectrum of the wood), without excluding the possibility of the existence also of other types of lignin–carbohydrate bonds.

The possibility of ether bonds of the benzyl ether type between lignin and carbohydrates in plant tissue was postulated by Freudenberg[87,88] on the basis of the preparation and investigation of a synthetic dehydropolymer[89–92]. Enzymatic dehydrogenation of coniferyl alcohol in aqueous methanol solutions results in the formation, together with other dimers and oligomers, of an α-*O*-methyl derivative of guaiacylglyceryl β-coniferyl ether (II, R=CH_3). The formation of this ether takes place via an intermediate quinomethane (I):



(I) (II)

If instead of methanol one uses a fairly concentrated solution of sorbitol or cane sugar, the corresponding α-*O*-derivative of guaiacylglyceryl β-coniferyl ether (II, R=$C_6H_{13}O_5$ or R = $C_{12}H_{21}O_{10}$) is formed. Calculations based on the content of methoxy-groups (10.21%) show that apparently two moles of quinomethane are combined with 1 mole of cane sugar. The sugar ether is readily hydrolysed by inorganic acids to (II, R = H), glucose, and fructose.

In a study of the effect of γ-radiation on wood, Hachihama and Takamuku[55] established that the amount of guaiacylmethanol groups increases in irradiated wood. Since the authors believe that γ-radiation leads to the cleavage of lignin–carbohydrate bonds, one may suppose that these bonds are of the benzyl ether type. In his review, Harkin[93] emphasises the central role of quinomethanes in the formation of the polymeric lignin molecule and of the bond between lignin and carbohydrates.

b. Phenyl Glycosidic Bonds

Hibbert and coworkers[94,95] synthesised a number of compounds simulating glycosides with aliphatic and phenolic aglycones: β-D-xyloside of α-hydroxypropiovanillone, β-o-xyloside of α-hydroxypropiosyringone, β-D-glucoside of α-hydroxypropioveratrone, β-D-xyloside of acetovanillone, β-D-glucoside of acetovanillone, β-D-cellobioside of acetovanillone, phenyl β-D-xyloside, phenyl β-D-glucoside, and guaiacyl β-D-xyloside. The rates of hydrolysis of these compounds and the conditions employed for the isolation of lignin from wood showed that the most likely type of bond between lignin and polysaccharides in plant tissues is the phenyl β-glycosidic bond.

By treating wood with acetic acid containing $MgCl_2$ as a catalyst, Freudenberg and Plankenhorn[96] isolated lignin acetate, which contained 11% of hexosan and after hydrolysis with alkali in an atmosphere of nitrogen yielded a product with a higher content of phenolic hydroxyls. Similar results were obtained by Pauly and coworkers[97,98], who treated wood powder in succession with methanol, 1.5% alkali at room temperature, and 85% acetic acid containing catalytic amounts of sulphuric acid and on the basis of the analysis of the preparations concluded that a phenyl glycoside bond is present between lignin and polysaccharides. Kawamura and Higuchi[99] demonstrated the presence of a lignin–xylose complex in dioxan-lignin isolated from beech wood. The dioxan-lignin obtained was separated by paper chromatography from sugars, exhaustively methylated, and hydrolysed with 5% hydrochloric acid. 2,3,4-Trimethylxylose, and not dimethylxylose, was isolated from the hydrolysis products by paper chromatography, which the authors believe to confirm the presence of glycoside bonds in lignin–carbohydrate complexes.

The work of Odintsov and Shishkova[100] on the cleavage of wood by enzymes, thermophilic cellulose bacteria, soil bacteria, and emulsion showed that the lignin–carbohydrate complex is cleaved, this being accompanied by the formation of new free phenolic hydroxyls. Häggroth and Lindberg[101] made a study whose aim was to explain the differences between sulphite and sulphate celluloses. According to McKinney's hypothesis[102], in sulphate pulping the residual hemicelluloses initially bound to lignin via phenyl glycoside bonds migrate to the cellulose chains of sulphate cellulose. In particular, the enhanced content of pentosans in sulphate cellulose is associated with this fact. Using phenyl β-D-xylopyranoside (III) as a model of the lignin–hemicellulose complex, Häggroth and Lindberg investigated its interaction with various alcohols and polysaccharides (methanol, glycerol, amylose, cotton cellulose). When compound (III) was treated with sodium methoxide in absolute methanol in nitrogen, a good yield of methyl β-D-xylopyranoside was obtained, while the interaction of (III) with sodium monoglyceride in anhydrous glycerol gave a mixture of glyceryl D-xylopyranosides. In the alkaline hydrolysis of compound (III) in the presence of both amylose and cotton cellulose, polysaccharides containing bound xylose were obtained. Thus, after the above treatment, cotton cellulose contained 2.4% of xylose. Hence the treatment of phenyl xylopyranoside in the presence of cellulose involves the cleavage of the phenyl glycosidic bond and xylose migrates to cellulose via transglycosidation, which confirms the McKinney hypothesis.

In the course of studies of lignin–carbohydrate complexes (xylolignin, acetylated xylolignin, complexes extracted with dioxan, 50% acetic acid, and dimethylformamide) isolated from wheat straw, Hayashi and Tachi[103,104] confirmed experimentally the presence of phenyl glycosidic bonds. In the alkaline hydrolysis of the complexes isolated an increase in the content of free phenolic hydroxyls was noted, as determined from the bathochromic shift in the ultraviolet spectrum (in the analogous treatment of lignin the amount of phenolic hydroxyls remains unchanged). Treatment of lignin–carbohydrate complexes with β-glucosidase increased the content of both phenolic hydroxyls of lignin and the reducing groups of sugar. Finally, in the alkaline pulping of lignin–carbohydrate complexes in the presence of cellulose, the migration of the carbohydrates of the complex to cellulose as a result of transglycosidation was observed (in the analogous treatment of a mixture of cellulose and freshly prepared holocellulose, transglycosidation was not observed).

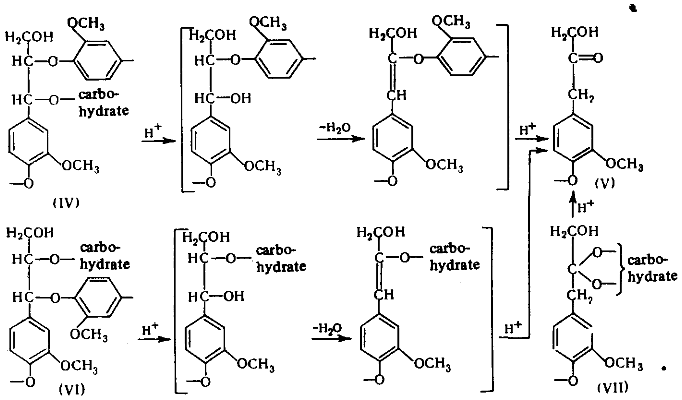
Kiryushina and Tishchenko[23] fractionated the lignins obtained as a result of brief sodium hydroxide digestion of maple wood with respect to their solubility in acetone. Analysis of the acetone-insoluble fraction showed[24] that it consists of lignin and carbohydrates (mainly pentosans) and behaves similarly as the chemically bound complex. Repeated soda pulping, acid hydrolysis, ozonolysis, and infrared spectroscopy confirmed experimentally[25] the hypothesis of the existence of a phenyl glycoside bond between lignin and carbohydrates in the acetone-insoluble fractions of the soda lignin. Moreover, the presence of a glycosidic bond, formed with a phenolic or aliphatic hydroxyl of lignin and the glycoside hydroxyl of the polysaccharides, has been indicated in the reviews of Richtzenhain[105] and Lindgren[106], who believed that this is one of the most probable types of the lignin–carbohydrate bond.

c. Acetal Bonds

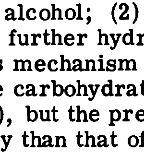
The hypothesis of the presence of an acetal (ketal) or hemiacetal (hemiketal) bond between lignin and hydrocarbons, formed by the carbonyl groups of the side chains of the phenylpropane structural elements of lignins and the hydroxy-groups of the polysaccharide chains, was put forward for the first time by Holmberg and Runius[107] on the basis of a study of the alcoholysis of wood. It is known that, when wood is treated with alcohol in the presence of an acid catalyst, the alcohol reacts with lignin to form an alcohol-soluble alcohol lignin. The authors suggested that the reaction consists in transacetalation: in wood lignin is linked to hydrocarbons, forming an acetal, while during alcoholysis the alcohol employed replaces the carbohydrate. To confirm this hypothesis, Maeda and Kobayashi[108] carried out experiments, which showed that before isolation from wood lignin does not contain free carbonyl or acid hydroxy-groups. To test these results, Nokihara et al.[109] subjected wood, holocellulose, and viscose cellulose to ethanolysis in the presence of hydroxylamine. The differences in the rates of reaction of these preparations suggested that the formation in wood of a lignin oxime is preceded by the hydrolysis of other compounds, tentatively identified as a lignin–carbohydrate complex, which incorporates an acetal bond. Berlin[110] carried out a series of experiments on the oxidation of wood with hydrogen peroxide and on the basis of the results concluded that the low-molecular component of natural lignin, localised in the secondary cell wall, is linked to carbohydrates via an acetal or hemiacetal bond, which is readily cleaved by hot water or dilute acids. The hypothesis of the presence of an acetal bond between the components of plant tissues was also supported by Shorygina[111] on the basis of the results obtained in the decomposition of lignin and wood by metallic sodium and liquid ammonia.

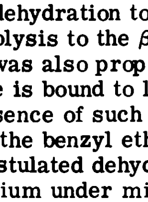
Recently this hypothesis received major support in a number of studies published by Bolker. As stated above, Bolker[57,58] observed that in the infrared spectra of isolated lignins there is an absorption band at 1710 cm^{-1}, which is absent from the spectra of different types of wood and wood celluloses containing residual lignin. This absorption band was assigned to a non-conjugated β-keto-group fromed in the isolation of lignin. Since β-keto-groups appear only in the course of the isolation of lignin, Bolker postulated that in wood and wood celluloses these groups are present as derivatives which do not absorb in the above region, i.e. in the form of acetal or enolic ether groups. Naturally, the spectra obtained do not show whether these groups are involved in intramolecular bonds of lignin (between phenylpropane units) or whether they are incorporated in the link between lignin and carbohydrates. However, the existence of a relation between the isolation of lignin and the accumulation in the latter of keto-groups and the finding that β-keto-groups are never observed in wood and wood celluloses is evidence, according to Bolker, in favour of the second possibility.

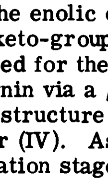
Bolker[112,113] proposed mechanisms for the decomposition of both the acetal (VII) and benzyl ether (IV) bonds between lignin and carbohydrate, resulting in the formation of β-keto-groups (V):



The mechanism of the decomposition of benzyl ether bonds (IV) postulated by Freudenberg[87,88] may, according to Bolker, consist of the following stages: (1) hydrolysis to benzyl alcohol; (2) dehydration to the enolic ether form; (3) further hydrolysis to the β-keto-group (V). An analogous mechanism was also proposed for the case where the carbohydrate is bound to lignin via a β-carbon atom (VI), but the presence of such a structure is much less likely than that of the benzyl ether (IV). As noted by Bolker himself, the postulated dehydration stage, occurring in an aqueous medium under mild conditions, is most vulnerable to criticism. In addition, Bolker put forward also a number of other, albeit indirect proofs, for the presence of an acetal bond between lignin and carbohydrates (the absence of the β-keto-group from lignins isolated by ethanolysis and their appearance after the acid hydrolysis of ethanol lignin[112]; the study of the rate of extraction of lignin from wood by non-aqueous acid mixtures of 2,2-dialkoxypropane and dioxane[113], etc.). In his subsequent communication Bolker[114] presents data on the interaction between two solvent systems: dioxane–2,2-dimethoxypropane–HCl and dioxan–methanol–HCl with the simplest models of the possible lignin–carbohydrate bonds: phenyl β-D-glucoside (VIII; glycoside bond), 1-ethoxy-2-(2″-methoxyphenoxy)-1-(3′,4″-dimethoxyphenyl)ethane (IX; benzyl ether bond), and 2-benzyl-2-methyl-1,3-dioxolane (X; ketal bond):


(VIII)


(IX)


(X) .

As was to be expected, the studies of the kinetics of these reactions did not yield any definite conclusions, although Bolker reports that work with more complex compounds simulating various types of lignin–carbohydrate bonds is being continued.

Bolker's data are of undoubted interest, although their interpretation gives rise to objections. In the first place the assignment of the band at 1710 cm⁻¹ to the β-keto-group is controversial[115–118]. In the second place, according to the data of Adler and coworkers[119–121], β-keto-groups may be formed as a result of the acidolysis of arylglyceryl β-aryl ethers, which may take place in the acid medium most often employed for the isolation of lignin.

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Apart from the types of lignin–carbohydrate bonds discussed above, Chudakov[122] postulates the presence of carbon–carbon bonds between lignin and carbohydrates, assuming that the work of Kratzl and coworkers[123], who showed that, on treating lignin with methanol (at 150°C, without the addition of inorganic catalysts), part of the alcohol alkylates the benzyl alcohol groups of lignin and part forms stable C–C bonds, constitutes indirect proof of this possibility.

It should be noted that the hypothesis of each of the lignin–carbohydrate bond types discussed above gives rise to some criticism based on the study of the stability of lignin–carbohydrate complexes under the conditions of different types of physical and chemical treatment[47,48,103,124]. Therefore, despite the relatively large number of studies concerning the problem of the lignin–carbohydrate bond type, the latter still remains open.

5. LIGNIN–CARBOHYDRATE BONDS AND THE PROBLEM OF THE HOMOGENEITY OF LIGNIN

It can now be regarded as firmly established that lignin is non-uniformly distributed in plant tissue. One of the first attempts to investigate the quantitative distribution of lignin in plant tissue was undertaken by Ritter[125,126], who treated 3 mm wood sections and then separated the lignin residue, which was determined by Klason's standard method. It was found that a large proportion of the lignin (about 75% of the total amount) is concentrated in the middle lamella, while the fraction in the secondary cell wall is much smaller and it should be noted that lignins localised in these two sites in plant tissue differ considerably in their content of methoxy-groups.

Bailey[127] separated by means of a micromanipulator 0.5 mg of the substance in the middle lamella from the wood of the Douglas fir and established that the preparation isolated contained 71% of lignin, 14% of pentosans, and 4% of cellulose. On the basis of data obtained in an ultraviolet microscope study, Lange[128] calculated the weight concentrations of lignin in the secondary cell walls and in the material of the middle lamella, which amounted to 16 and 73% respectively.

The problem of the distribution of lignin in the cell wall of plant tissue has been examined critically by Berlyn and Mark[129], who emphasised that the results of Bailey and Lange are diametrically opposed to those of Ritter. Noting that the volume of the material in the middle lamella in the wood of conifers amounts to only 10 to 12% of the volume of the woody tissue, Berlyn and Mark showed that, even if the middle lamella consisted entirely of lignin, it could not contain more than 40% of the total lignin in wood. This hypothesis was confirmed experimentally in a study by Goring and coworkers[130]. The method employed by the authors consisted of a combination of ultraviolet microscopy and densitometric analysis of the negatives of the ultraviolet photomicrographs obtained. Some of the results of these investigators are compiled in Table 2, which shows that the material of the middle lamella is more lignified compared with the secondary cell wall but nevertheless contains only a small proportion of the total lignin of wood.

Table 2. Distribution of lignin in tracheides of the fir (according to the data of Fergus et al.[130]).

Wood	Morphological differentiation	Relative u.v. absorption	Vol. of fraction, %	Lignin, % of total amount	Lignin concn., $g\,g^{-1}$
Early	SW	1	87.4	72.1	0.225
	ML (r) (t)	2.21	8.7	15.8	0.497
	ML (cc)	3.77	3.9	12.1	0.848
Late	SW	1	93.7	81.7	0.222
	ML (r) (t)	2.7	4.1	9.7	0.60
	ML (cc)	4.5	2.2	8.6	1.00

SW = secondary wall; ML = middle lamella; r = radial direction; t = tangential direction; cc = cell corners.

Interesting data on the distribution of hemicelluloses in plant tissue were obtained by Asunmaa and Lange[131]. They used a microspectrographic method and investigated the distribution of carboxy-groups in holocellulose isolated from fir wood and birch wood. It was established that the outer portions of the delignified fibres contained the greatest amount of carboxy-groups, while in the vicinity of the lumen (the cellular cavity of the fibre) their content is a minimum. It is well known that polyuronides containing carboxy-groups enter into the composition of hemicelluloses. On this basis, the authors concluded that in plant tissues the relative content of hemicelluloses diminishes almost linearly from the outer layers towards the lumen. Bearing in mind the analogous variation of the concentration of lignin, the results were interpreted in support of the presence of lignin–hemicellulose bonds. Asunmaa and Lange[132] investigated spectroscopically delignified fir and birch fibres esterified with *p*-phenylazobenzoyl chloride. It was shown that holocellulose is distributed approximately uniformly in the cell wall. However, while cellulose is most closely packed around the lumens, hemicelluloses are concentrated in the outer layers of the fibres (hemicelluloses constitute approximately 50% of the entire carbohydrate material in the outer layers of the fibre and only 10–20% around the lumen).

Thus the studies on the morphology of the cell wall demonstrated unambiguously a non-uniform distribution of lignin in plant tissues, which suggests that the composition and structure of the lignin–carbohydrate complexes localised in the middle lamella and in the secondary cell wall are different. This hypothesis was confirmed by the results of Aaltio[85,133], who carried out a series of nine butanol digestions of aspen wood. After preliminary extraction with acetone, the fine sawdust was pulped with a neutral buffered mixture of butanol and water for 4 h at 158°C and each digestive was carried out on the residue from the preceding one. The solubility of wood was followed by analysing the insoluble residue and the pulping solutions. Some of the results of this study are presented in Table 3.

These investigations showed that aspen wood consists partially of homogeneous lignin–uronide complexes. The first of these dissolves digestions readily, passing into solution in the course of the initial five digestions and is localised in the middle lamella. The ratio of lignin to pentosan uronides in this complex is about 0.75. The second complex dissolving in succeeding digestions is localised in the cell wall and is characterised by a lignin::pentosan uronide ratio of about 0.55. Cellulose is apparently closely associated with this complex. The carbohydrate component of the above complexes includes a homogeneous pentosan uronide in which the weight ratio of pentosans and uronic acids is approximately 7:1. Qualitative analysis of the sugar in the acid hydrolysates of the aqueous phases of various digested solutions showed that they contain D-xylose, 4-*O*-methylglucuronosidoxylose, aldobiuronic acid, D-galactose, D-galacturonic acid, L-arabinose, and traces of D-mannose, and L-rhamnose.

Table 3. Some results of a study on consecutive pulping of aspen wood by buffered aqueous butanol (according to the data of Aaltio[85]).

No. of digestions	Ratio of dissolved lignin to dissolved pentosan uronides	Content of CH_3O groups in dissolved lignin, %	
		found	calculated
1	1.05	21.4	21.7
2	0.75	—	21.3
3	0.77	20.1	20.2
4	0.73	—	21.4
5	0.74	17.9	17.9
6	0.59	—	15.3
7	0.55	15.0	15.0
8	0.54	—	15.0
9	0.55	14.9	12.0

The lignin fractions in both complexes are structurally different. While lignin in the readily soluble complex contains approximately 20–21% of CH_3O groups, the lignin in the more stable complex has a much lower methoxy-group content (about 15%). According to Aaltio's data, this difference is due to the different distribution of vanillin and syringin structures in the molecules of these lignin fractions. Aaltio interpreted his results on the basis that in the course of the first five digestions the pulping solution gradually acts upon the middle lamella, which leads to the isolation of the highly methoxylated lignin and pentosan uronides in proportions of 0.75 : 1. After the dissolution of the entire middle lamella, the material is freed from fibrous tissue and the secondary cell wall is acted upon in subsequent digestions. This leads to the isolation of lignin with a low methoxy-group content and pentosan uronides, again in constant proportions (0.55 : 1), which are however different from those found in the dissolution of the middle lamella.

It is noteworthy that, according to Aaltio, the greater part of lignin in the complex isolated from the middle lamella is in a free state and is not linked chemically to the carbohydrate components. This is consistent with the findings of Bailey[134], who concluded, on the basis of a study of the digestion of wood with a neutral aqueous butanol at 158°C, that in aspen wood the entire lignin is present in a free state, while in pine wood about 20% of the lignin is bound chemically to carbohydrates.

According to Björkman's hypotheses[36], lignin present in plant tissue may be divided into two fractions as regards its bonds with hemicelluloses. One fraction forms a very insignificant number of bonds with hemicelluloses or not at all and is probably localised in the middle lamella, where the concentration of lignin is a maximum. This fraction is isolated under mild conditions and corresponds to MGL obtained by Björkman's method. The second fraction is firmly bound to hemicelluloses, and may be isolated by more severe methods. This fraction corresponds to the lignin–carbohydrate complexes obtained by Björkman's method. The proportions of the fractions are approximately 1 : 1.

Brownell and West[46] also concluded, as a result of the experiments, discussed above, on the fractionation of hydroxyethylated wood dissolved in dimethylformamide and subjected to preliminary grinding in a ball mill, that in wood approximately three-quarters of the total amount of lignin is bound chemically to carbohydrates. About one-quarter of the lignin can be readily separated from carbohydrates. The authors suggest that this part of the lignin is not bound chemically to carbohydrates, although it is quite possible to postulate that the bonds are broken during the treatment of the wood in the ball mill.

As a result of his studies on the oxidation of wood with hydrogen peroxides, Berlin[110] concluded that the lignin in the intercellular material (i.e. localised in the middle lamella) has a higher molecular weight and is not bound to polysaccharides. Tishchenko[17] noted, on the basis of the results of a stepwise ozonolysis of fir wood in ethyl acetate, that the wood contains both free lignin (not less than 43% of the total lignin) and lignin bound chemically to carbohydrates.

All these data confirm partly the hypothesis of Purves[135] who suggested, as early as 1943, that the molecular weight and the relative amounts of "free" and "bound" lignin in plants can vary not only as a function of the plant species but also as a function of its age and conditions, and the even earlier hypothesis of Klason[72] of the presence in wood of two types of lignin: α- and β-lignins.

The data concerning the existence of various lignin–carbohydrate complexes localised in the middle lamella and in the secondary cell wall can explain to some extent why by pulping wood it is impossible to achieve complete delignification of cellulose and additional treatment, in particular bleaching, is necessary.

To some extent, the inhomogeneity of the lignin contained in plant tissue is confirmed by the determination of the molecular weights of preparations obtained by the fractional isolation of lignin using different methods: by sulphite pulping[136-138], by extraction with a dioxane–hydrochloric acid mixture[139], by sulphate pulping[140], and by nitrating with nitric acid in ethanol[141]. These data led to the hypothesis of the presence in plant tissue of two types of lignin: with low and high molecular weights, localised in different sites of the plant cell walls.

Summarising the foregoing, we may note that the "biological and structural role of lignin, the conditions of its formation, and the nature of its interaction with other components of the cell wall in the primary layer and in general in the middle lamella can, of course, differ from the role of lignin and the nature of its bond with other substances in the secondary cell wall. Therefore one must recognise that the attempts to establish a single relation governing the nature of the bond between cellulose and other polysaccharides on the one hand and lignin on the other in all parts of the cell wall without taking into account the characteristics of its structure and the mutual bonds between the components in its various parts are not justified".[142] In addition, one should bear in mind the irregularity of the lignin structure, which follows from its role in the plant and also from the characteristics of its biosynthesis. According to Freudenberg's data[89-92], only dehydrogenases which remove hydrogen from the phenolic hydroxyl of the monomer participate in the *in vitro* biosynthesis of lignin from coniferyl alcohol. The subsequent stages take place, without the participation of the enzyme, in accordance with stochastic laws, which give rise to a wide variety of intramolecular bonds in lignin as well as bonds between lignin and carbohydrates. Thus it is quite reasonable to suppose that the contribution of chemical bonds to the formation of a single complex of components of the plant tissue is different in the middle lamella and in the secondary cell wall. In addition, as stated above, one cannot exclude from consideration the presence of hydrogen bonds between lignin and carbohydrates and also the possibility of the formation of three-dimensional network structures of lignin immobilising the carbohydrate chains.

The problem of the type of chemical bond between lignin and carbohydrates in plant tissues can be solved most probably only as a result of parallel experiments on lignin–carbohydrate complex preparations isolated from wood and compounds simulating the above possible types of chemical lignin–carbohydrate bonds. The behaviour of compounds of these types in different kinds of treatment under otherwise identical conditions will undoubtedly yield information which will permit a first approximation solution of this problem, which is one of the most interesting in the chemistry of wood.

Finally, returning to the problem of the homogeneity of lignin, it is noteworthy that, according to the valid comment by Freudenberg[143], when only part of the lignin in plant tissues is bound to carbohydrates both the incrustation theory and the theory postulating the presence of lignin–carbohydrate bonds are correct and not mutually exclusive as appeared previously.

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Zelinskii Institute of Organic
Chemistry, USSR Academy
of Sciences, Moscow

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Stepwise Enzymatic Synthesis of the Specific $C_{(3')}$ - $C_{(5')}$ Internucleotide Bond

S.M.Zhenodarova

The review deals with the methods of synthesis of low-molecular-weight oligoribonucleotides based on the use of various ribonucleases and polynucleotide phosphorylase, whereby oligonucleotides can be obtained rapidly and in fairly high yields by a gradual (stepwise) growth of the oligonucleotide chain. The possibilities of this comparatively new field in the synthesis of oligonucleotides and the prospects for its development are discussed.
The bibliography includes 72 references.

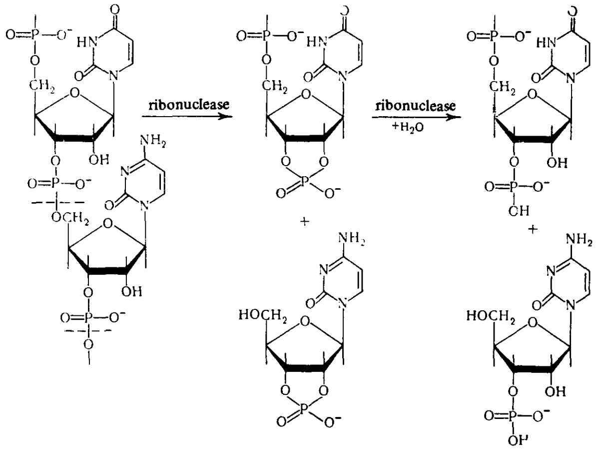
CONTENTS

I. INTRODUCTION

Since the publication of the review of methods for the stepwise synthesis of the specific $C_{(3')}-C_{(5')}$ internucleotide bond[1] several years have elapsed. In this period studies on further elaboration and improvement of these methods have developed widely and effectively (see, for example, Refs. 2–13) and very important results have been obtained. In particular 64 trinucleoside diphosphates containing the usual nucleotides in all possible combinations were synthesised[14], which permitted the final elucidation of the aminoacid code[2]. Studies on the synthesis of the gene coding for an alanine *t*RNA are also being successfully continued. However, it should be noted that the chemical methods for the synthesis of oligonucleotides consist of many stages and are fairly laborious. At the same time the need for oligonucleotides increases continuously in connection with the expansion of research in which they are employed: the study of the mechanism of protein synthesis, the study of substrate specificity and kinetics of enzymatic reactions catalysted by various nucleotidases, etc. Therfore the search for simpler and more effective methods of synthesis of oligonucleotides is continued and at present, together with chemical procedures, enzymatic methods are being increasingly employed. This review deals only with such enzymatic reactions, involving the *stepwise* synthesis of the $C_{(3')}-C_{(5')}$ internucleotide bond—(the synthesis of low-molecular oligonucleotides), while reactions leading to the synthesis of polynucleotides (synthesis with RNA and DNA polymerases[2], polymerisation using polynucleotide phosphorylase[15], etc.) are not considered.

II. SYNTHESIS OF OLIGORIBONUCLEOTIDES USING RIBONUCLEASES

It is well know that the cleavage of the phosphodiester bonds in ribonucleic acids or polynucleotides catalysed by ribonucleases takes place in two stages: (1) cleavage of the bond between the phosphorus atom and the 5'-O atom of ribose with subsequent transphosphorylation and the formation of 2',3'-cyclic phosphates; (2) hydrolysis of 2',3'-cyclic phosphates with formation of 3'-phosphates[16].



Usually ribonucleases catalyse the cleavage of the phosphodiester bond with a specific type of nucleoside whose 3'-oxygen atom is involved in this bond. Thus pyrimidylribonucleases cleave at the highest rate the bond in which a pyrimidinenucleoside donates the 3'-oxygen atom. For example, pancreatic ribonuclease is a pyrimidylnuclease. Similarly guanylribonucleases require that the 3'-oxygen atom be donated by guanosine. For example, the T1 ribonuclease from Takadiastase is of this type. However, non-specific ribonucleases also exist. As early as 1955 Heppel et al.[17] showed that the first stage of this reaction is reversible and under certain conditions pancreatic ribonuclease can catalyse the synthesis of compounds containing the phosphodiester bond. Somewhat later it was established that T1-ribonuclease also exhibits transesterifying activity and is capable of synthesising oligonucleotides[18]. Analogous properties were found also in guanylribonuclease isolated from *Actinomyces aureoverticilatus*[19].

At the present time studies on the application of pancreatic T1 ribonuclease in oligonucleotide synthesis are developing fairly rapidly[20–25]. However, it must be emphasised that the use of specific enzymes permits the synthesis of oligoribonucleotides in which the sequence of monomeric units is determined by the specificity of the enzyme. Recently it was shown that in the synthesis of oligonucleotides and in particular dinucleotides it is desirable to employ ribonucleases without definite specificity, since it is then possible to obtain dinucleotides with any sequence of bases[26,27].

In a discussion of methods for the synthesis of oligonucleotides using ribonucleases it is convenient to examine separately the synthesis of dinucleotides and trinucleotides, although both these reactions are of the same type and have much in common. Longer oligonucleotides have not so far been obtained by this method (see p. 700).

1. Synthesis of Dinucleotides (Dinucleoside Mono- and Di-phosphates)

Since ribonucleases of all the types known at present cleave the phosphodiester bond by the same mechanism, it follows that the synthesis of the phosphodiester bond using ribonucleases also involves substrates of the same type, namely nucleoside 2′,3′-cyclic phosphates. Nucleoside 2′,3′-cyclic phosphates are obtained as a rule from the corresponding nucleoside 2′,3′-phosphates with the aid of dicyclohexylcarbodi-imide or ethyl chloroformate[28]. In certain cases they are isolated from a ribonuclease hydrolysate[29].

The synthesis of dinucleotides in the presence of ribonuclease can be represented by the following mechanism:

$$N{>}p + N' \xrightarrow{\text{ribonuclease}} NpN',$$

where N>p[†] is the substrate(nucleoside 2′,3′-cyclic phosphate) and N′ is an acceptor, which consists of a nucleoside derivative with a free 5′-hydroxy-group (nucleoside, nucleotide, nucleoside 2′,3′-cyclic phosphate). The reaction is usually carried out by incubating with the enzyme a mixture of the substrate and the acceptor dissolved in a buffer solution. At the same time nucleoside 2′,3′-cyclic phosphate is hydrolysed to nucleoside 3′-phosphate.

Substrates. The substrates employed in this reaction were the 2′,3′-cyclic phosphates of uridine[20–23,26,27], cytidine[17,20–23,26,27], adenosine[26,27], guanosine[18,19,24–27], inosine, and xanthosine[25] and also 5′-*O*-substituted nucleoside 2′,3′-cyclic phosphates: 5′-*O*-phosphoryl- and 5′-*O*-methylphosphoryl-uridine 2′,3′-cyclic phosphates[31], 5′-*O*-(α-n-butoxyethyl)-substituted 2′,3′-cyclic phosphates of uridine, cytidine, adenosine, and guanosine[32,33], 5′-*O*-acetyl-, 5′-*O*-methylphosphoryl-, 5′-*O*-sulphonyl-, and 5′-*O*-pyrophosphoryl-guanosine 2′,3′-cyclic phosphates[34], and the methyl ester of 2′,3′-cyclophosphoguanylyl-(5–N)-phenylalanine[35]. Pancreatic ribonuclease is known to be capable of cleaving phosphodiester bonds the 3′-oxygen atom of which belongs to minor (4-thiouridine[36]) or non-natural (6-azauridine, 6-azacytidine[37], 5-halogenouridine[38], etc.) nucleosides and also nucleosides containing an anomalous carbohydrate residue[39]. Therefore it may be supposed that the corresponding nucleoside 2′,3′-cyclic phosphates may function as substrates in the synthesis of oligonucleotides. Indeed it has recently been shown that 5-bromouridine 2′,3′-cyclic phosphate gives rise to 5-bromouridilyl-3′–5′)-uridine after incubation with uridine in the presence of pancreatic ribonuclease[40]. Evidently the number of substrates will increase as the study of the specificity of already known ribonucleases is extended and also as new ribonucleases, differing in the type of their activity from those already known, are discovered.

Acceptors. The second component of this reaction, the phosphate acceptor, may be a nucleoside containing a free 5′-hydroxy-group, a nucletide, and in the case of specific ribonucleases also a nucleoside 2′,3′-cyclic phosphate. Since the specificity of ribonucleases is determined by the donor of the 3′-hydroxy-group, the possibility of the reaction occurring should be independent of the type of heterocyclic base in the acceptor. Thus in syntheses with participation of pancreatic ribonuclease, one may use as phosphate acceptors, together with natural nucleosides, also the aza-analogues of uridine[40], guanosine[41], and 5-chlorouridine[40] and, in the case of T1 ribonuclease, 5-bromouridine, 6-azauridine, $N_{(3)}$-methyluridine, and 5-methyluridine[40]. Heppel et al.[17] noted that in the case of pancreatic ribonuclease nucleotides are poor acceptors and nucleosides and cyclic phosphates are most effective. On the basis of these data and later studies[19], it is asserted that pancreatic ribonuclease uses nucleotides as acceptors to only a slight degree. However, this is erroneous, since Tikhomirova-Sidorova and coworkers[22,23] synthesised under analogous conditions UpUp (10–30%), UpCp (40%), CpCp (9%), and CpUp (29%). Heppel's conclusion that thymidine cannot serve as an acceptor in this reaction also proved to be incorrect: uridilyl-(3′–5′)-thymidine was obtained in about 12% yield from uridine 2′,3′-cyclic phosphate and thymidine[40].

Substrate concentration, ratio of substrate and acceptor concentrations, and effect of solvent. The substrate concentration and also the ratio of the substrate and acceptor concentrations in the reaction mixture are very important for the synthesis of dinucleotides in this reaction. In the studies of various investigators the substrate concentration varied from 0.02–0.08 to 1 M. In a study of the effect of substrate concentration on the synthesis of dinucleoside monophosphates in the presence of pancreatic ribonuclease A, Bernfield[20] established that the yield is proportional to substrate concentration below 0.3 M and is a maximum at a concentration of 0.4 M. It is quite likely that in the presence of other enzymes a different substrate concentration will be optimum, but such data are not at present available.

[†] To abbreviate the naming of the nucleosides, nucleotides, and oligonucleotides, the rules developed by the IUPAC Commission on Biochemical Nomenclature[30] and also the notation proposed by Holý and Smrt[9] have been employed: A = adenosine, C = cytidine, G = guanosine, U = uridine, X = xanthosine, I = inosine, N = nucleoside, and aza N = aza-analogue of nucleoside; p = phosphoric acid residue; when p (or the symbol for any other substituent) is written to the right of the nucleoside symbol, the phosphate group is in the 3′-position or ribose and when it is written to the left of the nucleoside symbol the phosphate group is in the 5′-position; p interposed between two nucleoside symbols denotes a 3′–5′ internucleotide bond; the symbol >p denotes a 2′,3′-cyclic phosphate; HSO_3 = sulphonate group; 5ClU = 5-chlorouridine; 5BrU = 5-bromouridine; T = thymidine; Me = methyl; Be = α-n-butoxyethyl; MeOPhe = methyl ester of phenylalanine.

The dependence of the yield of dinucleoside mono- or di-phosphates on the ratio of the substrate and acceptor concentrations has been investigated somewhat more thoroughly. It has been shown that a ratio close to 1/4 is optimum[25,27,33], but in some cases further increase of the excess of the acceptor increases the yield of dinucleotide. As an example, one may quote the syntheses of ApC and GpC catalysted by the non-specific ribonuclease from *Aspergillus clavatus*[27]. In the synthesis of ApC a large excess of the acceptor (tenfold and more) retards both the cleavage of the substrate and the formation of dinucleoside monophosphate, while in the second case an increase in acceptor concentration leads only to an increase of the yield of dinucleoside monophosphate (27% for a threefold excess and 46% for a tenfold excess). On the other hand, if the reaction mixture contains an excess of the substrate, then monotonic oligonucleotides of various lengths are obtained together with the dinucleotide[20,21].

It is noteworthy that in the case of sparingly soluble nucleosides or nucleotides (adenosine, guanosine, etc.) it is virtually impossible to obtain the required concentrations of the substrate and acceptor, which leads to low yields of dinucleosides. The present author believes that, in order to increase the concentration, it is necessary to employ acceptors in the form of their more soluble derivatives. Such derivatives must meet the following requirements: (1) high solubility in the appropriate buffer; (2) the substituent used to enhance the solubility must be easily introduced into the nucleoside (nucleotide) and easily eliminated; (3) the substituent must not affect the reaction. Preliminary studies showed that one may employ as compounds of this kind the *N*-dimethylaminomethylene derivatives, which are obtained in quantitative yield when the nucleoside (nucleotide) is treated with the dimethyl acetal of dimethylformamide[43,44], are readily soluble in various solvents, and easily lose the dimethylaminomethylene group under mild conditions, for example during chromatography in solvent systems containing ammonia. UpG,[32] ApG, GpG, and GpA [27] have been synthesised using as acceptors the *N*-dimethylaminomethylene derivatives of guanosine and adenosine.

Another method for increasing the acceptor concentration (and if necessary also the substrate concentration) consists in the replacement of aqueous buffers by buffer solutions containing organic solvents. Usually oligonucleotides are synthesised in the presence of ribonucleases in an aqueous buffer at pH 7 – 8. Trishydroxymethylaminomethane (Tris) or phosphate salts are normally employed as buffers, the buffer concentration varying in the range 0.05 – 0.15 M (Tris) and 0.01 – 0.025 M (phosphate). The synthesis of UpazaG and CpazaG in the presence of pancreatic ribonuclease in 50% pyridine was described recently[41]. In the present author's laboratory the effect of various solvents (dimethylformamide, pyridine, acetonitrile) on the synthesis of CpC was investigated. The results presented in Table 1 show that ribonuclease catalyses the synthesis of dinucleoside monophosphate in all cases but in the presence of an organic solvent the reaction is slower and as a rule the yield is lower. The hydrolysis of the substrate is also retarded in the presence of dimethylformamide and acetonitrile, while pyridine accelerates it.

The use of buffer systems containing various organic solvents may prove to be very interesting and useful also in another connection. As already mentioned, when the reaction mixture is incubated with the enzyme, the synthesis of the dinucleotide is accompanied by the hydrolysis of the nucleoside 2,3′ -cyclic phosphate to the 3′-phosphate, the latter reaction often predominating. Therefore it is of interest to find ways of inhibiting the hydrolysis while maintaining the synthesis. All such procedures involve the use of organic solvents. Pancreatic ribonuclease is known to retain its activity at high concentrations of alcohols, which, however, inhibit the enzymatic hydrolysis of cyclophosphate substrates[45]. Alcoholysis of the substrate catalysed by ribonuclease takes place only in the presence of the alcohols satisfying certain structural requirements for the formation of the ester. In particular, it is known that secondary alcohols do not participate in the alcoholysis[45,46]. Therefore a study has been made of the synthesis of oligoribonucleotides in the presence of ribonuclease A in isopropyl alcohol[20], i.e. under conditions where the hydrolysis of cytidine 2,3′-cyclophosphate is inhibited and alcoholysis does not occur. It was found that the yield of oligonucleotide increases with the concentration of the alcohol, but falls sharply at a concentration of 8.7 M. In 7.2 M isopropyl alochol the yield of oligonucleotide is 72% compared with the aqueous buffer and the hydrolysis takes place to the extent of only 42%. It is also extremely interesting that the effect of temperatures on the synthesis of oligonucleotides in isopropyl alcohol and water is not the same: in 7.2 M isopropyl alcohol at 10°C a greater amount of oligonucleotide is formed than at 0°C and more than at 0°C in water. At 24°C the yield of the synthesis in isopropyl alcohol is lower than at 0°C but higher than in water at the same temperature. In the presence of various amounts of methanol, glycerol, ethylene glycol, butane-2,3-diol and also mixtures of isopropyl alcohol with dioxane or formamide the yield in the synthesis did not exceed the level attained in water[20].

Table 1. Effect of organic solvent on the synthesis of CpC in the presence of pancreatic ribonuclease.

Buffer solution	Content of CpC and C>p in reaction mixture, %							
	0.5 h		1 h		2 h		4 h	
	CpC	C>p	CpC	C>p	CpC	C>p	CpC	C>p
0.05 M tris-HCl in water (pH 7.6)	19.5	65.4	17.2	60.6	17.0	57.0	12.4	45.8
0.05 M tris-HCl in 50% dimethylformamide (pH 7.5)	9.6	82.0	11.9	71.4	11.6	66.4	10.2	54.1
0.05 M tris-HCl in 50% acetonitrile (pH 7.6)	15.6	72.6	18.0	61.0	14.9	64.9	18.7	53.2
10% pyridine	14.3	67.0	15.1	59.0	15.2	50.9	10.5	38.3
30% pyridine	12.2	66.7	11.9	60.5	12.0	52.3	10.1	40.0

In the discussion of problems associated with the solubility of the reaction components we must finally draw attention to the fact that the substrate may be used in the form of various salts: ammonium[20,22,25,27], sodium[26,27], potassium[19], dicyclohexylguanidinium, pyridinium, tributylammonium[27], and triethylammonium[27,41]. However, preliminary data obtained in our laboratory showed that the nature of the cation in the substrate influences not only its solubility in the buffer but also the course of the synthesis. In particular, the pyridinium salt of adenosine 2′,3′-cyclic phosphate is cleaved more rapidly under the conditions of synthesis of ApC.

Temperature. The synthesis of oligonucleotides with participation of ribonucleases takes place usually at temperatures close to 0°C. In Heppel's studies[17] it was already noted that the reaction takes place better at a low temperature, while at a higher temperature (37°C) the substrate is rapidly cleaved. These data were confirmed later in other investigations[20,22] for pancreatic ribonuclease and for the non-specific ribonuclease from *Aspergillus clavatus*[27].

Concentration of ribonuclease. The concentration of ribonuclease used in the synthesis is as a rule low and varies in the range from 10 to 40 $\mu g\ ml^{-1}$. In the presence of pancreatic ribonuclease the synthesis varies linearly with enzyme concentration in the range not exceeding 40 $\mu g\ ml^{-1}$ [20] and falls on further increase of concentration. An increase in the concentration of guanylribonuclease from *actinomycetes* accelerates the synthesis and increases the yield of oligonucleotides[19]. In the case of 5-*O*-substituted substrates the synthesis of the oligonucleotide in the presence of pancreatic ribonuclease reaches a plateau at an enzyme concentration of 40 $\mu g\ ml^{-1}$.[31]

Duration of reaction. The dependence of the yield of oligonucleotides on the duration of incubation of the reaction mixture has been investigated. Heppel noted an increase of the yield of dinucleotide with incubation time[17]. Later studies of reactions with participation of pancreatic ribonuclease showed that the synthesis of dinucleotides largely terminates after 3–4 h when the substrate is cytidine 2',3'-cyclic phosphate[20,23] and after 5–6 h when the substrate is uridine 2',3'-cyclic phosphate[22]. However, the hydrolysis of the substrates continues when the acceptor is a nucleoside. When the acceptor is a nucleotide, the synthesis and the hydrolysis terminate simultaneously. Therefore, it has been suggested that the cytidylic or uridylic acid formed in the reaction inhibits the synthetic function of ribonuclease in the first place[22]. It must be emphasised that these results are valid only for this particular enzyme. The synthesis of dinucleotide monophosphate catalysed by the non-specific ribonuclease from *Aspergillus clavatus* is slower and reaches a maximum after 24–48 h, depending on the nature of the substrate[27]. Moreover it has been found that the curves relating the yield of dinucleoside monophosphate to time are influenced by the ratio of the concentrations of the substrate and acceptor in the reaction mixture[27].

Effect of the pH. According to Heppel's data[17], the synthesis in the presence of pancreatic ribonuclease is independent of the acitidity of the medium in the pH range between 5 and 9. In the cases of guanylribonuclease from *Actinomyces*, at pH 5.5 the synthesis takes place at a lower rate than at pH 7.2.[19] In a study of the non-specific ribonuclease from *Aspergillus clavatus* in the synthesis of GpC it was shown that the optimum pH for the synthesis and hydrolysis is the same[27].

Thus it follows from the data examined that it is now possible to synthesise dinucleotides of any composition and with any sequence of nucleic acid bases using a set of ribonucleases or a single non-specific ribonuclease. The synthesis is achieved in one stage and may be carried out on a preparative scale. Table 2 lists all the dinucleoside mono- and di-phosphates synthesised in this way.

The compounds synthesised by this procedure were isolated by preparative paper chromatography in standard solvent systems: 2-propanol–conc. ammonia–water (7 : 1 : 2),[33] 1-propanol–conc. ammonia–water (55 : 10 : 35),[20–23] 1-butanol–acetic acid–water (5 : 2 : 3),[25] and isobutyric acid–0.5 *N* ammonia (10 : 6),[19] with a subsequent check of purity by paper electrophoresis. The converse procedure has also been used: the reaction mixture was separated by paper electrophoresis in 0.05 M triethylammonium bicarbonate and then additionally purified by chromatography in a particular standard system[23,26,32]. The separation of the reaction mixture by chromatography on ion-exchange resins or molecular sieves is promising for syntheses on a preparative scale.

Table 2. Dinucleoside mono- and di-phosphates synthesised in the presence of ribonucleases*.

Substance	Yield (in relation to substrate), %	References	Substance	Yield (in relation to substrate), %	References
UpU	25; 13	21; 22	UpT	12.0	40
	14.0	40	5BrUpU	14.5	40
UpC	23.0	22	UpUp	10—30	22
CpC	25.0	23	UpCp	40.0	22
	27.0	21	CpCp	9.0	23
CpU	2.3	27	CpUp	29.0	23
ApC	24.0	27	GpUp	40.0	19
ApU	4.5	27	GpCp	50.0	19
ApG	13.8	27	GpAp	25.0	19
ApA	6.1	27	pUpU	7.0	31
GpC	56.0	27	MepUpU	8.0	31
	50.0	19	BeUpU	13.0	33
GpU	50.0	19	BeUpC	15.0	33
	13.0	27	BeApC	13.0	33
	24.5	34	BeCpC	20.0	33
GpG	4.3	27	BeGpC	19.0	33
GpA	13.4	27	MepGpU	24.0	34
IpU	25.0	61	PGpU	60.0	34
XpU	10.0	61	MepGpU	25.0	34
Up8azaG	13.5	41	ppGpU	1.5	34
Cp8azaG	13.5	41	HSO_3GpU	1.5	34
Up 6aza U	11.3	40	MeOPhepGpU	10.0	35
Up 5ClU	15.6	40			

*The Table does not list the dinucleotides for which the yield is not quoted in the original paper.

2. Synthesis of Trinucleotides (Trinucleoside Di- and Tri-phosphates)

The stepwise synthesis of trinucleotides may be achieved in two ways:

$$N > p + N'pN'' \rightarrow NpN'pN'' , \qquad (I)$$

$$NpN' > p + N'' \rightarrow NpN'pN''. \qquad (II)$$

One of the principal characteristics of this synthesis is the presence of the phosphodiester bond in the acceptor [reaction (I)] or in the substrate [reaction (II)], which makes it necessary in such cases to choose the enzyme catalysing the synthesis, or other reaction conditions, in such a way that the cleavage of the bond is reduced to a minimum.

The mechanisms quoted show that the substrates should be 2',3'-cyclic phosphates of nucleosides or of dinucleoside monophosphates. Compounds of the first type are readily available[28,29], but the introduction of the 2',3'-cyclic phosphate group into nucleotides is more difficult. Three methods have now been proposed for the synthesis of compounds of the type NpN'>p: (1) selected phosphorylation of dinucleoside monophosphates with triethyl phosphite and subsequent oxidation with hexachloroacetone[47]; (2) cyclisation of the terminal 3'-phosphate in dinucleotides with the aid of cyclohexyl-β-(*N*-methylmorpholino)ethylcarbodi-imide *p*-toluenesulphonate[48]; (3) cyclisation of the terminal 3'-phosphate with ethyl chloroformate[69].

There exists also a third method for synthesising trinucleotides: incubation of an excess of a nucleoside 2′,3′-cyclic phosphate (N>p) with a nucleoside, which leads to the formation of trinucleoside diphosphates of the type NpNpN′ [reaction (III)]. The first trinucleotides were in fact obtained by this procedure in enzymatic reactions with participation of ribonucleases:

$$2N>p+N' \rightarrow NpNpN'. \qquad (III)$$

Heppel et al.[17] already noted that, at high concentrations of cytidine 2′,3′-cyclic phosphate (> 0.1 M) and cytidine, their incubation with ribonuclease at 2°C leads to the formation (together with CpC, CpCp, CpC>p) of CpCpC and CpCpC>p. When reaction mixtures containing about 0.5 M substrate and acceptor are incubated, oligonucleotides with longer chains are formed. Bernfield and Nirenberg[49] reported the synthesis of UpUpU (12%), UpUpC (8%), and CpCpC (10%), and later[21] of CpCpU (8%) and CpCpA (2%). Each synthesis involved the reaction of two molecules of pyrimidine 2′,3′-cyclic phosphate with a nucleoside.

In 1964 the first communication[24] on the synthesis of the trinucleoside diphosphate GpUpC from a nucleoside 2′,3′-cyclic phosphate (G>p) and a dinucleoside monophosphate (UpC [see reaction (I)] was published. The synthesis was achieved by thermostatting 6.5 micromoles of G>p and 20 micromoles of UpC in 0.1 ml of 0.05 M tris buffer (pH 7) with 1 μg of T1 ribonuclease at 2°C and 24 h.

A series of papers by Grünberger, Holý, and Šorm[25,41,50-54] described the synthesis of 66 different trinucleoside diphosphates with participation of T1 ribonuclease. The synthesis was achieved by reactions (I) and (II) and the substrates were the 2′,3′-cyclic phosphates of guanosine, inosine, 8-azaguanosine, and xanthosine; the reactions of dinucleoside monophosphates with guanosine, inosine, and 8-azaguanosine at the 3′-end were also employed. It was found that in reaction (I) G>p and I>p were more effective substrates than 8-azaG>p or X>p. The acceptors in these reactions were dinucleoside monophosphates without guanosine, inosine, 8-azaguanosine, or xanthosine at the 5′-end and consequently incapable of being cleaved by T1 ribonuclease.

The synthetic activity of T1 ribonuclease depends on the nature of both nucleosides in the dinucleoside monophosphate acceptor, but the effect of the nucleoside at the 5′-end is more pronounced. Other conditions being equal, the yield of the oligonucleotide diminishes in the series C > U > A when the 5′-terminal nucleoside is varied. These results differ from the known sequence of the rates of cleavage of the corresponding internucleotide bonds[55]. GpGpU could not be obtained from G>p and GpU, since in the course of incubation GpU is cleaved more rapidly than the trinucleoside diphosphate synthesised. When the 3′-terminal nucleoside is altered, the yield varies in the series C > U > A > I > G.

Certain other types of oligonucleotides containing anomalous bases (5-methyluracil, $N_{(3)}$-methyluracil, $N_{(1)}$-methylinosine, 5-bromouracil, and 5-iodouracil)[54] or analogues of phosphodiester bonds have been obtained by the same procedure[56].

A reaction of type (II) has been carried out with the substrates CpG>p, UpG>p, CpI>p, and UpI>p in the presence of a tenfold excess of a nucleoside acceptor (C, U, or A‡). Higher yields were obtained in those cases where the 3′-terminal nucleoside was inosine. In a discussion of the synthesis of oligonucleotides with participation of T1 ribonuclease, mention should be made of the report of Podder and Tinoco[57], who observed that under certain conditions (incubation of G>p with T1 ribonuclease at room temperature) T1 ribonuclease catalyses the formation of 2′–5′ phosphodiester bonds. If this result is not an artifact, it is necessary to ensure a particularly rigorous control of the conditions of synthesis and to analyse carefully the oligonucleotides obtained with participation of ribonucleases§.

Comparison of all three versions of the synthesis of trinucleotides shows that pathway (III) is simplest but is also the most restricted, since it yields only trinucleotides containing two identical nucleosides at the 3′-end of the molecule. Moreover, the reaction mixture contains in this case a considerable amount of monotonic oligonucleotides, which makes their separation difficult. Pathways (I) and (II) both require preformed dinucleotides and in the second case there is an additional requirement of the introduction of a 2′,3′-cyclic phosphate group into the dinucleotide. Therefore we believe that pathway (I) is to be preferred, and, for a more complete utilisation of the acceptor dinucleotide, it is desirable to introduce an excess of the substrate into the reaction mixture. In order to avoid the formation in a side process of a series of monotonic oligonucleotides, it is suggested that substrates with a blocked 5′-OH-group be used[31-33]. The synthesis of oligonucleotides in the presence of ribonucleases using substrates of this type has so far been comparatively thoroughly investigated only at the level of dinucleoside monophosphates[31-35]. In these investigations it has been shown convincingly that 5′-*O*-substituted nucleosides 2′,3′-cyclic phosphates may serve as substrates for pancreatic[31-33], guanyl-[34,35] and non-specific ribonuclease from *Aspergillus clavatus*[33] and that the use of an excess of a 5′-*O*-substituted substrate really does not lead to the formation of a mixture of oligomers[34]. The synthesis of pGpApU and pGpUpU from pG>p and the corresponding acceptor in the presence of T1 ribonuclease has also been briefly reported[42].

As already stated, in the synthesis of trinucleoside diphosphates via pathways (I) and (II), under certain conditions the formation of the oligonucleotide and the cleavage of the 2′,3′-cyclic phosphate group in the substrate may be accompanied by the cleavage of the phosphodiester bond in the acceptor [reaction (I)] or the substrate [reaction (II)], which complicates the composition of the reaction mixture and hinders the preparation of the trinucleotide. To avoid this, Bernfield[20] suggested the use of derivatives of pancreatic ribonuclease with synthetic activity but hydrolytically inactive. Thus, it has been established that S-protein[58], 1-carboxymethylhistidine-119-ribonuclease[59], and ε-dinitrophenyl-lysine-41-ribonuclease[60] exhibit synthetic activity (Table 3) but virtually do not hydrolyse C>p and RNA with a high molecular weight.

In the study of the synthesising activity of these derivatives it was established that the substrates for S-protein may be cytidine and uridine 2′,3′-cyclic phosphates. The optimum pH in the syntheses with participation of S-protein and 1-carboxymethylhistidine-119-ribonuclease proved to be 8.0 and the optimum reaction temperature is 23°C.[20] The synthesising activity of the derivatives is

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‡ In the case of adenosine, a tenfold excess could not be achieved because of the low solubility of adenosine in tris buffer.

§ Later, in a special study Rowe and Smith[71] showed that, under conditions optimum for synthesis, T1 ribonuclease gives rise to the formation of 3′–5′ internucleotide bonds only.

inhibited by lower concentrations of nucleoside 3′-phosphate than in the case of ribonuclease A. The relative initial rates of synthesis for ribonuclease A, S-protein, and 1-carboxymethylhistidine-119-ribonuclease are 100, 21, and 7 respectively. In all cases the dependence of the synthesis on enzyme concentration is linear in the range up to 60 μg ml^{-1}.

Table 3. Depolymerase and synthetic activities of derivatives of ribonuclease A.[20]

Enzyme or derivative	Depolarisation, %	Synthesis, %	Ratio of synthesis to depolymerisation
Ribonuclease A	100	100	1.0
Ribonuclease S	108	103	0.96
S-Protein	5.2	17	3.3
S-Peptide	0	0	0
Carboxymethylhistidine-119-ribonuclease	0.98	5.5	5.6
Ribonuclease inactivated by pepsin	0	0	0
Poly-DL-alanylribonuclease prepared in bicarbonate buffer	10—21	9—22	1
Poly-DL-alanylribonuclease prepared in phosphate buffer	12	14	1.2
ϵ-dinitrophenyl-lysine-41-ribonuclease	4.4	38	8.6

Comparison of the hydrolytic activities of ribonuclease A and S-protein in the reaction mixtures U>p−UpC and C>p−UpC showed that S-protein cleaves UpC 4−5 times more slowly than ribonuclease A and may be used in the synthesis of trinucleotides via pathway (I) using as an acceptor a dinucleotide with a pyrimidine nucleoside at the 5′-end of the molecule[21].

The activities of ribonuclease A and S-protein have also been compared in the reaction with U>p + ApA and C>p + ApA. It has been established that S-protein catalyses the synthesis of UpApA about three times more effectively than ribonuclease A—the reaction is rapid and begins to slow down after 4 h. The yield of UpApA reaches 10% after 48 h.

Thus in the synthesis of trinucleotides via reaction (I) S-protein has certain advantages over ribonuclease A. Bernfield noted[21] that, for a given substrate, the yield of the trinucleotide depends on the nature of the nucleosides at the 3′-end of the acceptor molecule and is low when the cyclic nucleotide and the nucleoside at the 3′-end of the acceptor molecule are complementary (for example, U>p + CpA). The low yields in those cases where the pyrimidine nucleoside is at the 5′-end of the molecule are probably due to the admixtures of ribonuclease in the S-protein.

Evidently the cleavage of the dinucleotide introduced into the reaction may be avoided also by other methods, for example by introducing a blocking group in the 2′-position of the 5′-terminal nucleotide, since it is known that in this case ribonuclease does not cleave the phosphodiester bond. As usual, in the blocking of a particular functional group it is necessary that the blocking group should be readily introduced into the oligonucleotide, should be stable under the conditions of enzymatic synthesis, and should be readily eliminated. However, no studies on these lines have so far been published.

The trinucleotides synthesised with participation of ribonucleases (Table 4) are isolated and identified in the same way as the dinucleotides (see p. 698).

Summarising the discussion of the methods of synthesis of trinucleotides in the presence of ribonucleases, it should be said that in order to obtain trinucleotides of any composition and any sequence of nucleic acid bases, it is necessary to have at one's disposal a set of highly specific ribonucleases (such as guanylribonucleases) or to find conditions under which the preferential synthesising activity of the enzyme will be shown and its hydrolytic activity will be suppressed. Already, using only the known and more or less available ribonucleases or their derivatives, it is possible to synthesise a large number of various trinucleoside diphosphates via pathways (I), (II), or (III), depending on which sequence of nucleic bases it is to be obtained.

Table 4. Trinucleotides synthesised in the presence of ribonucleases.

Substance	Yield, % (reaction)	References	Substance	Yield, % (reaction)	References
CpCpC	10.0 (III)	21	GpCpU	23.0 (I)	25
UpUpU	12.0 (III)	21	GpCpA	14.0 (I)	25
CpCpU	8.0 (III)	21	GpCpI	11.2 (I)	25
CpCpA	2.0 (III)	21	GpCpG	8.3 (I)	25
UpUpC	8.0 (III)	21	IpCpC	20.0 (I)	25
GpUpC	6.5 (I)	24	IpCpU	19.2 (I)	25
	19.2 (I)	22	IpCpA	15.0 (I)	25
GpCpC	27.0 (I)	25	azaGpUpG	2.4 (I)	25
IpCpI	7.1 (I)	25	azaGpApC	6.5 (I)	25
IpCpG	6.8 (I)	25	azaGpApU	2.5 (I)	25
GpUpU	18.0 (I)	25	XpUpU	7.0 (I)	25
GpUpA	8.4 (I)	25	XpApC	2.2 (I)	25
GpUpI	5.2 (I)	25	**GpCp8azaG**	3.7 (I)	41
GpUpG	4.1 (I)	25	**GpUp8azaG**	1.3 (I)	41
GpApC	8.2 (I)	25	aza GpUp aza G	1.0 (I)	41
GpApU	6.0 (I)	25	CpGpC	8.0 (II)	25
IpUpC	16.9 (I)	25	CpGpU	7.8 (II)	25
IpUpU	17.0 (I)	25	CpGpA	2.9 (II)	25
IpUpA	7.5 (I)	25	CpIpC	23.0 (II)	25
IpUpI	4.1 (I)	25	CpIpU	12.0 (II)	25
IpUpG	3.2 (I)	25	UpGpC	6.0 (II)	25
IpApC	7.0 (I)	25	UpGpU	3.1 (II)	25
IpApU	5.0 (I)	25	UpIpC	17.0 (II)	25
azaGpCpC	8.2 (I)	25	UpIpU	14.5 (II)	25
azaGpCpU	7.0 (I)	25	UpIpA	2.3 (II)	25
azaGpCpA	5.0 (I)	25	CpazaGpU	2.2 (II)	41
azaGpCpG	3.0 (I)	25			
azaGpUpC	8.5 (I)	25			
azaGpUpU	8.0 (I)	25			
azaGpUpA	5.0 (I)	25			

Table 5. Trinucleoside diphosphates synthesised in the presence of S-protein[21].

Substance	Yield, %	Substance	Yield, %
CpApA	8.0	UpCpU	5.0
UpApA	5.0	CpGpA	8.0
CpApC	10.0	UpGpA	6.0
UpApC	7.0	CpUpC	2.0
CpApG	4.0	CpUpG	2.0
UpApG	6.0	CpUpU	5.0
UpCpC	4.0		

Evidently, by combining any of the methods and approaches under discussion, it is possible to synthesise in the presence of ribonucleases also longer oligonucleotides, although the experimental data concerning such syntheses are still unavailable, apart from the reports of the formation of tetranucleotides and longer oligonucleotides by incubating an excess of the substrate with pancreatic ribonuclease[17,20].

After the present review had been sent to the editors, a paper was published by Mohr and Tach[69] in which they report the synthesis of 8 tetranucleotides (ApUpGpU, ApUpGpC, ApUpGpA, ApApGpU, ApUpGpUp, ApUpGpCp, and ApUpGpAp) in yields of 5–37%, 5 pentanucleotides (ApUpGpCpC, ApUpGpUpC, ApUpGpApA, ApUpGpApC, and ApUpGpApU) in yields of 11–25%, 3 hexanucleotides (ApUpGpApApA, ApUpGpApUpG, and ApUpGpUpUpUp) in yields of 8–15%, 2 heptanucleotides (ApUpGpApApApA and ApApApGpApApA) in 5% yields, and 1 octanucleotide ApUpGpApApApApA in 3% yield from oligonucleotide donors and acceptors in the presence of guanyl-specific T1 ribonuclease.

III. SYNTHESIS OF OLIGORIBONUCLEOTIDES USING POLYNUCLEOTIDE PHOSPHORYLASE

The possibility of adding one or more nucleotide residues from a nucleoside 5′-diphosphate to a preformed oligonucleotide in the presence of polynucleotide phosphorylase from *Micrococcus lysodeicticus* was first demonstrated by Singer et al.[62], who obtained and characterised nucleotides such as pApApApU and pApApApGpG.

Table 6. Trinucleoside diphosphates synthesised in the presence of polynucleotide phosphorylase from *Micrococcus lysodeicticus*[63].

Substrates for synthesis			
Dinucleoside monophosphate	Nucleoside diphosphate	Trinucleoside diphosphate	Yield, %
ApA	ppC	ApApC	6.0
ApA	ppG	ApApG	12.0
ApA	ppU	ApApU	32.0
ApU	ppC	ApUpC	6.0
ApU	ppG	ApUpG	4.0
ApU	ppU	ApUpU	15.0
ApC	ppG	ApCpG	3.0
ApG	ppC	ApGpC	21.0
ApC	ppU	ApCpU	12.0
ApG	ppU	ApGpU	27.0
ApG	ppA	ApGpA	13.0
GpA	ppU	GpApU	14.0
UpA	ppU	UpApU	5.0
GpC	ppU	GpCpU	6.0

Leder et al.[63] suggested that trinucleoside diphosphates be synthesised by the addition of a nucleotide residue from a nucleoside 5′-diphosphate to a dinucleoside monophosphate according to the following mechanism

$$\mathrm{N'pN''} + \mathrm{ppN} \xrightarrow{\text{polynucleotide phosphorylase}} \mathrm{N'pN''pN} + \mathrm{P}_i\ ,$$

where ppN is a nucleoside 5′-diphosphate, N′pN″ a dinucleoside monophosphate, and P_i inorganic phosphate. This method may be used for the synthesis of oligonucleotides with any sequence of monomeric units. The reaction was carried out by incubating the substrates with an enzyme at 37°C for 2 h. The trinucleoside diphosphates were isolated from the reaction mixture by paper chromatography and paper electrophoresis. The trinucleoside diphosphates synthesised in this way are listed in Table 6.

The data in Table 6 show that the yields of trinucleoside diphosphates vary from 3 to 30%, depending, according to the authors, on several factors. Thus, at a high concentration of nucleoside 5′-diphosphate, polynucleotides with a long chain (10 or more units) accumulate and shorter oligonucleotides are not formed. Such tendency towards the formation of polynucleotides with a large number of units is particularly typical for adenosine 5′-diphosphate and less so for cytidine 5′-diphosphate. However, even under the most favourable conditions, tetra-, penta-, hexa-, and hepta-nucleotides are formed in addition to the trinucleoside diphosphate. The yield of trinucleotide depends also on the nature of the nucleoside 5′-diphosphate: uridine 5′-diphosphate gives the highest yield. In those cases where the substrates used in the synthesis contain complementary bases, the yield of trinucleotide may be improved by heating the reaction mixture to 70°C before adding the enzyme.

This method was subsequently used for preparative purposes[64]. After incubating for 12 h, the reaction is stopped by adding alkaline phosphatase and the reaction mixture is separated on a column with DEAE cellulose with subsequent purification of the oligonucleotide fractions by paper chromatography. The yields of trinucleoside diphosphates were 5–40% in relation to the initial dinucleoside monophosphate.

An advantage of the method consists in the fact that polynucleotide phosphorylase does not cleave dinucleoside monophosphates[66] and therefore, on the one hand, there can be no rearrangement of the nucleotide sequence in the dinucleoside monophosphate as a result of cleavage and resynthesis and, on the other hand, dinucleoside monophosphates may be regenerated. As already mentioned, a disadvantage of the method is the fact that the reaction mixture contains, together with the trinucleoside diphosphate, also longer oligonucleotides, which reduces the yield of the trinucleoside diphosphate and hinders its isolation.

Comparison of the method of synthesis of oligonucleotides in the presence of polynucleotide phosphorylase with methods based on the application of various ribonucleases shows that both types of method have their advantages and disadvantages; bearing these in mind, the procedures must be regarded as fully of equal value in the stage involving the preparation of oligonucleotides longer than dinucleotides and may be used depending on which substrates and which enzyme are more available in each particular situation. In the synthesis of dinucleotides only the "ribonuclease method" may be employed.

The data discussed above suggest that the methods of synthesis of oligonucleotides based on the use of enzymes, particularly ribonucleases, are more advantageous and therefore more promising than chemical methods. The principal advantages of enzymatic methods are as follows: the relative availability of the initial components (substrates and acceptors), the elimination of the need to block reversibly the "superfluous" functional groups of these components and hence a significant shortening of the time required for the synthesis, the simplicity of separation of the reaction mixture, and in the majority of cases a higher yield of the oligonucleotide.

Further development and propagation of these methods should be accompanied by an increase in the number of enzymes with suitable catalytic properties and also by the development of methods necessary for the rapid and simple separation of large amounts of reaction mixtures. Special mention should be made of the necessity to seek analogous approaches to the synthesis of oligodeoxyribonucleotides, which will significantly extend the scope of enzymatic methods for the stepwise synthesis of the $C_{(3')}-C_{(5')}$ bond between specific nucleotides.

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Institute of Biological Physics,
USSR Academy of Sciences,
Pushchino on Oka

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Effect of a Solid Surface on Relaxation and Structure-formation Processes in Polymer Layers Adjoining the Walls

Yu.M.Malinskii

Data on the characteristic properties, in particular crystallisation properties, of low-molecular substances in layers adjoining the walls are briefly discussed. The methods for and the results of the determinations of the thickness of wall layers of solutions and melts of many polymers are quoted. Data on the effect of a solid surface on the rate of relaxation processes and the properties of the polymers due to them are reviewed.

The effect of artificial nucleating agents on the structure (and properties) pf polymers, the suppression of structure formation in thin layers in certain systems, and epitaxy are discussed.

The experimental data presented are treated from the standpoint of the hypothesis of the packet structure of polymers and the effect of the interaction between the solid surface and the polymer on the enthalpy and entropy of the system.

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CONTENTS

1. INTRODUCTION

The specific features of thin layers of polymers (1 – 20 μm thick) in contact with a solid surface have increasingly attracted the attention of investigators in recent years. The physicochemical foundations of recipes for and the technology of the processing and applications of filled polymeric materials, adhesives, and paint and varnish coatings would be impossible without an understanding of the structural characteristics of such layers and their behaviour under conditions of use.

As early as 1935–1936, Rebinder related the effectiveness of the filler to the fraction of the polymer, which, as a result of adsorption interaction with the filler surface, passes into a "special film state" with enhanced mechanical properties[1,2].

In recent years, particularly in the last decade, numerous observations have accumulated, showing that surface layers of the polymer (or layers adjoining the walls), arising when it comes into contact with another (particularly solid) phase, differ in structure and properties from the polymer at a fairly large distance from the phase boundary, and have a thickness, which sometimes reaches many micrometres.

A chemically inert solid surface acts on the surface layers of polymers (and low-molecular substances) via intermolecular attraction and repulsion forces; these forces are responsible for adsorption interaction between the system components and for the purely geometrical restriction on the space available for migration by the kinetic units of the substance in the wall layer.

The unusual properties of the structure of surface layers are a consequence not only of the interaction between the atoms and molecules of the solid and the polymer layer located directly on its surface but also on the transmission of this interaction (more precisely its results) from the layers nearest to the surface to more remote layers. The effect of one phase on another via an interface theoretically extends throughout the entire bulk of the phase and on moving away from the phase boundary, the value of a property of the phase approaches asymptotically the value characteristic of the phase in the absence of such influence[3]. Therefore, the thickness of the wall layers determined in any experiment is only an effective thickness characterising the behaviour of the system under the conditions of the given experiment; the effective thickness varies with the property investigated and the sensitivity of the method employed. The gigantic size of polymer molecules and the presence of supermolecular formations results in a much greater thickness of wall layers in polymers than in low-molecular substances. This fact is of great practical importance in the study of wall layers of polymer systems.

In the vast majority of investigations which have been made, the surface layers of polymers were examined not by direct study of the layers themselves but by studying the properties of complex systems in which the behaviour of certain polymer layers plays a significant role. Quantitative relations governing the effect of an extraneous surface on the structure and properties of a polymer wall layer are not as yet available and qualitative generalisations have been made only concerning certain aspects. The results obtained by different investigators are sometimes contradictory and the reasons for such contradictions are not always clear.

In the present paper an attempt is made to describe the available literature data on the principal properties of polymer wall layers from the standpoints of the energy and geometrical effects of the solid surface on a structured (in packets or crystallites) polymer.

2. PROPERTIES OF WALL LAYERS OF LOW-MOLECULAR SUBSTANCES

In a series of investigations Deryagin and coworkers showed that the wall layers of a number of low-molecular liquids under the influence of the surface forces of the solid acquire properties different from those of the bulk-phase liquid. Thus it was found[4] that the elasticity of water in a layer adjoining a glass surface becomes equal to that of the bulk-phase water only at a distance of about 0.07 μm and the shear elasticities of wall layers of water, acetone, hexanol, and octanol on quartz are about a factor of ten higher than the bulk-phase values[5]. In the thin pores (diameter about 0.01 μm) of amorphous silica water does not exhibit the anomalous thermal expansion (in the range 0−36°C)[6]; similar results were obtained in studies on the behaviour of water in glass capiliaries[7,8] and in carbon pores[9]. The heat capacity of nitrobenzene mixed with a glass powder (activated by treatment in a glow discharge), where the average thickness of nitrobenzene layers was 0.2−0.3 μm, was lower than the bulk-phase value approximately by 10%[†].

Purified mineral oils in a gap between steel surfaces begin to exhibit boundary mechanical properties when the gap thickness is less than 0.3 μm and in gaps 0.1 μm thick, the layer begins to show elastic properties[11].

The unusual properties of liquids in wall layers are caused not only by direct interaction with the surface of another phase but, at least in the majority of cases, by the orientation of molecules in this layer. One may refer, as examples, to the orientation, demonstrated by electron diffraction, in thin films of certain straight-chain hydrocarbons on copper, rock salt, and glass[12] and of lubricating oil (mixtures of saturated and unsaturated hydrocarbons) on a number of metals and alloys[13]; the electron diffraction patterns of the surface layer of the mercury meniscus (at the boundary with air) also show a distinct texture[14].

The effect of the solid surface on the structure and mobility of the wall layer of a liquid cannot fail to influence also its crystallisation. Indeed, in the crystallisation of piperine[15] and betol[16] in a layer with a thickness of several tenths of a millimetre between glass surfaces and also in the case of piperine between mica surfaces, the curves for the temperature variation of the rate of nucleation show two maxima. The authors of these investigations attribute the low-temperature maximum (at a distance of several degrees from the high-temperature maximum) to the effect of the solid surface, in the vicinity of which the molecules of the liquid are in a more ordered state than in deeper layers. The curves relating the rate of nucleus formation in betol to the distance from the surface of glass show a maximum, the effect of the surface extending over a distance of the order of several micrometres[17]. Brief treatment of glass surfaces with hydrogen fluoride, coating of the surface with a thin layer of lactic acid[17], and the application of a magnetic field[18] weaken the effect of the surface on the rate of nucleation while coating of the surface with a layer of collodion (10 μm thick) completely eliminates the surface effect[17][‡].

The results of many investigations demonstrate the dependence of the structure of thin metallic films, obtained by vacuum deposition on a solid support, on their thickness. Under certain experimental conditions, silver telluride (Ag_2Te) films with a thickness less than 300−350 Å are structureless, in films with a thickness of between 350 and 700 Å spherulites 100 μm and above in diameter are formed, while in still thicker layers the spherulite structure is gradually suppressed by microcrystals growing in increasing numbers[19]. Beryllium, vanadium, nickel, chromium, and cobalt films give rise to electron diffraction patterns which coincide with those of the massive specimens only when the thickness is in excess of 70−80 Å; for smaller thicknesses, the diffraction patterns show additional lines and when the thickness is 20−30 Å only diffuse rings are seen[20]. In silver films 40−50 Å thick two phases coexist at room temperature—a face-centred cubic phase and a hexagonal phase, while in thicker films (of the order of 100 Å) the hexagonal modification is unstable[21].

The above data by no means exhaust the abundance of observations on the properties of wall or surface layers of low-molecular substances and are quoted only to assist the reader gain an idea about the general occurrence of the phenomena under discussion for both high-molecular and low-molecular substances. Extensive evidence concerning the unusual properties of the wall layers of low-molecular liquids is presented in a detailed review by Henniker[22].

3. THE THICKNESS OF POLYMER WALL LAYERS AND METHODS FOR ITS DETERMINATION

Recently Kargin and coworkers demonstrated the possibility of forming large supermolecular polymer species in dilute solutions. In solutions of poly-α-butylene ($M = 180\,000$) in rosin at a concentration of 0.1% and above supermolecular species with a length of the order of 1 μm were observed[23], while in solutions of the same polymer in propane species with a length of several tenths of a micrometre were observed at concentrations as low as 0.05%[24]; in solutions of atactic polypropylene ($M = 35\,000$) in propane at concentrations as low as 0.2% particles with dimensions of the order of a micrometer were found[25].

So far it has not proved possible to observe directly supermolecular formations in polymer melts but there is much reliable evidence for their existence. This includes electron diffraction data showing the presence of a high degree of order in the distribution of polymeric molecules in the melt[26,27], results of studies on the sorption properties of polymers above their melting points[28], certain rheological characteristics of melts[29-34], the retention of the steric distribution of the spherulite centres after repeated fusion[35], and the high rate of crystallisation of melts[36].

The existence in melts and solutions of polymers of supermolecular formations must inevitably result in high-molecular substances having much thicker wall layers (with properties differing from those in the bulk-phase) than low-molecular compounds.

We shall examine briefly the methods used to determine the thickness of the wall layers of polymers in systems comprising a polymer solution or melt and a solid surface. Various methods for the determination of the weight of the polymer adsorbed on the surface from its solution are widely employed. Since these methods have been widely discussed in a review by Patat et al.[37], we shall not deal with them.

Viscometry

Viscometric methods are simplest; with their aid, it is possible to determine the effective change in capillary

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[†] We restrict the review of the work of Deryagin's school to the publications quoted above, which contain the bibliography of other papers by this school on the properties of the wall layers of low-molecular liquids.

[‡] In the publications quoted above[15-18] there is a bibliography of other investigations at Odessa University on the effect of surface on the crystallisation of low-molecular organic liquids.

diameter caused by the appearance of an adsorbed layer[38-42] or in the dimensions of adsorbent particles suspended in a solution or melt of the polymer[43-48].

Öhrn[38] measured the flow times of a polymer solution using a viscometer with two parallel capillaries of different diameters (0.5 and 0.2 mm). The following considerations were employed to calculate the effective thickness of the adsorbed layer. If, for a capillary with a radius r and a thickness of the adsorbed layer δ, the apparent (observed) relative viscosity of the solution is denoted by η^*_{rel}, the true relative viscosity of the solution $\eta_{\text{rel}} = \eta_{\text{soln}}/\eta_{\text{solvent}}$ is given by

$$\eta_{\text{rel}} = \eta^*_{\text{rel}} \left(\frac{r-\delta}{r}\right)^4 = \eta^*_{\text{rel}} \left(1 - \frac{4\delta}{2}\right) + \cdots$$

We shall retain only the first term in the expansion and, on converting to the viscosity number (term recommended by IUPAC), we obtain the expression

$$\eta^*_{\text{sp}}/c = \eta_{\text{sp}}/c + (\eta_{\text{rel}}/c)(4\delta/r) \ .$$

If we assume that for a given concentration the effective thickness of the adsorbed layer δ is independent of the dimensions of the capiliary§, then δ may be calculated from the slope of the linear plot of η^*_{sp}/c against $1/r$.

The thickness of the adsorbed layer may be calculated also directly from the flow times of the solution in two capillaries of different diameters[40], and from the formula[42]

$$\delta = \frac{r\,\Delta t}{4t} \quad ,$$

where r is the capillary radius, t the flow time of the solvent until the viscometer is filled by the test solution, and $t + \Delta t$ the flow time of the solvent after the viscometer had been used for the test solution and then washed with the solvent. The thickness of the adsorbed layer obtained by the last method is probably somewhat too low, since it is very likely that part of the adsorbed polymer is removed from the walls of the capillary when it is washed.

In the determination of the thickness of the adsorbed layer from the change in the dimensions of adsorbent particles suspended in a liquid, measurements were made either of the viscosity of such a system using the Einstein equation[43,45-49] or the rate of sedimentation of the particles[44]. The familiar Einstein equation for the viscosity of suspensions of rigid spherical particles in a Newtonian liquid[50,51] is of the form

$$\eta = \eta_0 (1 + K\varphi) \ ,$$

where η is the viscosity of the suspension, η_0 the viscosity of the pure liquid, φ the volume fraction of the particles, and K a constant. If the particles are spherical and the liquid merely wets them, then $K = 2.5$. When an adsorbed layer is formed on the particles of the suspension, their effective volume increases and the viscosity of the system is described by the Einstein equation in which K (in this case the constant may be denoted by K_{eff}) is greater than 2.5. When the form of the particle deviates from the spherical, K also proves to be greater than 2.5. If this deviation is slight, the value of K characteristic of particles of a given form (it will be denoted by K_0) may be determined by measuring the viscosity of the suspensions in a suitable low-molecular liquid (transformer oil, for example, has been used for this purpose[48]).

Knowing the particle diameter d and the experimental values of K_0 and K_{eff}, it is easy to calculate[47] the thickness of the adsorbed layer δ:

$$\delta = \frac{d}{2}\left(\sqrt[3]{\frac{K_{\text{eff}}}{K_0}} - 1\right) .$$

If a polydisperse absorbent with a specific surface S_{sp} is used, then, having calculated the effective increase of its volume in the suspension per unit weight ($\Delta\varphi_{\text{eff}}$) due to adsorption, it is possible to calculate also the thickness of the layer $\delta = \Delta\varphi_{\text{eff}}/S_{\text{sp}}$. An advantage of this method is the possibility of applying it in studies on concentrated solutions and polymer melts; the measurements must be made for low values of φ and under conditions ensuring Newtonian behaviour of the system.

The following two methods for the determination of the thickness of the wall layer based on its enhanced viscosity may also be included among viscometric methods. The dependence of the viscosity of polymer wall layers on the distance from the solid surface has been investigated by the so called "blowing off" method[52]. The essential features of this method have been described in detail in a number of papers[53-55] and are as follows. A jet of air directed onto a slit between two flat surfaces containing the liquid produces a tangential force causing the profile of the film to assume a definite form reflecting the property investigated. The steepness of the film profile at each point is proportional to the viscosity of the liquid at the corresponding distance from the surface. If the viscosity is independent of the distance from the surface, then the profile of the wedge-shaped film is linear; the increase of viscosity on approaching the surface leads to the "blunting" of the wedge. The steepness of the profile can be comparatively simply determined from the distance between the interference bands obtained on illuminating the film with monochromatic light.

Tsvetkov et al.[56] employed in the investigation of polymers a previously developed method[13,57] for the determination of the thickness of the boundary layer in low-molecular liquids. The essential feature of the method consists in the study of the variation with time of the thickness of a layer of the liquid between the parallel plates of a planar plastometer compressed by a constant force. Extrapolation of the relation to infinite times permits the estimation of the thickness of this rigid "non-fluid" layer, which may be regarded as the wall layer. It has been shown for low-molecular liquids[13,57] that the thickness of this layer depends on the pressure on the plates of the plastometer, the nature of the liquid and of the surface of the plates, and the experimental temperature. There is no doubt that these factors influence also the thickness of the polymer layer. However, one may question the validity of the extrapolation of data obtained over a period of 15 min for the highly viscous polymer melts of the kind investigated by Tsvetkov[56].

Ellipsometry

Ellipsometry is a satisfactory method permitting the measurement of the thickness of the adsorbed layer with an accuracy of several ångstroms. This procedure uses the fact that the formation of a film on the solid surface influences the optical properties of the latter—there is a change in the phase difference and the amplitude ratios of the components of the elliptically polarised light reflected

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§ The velocity gradient in both capillaries of Öhrn's viscometer was the same and $r \gg \delta$.

from it. The accuracy of this method is considerably reduced if the refractive indices of the film and the solution adjoining it are similar. A method has been described for the calculation (using computers) of the thickness of adsorbed films of low-molecular and polymeric substances from data obtained with the aid of an ellipsometer[58,59]. To improve the precision of the measurements, the incident beam was reflected three times from the test surfaces. Ellipsometry has been used to investigate adsorption from dilute polymer solutions[58–61]; the use of this method to investigate adsorption from polymer melts would be of great interest.

The somewhat arbitrary nature of the ellipsometric values obtained for the thickness of the wall layer is a consequence not only of the fact that these values, as in measurements by any other method, constitute merely effective quantities but also because in the calculation it is necessary to take into account the refractive index (and hence the density) gradient within the layer. In the first studies by Stromberg and coworkers[58–60] the simplest hypothesis was adopted, namely that the adsorbed film is homogeneous and that the refractive index gradient within the layer is zero. Subsequently[61] in the calculation of the thickness it was also postulated that the density gradient is exponential. The refractive index gradient in the film is at present unknown; statistical calculations show that, even for the simplest model (an isolated macromolecule of finite[62] and infinite length[63]), there is a fairly complex relation between the density of the adsorbed layer and the distance from the surface of the support, the relation being influenced by the rigidity of the chain and the adsorption energy.

Table 1. Thicknesses of polymer wall layers in various systems.

Polymer; 10^{-5} mol. wt.	Soln. concn., g litre^{-1}	Thickness of wall layer, μm	Methods for determination of layer thickness	References
Polystyrene				
4—6.2	0.2—2.0	0.08—0.25[a]	viscometric	38, 39
0.6—14	not indicated[b]	0.01—0.07[a]	ditto	47
0.8	0.18	~0.008	ellipsometric	59
0.8	2—9.7	~0.02	ditto	59
5.4—33	1—2	0.04—0.09	”	61
2.9	up to 10	up to 0.001[c]	from weight of adsorbed layer	67, 68
6	6.6—25.7	0.087—0.5[a,d]	ditto	69
Not indicated[e]	20	0.3	viscometry of suspensions	48
Not indicated	1.6—14	0.03—1[a,d,f]	from weight of adsorbed layer	70, 71
4.4 and above	melt; 227° melt; 296°	7—9 ~2	extrapolation of distance between plates of plastometer	56
Poly(vinyl acetate)				
8.8	0.11—0.18	0.47—0.66	viscometric	40
0.8—12	not indicated	0.01—0.09	ditto	41, 47
0.45—9	0.35—2.0	0.025—0.074[g]	from weight of adsorbed layer	72; 73
7.7	not indicated	0.15[d]	ditto	75
7.7	2.7—31.0	0.06—0.72[a,d]	”	69
0.32	80	2[r]	”	66
Poly(methyl methacrylate)				
0.75—66	not indicated	0.01—0.4[h]	viscometric	47, 74
0.44—15	3.3—56.2	0.048—0.72[d]	from weight of adsorbed layer	69, 75
Not indicated	0.3—13.1	0.02—0.76[d,f]	ditto	70, 71
Poly(lauryl methacrylate) 3.3 or 11.9	not indicated	0.0025	from measurement of of rate of sedimentation	44
Copolymer of stearyl methacrylate and *N*-vinyl-2-pyrrolidinone (5 : 1)	not indicated	0.021	ditto	44
Polyvinylpyrrolidinone 6	18	0.75[d]	from weight of adsorbed layer	69, 75
Poly(vinyl chloride) 0.7-0.8	0.01—0.5	0.14—0.33	viscometric	76
Poly(vinyl alcohol)				
Not indicated	not indicated	1.2[d]	from weight of adsorbed layer	75
Polyisoprene 0.22-0.32	70	>2.7[d]	ditto	66
Guttapercha	20—40	0.9—3.6	viscometry of suspension	48
Ditto	melt; 75°	3.2—8[i]	ditto	48
Butadiene-styrene (GR=S)	0.1—0.2	0.015—0.010	”	43
Poly(ethylene glycol) 0.3	90	>3[d]	from weight of adsorbed layer	66
Poly(butyl vinyl ether) 0.006	melt	>5[k]	“blowing off” of film	52
	ditto	up to 18[l]	ditto	52
Poly(neopentyl phthalate) 0.02	0.1—10	0.0004—0.0035[c]	from weight of adsorbed layer	77
Polyepoxide [from 4,4′-bisglycidylphenyl-2,2′-propane and hexane-1,6-diamine]	filled system	0.05—0.15	from sorption of solvent vapour	64, 78
Cellulose trinitrate 22	0.005—0.12	0.05—0.1	viscometric	42

a. This range of thicknesses includes results obtained using various solvents.

b. Concentration not indicated in the paper; however, there is no doubt that the behaviour of dilute solutions was investigated.

c. The thicknesses are much too low, since in the calculations the authors assumed that the entire surface of the sorbent (carbon black, titanium dioxide, etc.), determined from the extent of adsorption of nitrogen, is available for the adsorption of the polymer and the density of the adsorbed layer is equal to that of the solid polymer.

d. Thickness of the layer estimated assuming that its density does not differ from that of the solid polymer; this method of estimation yields low results.

e. Isotactic polymer.

f. This range of thicknesses includes results obtained at different temperatures.

g. The layer thickness was estimated by the present author from the weight adsorbed per unit surface area of the adsorbent using[40] 0.17 g ml^{-1} as the density of the layer.

h. It has been stated[74] that the layer thickness fails with increasing concentration of the solution; this range of thicknesses includes the results obtained by extrapolation to zero concentration.

i. The layer thickness decreases with increasing shear stress.

j. From the difference between the viscosities of the wall layer and the bulk-phase polymer.

k. From the zone corresponding to the breakdown of interference bands.

Sorption

An unusual method for estimating the thickness of polymer layer immobilised by the surface of a filler is based on the extent of sorption of the solvent vapour by the filled system at a temperature greater than T_g for the polymer[64]. In the calculation it was assumed that at the experimental temperature the immobilised polymer layer sorbs like the initial polymer in the vitreous state and the remaining polymer in the filled system does not differ in its sorption capacity from the unfilled polymer; it was also assumed that, for low vapour pressures, sorption by the vitreous polymer may be neglected. It is noteworthy that these assumptions lower the thickness of the immobilised layer.

Table 1 presents data for the thicknesses of the wall layers of various polymer – solid surface systems obtained by different methods. A striking feature of the results in Table 1 is their considerable scatter, which is due primarily to the different concentrations of the polymers in the systems to which the particular data refer. Layer thicknesses of the order of tenths and hundredths of a micrometer occur in dilute polymer solutions at concentrations ranging from a fraction of a gramme to several grammes per litre; in all cases where melts were investigated the thickness of the wall layer amounted to several micrometers. It is appropriate to mention here that, in the determination of the extent of adsorption of the polymer from solution over a wide range of concentrations, saturation was not observed with increase in concentration[65,66]. The thickness of the wall layer depends not only on the concentration of the solution, the nature of the solid surface, the molecular weight, and the nature of the polymer and solvent (if it is present in the system) but also on experimental conditions such as temperature, pressure, shear stress and shear velocity, and the method used to determine it (see above, p. 704). It may be supposed that in those cases where the thickness of the wall layer of the polymer is comparable to the dimensions of the solid particles round which the layer is formed (for example in systems with a highly dispersed filler), the thickness of the layer is directly related to the particle diameter.

Table 1 shows also the extreme paucity of information at present available about the thickness of the wall layer in polymer melts.

4. CHARACTERISTICS OF RELAXATION PROCESSES IN POLYMER WALL LAYERS

A solid surface in contact with a polymer can influence the wall layer via two mechanisms¶: as a result of a purely steric effect—by restricting the volume occupied by the units of the macromolecule and the larger kinetic units during their thermal motion, and as a result of an energy effect—by bonding via an intermolecular interaction directly to certain units of the macromolecules adjacent to the surface, via chemical bonding to macromolecules comprising these units, and via intermolecular bonding to supermolecular formations (naturally not only those of which such molecules are constituent parts but also the adjacent formations). As a result, the majority of the relaxation processes in the wall layer are slower than in the bulk of the polymer.

The data on the relaxation times and activation energies for isothermal compression obtained in the study of the unfilled systems poly(methyl methacrylate) – nitron or fibre glass and polystyrene – quartz or nitron lead to the conclusion that in these systems the principal factor responsible for the reduced mobility of the structural units in the polymer wall layers is the decrease of the number of possible conformations of the macromolecules and not their energy interaction with the surface[84]. However, it may be supposed that in certain other systems this energy factor will predominate. The reduced mobility in polymer wall layers is associated with the expansion of the relaxation spectrum towards longer times[85-87].

Effect of the Solid Surface on the Packing Density and Orientation in Wall Layers

The lack of correspondence between the steric disposition of the centres of intermolecular interactions on the solid surface on the one hand and in the polymer on the other, which usually obtains, leads to a lowering of the packing density of the polymer in its wall layers compared with bulk phase. The results of sorption measurements[84,88-90], direct determinations of the deviation of the density of the mixture from addivity[84,88,91,92], and the increase in the coefficient of volume expansion on filling[93] indicate a loosening of the polymer bulk phase in the systems poly(vinyl acetate)[92] and vinyl acetate-vinyl chloride copolymer[88] – titanium dioxide, polystyrene and poly(methyl methacrylate) – fibre glass[89] or quartz powder[84,93], isotactic polypropylene – glass powder[90], and natural rubber – zinc oxide[91] †. The increase of the rate of dissolution of small particles of dye in the melt of isotactic polypropylene on increasing the distance between such a particle and a glass surface, starting with a distance of 30 μm, observed in our experiments[90], also confirms that the density of the polymer in the wall layer is reduced.

A solid surface interacting fairly strongly with the polymer can orient to some extent its molecules and supermolecular formations in the wall layer. In the limiting case this orientation leads to epitaxy‡, which will be considered in the next section. It has been established by electron diffraction that guttapercha is oriented on aluminium[94]; Kozlov et al.[95] concluded, on the basis of studies of the strength, swelling, and contraction of films of cellulose ethers on the surface of glass that the orientation of such films is planar. Calculation, based on data for the sorption of water showed that, when a polyepoxide [from 4,4′-bisglycidylphenyl-2,2′-propane and hexane-1,6-diamine] is filled with titanium dioxide (arutile modification with an average particle size of 0.2 μm), there is a

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¶ We are not discussing here the chemical interaction between the polymer and the material with which it is in contact nor the effect of the solid surface on polymerisation, polycondensation, and cross-linking processes, which have been described in a number of publications[79-83].

† The observed[92] decrease of the coefficient of volume expansion of poly(vinyl acetate) at 40°C (slightly above the glass point T_g) as a result of the introduction of 12.1% of titanium dioxide is not inconsistent with the hypothesis that the density of the polymer decreases on filling. If at a temperature below T_g the free volume of a filled polymer is significantly greater than that of an unfilled polymer, then, despite the decrease of the coefficient of volume expansion, there is a certain range of temperatures fairly close to T_g where the free volume of the filled polymer will still remain higher than that of the unfilled polymer.

‡ Epitaxy is the formation at the boundaries of the crystals of one substance of oriented crystals of another.

decrease of the free energy and enthalpy (by 2 cal g^{-1}) and of entropy (by 5×10^{-3} cal g^{-1} deg^{-1}) of the polymer, which also indicates some ordering of the latter[78].

The conclusion that the configurational entropy of poly(vinyl acetate) may increase when it is filled with titanium dioxide was also based[92] on a considerable (almost by a factor of 2) decrease of the activation energy for the diffusion of oxygen and argon (at temperatures above T_g) on filling.

The orientation obtained when the polymer is extended may lead to both an increase and a decrease of the packing density of the polymeric molecules[96,97]. By analogy, we must suppose that the orienting effect of the solid surface on the polymer can also lead either to an increase or a decrease of the packing density of the wall layer. Since the molecular attractive forces of the solid act not only on the nearest layer of units of the macromolecules but also on the more remote layers, an enhancement of the interaction between the polymer and the solid surface should favour an increase in packing density; more favourable conditions for relaxation have a similar effect. It can also be supposed that in certain cases filling leads to an increase in the packing density of the polymer at temperatures above T_g, but lowers it below T_g. Indeed, it has been established in a number of studies that above T_g the swelling of the polymer or the sorption of water vapour decrease on filling. This has been observed in the study of the systems natural rubber or polyisobutylene – colloidal nickel or cobalt[98], natural rubber – carbon black[99], poly(vinyl acetate) or polyepoxide – titanium dioxide or copper-phthalocyanine[64], and gelatine – glass[100] (in the last case gelatine sorbed such an amount of water long before the attainment of equilibrium swelling that T_g fell considerably below the experimental temperature).

The packing density of the wall layer can also be influenced by the conditions of its formation. Thus it has been shown[101] that, when a mixture of poly(methyl methacrylate) or polystyrene with a glass powder is obtained from solutions in different solvents (by evaporating the solvent), then, as a rule, with enhanced thermodynamic effectiveness of the solvent (estimated from the second virial coefficient of the osmotic pressure), the packing density of the polymer falls and the capacity for swelling increases correspondingly. This is due to the fact that in thermodynamically more effective solvents the macromolecules are in more extended conformation than in less effective solvents and it has been established by electron microscopy[102] that the initial conformation of the polymeric chains influences their interaction with the solid surface. It has also been observed[99] that the introduction of carbon black into a solution of natural rubber with subsequent evaporation of the solvent yields a mixture which swells much less than the mixture obtained by rolling. It is interesting to note that, after standing at room temperature, the density and degree of ordering of rubber in the mixture increase in the first tens of minutes after the termination of rolling (as shown by the decrease of the capacity for swelling).

Effect of the Solid Surface on Relaxation Processes in Wall Layers

The solid surface, which interacts with polymers and restricts by its steric effect the mobility of the macromolecules and supermolecular structural elements (as already mentioned above), retards the relaxation processes in the wall layer. The decrease in packing density in the polymer wall layer (which occurs at temperatures below T_g) has the opposite effect on relaxation processes, accelerating them[103-105]. The opposing effects of these factors which act simultaneously (the packing density also depends on the polymer – solid surface interaction) greatly complicates the observed situation.

The study of the temperature variation of the tangent of the dielectric loss angle of poly(methyl methacrylate) ($M \simeq 8 \times 10^4$) and polystyrene ($M \simeq 8 \times 10^5$) filled with a quartz powder having a particle diameter of about 4 μm showed[86] that filling (up to 24 vol.%—average distance between particles 4 μm) hardly affects the temperature of the maximum dipole – elastic losses in poly(methyl methacrylate) and greatly increases this temperature in polystyrene; at the same time the temperature of the maximum of the dipole – radical losses for [poly(methyl methacrylate)] falls. These results apparently contradict the dilatometric data showing a considerable increase of T_g for poly(methyl methacrylate) ($M_{visc} \simeq 3 \times 10^4$ and 6×10^6) filled by the same quartz powder[93], according to which the introduction of 30 wt.% of quartz increases T_g by 24°C. These findings found a natural explanation based on the concept of the packet structure of polymers[36,106], taking into account the contribution by the mobility of particular structural units of the polymer to the observed effect.

Not only segments and macromolecules but also various supermolecular formations (packets and in certain cases more complex species) interact with the solid surface, only a small fraction of the functional groups of the polymer being linked directly to the surface§. The side chains of the macromolecules containing the remaining functional groups are not directly influenced by the surface and therefore, on lowering the packing density with the associated increase of free volume[93], may exhibit in the vicinity of the solid surface a greater mobility than further away from it. The increase of the mobility is responsible for the decrease of the corresponding dielectric relaxation time, which is reflected in a lowering of the temperature of the maximum in dipole – radical losses[110].

As already mentioned above, the interaction of the solid surface with the functional groups of the polymers leads to a lowering of the mobility of the packets (and larger structural formations if they are present); Lipatov[86] in fact explained the observed increase of T_g of a polymer interacting with a solid surface by such lowering of the mobility of the packets.

The lack of dependence on the degree of filling of the temperature of the maximum dipole – elastic losses for the systems investigated[86] of shows, that, despite the decrease of the mobility of the packets, the mobility of the segments of the macromolecules in the wall layers does not change or changes only slightly.

The conclusion that there is a sharp decrease in the mobility of the structural elements of the wall layers of polymers also follows from the results of Deryagin and coworkers[111], who investigated the self-adhesion of thin

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§ Since the thickness of the wall layer exceeds by several powers of ten the diameter of the macromolecules, only a small fraction of the functional polymer groups present in this layer can interact directly with the surface. This conclusion is also a direct result of a number of experimental studies[44,107-109].

layers of natural or butadiene rubbers deposited on quartz filaments. For films with a thickness less than 0.3 μm, the adhesive force was small and, in contrast to thicker films, hardly changed with the duration of contact. Such a weak dependence of the adhesive force on the duration of contact can be accounted for by a considerably reduced mobility of the structural elements in films with this thickness, which leads, on the one hand, to a virtually unchanged area of contact of the films and, on the other hand, to a suppression of the diffusion of macromolecules and their segments, which is known to be responsible[112] for the dependence of the effect of the adhesive bond on the duration of contact of the test specimens.

The results of studies on stress relaxation by the method described previously[114] in the system polyarylate N-1 (obtained from phenolphthalein and the chloride of isophthalic acid[113]) – copper powder showed that the initial activation energy for the relaxation process U_0[¶] diminishes with increasing degree of filling up to a certain limit and then remains virtually unchanged[117]. A similar variation of the activation energy for deformation with the degree of filling was established for the system polystyrene–fibre-glass[118]. The curve relating the constant γ to the filler content in compositions based on polyarylate N-1 passes through a minimum corresponding approximately to 40 wt.% of the copper powder[117]. This form of the curve may be due to the fact that for comparatively low contents of the filler, partial breakdown of the supermolecular structural elements produces a more uniform distribution of stresses despite the appearance of inhomogeneities such as the filler particles. When the filler content is greater than 40 wt.%, the effect of the concentration of stresses in the vicinity of filler particles predominates.

Effect of the Specific Features of the Relaxation Processes in Wall Layers on Certain Properties of Heterogeneous Polymeric Systems

The expansion of the spectrum of relaxation times towards longer times caused by the solid surface of the filler particles or of the support produces significant change in many properties of polymers.

The glass point of the majority of the systems investigated increases with the filler content. This happens in the systems polystyrene–fibre-glass[118], glass powder[122], kaolin[119], colloidal lead[120], and bentonite[121], poly(methyl methacrylate)–glass powder[101,122], bentonite[121,123,124], and kaolin[119], poly(vinyl alcohol), polyvinylbutyraldehyde, and poly(vinyl acetate)–fibre-glass[125], polyisobutylene–glass microspheres[85,126], polyurethane rubber–glass microspheres[126] and sodium chloride[127], polyamide 6,6–fibre-glass[128], phenolformaldehyde resins–highly dispersed iron powder[129] and graphite[130], poly(vinyl chloride)–graphite[130], alkyd-melamine resin–titanium dioxide[131], and epoxy-resin–titanium dioxide[132].

In many cases T_g is found to remain constant or to decrease on introduction of a filler. Thus T_g did not change or changed only slightly on introduction of carbon black into the following elastomers: natural rubber (up to 18 vol.% of carbon black)[133], polyisobutylene (up to 50%) [134], butadiene–styrene (SKS-30) and nitrile (SKN-40) vulcanised rubbers (up to 30 vol.%) [135,136], and fluororubber SKF-6 (up to 15 vol.%) [135]. Similarly chalk, kaolin, and lithopone (20 vol.%) hardly altered T_g for SKS-30 vulcanised rubber; chalk (20 vol.%) T_g had very little effect on T_g for SKN-40 vulcanised rubber[135,136]. Introduction of up to 50 parts by weight of aluminium powder into 100 parts of SKMS-10 butadiene–methylstyrene vulcanised rubber mixture did not increase T_g. [135]

The introduction of 10% of chalk into poly(methyl methacrylate) reduced T_g by 10 deg [137]; when the polymer is plasticised to some extent, the filling of polystyrene and poly(methyl methacrylate) with glass powder also lowers T_g. [122] Carbon black slightly decreased T_g for vulcanised *cis*-polybutadiene[134]. It has been reported that the introduction into polystyrene of 30% of iron powder appreciably lowered T_g for the composition[138], but the lowering is undoubtedly due to the degradation of the polymer on mixing with the filler.

There is no doubt that the absence of an effect or only a slight effect of inert fillers (chalk, kaolin, aluminium powder) on T_g for rubbers is due to the absence of a strong interaction between the rubber molecules and the surface of the fillers. The paucity of the experimental data precludes at present a reliable explanation of the independence of T_g for rubbers of the carbon black content over a fairly wide range of concentrations and there are even fewer grounds for an explanation of the lowering of the temperature as a result of the introduction of carbon black. Possibly the reason for this consists in the high flexibility of rubber macromolecules; another explanation is based on the hypothesis that in filled vulcanised rubber the density of cross-links is somewhat lower than in unfilled rubbers, or they are distributed less regularly[134].

Table 2. Effect of the filler (TiO_2) on the glass points of the vinyl acetate–vinyl chloride copolymer[109].

TiO_2 content, vol.%	0	1,1	3,0	4.8	6,5	12.8	19,1
Glass point, °C	30 and 77	32 and 73	27 and 62	28	48	51	51

* The volume concentration was calculated for 25°C.

An unusual effect of fillers on the glass point of copolymers was observed in dilatometric studies on the system vinyl chloride–vinyl acetate (9 : 1 molar ratio) copolymer–rutile (with a mean particle diameter of 0.220 μm) [109]. Table 2 shows that, for a comparatively low degree of filling (up to 4.8 vol.%), the upper T_g, due to the presence of vinyl chloride units, increases, while the lower T_g, reflecting the mobility of the vinyl acetate units, changes only slightly. Further increase of the filler content leads to some increase in the glass point (now a single point) for the system and finally to its independence of the degree of filling. According to the authors[109], the lowering of the upper T_g can be accounted for by the adsorption of the acetyl group on the filler and the dissociation of the intermolecular bonds formed by these groups, thereby increasing the mobility of the vinyl chloride units. An increase of

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[¶] One of the constants of the familiar Aleksandrov–Gurevich equation[115,116] $\tau = \tau_0 \exp [(U_0 - \gamma\sigma)/RT]$, where τ is the relaxation time, σ the stress, T the temperature, R the gas constant, and U_0, γ, and τ_0 are constants characterising the relaxation properties of the polymeric material.

the TiO_2 content above 4.8 vol.% leads to the binding of a large number of acetyl groups and an increase of the lower T_g. One may expect that different effects of the filler on the upper and lower glass points will be shown also on filling other copolymers the units of the macromolecules of which differ appreciably in chemical nature and polarity.

The present author's investigations[139-141] established that the temperature variation of the strength of adhesive junctions tested under conditions of a very non-uniform distribution of stresses (tearing away, separation of separate layers, etc.) passes through a maximum in the region of glass formation. The presence of this maximum was explained by the fact that, on approaching the glass formation region from the low-temperature side, the rate of decrease of excess stresses increases in the vicinity of the apex of the growing crack as a result of the acceleration of relaxation processes and the decrease of such stresses leads to an increase of the load necessary to break the specimen. On further increase of temperature, the breaking load diminishes in consequence of the usual temperature-induced decrease of cohesive or adhesive strength. It was found that a decrease in the thickness of the layer of polymeric adhesive in the junction from 30 to 3 μm increased the temperature of the maximum strength of the junction by 10 deg. A similar effect was obtained when, instead of a homogeneous adhesive, a filled adhesive was employed, in which the average distance between the filler particles was close to 2 μm. [140] The observed increase in the temperature of maximum strength can be reasonably attributed to the retardation of relaxation processes in the vicinity of the solid surface.

The yield point (T_y) of filled polymeric systems is even more sensitive to filling than the glass point. This is because fairly large doses of filler in many cases produce a three-dimensional network apart from changing the number of conformations of the macromolecules and the spectrum of relaxation times[125,142-145]. The ability to form a three-dimensional structural network is clearly shown by fibrous and carbon black fillers. Thus the introduction into polystyrene of 20% fibre-glass hardly alters T_g but increases T_y by 40–50 deg [145,146]. The introduction of a filler increases T_y in the systems poly(methyl methacrylate)–fibre-glass[125], kaolin[119], and bentonite[121,124,137], polyisobutylene–Lavsan fibres[147] [a variety of nylon produced in the USSR (Ed. of Translation)], and mixed polyamide G-548–powdered metal oxides in large amounts (CaO, ZnO, MgO, and VO_3). [148] In certain systems the curve relating T_y to the filler content passes through a minimum in the region of low concentrations. This happens in mixtures of poly(methyl methacrylate) with kaolin[119], of polystyrene with bentonite[121], of polyisobutylene with very short (length 25–75 μm) Lavsan fibres[149], and of polystyrene containing 5% of a plasticiser with fibre-glass[146]; the introduction of 10% of chalk lowers T_y for poly(methyl methacrylate) approximately by 25 deg. [137] It may be that at least in some if not all systems the decrease of T_y is caused by the disruptive effect of the filler on the supermolecular structural formations in the polymer[149]. It must be emphasised that the introduction into polyisobutylene of longer Lavsan fibres (3 and 10 mm) as well as filling with fibre-glass of polystyrene not containing a plasticiser or containing more than 10% of a plasticiser inevitably leads to an increase of T_y.

It is known that in the deformation of homogeneous polymers in the state corresponding to rubber elasticity intermolecular bonds are broken as are a certain number of chemical bonds[150]. During the deformation of filled polymeric systems some of the polymer–filler bonds are also broken and in certain cases, in particular in rubbers filled with carbon black, also of filler–filler bonds[151]). After the removal of the load, the relaxation process tending to return the system to the initial state is accompanied by the reformation of the polymer–filler bonds (and also of the bonds between the filler particles in the relevant systems). Then part of the macromolecules and their aggregates are fixed in non-equilibrium positions. As a result, filled polymers exhibit some thixotropy[143,145,152]; the dissociation and reformation of the bonds and the fixation of a certain fraction of deformations of the rubber-elastic type result in a greater similarity of the behaviour of filled systems to that of polymeric materials under conditions of "chemical flow"[36,153-156].

Since the polymer interacts with the surface of solid particles, an increase of the degree of dispersion of the filler enhances its influence on the relaxation properties of the system. This was observed, in particular, in mixtures of poly(methyl methacrylate) or polystyrene with bentonite or kaolin[157] and on introduction of aminated bentonite into methyl methacrylate and subsequent polymerisation of the monomer[158]; for mixtures of polyethylene or butadiene–styrene or natural rubber with a number of mineral fillers, a linear relation has been established between certain properties associated with strength and deformation and the reciprocal of the filler particle dimensions (in the range of dimensions <0.2 μm) [159].

5. CHARACTERISTICS OF STRUCTURE-FORMATION PROCESSES IN POLYMER WALL LAYERS

In the previous section it was shown that wall layers differ from the bulk phase of a polymer in packing density and orientation and by a reduced rate of relaxation. These differences must influence also the structure-formation processes†. The looser packing and lower rate of relaxation should hinder both the formation of crystal nuclei and the growth of crystalline structures; on the other hand, orientation may favour crystallisation. The surface of an extraneous solid may affect the nucleus-formation processes also by influencing the change in surface energy on formation of a nucleus of the crystalline phase. As a result of the different contributions by these factors in various systems, in some cases the solid phase favours crystallisation to some extent while in others it hinders it up to complete suppression; in a comparatively small number of systems polymer crystals oriented in accordance with the crystal structure of the support (epitaxy) are formed at the crystal–support boundaries.

Promotion of Crystallisation in Wall Layers and Its Influence on the Properties of Polymeric Materials

In recent years the possibility of regulating the dimensions (and number) of spherulites in polymeric materials by introducing into the polymers a small amount of a finely dispersed additive[160-204] has been attracting the

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† We are not considering the differences in the structures and properties of wall layers caused by the differences in the thermal history of these layers and the bulk phase of the polymer (in many cases the rates of change of the temperature of wall and bulk-phase layers differ significantly).

attention of investigators and technologists to a considerable degree. Kargin, Sogolova, and coworkers[174,175,182-184,187,190] showed that the mechanism by which these additives act involves the formation (by adsorption) on the surface of the solid particles of the nucleating agent of ordered regions of the polymer, which act as crystallisation centres. Such ordered regions are retained on the surface of the nucleating agent at high temperatures of the polymer melt when homogeneous crystallisation centres (in the bulk of the melt) are completely decomposed. When the number of added particles is sufficiently large, the number of heterogeneous centres of the surface greatly exceeds the number of homogeneous centres formed in the bulk of the polymer throughout the crystallisation. It has been shown that nucleus-forming agents do not affect the rate of the linear growth of spherulites. An increase in the number of crystallisation centres in combination with a constant rate of linear growth in fact leads to a decrease of the dimensions of the spherulites[‡] and an increase of the rate of crystallisation. It is interesting to note that nucleating agents which alter the dimensions of polyethylene spherulites altogether fail to influence the formation and dimensions of its single crystals.[190]

Several hundreds of compounds, mainly organic[161-163,166,168-175,178,183-186,195,202], have been tested as nucleating agents. These investigations established that the effectiveness of the nucleation depends primarily on the physicochemical nature of the polymer and the nucleator. The particles of a satisfactory nucleating agent should be readily wetted by the polymer melt above its melting point (T_f) and should interact fairly strongly with it below T_f, but they should not dissolve in the polymer at T_f or below it; the melting point of the nucleus-forming agent should be higher than that of the polymer[§]. The similarity between the crystal structures of the polymer and the nucleating agent is not essential.

It has been noted[206-208] that carbon black present in considerable amounts (tens per cent) promotes the crystallisation of vulcanised rubbers and in some cases[206] larger crystals with more regular shapes are formed in carbon-filled rubbers on extension than in unfilled vulcanised rubbers. Possibly the higher rate of crystallisation in vulcanised rubbers is due to the lowering of the density of cross-links in them as a result of the adsorption of vulcanising agents on the carbon black[208].

The considerable reduction of the dimensions of supermolecular formations achieved by the use of nucleating agents leads to a significant improvement of a number of properties of finished articles. There is an increase in transparency[160,164,169-172,176,178,185,186,197], strength and capacity for deformation and extension[169,173,176,181,183-187,198,200], stress resulting in the formation of a "neck"[176,200], resistance to long-acting[199] and impact loads[164,166,168-172,176,188], hardness[161,169,176,186], and resistance to wear[188] and there is a decrease in the coefficient of friction[164] and in the evolution of heat on cyclic application of loads[200]. The presence in the polymer system of nucleating particles stabilises the supermolecular structure and properties of the material at elevated temperatures[184]; it has been shown that thermal-oxidative degradation of polyethylene takes place more slowly when an antioxidant with a nucleating action is introduced into the polymer[201]. This is evidence that the use of nucleating agents improves certain technological properties of polymeric materials[169,176,186], but an increase in the viscosity of the polymer melt has also been observed following the introduction of nucleating agents[191-195].

Inhibiting Effect of the Solid Surface on the Crystallisation of Polymers in Wall Layers

Apart from the present author's investigations[90,209,210], it was possible to find only a few unsystematic data concerning the retarding effect of the solid surface on crystallisation in the adjacent layer of polymer. To account for the protecting effect of carbon black in the thermal oxidation of polyethylene, it was suggested[211] that near the surface of the carbon black particles the concentration of the amorphous polymer phase is above average. On the basis of a study of the mechanical properties of mixtures of polyarylate F-1 with powders of various metals and mineral fillers, Korshak and Slonimskii concluded that the filler particles to some extent prevent the natural development of structure-formation processes in the polymers[117,212]. In contrast to the effect of carbon black on vulcanised rubbers mentioned above, the introduction of 50 wt.% of particles of carbon black into non-vulcanised natural rubber reduced the rate of its crystallisation (the introduction of 2% of carbon black did not alter appreciably this rate)[213]. This observation is related to the conclusion, based[214] on the results of an electron-microscope study of mixtures of natural rubber with carbon black and activated silica gel, that in the vicinity of the particles of these fillers there is a layer 0.03 – 0.05 μm thick in which rubber does not crystallise[¶]. Schoon and Adler[214] suggested that crystallisation is hindered by mixtures adsorbed on the surface of the filler but did not put forward any facts in support[†].

The effect of the thickness δ of the polymer layer between two glass surfaces on the kinetics of the crystallisation of certain polymers has been investigated[90] by microcinematographic techniques. The Figure presents curves characterising this effect for isotactic polypropylene; similar curves were obtained for guttapercha and cellulose tribenzoate. Curve *2* shows that a linear rate of growth of spherulites, which is low at low values of δ, increases with δ, and, for a certain thickness of the film when the effect of the surface no longer operates, ceases to depend on δ.

The minimum in curve *3* describing the effect of δ on the rate C_3 of nucleus formation calculated per unit volume of the polymer can be explained as follows. C_3 is the sum of the rates of nucleation on the polymer – glass interface and in the bulk of the film. Nucleus formation on the surface is slower than in the bulk phase. In the region of low values of δ surface nucleation predominates; in this range of thicknesses, an increase of δ favours a more

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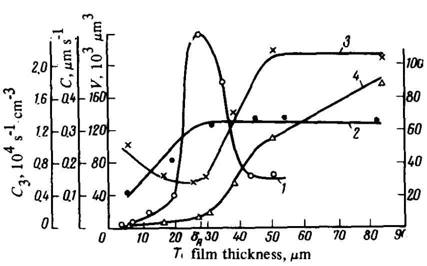
[‡] The method of modifying the structure and properties of polymeric materials by introducing into the polymer surface-active substances[205] yields a result similar in many respects, but it is based on a different mechanism of action on crystallisation.

[§] Amorphous polymers, liquids, and even air exhibit some nucleus-forming properties[184,187,192,193,195].

[¶] The photographs quoted by Schoon and Adler[214] are insufficient to determine the validity of this conclusion.

[†] There exist data of the opposite kind[199] — crystals of natural rubber which do not melt up to 125°C (the usual crystals of natural rubber melt[215] at 28°C) grow on the surface of amorphous carbon.

rapid increase in the volume of the film than in the number of nuclei and the C_3 curve moves downwards. The minimum in curve *3* corresponds to a thickness δ_A for which the contribution of the bulk-phase nucleus formation to C_3 begins to increase sharply. For sufficiently thick films, bulk phase nucleation plays a significantly more important role than surface nucleation and the number of nuclei in the film increases in proportion to its thickness, like its volume. This results in C_3 being independent of δ. This explanation is confirmed by the form of curve *4*, which shows the variation of the rate of nucleation C_S, calculated per unit surface, with δ. C_S is almost independent of film thickness up to δ_A and, when δ_A is reached, the slope of curve *4* rises sharply.



Effect of the thickness of the polypropylene layer, on the volume of spherulites (V, curve *1*), linear rate of growth of spherulites (C, curve *2*), and rate of nucleus formation (C_3, curve *3*—rate calculated per unit volume of the polymer; C_S, curve *4*—rate calculated per unit surface of the specimen).

The variation with thickness of the rate of linear growth of spherulites (curve *2*) and nucleus formation (C_3; curve *3*) is responsible for the maximum (observed in this investigation and previously[209]) in the curve relating the volume of the spherulites to δ (curve *1*) in the region of thicknesses for which the crystallisation behaviour of the polymer layer is determined by the crystallisation in surface layers.

In the case of isotactic polystyrene the linear rate of growth of spherulites depends on δ similarly, but, probably owing to the low rate of homogeneous nucleus formation in this polymer[183], C_S is independent of δ.

The decrease in the thickness of the polypropylene layers achieved by increasing the extent of its filling with glass powder influences the crystallisation kinetics in the same way as the decrease (described above) of the distance between the comparatively large glass surfaces confining the film.

The same surface may influence in opposite ways the crystallisation of different polymers. Thus the inhibiting effect of the glass surface on the crystallisation of certain polymers has been described. However, in the study of a film of polyamide 66 compressed between glass surfaces it was established that a decrease of its thickness from 30 to 10 μm results in an increase of the rate of linear growth of spherulites[216].

A solid surface can influence not only the rate of crystallisation processes but also the morphology of thin films. Thus in guttapercha[90,209,217], cellulose tribenzoate, and isotactic polypropylene and polystyrene[90,217] films with a thickness less than several micrometres imperfect crystalline formations were observed, while spherulites were formed in thick layers. For $\delta < 1-1.5$ μm, no structures could be observed at all with the aid of a light microscope. Similarly, films of many polymers with a thickness less than 0.1 μm on metallic surfaces did not exhibit a spherulite structure, in contrast to thicker films[218]. In films of mixtures of poly(ethylene adipate) or poly(ethylene sebacate) with poly(methyl methacrylate) or certain other amorphous polymers with a thickness amounting to several hundreds of ångstroms, no structure was observed either, while films with a thickness in excess of 20–30 μm were crystalline[219]‡.

The crystallinity of polypropylene films with a thickness of 1–1.5 μm was also not observed in the studies of polypropylene by differential thermal analysis and by X-ray diffraction[90,217]. Crystallisation does not occur in such thin films, possibly as a result of the strong interaction of the macromolecules, packets, and other structural elements of the melt with the solid surface, which is so pronounced that the activation energies for nucleus-formation processes become very high and the rates of these processes are correspondingly negligible. It is also possible that the change in surface energy in certain solid–polymer systems during the crystallisation of the polymer in thin layers is so great that this phase transition becomes thermodynamically unfavourable.

It may be supposed that in the presence of a very weak interaction between the polymer and the surface of an extraneous body the surface does not affect the crystallisation processes, when the interaction is very pronounced the processes are retarded, and for moderate interactions the surface exhibits a nucleus-forming effect§.

Epitaxy of Polymers

As already mentioned above, in certain systems thin polymer films have an epitactic structure. Thus on freshly cleaved (001) surfaces of the crystals of certain alkali metal halides, usually sodium chloride, oriented crystallisation of polyethylene[222-226], isotactic polypropylene[226,227], poly-3,3-bischloromethylcyclobutane (pentone), poly(ethylene terephthalate), isotactic polystyrene[226], polyoxymethylene and polyoxypropylene[227], polyamides 6.66 and 610,[228] polyamides 7 and 8,[229] polyacrylonitrile[230], and polyurethane[229] was observed. Epitactic crystallisation of polyacrylonitrile on a freshly etched surface of crystalline quartz has also been observed[231]. A case of the epitaxy of polyethylene on stretched films

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‡ These relations are closely related to the findings described above (p. 704) namely a sharp transition from a structured film of silver telluride on glass to a structureless form when the thickness is 300–350 Å and the variation of the structure of vacuum-deposited films of a number of metals with their thickness in the range up to 70–80 Å; a similar variation is observed also for tantalum up to a thickness of 250 Å.[220]

§ This hypothesis is fully consistent with the results of the calculations of Moazed[221], who showed that a stable epitactic nucleus of a low-molecular substance can be formed from its vapour only when the angle between the surfaces of the nucleus and the substrate is in the range 10–40°.

of polyoxymethylene has been described, the needlelike crystals of polyethylene being oriented perpendicular to the direction of the stretching of the support[232].

The crystallisation of polyethylene, pentone, and polystyrene (on alkali metal halides) begins with the formation of needlelike crystals arranged along the [110] direction on the support; subsequently these crystals grow, giving rise to an oriented network structure. Polypropylene forms squares with dimensions of up to 20 × 20 μm with the sides parallel to the [100] and [010] directions of the salt crystals and poly(ethylene terephthalate) and polyoxymethylene form long (up to 100 μm for PETP and up to 6 μm for POM) needles along the [110] direction on the alkali metal halide crystals. It has been established by electron diffraction that molecular chains in polyethylene, polystyrene, and pentone crystallites are oriented preferentially parallel to the surface along the [110] direction of the support, while in polyoxymethylene, polypropylene, and polyoxypropylene crystallites the chains are arranged perpendicular to the surface of the support.

Two explanations are possible for the orienting effect of the surface of alkali metal halide crystals[227]. One possibility involves the attribution of the orienting effect to sequences of similarly charged ions arranged along the [110] direction of the (001) plane. Another explanation is based on the nucleus-forming effect of dislocations, formed in large amounts when small crystals are cleaved, extended along the [110] direction; each of these dislocations contains a multiplicity of sections with an enhanced surface energy.

For epitaxy (as for the nucleus-forming agent–polymer systems), there is apparently no obligatory requirement of a correspondence between the dimensions of the crystal lattices of the support and the polymer. Thus polyethylene exhibits epitaxy on lithium fluoride, sodium chloride, sodium bromide, sodium iodide, potassium chloride, and potassium iodide despite the considerable differences in the lattice dimensions of these crystals (the lattice constant a_0 for the crystals varies from 4.01 to 7.05 Å).[226]

As a result of the presence in polymers of supermolecular formations, each of which behaves in many processes as a single kinetic entity, the wall layers of the polymer at its boundary with the solid surface differ in some of their properties from the bulk-phase layers and their thickness may exceed that of wall layers in low-molecular substances.

The relaxation processes in the wall layers of the polymer are retarded. This is because the solid surface in contact with the polymer not only restricts the volume accessible to the kinetic units of the polymer in their thermal motion, but also combines with them via intermolecular interaction forces. Interaction of the solid surface with the polymer can result in a partial orientation of the polymer in the wall layer and also in a lowering of the packing density.

The different contributions of these factors (rate of relaxation and orientation and packing density) in various polymer–solid surface systems give rise to a wide range of effects of solid surfaces on relaxation and structure-formation processes in wall layers of polymers. In some systems the solid surface promotes to some extent the crystallisation of the polymer while in others it either retards or even completely suppresses the crystallisation.

Further theoretical and experimental studies of wall layers of polymers are essential, in particular with the aid of methods such as nuclear magnetic resonance, infrared spectroscopy, radiothermoluminescence, and a combination of these methods, and also electron and light microscopy together with the investigation of the mechanical, electrical, and physicochemical properties of heterogeneous polymeric systems. Such study will not only throw light on certain fundamental characteristics of polymers but will help develop technological processes for the preparation of new materials of importance in engineering.

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Karpov Physicochemical Institute,
Moscow

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Aminoacids and Peptides Containing the Di-(2-chloroethyl)amino-group

L.Rasteikiene, M.Dagiene, and I.L.Knunyants

The review deals with studies on the relation between the antitumour activity of di-(2-chloroethyl)amino-derivatives of aminoacids and peptides and their chemical structure.
The bibliography includes 236 references.

CONTENTS

I. INTRODUCTION

The incorporation of the di-(2-chloroethyl)amino-group in biologically important compounds such as aminoacids, peptides, sugars, and various metabolites or physiologically active substances frequently yields antitumour preparations. Research on the synthesis and properties of cytotoxic derivatives of aminoacids and peptides is being pursued on a particularly wide front.

The properties of the di-(2-chloroethyl)amino group and the mechanisms of biological alkylation have been fairly widely described in Ross's monograph[1]. Among later publications, mention should be made of Wheeler's paper[2].

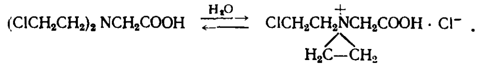
II. DI-(2-CHLOROETHYL)AMINOACIDS AND THEIR DERIVATIVES

The most thoroughly investigated representatives of this series of compounds are di-(2-chloroethyl)glycine (R = H) and di-(2-chloroethyl)alanine (R = CH_3):

$$(ClCH_2CH_2)_2NCHRCOOH\,.$$

Analogous derivatives of other aminoacids are also known (Table 1)†.

In water these acids are readily cyclised into aziridinium salts, which are less stable than the ions derived from di-(2-chloroethyl)methylamine (Embichin)[19]:



$$(ClCH_2CH_2)_2NCH_2COOH \xrightleftharpoons{H_2O} ClCH_2CH_2\overset{+}{N}(CH_2CH_2)CH_2COOH \cdot Cl^-\,.$$

It is believed that the alkylating properties of such acids depend on the pH in the tissues[20]. When the distance between the carboxyl and the di-(2-chloroethyl)amino-group is increased, the reactivity of the chlorine atoms in these acids rises. This accounts for the enhanced toxicity of di-(2-chloroethyl)-β-alanine[12].

Di-(2-chloroethyl)aminoacids with free carboxyls are less toxic than their amides or esters, the toxicity of which

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† We believe that this group of compounds should be regarded as Embichin derivatives rather than those of aminoacids; nevertheless the terminology of the authors quoted is retained in the review.

approaches that of di-(2-chloroethyl)methylamine (Embichin), probably owing to the presence of the free electron pair at the nitrogen atom of the di-(2-chloroethyl)amino-group. In compounds with a carboxy-group, this electron pair is protonated to give a zwitter ion[21,22]. For this reason, the chlorine atoms in di-(2-chloroethyl)-aminoacids are less mobile than in other di-(2-chloroethyl)amino-derivatives[22].

Table 1.

Aminoacid or its derivative	Refs.	Aminoacid or its derivative	Refs.
—Gly—OH; —OEt; —NH_2	3—7	—(Ala—OCH_2)$_2$	6
(Gly—OCH_2)$_2$	6	—Ala—NH_2(*DL* and *L*, *D*)	3, 4, 10
—Gly—NHC_6H_4F-*m*	7	—Ala—$N(CH_3)C_6H_5$	11
—Gly—NHC_6H_4OMe-*p*	7	—β-Ala—OH; —OEt; —NH_2	12
—Gly—$NHC_6H_3(OCH_3)_2$-2,4	7	—β-Ala—OC_6H_5	13
—Gly—$NHC_6H_2(OCH_3)_3$	7	—Phe—OH; —NH_2	14
—Gly-emetine	8	Phe—PhGly—NH_2	4, 5, 10
—Gly—Phe-emetine	8	—Glu—$(OH)_2$	15
—Gly—Try-emetine	8	Orn-α(NH_2)—OH	12
—Gry—Pro—Pro-emetine	8	Lys-α(NH_2)—OH	12, 16, 17
—Gly-6-amino-		Abu—NH_2	12
penicillanic acid	9	γ-Abu—OH	12
—Ala—OH; —OEt	3	Pro—OH	18

It has been suggested that the formation of a metal complex via the unshared electron pair of the nitrogen atom would reduce the toxicity of di-(2-chloroethyl)aminoacids. Therefore tests were made on the biological activity of complex copper(II) salts of di-(2-chloroethyl)glycine and di-(2-chloroethyl)alanine. The toxicity of these compounds was in fact reduced, but their antitumour activity was not improved[23].

After a single administration to mice with Yoshida sarcoma, di-(2-chloroethyl)alanine temporarily reduced the amount of nucleic acids in the cancer tissues as well as the number of the cancer cells themselves[24]. Di-(2-chloroethyl)glycine and di-(2-chloroethyl)alanine prolonged the life of mice with leukaemia *L* 1210 by 20 and 19% (if the activity of amethopterin is taken as 100%).[25] The amides of these acids are more effective although their chemotherapeutic index is lower. *In vitro* they showed a lower cytotoxic activity compared with the free acids, which the authors[11] believe to be due to the stability of the amides in water.

The antitumour activities of the diastereoisomers of di-(2-chloroethyl)alanine amide were compared but no differences were found in the biological properties of the L- and D-forms[26].

Di-(2-chloroethyl)alanine arrests the incorporation of labelled aminoacids into the proteins of the tumours in rats affected by Walker carcinosarcoma 256; this constitutes their advantage over Embichin, which arrests the incorporation of aminoacids also into the normal tissues of the organism. Di-(2-chloroethyl)alanine arrests the incorporation not only of alanine but also of other aminoacids: lysine and methionine. This shows that it does not behave as an antimetabolite but as an alkylating agent. The incorporation of labelled aminoacids into the acid-insoluble fraction of nuclear proteins is arrested particularly markedly, which is evidence of the importance of this fraction in the growth of tumours[27].

It has been shown that the phenyl ester of di-(2-chloroethyl)-β-alanine has a powerful mutagenic activity[13].

Di-(2-chloroethyl)glycine, di-(2-chloroethyl)-α-alanine and its amide, and di-(2-chloroethyl)-β-alanine all exhibited cholinergic and leukopenic activity[28].

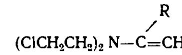
Comparison of the antitumour properties of di-(2-chloroethyl)aminoacids revealed that di-(2-chloroethyl)-alanine has the best chemotherapeutic index[12,29]. It was tested in several clinics in Japan on leukaemic patients[30-33]. Clinical tests on 69 patients with different forms of cancer showed that objective improvement was observed only in the case of lymphoma. The authors concluded that under clinical conditions di-(2-chloroethyl)alanine is not superior to Embichin[34].

Other di-(2-chloroethyl)aminoacids have been less widely investigated. They too are probably not promising anticancer agents.

N-Di-(2-chloroethyl)phenylalanine and its amide showed no antitumour activity at all[14]. 4-Di-(2-chloroethyl)-amino-L-proline was less effective than Sarkolysin in tests on a wide spectrum of tumours[35]. Analogous lysine derivatives—a mixture of N_α- and N_ϵ-di-(2-chloroethyl)-lysine called "Lysepsin"—were also investigated. It was shown that the L-form is less active than Sarkolysin[36,37]. This preparation arrested the incorporation of [^{14}C]lysine and phenylalanine into the tumour proteins of sarcoma 45 in rats[38].

Di-(2-chloroethyl)glycyl-6-aminopenicillanic acid was less toxic but showed also a less pronounced antitumour activity than di-(2-chloroethyl)glycine.[9]

Several unsaturated di-(2-chloroethyl)amines and di-(2-chloroethyl)-derivatives of unsaturated aminoacids and peptides with the general formula[39]



$$(ClCH_2CH_2)_2N{-}\overset{R}{C}{=}CHR'$$

where R = H, $COOCH_3$, $COOC_2H_5$, $CONH_2$, CO–Gly–OC_2H_5, CO–Val–OC_2H_5, CO–L-Phe–OCH_3, CO–L-Tyr–OC_2H_5, $COOC_2H_5$, or *p*-$NO_2C_6H_4$ and R′ = $COOCH_3$, $COOC_2H_5$, $COO(CH_2)_nCH_3$ (*n* = 2, 4, or 6), $CONH_2$, H, or C_6H_5, were synthesised. Most of these compounds did not show antitumour activity.

On oxidation, di-(2-chloroethyl)aminoacids are converted into the corresponding *N*-oxides[40]:

$$(ClCH_2CH_2)_2N(O)CHRCOR'$$

where R = H or CH_3 and R′ = OH, OC_2H_5, or NH_2. The antitumour activity of these derivatives was lower than that of the corresponding di-(2-chloroethyl)aminoacids. In water they are converted into 1,2-dimethyleneoximmonium ions[19]. *N*-Di-(2-chloroethyl)hydrazinocarboxylic acids,

$$(ClCH_2CH_2)_2NNHCH(R)COOH,$$

where R = CH_3, C_2H_5, or n-C_3H_7, have been synthesised, but their biological properties have not been described[41].

III. AMINOACID DI-(2-CHLOROETHYL)AMIDES

A series of known di-(2-chloroethyl)amides of aminoacids and their *N*-acylated derivatives are listed in Table 2.

Aminoacid di-(2-chloroethyl)amides are unstable, rearranging to esters in the presence of traces of moisture[44-49]:

$$NH_2CH(R)CON(CH_2CH_2Cl)_2 \rightarrow NH_2CH(R)COOCH_2CH_2NHCH_2CH_2Cl \cdot HCl\ .$$

Aminoacid amides containing the di-(2-chloroethyl)amino-group in the benzene ring have been synthesised[49-52]:

$$RNH(R')_2CONHC_6H_4N(CH_2CH_2Cl)_2\text{-}p\ ,$$

where R = H or $C_6H_4(CO)_2$ and R' = CH_2, CH_2CH_2, CH_3CH, $CH_2CONHCH_2$, or C_6H_5CH.

Glycine and phenylalanine derivatives did not exhibit antitumour activity[50]. Among glutamic acid derivatives[53], the compound with a free γ-carboxy-group was less active than the derivative in the L-form with a free α-carboxy-group. However, the activities of these compounds were lower than that of Melphalan[54].

Table 2.

Compound	Refs.
H—; Bz—; Phth—Gly—N $(CH_2CH_2Cl)_2$	42—46
Phth—Gly—Gly—N $(CH_2CH_2Cl)_2$	46
H—; Ac—; Bz; Phth—Ala—N $(CH_2CH_2Cl)_2$	45, 47
$CHCl_2CO$—Ala—N $(CH_2CH_2Cl)_2$	45
Phth-β-Ala—N $(CH_2CH_2Cl)_2$	45
Ac—Val—N $(CH_2CH_2Cl)_2$	45
H—; Ac—Leu—N $(CH_2CH_2Cl)_2$	45
$CHCl_2CO$—Ser (O—Me)—N $(CH_2CH_2Cl)_2$	45
Ac—Met—N $(CH_2CH_2Cl)_2$	45
$CHCl_2CO$—Met—N $(CH_2CH_2Cl)_2$	45
H—; Ac—; Bz—Phe—N $(CH_2CH_2Cl)_2$	45, 47, 48
$CHCl_2CO$—Phe—N $(CH_2CH_2Cl)_2$	45
CCl_3CO—Phe—N $(CH_2CH_2Cl)_2$	45

A number of aminoacid di-(2-chloroethyl)hydrazides are known:

$$RNHCH(R')CONH{-}N(CH_2CH_2Cl)_2 ,$$

where R = C_2H_5OCO and R' = H, $(CH_3)_2$, $CH(CH_3)_2$, $CH_2CH(CH_3)_2$, $CH(C_2H_5)CH_3$, $(CH_2)_2COOH$, or $CH_2C_6H_4OH$-*p*, but the biological properties of these compounds have not been described[55].

Several hydrazones of *p*-di-(2-chloroethyl)aminobenzaldehyde have been synthesised from the hydrazides of acetamidoacids:

$$(ClCH_2CH_2)_2NC_6H_4CH{=}N{-}NHCOCH(R)NHCOCH_3 ,$$

where R = $CH_2C_6H_5$, $CH_2C_6H_4OH$-*p*, $CH_2CH_2SCH_3$, or CH_2-β-indole. They did not exhibit antiviral activity[56].

Among compounds of this group, *N*-di-(2-chloroethyl)-carbamoylaminoacids, which exhibit antitumour activity, were examined:

$$(ClCH_2CH_2)_2NCONHCH(R)COOC_2H_5 ,$$

where R = H, $CH_2CH(CH_3)_2$, CH_2COOH, $CH_2C_6H_5$, or $(CH_2)_2SCH_3$.[57] Under the action of water, they are rearranged to urethanes:

$$ClCH_2CH_2NCH_2CH_2OCONHCH(R)COOR' \cdot HCl .$$

NN-Di-(2-chloroethyl)carbamoyl derivatives of serine and threonine are also known[58]:

$$(ClCH_2CH_2)_2NCOOCH(R)CH(NH_2)COOC_2H_5 ,$$

where R = H or CH_3.

Tests of the antitumour activity of *O*-derivatives of serine in relation to Walker carcinosarcoma 256 showed that the L-form is more active than the racemate. *O*-Derivatives of threonine are inactive[58]. The study of the diffusion of these compounds through the membrane of intestinal cells showed that, despite their different antitumour activities, the permeability of the membrane in relation to them is the same[59]. This finding casts doubt, according to Evered and Randall[59], on the theory of the cytotoxic group carrier according to which the aminoacid component of the molecule behaves as a kind of transferring agent for the di-(2-chloroethyl)amino-group across the cell membrane and the antitumour activity is regarded as a direct function of the permeability.

O-Di-(2-chloroethyl)carbamoylserine arrested the incorporation of labelled methionine and serine into the nucleoproteins of Walker's tumour 256.[60]

IV. AROMATIC AMINOACIDS AND THEIR PEPTIDES CONTAINING DI-(2-CHLOROETHYL)AMINO-GROUPS IN THE BENZENE RING

The first aminoacid in which the di-(2-chloroethyl)-amino-group was introduced into the benzene ring was phenylalanine. This resulted in antitumour preparations (Sarkolysin and Melphalan) which have since been used in many oncological clinics in the treatment of certain forms of neoplasm. The high antitumour activity of these preparations stimulated a whole series of investigations on the specific synthesis of antitumour compounds containing the phenylalanine residue.

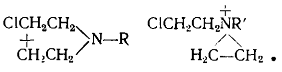
1. *p*-Di-(2-chloroethyl)aminophenylalanine

p-$(ClCH_2CH_2)_2NC_6H_4CH_2CH(NH_2)COOH$

This compound was synthesised and studied almost simultaneously by two groups of investigators: in England by Bergel and Stock as the L-enantiomer (Melphalan, abbr. Mel.), the D-enantiomer (Medphalan, abbr. Med.), and the DL-racemate (Merphalan, abbr. Mer.)[61,62] and in the Soviet Union by Khokhlov and coworkers under Larionov's supervision as the racemate under the name "Sarkolysin"[63] (abbr. Sark.).[61-71]

Together with high antitumour activity in relation to a number of transplantable tumours, Sarkolysin exhibited also high toxicity[72]. Sarkolysin is employed in clinical practice in the treatment of certain forms of neoplasm. However, it does not affect the majority of neoplasms. Sarkolysin has also shown a carcinogenic effect more pronounced than that of Embichin[73]. For a description of the biological and clinical tests of this widely known preparation, see Larionov[72]. This review deals only with the comparison of Sarkolysin with other similar compounds.

Sarkolysin contains the di-(2-chloroethyl)amino-group in the aromatic ring. It has been reported that, in contrast to aliphatic di-(2-chloroethyl)amines, such compounds undergo the alkylation reaction vis an S_N1 mechanism. An attempt was made to explain thereby the reduced toxicity of aromatic di-(2-chloroethyl)amines, including Sarkolysin[1]. However, a paper was published recently[74], where it was shown experimentally that *p*-di-(2-chloroethyl)-aminophenylalanine does not alkylate via a carbonium ion but via the formation of an unstable immonium ion, as in the case of aliphatic derivatives:



The rate of hydrolysis of the chlorine atoms in Sarkolysin and its derivatives has been investigated in aqueous alcohol[75-78]. It has been shown that the chlorine atoms in Sarkolysin are hydrolysed at unequal rates[78] and that chloride ions retard this process[73,77]. A spectrophotometric determination of Sarkolysin has been described[79].

In an acid medium Sarkolysin is readily oxidised with formation of a comparatively unstable free radical:

$$(ClCH_2CH_2)_2\,NC_6H_4CH_2CH\,(NH_2)\,COOH\ .$$

It is suggested that the same radical is formed in tumour cells[80].

The mechanism of the biological action of Sarkolysin and the selectivity of its action on certain tumours have not so far been elucidated.

It has been noted that D-Sarkolysin is deaminated and inactivated by D-amino-oxidase, the activity of which is appreciably greater in rat kidney tissue than in sarcoma 45. This is thought to account for the reduced antitumour activity of D-Sarkolysin on this tumour strain compared with the L-form[81].

Three modifications of radioactive Sarkolysin have been synthesised: (1) the derivative labelled in the aminoacid part of the molecule—*p*-di-(2-chloroethyl)amino-DL-[β-^{14}C]phenylalanine[82]; (2) the derivative labelled in the cytotoxic part of the molecule—*p*-di-(2-chloro-[β-^{14}C]-ethyl)amino-DL-phenylalanine[82]; (3) Melphalan labelled with tritium[83].

In a study of the distribution in the organism of normal rats and rats with a grafted tumour of Sarkolysin labelled in the aminoacid[84] and cytotoxic[85] groups and also of Melphalan labelled with tritium[83] it was shown that all the preparations administered in toxic doses are equally distributed in the rat organism. Selective accumulation of radioactivity in the tumour proteins was not observed.

It has been noted that labelled Sarkolysin is not converted in the organisms into tyrosine or phenylalanine[84]. In contrast to Sarkolysin, the labelled product of the hydrolysis of Melphalan [*p*-di-(2-hydroxy[β-^{14}C]ethyl)amino-L-phenylalanine] is not incorporated into the proteins of the blood or liver of rats; this suggests that Sarkolysin acts on proteins as an alkylating agent[86]. Other investigators arrived at a similar conclusion[34,87].

Melphalan and Sarkolysin arrest the incorporation of labelled aminoacids (phenylalanine, lysine, or methionine) into tumour proteins, particularly into the acid-insoluble fraction of proteins in the cell nucleus[34,39].

In a study of the effect of Melphalan on the incorporation of labelled methionine into tumour proteins of rats *in vivo* and *in vitro* in a tissue culture, it was concluded that different processes take place under the action of Melphalan in the organism and in an isolated tumour cell. Moreover, Melphalan causes a more pronounced arrest than its D-enantiomer of the incorporation of labelled methionine into tumour proteins[88]. It also arrests the incorporation of labelled aminoacids into microsomal proteins[89].

Sarkolysin alters the activity of enzymatic systems in the organism[2]. It reacts with cytochrome c *in vitro*[90] and acts in the organism on the enzymes and proteins containing sulphydryl groups[91]. Melphalan reacted with blood albumen *in vitro*[92]. Like other bifunctional alkylating agents, it affects the metabolism of nucleic acids or nucleoproteins[34,93-96]. In a study of the kinetics of the reaction of Sarkolysin with DNA *in vitro*, it was shown that Sarkolysin reacts with the phosphate groups of nucleic acids[97].

Sarkolysin exhibits mutagenic activity. It damages the gene locations in Drosophila which are resistant to the action of X-rays[98].

The antitumour activities of the L- and D-forms of *p*-di-(2-chloroethyl)aminophenylalanine were investigated, but the difference between the biological effects of the two forms has not as yet been completely elucidated. Possibly the difference depends on the nature of the tumour itself[99,100]. The L-enantiomer gave rise to marked leukopenia in rats, although its dose was smaller by a factor of 4 than that of its D-enantiomer[101]. In contrast to Sarkolysin, Melphalan lowered the amount of DNA in the intestine of experimental animals and was more toxic[102].

A number of derivatives of *p*-di-(2-chloroethyl)amino-phenylalanine substituted in the carboxy- and amino-groups have been synthesised (Table 3):

$$p\text{-}(ClCH_2CH_2)_2\,NC_6H_4CH_2CH\,(NHR)\,COR'.$$

The antitumour activity and toxicity of the lower esters differ little from those of Sarkolysin itself[101,124]. On the other hand, the *N*-acyl derivatives proved to be less toxic and the spectrum of their antitumour activity (their effect on various curable tumour strains in rodents) differed from that of Sarkolysin[101,124-128].

Table 3.

Optical configuration	R	R′	Refs.
DL	H	OCH_3	103
DL	H	OC_2H_5	104
L	H	OC_2H_5	105
DL	H	$OCH_2C_6H_5$	106
L	H	NH_2	105
DL	H	2-aminothiazole	107
DL	H	3-aminohomopiperidinone	108
DL	H	$NHNH_2$	109
DL	H	$NHNHCOCH_2C_6H_4N(CH_2CH_2Cl)_2$	109
DL	H	$NHN{=}CHC_6H_4N\,(CH_2CH_2Cl)_2$	109
DL	CHO	OH	110
DL	^{14}CHO	OH	111
L	CHO	OC_2H_5	105
L	CHO	NH_2	105
L	CHO	NHC_2H_5	105
DL	CHO	$NHC_6H_4COOC_2H_5$	103
DL	CHO	2-aminothiazole	107
DL	CHO	2-amino-1,3,4-thiadiazole	112
DL	CHO	*DL*-3-aminohomopiperidinone	108
D*L*	CHO	$NHNH_2$	109
DL	CHO	$NHNHCOCH_2C_6H_4N\,(CH_2CH_2Cl)_2$	109
DL	CHO	$NHN\text{-}CHC_6H_4N\,(CH_2CH_2Cl)_2$	109
DL	CH_3CO	OH	113
DL	CH_3CO	cholesterol	114
DL	CH_3CO	β-cytosterol	115
DL	CH_3CO	pregnolone	115
DL	CH_3CO	Δ^3-dehydroepiandrosterone	115
DL	CH_3CO	2-aminothiazole	107
DL	CH_3CO	2-amino-4-methylthiazole	107
DL	CH_3CO	piperidine	107
DL	CH_3CO	morpholine	107
DL	CH_3CO	2-aminomethylthiazole	116
DL	CH_3CO	4-aminomethylthiazole	116
DL	CH_3CO	4-aminomethyl-2-methylthiazole	116
DL	CH_3CO	5-aminothiazole	116
DL	CH_3CO	2-amino-1,3,4-thiadiazole	112
DL	CH_3CO	3-amino-1,2,4-triazole	112
DL	CH_3CO	5-amino-1,2,3,4-tetrazole	112
DL	CH_3CO	*DL*-3-aminohomopiperidinone	108
DL	CH_3CH_2CO	OH	117
DL	CH_3CH_2CO	OCH_3	117
DL	$CH_3\,(CH_2)_2CO$	OH	117
DL	$CH_3\,(CH_2)_2CO$	OCH_3	117
DL	$CH_3\,(CH_2)_3CO$	OH	117
DL	$CH_3\,(CH_2)_3CO$	OCH_3	117
DL	$CH_3\,(CH_2)_{14}CO$	OH	117
DL	$CH_3\,(CH_2)_{14}CO$	OCH_3	117
DL	$CH_3\,(CH_2)_{14}CO$	OC_3H_7-iso	117
DL	$CH_3\,(CH_2)_{14}CO$	$OCH_2C_6H_5$	117
DL	$CH_3\,(CH_2)_{16}CO$	OC_3H_7-iso	117
DL	$HOOC\,(CH_2)_2CO$	OCH_3	117
DL	nicotinoyl	OH	117
DL	nicotinoyl	OCH_3	117
DL	nicotinoyl	OC_3H_7-iso	117
DL	nicotinoyl	$OCH_2C_6H_5$	117
DL	$ClCH_2CO$	OC_3H_7-iso	113
DL	ICH_2CO	OH	118
DL	ICH_2CO	OC_3H_7-iso	113
L	$COCH_2CO$	OC_2H_5	105
DL	C_6H_5CO	NH_2	119
DL	C_6H_5CO	NHC_2H_5	119
DL	C_6H_5CO	NHC_6H_{11}	119
DL	*p*-$(ClCH_2CH_2)_2NC_6H_4CH_2CO$	OC_2H_5	120
L	1-$(CH_3)_2N$—naphthyl–5-SO_2	OH	121
L	1-$(CH_3)_2N$—naphthyl–5-SO_2—$NHCH_2CO$	OH	121
L	1-$(CH_3)_2N$—naphthyl–5-SO_2NHCH_2CO	OC_2H_5	121
DL	$HN\,(CH_2)_3OP(O)$	OC_2H_5	122
DL	tetracyclinemethylene	OH	123
DL	hydroxytetracyclinemethylene	OH	123

In a study of the reaction of *N*-formyl- or *N*-acetylsarkolysin with blood plasma it was found that these preparations are bound to the plasma to the extent of 60%, while Sarkolysin is bound only to the extent of 24%.[129]

Labelled *N*-[^{14}C]formylsarkolysin was synthesised and its metabolism in the rat organism was investigated[111]. When administered in a dose eight times as large as that of Sarkolysin, *N*-formylsarkolysin arrested the incorporation of labelled phosphorus into nucleic acids in rat spleen, into Erlich ascites carcinoma of mice, and into the DNA of Yoshida sarcoma[130].

N-Formylsarkolysin and *N*-acetylsarkolysin proved to be active mutagenic agents for Actinomyces. Their activity greatly exceeds that of Sarkolysin[131].

Preliminary data on the application of *N*-formylsarkolysin in clinical practice have been established. It has proved active in the treatment of the seminoma of testicles[132]. *N*-Methylsarkolysin was also tested under clinical conditions. Its antitumour activity proved to be similar to that of Sarkolysin[133].

2. Peptides of *p*-di-(2-chloroethyl)aminophenylalanine

The comparatively low selectivity of the antitumour action of Sarkolysin and its simplest derivatives made it desirable to search for more effective preparations. The research begun by Knunyants and Kil'disheva and coworkers in 1956 on the synthesis of Sarkolysin peptides proved to be particularly fruitful[110]. Somewhat later Bergel and Stock published a paper describing the synthesis of peptides of *N*-benzoyl-melphalan[119]. Knunyants and Kil'disheva and coworkers investigated mainly the peptides of Sarkolysin formed via its carboxy-group, while Bergel and coworkers studied Melphalan peptides formed via its amino-group.

So far many peptides of *p*-di-(2-chloroethyl)aminophenylalanine, where it is the *N*- or *C*-terminal aminoacid or is located in the centre of the chain, have been synthesised and investigated. Peptides with a free amino-group of Sarkolysin or another aminoacid as well as those where the amino-group is protected by an *N*-acyl group are known (Table 4).

It was shown that the antitumour activity of these peptides is almost independent of whether the terminal aminoacid has a free carboxy-group or whether the latter is protected by the formation of an ester or an amide[101,105].

The role of the free amino-group in Sarkolysin peptides proved to be very important. The investigators arrived at the interesting conclusion that the toxicity and antitumour activity of Sarkolysin peptides containing a free amino-group are indistinguishable from those of Sarkolysin itself. This phenomenon was noted in a series of peptides where Sarkolysin is the *N*-terminal aminoacid[147] and the peptides where the free amino-group is in the residue of another aminoacid[53,101,105,145]. The only exception was the ethyl ester of Sarkolysylphenylalanyl-leucine, which, in the form of a salt of methylenedi-(*β*-hydroxynaphthoic) acid, showed a superior effect to that of Sarkolysin in relation to sarcoma 45 and Jensen sarcoma[148].

When the amino-group in peptides with *N*- or *C*-terminal Sarkolysin is protected by an *N*-formyl or *N*-acetyl residue, the biological activity is altered sharply. Such peptides are much less toxic than Sarkolysin and their chemotherapeutic indices are better[105,149,150]. One preparation of this series—the ethyl ester of *N*-acetylsarkolysylvaline (Asaline) was tested under clinical conditions on 49 patients with different forms of cancer. It proved to be less toxic than Sarkolysin, had a less pronounced effect on the blood generating system, and showed an objective effect on reticulocytic sarcoma and myeloma[151].

It is interesting to note that, although the biological activity of Sarkolysin differs from that of its *N*-acyldipeptides, the mobility of the chlorine atoms remains the same[101,105].

Table 4.

Compound	Configuration of aminoacid	References
H—Sarc—Val—OH; —OEt	*Dl*, *L*	106, 131
H—Sarc—Met—OEt	*DL*	103
H—Sarc—Phe—OEt	*DL*	103
H—Sarc—Glu—(OEt)$_2$	*DL*	135
H—Sarc—Abu—OH; —OEt	*DL*	136
H—Sarc—β-Abu—OH; —OEt	*DL*	137
H—Sarc—Hyp—OEt	*DL*	18
H—Sarc—Arg—OMe	*DL*	138
Form—Sarc—Gly—OEt	—	110, 120
Form—Mel—Gly—OEt		105, 110, 134
Form—Sarc—Val—OH; —OEt	*DL*	110
Form—Sarc—Leu—OEt	*DL*	110
Form—Sarc—Phe—OEt	*DL*	110
Form—Sarc—Try—OEt	*DL*	110
Form—Sarc—Met—OEt	*DL*	120
Form—Sarc—Glu— (OEt)$_2$	*DL*	135
Form—Sarc—Pro—OEt	*DL*	103
Form—Sarc—Hyp—OEt	*DL*	18
Form—Sarc—β-Ala—OEt	*DL*	110
Form—Sarc—Abu—OH;	*DL*	136
Form—Sarc—β-Abu—OH	*DL*	137
Form—Sarc—Cys (S—ClCH$_2$CH$_2$—)—OEt	*DL*	120
Form—Sarc—Homocys (Bz)—OEt	*DL*	120
Ac—Sarc—Gly—OEt	—	139
Ac—Sarc—Ala—OEt	*DL*	140
Ac—Sarc—Val—OH; —OEt	*DL*	134, 140, 141
Ac—Mel—Val—OEt	*L* and *D*	142
Ac—Med—Val—OEt	*L* and *D*	142
Ac—Sarc—Leu—OEt	*DL*	143
Ac—Sarc—Ile—OEt	*DL*	143
Ac—Sarc—Phe—OEt	*DL*	139, 140
Ac—Mel—Phe—OEt	*L* and *D*	141, 142
Ac—Med—Phe—OEt	*L* and *D*	141, 142
Ac—Sarc—Met—OEt	*DL*	140
Ac—Mel—Met—OEt	*L* and *D*	141
Ac—Med—Met—OEt	*L* and *D*	141
Ac—Sarc—Cys—OEt	*DL*	140
(Ac—Sarc)$_2$—(Cys—OEt)$_2$	*L*	108
Ac—Sarc—Pro—OEt	*L*	108
Ac—Sarc—Hyp—OEt	*DL*	18
Ac—Sarc—Thr—OEt	*DL*	108
(Ac—Sarc)$_2$—Lys—OEt	*DL*	108
Ac—Sarc—Gly—(OEt)$_2$	*DL*	135
Ac—Sarc—Arg (No$_2$)—OMet	*DL*	138
Ac—Sarc—Tyr—OEt	*L* and *D*	144
Ac—Sarc—3-Hytyr—OEt	*DL*	144
Bz—Sarc—Phe—OEt	*DL*	119, 139
Bz—Sarc—Gly—OH		119
Bz—Sarc—Ala—OH	*DL* and *L*	119
Bz—Sarc—Leu—OEt	*L*	119
p-(ClCH$_2$CH$_2$)$_2$NC$_6$H$_4$CH$_2$CO—Sarc—Val—OH—OEt	*DL* and *L*	106
H—Gly—Mel—OEt		105
H—Ala—Mel—OEt	*L* and *D*	105
H—Val—Mel—OH	*L*	105
H—Val—Sarc—OH	*L*	106
H—Lei—Mel—OEt	*L*	105
H—Phe—Mel—OEt	*L*	105
H—Ser—Mel—OEt	*L*	53
(H—Cys)$_2$—(Mel—OEt)$_2$	*L*	105
H—Glu—α-(Mel—OEt)—γ-OH	*L* and *D*	53
H—Glu—α-(OH)-γ-(Mel—OEt)	*L* and *D*	53
H—Glu—α, γ-(Mel—OEt)$_2$	*L*	53
H—Asp—α-(Mel—OEt)—β-(OH)	*L*	53
H—Asp—α-(OH)—β-(Mel—OEt)	*L*	53
H—Arg—Mel—OEt	*L*	145
H—Abu—Mel—OH	*DL*	136
H—β-Abu—Mel—OH	*DL*	137
H—Val—Gly—Mel—OEt	*L*	105
H—Val—Leu—Mel—OEt	*L*—*L*	105
H—Ala—Leu—Mel—OEt	*L*—*L*	105
H—Glu—γ-(OH)—Glu—γ-(OH)—Mel—OEt	*L*—*L*	53
H—Val—Gly—Gly—Mel—OEt	*L*	105
H—Pro—Gly—Val—Phe—Mel—OEt	*L*—*L*—*L*	145
H—Val—Sarc—Val—OH	*L*—*L*	106
H—Val—Sarc—Gly—OEt	*L*	105
Form—Phe—Mel—OEt	*L*	146
Form—Abu—Sarc—OH	*DL*	136
Form—β-Abu—Sarc—OH	*DL*	137
Ac—Gly—Mel—OEt		137
Ac—Ala—Mel—OEt	*L* and *D*	137
Ac—Val—Sarc—OH	*L*	106
Ac—Val—Mel—OEt	*L* and *D*	137
Ac—Leu—Mel—OEt	*L* and *D*	137
Ac—Phe—Mel—OEt	*L* and *D*	105, 137
Ac—Phe (*p*-NO$_2$)—Mel—OEt	*L* and *D*	105, 137
Ac—Phe (*p*-NH$_2$)—Mel—OEt	*L*	105

Comparison of the biological activities of *N*-formyl- and *N*-acetyldipeptides of Sarkolysin on 35 strains of experimental tumours did not show an appreciable difference between their effects[152].

The dipeptide of *N*-formylsarkolysin, where the *C*-terminal aminoacid was tryptophan, proved to be completely inactive[149] even in large doses[152].

A difference was noted between the antitumour activities of the ethyl ester of α- and β-aspartyl-melphalan on the one hand and the analogous $\alpha\gamma$-glutamyldipeptides[53].

The optical configuration of the molecule has a marked effect on the antitumour activity of Sarkolysin in peptides. Five pairs of optically pure ethyl esters of Melphalan dipeptides were synthesised. Tests on Walker carcinosarcoma 256 showed that the dipeptides with the LL-configuration are a hundred times more active than those with the DL-configuration[146]. Analogous results were obtained for the enantiomers in the aspartyl- and glutamyl-melphalan dipeptide series[53].

All possible optical isomers of the dipeptides of *N*-acetylsarkolysin with phenylalanine, methionine, and valine have been tested. Among the dipeptides with phenylalanine and methionine, the isomers with the LL-configuration proved to be the most active and those with the DD-configuration the least active. The dipeptide with valine exhibited similar activity in relation to mouse sarcoma 37, but the same peptide proved to the most active in the LD- and DD-configurations in relation to rat sarcoma[153].

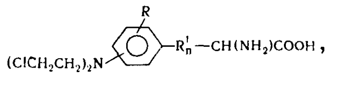
The following polypeptides of *p*-di-(2-chloroethyl)-phenylalanine have also been synthesised: $(\text{Sark.})_n$ (n = 10, 50–100),[154,155] $(\text{Mel.})_n$,[155] and $(\text{Am})_n-\text{Mel}-\text{OEt}$, where Am = Gly, Ser, Phe, Leu, SerGlu, or TyrGlu; acids with the L- and D-configurations were employed. Comparison of the antitumour properties of these polymers showed that preparations containing aminoacids with the D-configuration are less active[155]. The Sarkolysin polymer also proved to be less active[154].

3. *o*- and *m*-Di-(2-chloroethyl)aminophenylalanines

To investigate the effect of isomerism on biological activity, *o*-di-(2-chloroethyl)amino-DL-phenylalanine[104,156,157], the *meta*-derivative[65,158–161], the L- and D-enantiomers of the *meta*-isomer, and the *N*-formyl derivative[161] were synthesised. The *ortho*-isomer was more toxic than Sarkolysin and showed a similar spectrum of antitumour activity[163]. The chlorine atoms in the *ortho*- and *meta*-isomers are more easily hydrolysed than in the *para*-isomer[77]. The *meta*-isomer was more effective than Melphalan in relation to experimental tumours[158,164–166]. In a study of the antitumour activity of enantiomers of the *meta*-isomer, no difference was found between the L- and D-forms[162].

Preliminary clinical tests with the *meta*-isomer of Sarkolysin on 40 patients with cancer in different locations showed that this preparation differs little from Sarkolysin itself[167].

Other derivatives of di-(2-chloroethyl)aminophenylalanines and aminoacids with the general formula (Table 5)



were also synthesised.

Derivatives of *p*-di-(2-chloroethyl)aminophenylalanine containing halogens in the benzene ring did not show antitumour activity[185] and only 3-di-(2-chloroethyl)amino-2-fluorophenylalanine had an antitumour activity superior to that of Sarkolysin[186].

Tests on the antitumour activities of β-alanine derivatives [*p*- and *m*-di-(2-chloroethyl)aminophenyl-β-alanines] showed that they are more toxic and less effective than the analogous derivatives of α-alanine[65,174,175,187].

Table 5.

$(\text{ClCH}_2\text{CH}_2)_2N$	R	R′	n	References to syntheses
4-	2-F	CH_2	1	168
4-	2-Cl	CH_2	1	168, 169
4-	2-Br	CH_2	1	168, 169
4-	2-I	CH_2	1	161
4-	3-Cl	CH_2	1	161
3-	6-F	CH_2	1	170
4-	H	$CHNH_2^a$	1	171–173
3-	H	$CHNH_2^a$	1	65, 174, 175
3-	H	—	—	104
3-	H^f	—	—	104
4-	H	—	—	176
4-	H	CH_2	2	71,177
4-	H	CH_2^b	2	71
4-	H	CH_2^c	2	178
4-	H	CH_2^d	2	71
4-	H	CH_2^b	2	178
4-	H	CH_2	3	71, 176
4-	H	$(CH_2)_2CHNH_2^a$	1	179
4-	H	SCH_2	1	180
4-	H	SO_2CH_2	1	180
4-	H	$CH_2SCH_2^b$	1	180
4-	H	$CH_2SO_2CH_2^b$	1	180
4-	H	$CH_2S(CH_2)_2$	1	180
3-	$6\text{-}CH_3^e$	—	—	181
3-	H^e	—	—	181
4-	H^e	—	—	181
2-	$5\text{-}CH_3$	CH_2	1	182
2-	$5\text{-}NO_2$	CH_2	1	183
4-	H	CH_2^g	1	184

[a] In the general formula $NH_2 = H$; [b] ethyl ester; [c] L-enantiomer; [d] D-enantiomer; [e] *N*-acetyl; [f] CH_3 instead of H in the general formula; [g] $(ClCH_2CH_2)_2NCOO$ group instead of $(ClCH_2CH_2)_2N$.

In an attempt to find aromatic di-(2-chloroethyl) amines with a more selective activity, *p*-di-(2-chloroethyl)aminophenylalkanoic acids were synthesised[176]:

$$p\text{-}(ClCH_2CH_2)_2NC_6H_4(CH_2)_nCH(NH_2)COOH \quad (n = 0;\ 2;\ 3).$$

L- and D-forms of *p*-di-(2-chloroethyl)aminophenyl-α-aminobutyric acid were isolated. The L-isomer showed an antitumour activity in relation to mouse melanoma five times greater than the D-isomer, but its activity did not exceed that of Melphalan[71]. The analogous derivative of α-amino-Δ-phenylvaleric acid proved to be very toxic (n = 3). Comparative tests on *p*-di-(2-chloroethyl)aminophenyl-α-aminobutyric acid (under the name "aminochlorambucil") and Melphalan were carried out under clinical conditions on 47 patients with different forms of cancer. Both preparations proved to be equally active in relation to reticulosarcoma but did not exhibit any activity in other types of cancer[100].

A number of homologues of *S*-*p*-di-(2-chloroethyl)aminophenylcysteine showed a weak antitumour activity[180,188]:

$p\text{-}(ClCH_2CH_2)_2N(CH_2)_nC_6H_4S(CH_2)_mCH(NH_2)COOH \quad (n = 0;\ 1;\ \ m = 1;\ 2).$

A low antitumour activity of the corresponding *N*-benzylleucine derivative was noted[189]:

$p\text{-}(ClCH_2CH_2)_2NC_6H_4CH_2NHCH(COOEt)CH_2CH(CH_3)_2.$

4. Di-(2-chloroethyl)aminomethylenephenylalanines

All three isomers (*o*-, *m*-, and *p*-) of di-(2-chloroethyl)aminomethylenephenylalanine

$(ClCH_2CH_2)_2NCH_2C_6H_4CH_2CH(NH_2)COOH$[185,190]

and 2′-di-(2-chloroethyl)aminomethylene-5′-nitrophenylalanine[191] were synthesised and their biological activity was tested. The antitumour activities of these compounds proved to be equal to that of Sarkolysin[190].

5. Di-(2-chloroethyl)aminotyrosines

In view of the important role of tyrosine in the living organism and its enhanced content in melanoma, di-(2-chloroethyl)amino-derivatives of tyrosine were synthesised and investigated (Table 6):

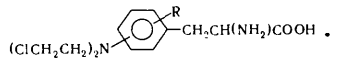


Table 6.

Position of $(ClCH_2CH_2)_2N$ group	R	References to syntheses	Position of $(ClCH_2CH_2)_2N$ group	R	References to syntheses
2-	4-OH	192	4-	2-OCH_3	168
3-	4-OH	193	4-	2-OCH_3[e]	168
3-	4-OH[a]	193	4-	2-OCH_3[e, f]	168
2-	4-OH[b]	194	4-	2-OCH_3[e, g]	168
3-	4-OH[b]	194	4-	2-OC_2H_5	168
2-	4-OCH_3	192	4-	2-OC_3H_7	168
3-	4-OCH_3	195	4-	2-OC_4H_9	168
3-	4-OCH_3[c, d]	195	5-	2-OCH_3	196
4-	2-OH	168	4-	H[h]	197

[a] L-enantiomer; [b] di-(2-chloroethyl)aminomethylene group in benzene ring; [c] *N*-phthaloyl; [d] methyl ester; [e] *N*-formyl; [f] peptide with ethyl ester of DL-valine; [g] peptide with ethyl ester of DL-phenylalanine; [h] *p*-di-(2-chloroethyl)aminophenoxy-group in benzene ring.

The chlorine atoms in 2-di-(2-chloroethyl)aminotyrosine are hydrolysed more rapidly than in Sarkolysin[193].

Di-(2-chloroethyl)aminomethylenetyrosines proved to be active in relation to Erlich ascites carcinoma in mice[194].

The antitumour activity of 2-hydroxy-4-di-(2-chloroethyl)aminophenylalanine and its alkoxy-derivatives fell with increasing size of the alkoxy-group. The 9-methoxy-derivative, which was most active, was tested under clinical conditions on 30 cancer patients[168].

N-Formyl dipeptides of this compound with ethyl esters of valine and phenylalanine were synthesised[168].

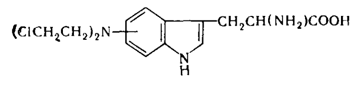
O-[*p*-Di-(2-chloroethyl)aminophenyl]-DL-tyrosine

$p\text{-}(ClCH_2CH_2)_2NC_6H_4OC_6H_4CH_2CH(NH_2)COOH$

initially did not exhibit any activity on the growth of Walker carcinosarcoma 256.[197] However, when tested in large doses on six strains of transplantable tumours, its antitumour activity proved to be considerable[144].

6. Di-(2-chloroethyl)aminotryptophans

In view of the important biological properties of tryptophan, di-(2-chloroethyl)amino-derivatives of this aminoacid were synthesised. At the present time three DL-isomers of this type are known: 5-di-(2-chloroethyl)-aminotryptophan[198,199] and 6- and 7-di-(2-chloroethyl)-aminotryptophans[200]:



Comparison of the antitumour activities of these compounds showed that the 7-isomer is more active in relation to sarcoma 180 than the 5-isomer[200]. However, the 5-isomer is more readily available and therefore its biological properties have been more thoroughly investigated. The DL-form of this compound was tested on 32 strains of transplantable tumours and its activity proved to be higher than that of Embichin and close to that of Melphalan[199]. It arrested the incorporation of labelled aminoacids into the proteins of Walker carcinosarcoma 256, particularly into the proteins of the cell nucleus[201].

The distribution of tritium-labelled 5-di-(2-chloroethyl)amino-DL-tryptophan in the organism of rats with a grafted Jensen sarcoma was investigated. The highest radioactivity was found in the kidneys and the lowest in the tumour[202].

5-Di-(2-chloroethyl)aminotryptophan was tested in clinical trails. It proved to be toxic but the authors concluded that it may be employed as a chemotherapeutic preparation for the treatment of melanoma[203].

7. Di-(2-chloroethyl)amino-derivatives of Non-natural Aminoacids

Derivatives of aromatic unsaturated aminoacids were synthesised:

$p\text{-}(ClCH_2CH_2)_2NC_6H_4CH{=}C(NHCOC_6H_5)COR,$

where R = OCH_3,[204] NH_2, NHC_2H_5, NHC_6H_{11}, Gly-OH, Gly-OEt, DL- and L-Ala-OH, L-Val-OH, L-Leu-OEt, and DL-Phe-OEt. However, no information about the antitumour activities of these compounds has been reported[119].

1-Amino-6(and 7)-di-(2-chloroethyl)aminoindan-1-carboxylic acids, 2-(and 1-)amino-7-di-(2-chloroethyl)-amino-1,2,3,4-tetrahydro-2-(and 1-)naphthoic acids, and the hydantoins derived from them were synthesised and tested. They all showed a slight antitumour activity[104,205].

Heterocyclic derivatives of alanine have been synthesised: β-[7-(4-)-di-(2-chloroethyl)aminobenzo-1,2,3-thiadiazol-4-yl-(and -5-yl)]alanine[206] and β-[5-di-(2-chloroethyl)aminobenzimidazol-2-yl]alanine and their esters[207], but data on their antitumour activities have not so far been reported.

V. AMINOACIDS AND PEPTIDES ACYLATED BY *p*-DI-(2-CHLOROETHYL)AMINOPHENYLALKANOIC ACIDS

A large number of *N*-di-(2-chloroethyl)aminoacids and their derivatives of the type $(ClCH_2CH_2)_2NC_6H_4(CH_2)_nCO$-aminoacid (its ester or peptide), with $n = 0-3$, have been synthesised and investigated. The initial di-(2-chloroethyl)aminophenylalkanoic acids exhibit antitumour activity but are toxic. A clinical application has been found for *p*-di-(2-chloroethyl)aminophenylbutyric acid, which is used under the name "Chlorobutin", "Chlorambucil" or "Leukeran" in the treatment of certain forms of leukaemia[72].

1. Aminoacids Acylated by Di-(2-chloroethyl)aminobenzoic Acids

Glycine[208,209], γ-aminobutyric acid[208], DL-[210] and L- and D-glutamic acids[211,212], the ethyl esters of these acids, and the mono-ethyl ester of the α-(*p*-ethoxycarbonylanilide) of glutamic acid[213] were acylated by *o*-, *m*-, and *p*-di-(2-chloroethyl)aminobenzoic acids.

The *ortho*-isomer of di-(2-chloroethyl)aminobenzoyl-L-glutamic acid proved to be most active in relation to Erlich ascites tumour in mice and in a tissue culture. It also showed a high activity in relation to microbiological systems. The activity of the free acids did not differ from that of the ethyl esters. Among the compounds tested, the *para*-D-isomer proved to be the least active.

The *ortho*-isomers are the most active in the case of di-(2-chloroethyl)aminobenzoylglycine and γ-aminobutyric acid[208].

The toxicity of *p*-di-(2-chloroethyl)aminobenzoyl-6-aminopenicillanic acid, which shows antibacterial activity, is lower than that of the initial *p*-di-(2-chloroethyl)aminobenzoic acid[9].

2. Aminoacids and Peptides Acylated by *p*-Di-(2-chloroethyl)aminophenyl-acetic, -propionic, and -butyric Acids

A number of such compounds have been synthesised (Table 7). One derivative of 6-aminopenicillanic acid acylated by *p*-di-(2-chloroethyl)aminophenylacetic acid is known[9].

Only the derivatives of natural aminoacids showed antitumour activity. *p*-Di-(2-chloroethyl)aminophenylacetylhexafluorovaline and -phenyl-β-alanine proved to be inactive[221]. Natural aminoacids and their esters or peptides acylated by *p*-di-(2-chloroethyl)aminophenylacetic acid are as a rule less toxic than the initial acid (by a factor of 6–19). The activity of these compounds as well as its spectrum depends on the *C*-terminal aminoacid[221–223] as in the case of *N*-acylsarkolysin peptides.

p-Di-(2-chloroethyl)aminophenylacetyl-DL-phenylalanine (Lophenal) proved to be an effective chemotherapeutic preparation for the treatment of patients with cancer of the uterus and certain forms of leukosis[224].

NN'-$\alpha\alpha'$-di-[*p*-di-(2-chloroethyl)aminophenylacetamido]propionic acid[219]

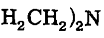
$$[(ClCH_2CH_2)_2NC_6H_4CH_2CONH]_2C(CH_3)COOH$$

showed antitumour activity. This preparation was tested under the name "Lonin 4" in clinical trials and proved to be effective in the treatment of malignant diseases of the lymphoreticular system but it also had a supressive effect of haemopoeisis[225].

Only one derivative of *p*-di-(2-chloroethyl)aminophenylpropionic acid—*NN'*-$\alpha\alpha'$-di-[*p*-di-(2-chloroethyl)aminophenylpropionamido]propionic acid—is known, but its biological properties have not been investigated[217].

Among the aminoacids acylated by *p*-di-(2-chloroethyl)aminophenylbutyric acid, antitumour activity was investigated only for the ethyl ester of valine. It proved to be less toxic than Chlorobutin itself but less active than the analogous derivative of phenylacetic acid[226].

A limited number of studies have been made in which the biological activities of Sarkolysin peptides were compared with those of peptides acylated by di-(2-chloroethyl)aminophenylalkanoic acids.

Table 7. $(ClCH_2CH_2)_2N-$$-(CH_2)_n-CO-$aminoacid, its ester, or peptide.

Aminoacid or peptide (n = 1)	Refs	Aminoacid or peptide (n = 1)	Refs.
Gly—OMe	120	Sarc—OEt	120
Leu—OEt	120	Leu—Phe—OEt	216
Val—OH; —OEt	120, 211	Phe—Lei—OEt	216
Phe—OH; —OEt;	120, 211	Phe—Met—OEt	216
Phe—$OC_2H_4N(Et)_2$	214, 215	Phe—Phe—OEt	216
Met—OH; —OEt	215	Leu—Met—OEt	216
Glu—$(OH)_2$;—$(OMe)_2$	215, 216	Leu—Leu—OEt	216
Glu—α-(OH)—γ-OEt	217	Phe—Val—OEt	216
Glu—α-(OH)—γ-OMe[a]	217	Met—Phe—Val—OEt	216
Pro—OEt	216	$\alpha\alpha'$-Diaminopropionic acid[b],	220
His—OMe[a]	218	Aminoacid or peptide (n = 3)	
Lys—$\varepsilon(NH_2)$—OH	215	Val—OH; —OEt	120
Arg(NO_2)—OH; —OMe	138	Phe—OH; —OEt	120, 211
β-Phe—OEt	120	Glu—$(OMe)_2$	216
+Ala—(β-Cl)—OMe	120	His—OMe	218
Homomet—OEt	120	Arg(NO_2)—OMe	138
Homocys(S—Br)—OEt	120	ϵ-*Amino-oenanthic* acid	216
Cys(S—$ClCH_2CH_2$)—OEt	120	*p*-NHC_6H_4COOEt	216
Hexafluorovaline-OEt	216	Phe—Leu—OEt	216
p-NHC_6H_4COOEt	216	Phe—Phe—OEt	216
$\alpha\alpha'$-Diaminopropionic acid	219	Leu—Leu—OEt	216
6-Aminopenicillanic acid	9	Met—Leu—Phe—OEt	216
		Leu—Phe—Met—OEt	216

[a] L-enantiomer; [b] n = 2.

Thus *p*-di-(2-chloroethyl)aminophenylacetylphenylalanine showed a different spectrum of antitumour activity than the ethyl ester of *N*-formylsarkolysylphenylalanine[147]. A Sarkolysin peptide with a free amino-group (the ethyl ester of sarkolysylphenylalanyl-leucine) showed a more potent antitumour activity than the ethyl ester of *p*-di-(2-chloroethyl)aminophenylacetylphenylalanyl-leucine[148].

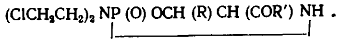
The ethyl ester of *p*-di-(2-chloroethyl)aminophenylacetylmethionine suppressed the regeneration of the liver like the initial *p*-di-(2-chloroethyl)aminophenylacetic acid or Chlorobutin, while Sarkolysin itself and certain dipeptides of *N*-acetylsarkolysin did not show such activity[227].

VI. AMINOACIDS ACYLATED BY *p*-DI-(2-CHLOROETHYL)PHOSPHORAMIDIC ACID

The higher antitumour activity and chemotherapeutic index of Endoxan (Cyclophosphamide, Cyclophosphan)—a cyclic ester of *NN*-di-(2-chloroethyl)-*N'*-γ-hydroxypropyldiamide of phosphoric acid[72]—stimulated research on other derivatives of this type including derivatives formed with aminoacids. A number of compounds with the general formula $(ClCH_2CH_2)_2NP(O)RR'$ were synthesised (Table 8).

The biological properties of only two compounds of this series have been described[234]. The compound with R = R' = Gly-OEt showed antitumour activity. The analogous thio-derivative was inactive.

Cyclic derivatives of di-(2-chloroethyl)aminophosphorylaminoacids and peptides have also been synthesised (Table 9):



$(ClCH_2CH_2)_2NP(O)OCH(R)CH(COR')NH$.

Table 8.

R	R′	Refs.
Gly—OEt	—Cl	228
DL—Leu—OEt	—Cl	228
Gly—OEt	—OPh	228
p-NH$_2$—DL—Phe—OH	—OPh	229
DL-Homoser-NHC$_6$H$_{11}$	—OPh	230
Gly—OEt	—N(CH$_2$)$_2$	228
DL—Leu—OEt	—N(CH$_2$)$_2$	228
Gly—OEt	—NHC$_6$H$_{11}$	231
Gly—OMe	R	231
Gly—OEt	R	228, 231, 232
Gly—OEt[a]	R	233
DL-Ala—OEt	R	232
β-Ala—OEt	R	228
DL-Val—OEt	R	232
DL-Leu—OEt	R	228, 232
DL-Phe—OEt	R	232
DL-Asp—OEt	R	232
DL-Gly—OEt	R	232

[a] O = S.

Table 9.

R	R′	References
—H	—OH	233, 235
—H[a]	—OH	236
—H[b]	—OH	
—H	—OMe	233
—H	—OEt	232, 235
—H[c, d]	—OEt	235
—H	-*DL*-Ser—OEt; -*DL*-Ser—OCH$_2$Ph	233
—H	-*DL*-Thr—OMe	233
—H	-*DL*-Phser—OCH$_2$Ph	233
—H	—γ-Abu—OEt	231
—H	—*p*-NHC$_6$H$_4$CH$_2$CO—OEt	233
—H	—*p*-NHC$_6$H$_4$(CH$_2$)$_3$CO—OEt	233
—Me	—OH	236
—Ph[e, f]	—OH; —OEt	235
—CH$_2$CO—OEt	—OEt	235

[a] L-enantiomer; [b] D-enantiomer; [c] O = S in ring; [d] O = NH in ring; [e] *threo*-; [f] *erythro*-.

Other compounds synthesised are the cyclic derivative of phenylserine with the DL-, LL-, and DD-configurations[236] and polyserine containing di-(2-chloroethyl)aminophosphoryl groups[236].

Tests on the antitumour activity of such cyclic derivatives of serine, serylserine, and polyserine with various optical configurations showed that they exhibit an appreciable antitumour effect and that the optical configuration is very important for biological activity[71,220]. The antitumour activity is also related to the length of the peptide component of the molecule. The polyserine derivative was less toxic and its chemotherapeutic index was higher than that of the analogous serylserine derivative[54].

Cyclic *ON*- and *SN*-derivatives of serine[54,218] and cysteine[185] respectively proved to be less active.

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The above review reveals certain regularities in the behaviour of Sarkolysin peptides and aminoacids and peptides acylated by di-(2-chloroethyl)aminophenylalkanoic acids. Sarkolysin peptides with a free amino-group exhibit a low selectivity in their effect, destroying to an equal extent not only tumour but also normal cells of the organism. Protection with *N*-formyl and *N*-acetyl groups sharply increases the selectivity of action of the compounds. The carboxy-group is not so important. Compounds with non-natural aminoacids have almost no antitumour activity.

The steric configuration of the aminoacids is extremely important. In the majority of the cases investigated peptides of the L-series showed much more pronounced antitumour activity. However, the mechanism of the biological action of these compounds has still been little investigated.

Research on the specific synthesis of antitumour preparations is only beginning and it is to be hoped that the combined efforts of chemists, biologists, and physicians in this interesting and important field will lead to useful discoveries.

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Institute of Biochemistry of
the Academy of Sciences of
the Lithuanian SSR, Vilna

Institute of Organic Derivatives
of the Elements, USSR Academy
of Sciences, Moscow

U.D.C. 547.314

The Favorskii Rearrangement

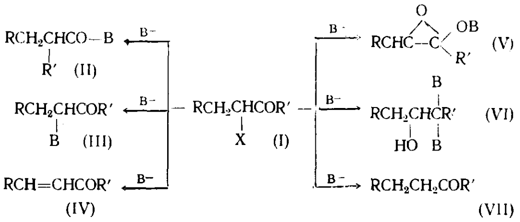
A.A.Akhrem, T.K.Ustynyuk, and Yu.A.Titov

The skeletal rearrangement of α-halogeno-ketones, which is known as the Favorskii rearrangement, is met most frequently in aliphatic monocyclic, and polycyclic halogenated ketones. This molecular rearrangement is used in the synthesis of branched carboxylic acids and *cis*-αβ-unsaturated acids and for obtaining smaller rings in alicyclic and to a less extent heterocyclic compounds. The sterochemistry and the mechanism of the Favorskii rearrangement are also considered, these being of great interest for theoretical organic chemistry. A list of 261 references is included.

CONTENTS

I. INTRODUCTION

The rearrangement of the carbon skeleton of α-halogeno-ketones (I) (here and subsequently X denotes a halogen and B^- the anion of a base), which occurs under the influence of bases, is termed the Favorskii rearrangement. Various derivatives of carboxylic acids (II) containing the same number of carbon atoms as in the initial ketone can be formed depending on the base used and the number of halogen atoms in the ketone. The α-halogeno-ketones are extremely reactive compounds, and in the presence of bases they yield also products in which the halogen has been replaced (III) or eliminated (IV), oxides (V), α-hydroxy-acetals (VI), saturated ketones (VII), etc. Which reaction occurs depends on the structure of the initial ketone and the conditions.



The rearrangement of the carbon skeleton of α-halogeno-ketones was described for the first time as a general reaction by Favorskii[1-3] in 1892, although isolated examples of such rearrangements had been known earlier[4-6]. There have been several reviews[7-12] of the Favorskii rearrangement, covering the literature up to 1959.

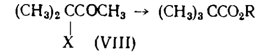
II. THE FAVORSKII REARRANGEMENT AS A SYNTHETIC METHOD

The chief synthetic uses of the Favorskii rearrangement are the preparation of branched carboxylic acids, the stereospecific synthesis of *cis*-αβ-unsaturated acids, ring contraction in alicyclic and heterocyclic compounds, and the modification of steroids.

The Favorskii rearrangement is usually effected by adding the halogeno-ketone to a solution or a suspension of the base. Hydroxides of alkali or alkaline-earth metals, alkoxides, alkali-metal carbonates and hydrogen carbonates, ammonia, and amines are used as the bases. The first two groups are strong bases, and the latter two weak bases. The solvents used can be divided into protic (water, alcohols) and aprotic (ether, dioxan, dimethoxyethane). The course of the reaction depends primarily on the structure of the initial halogeno-ketone; hence no general recommendations can be given on the choice of optimum conditions for the reaction: they must be chosen separately for each type of ketone.

1. Aliphatic Halogeno-ketones

This is the most numerous group of halogeno-ketones. Favorskii's first work on α-monochloro-ketones was done as early as 1901[13]. The principal synthetic application of these compounds is to the preparation of branched aliphatic acids, which can be illustrated by the preparation of derivatives of αα-dimethylpropionic acid from the ketone (VIII: X = Br, Cl). Sodium methoxide in ether, the prop-2-oxide, and the phenoxide give yields of 61%, 64%, and 47% of the corresponding esters[14,15]. The free acid can be obtained in 30–40% yield by reaction of the ketone (VIII) with alkalis[16,17]:

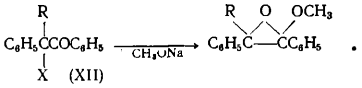


$$(CH_3)_2\underset{X}{C}COCH_3 \rightarrow (CH_3)_3CCO_2R \quad \text{(VIII)}$$

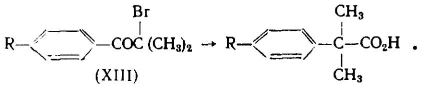
Increasing the degree of substitution at the α-carbon atom (to which the halogen is attached) usually favours the Favorskii rearrangement by lowering the rate of side-reactions, whereas substitution on the α′-atom hinders rearrangement[14,18-20]. Nevertheless, these principles are structurally equivalent: i.e. independently of the position of the halogen relative to the keto-group in compounds (IX) and (XI), the action of bases on them leads to derivatives of the same acid (X). Thus when $R^1 = R^2 = C_6H_5$, the action of sodium ethoxide on the ketone (IX) yields the acid (X: $R = C_2H_5$) in 85% yield, and on ketone (XI) in 69% yield[21]. Similar results are obtained with ketones of the types (IX) and (XI) when $R^1 = C_6H_5$, $C_6H_5CH_2$, Alk and $R^2 = H$[19,22-25]. In this case substitution of the halogen (Cl by Br) has no significant effect on the yield of the acid (X).[26,27] The equivalence of the α- and α′-positions is important in the synthetic application of the Favorskii rearrangement: it enables ketones to be brominated directly and the resulting mixture of α-bromo- and α′-bromo-isomers to be subjected to rearrangement without separation, with the formation of a single reaction product[20].

(IX) (X) (XI)

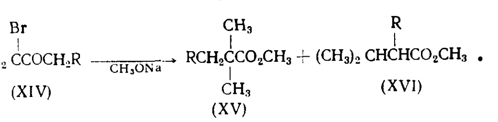
In the case of the ketones (VIII), (IX), and (XI) it has been shown that the Favorskii rearrangement takes place with both alkylated and arylated ketones. However, when aryl substituents are present on both α- and α′-carbon atoms (XII: X = Cl, Br; R = H, Alk, Ar), rearrangement is replaced by formation of the corresponding alkoxy-oxides[26,28–32]:



In the above examples the α-halogeno-ketones contained an α′-hydrogen atom. However, cases are known in which rearrangement takes place in ketones containing no α′-hydrogen, e.g. in compounds of the type (XIII: R = H, C_6H_5):[33–35]

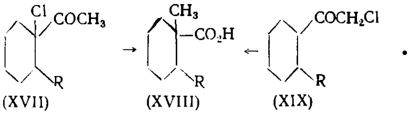


Sometimes the Favorskii rearrangement of monohalogeno-ketones yields a mixture of structural isomers. Thus ketones of the type (XIV) gave a mixture of the esters (XV) and (XVI), the proportion of the latter ester increasing from 16% to 80% with increase in the bulk of the alkyl radical R from methyl to isopropyl[36]:



Possible reasons for this are discussed in Section III.

Many halogenated ketones undergoing the Favorskii rearrangement contained the keto-group in a side-chain attached to a cyclic residue. An example is the rearrangement of compounds of the type (XVII: R = H, CH_3) to the corresponding acids (XVIII)[15,37,38]. In conformity with the above equivalence of the α- and α′-positions the same acids are formed from isomeric ketones of the type (XIX: R = H, CH_3)[39,40] (see, however, Ref. 41):

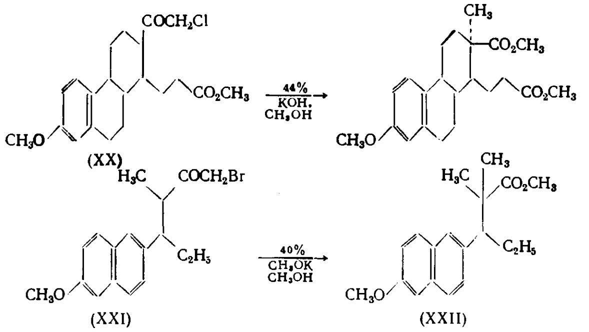


(XVII) (XVIII) (XIX)

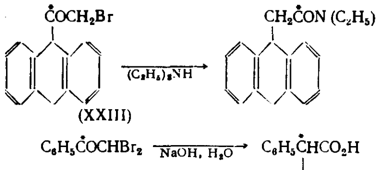
Replacement of the chlorine atom in (XIX) by bromine favours the Favorskii rearrangement but not side-reactions[39]. Other results indicate[37] that brominated ketones of the type (XIX) form only hydrolysis products with bases.

When R = CH_3, two isomeric acids (XVIII) can be formed from (XVII). It was shown initially that with sodium benzyloxide in ether the rearrangement proceeds strictly stereospecifically, with inversion of configuration at the carbon atom to which the halogen is attached[42]. Later, however, it appeared that this stereospecificity (which was not altogether exact) is observed only in aprotic solvents such as dimethyoxyethane and dimethyl sulphoxide, whereas in methanol or water a mixture of approximately equal quantities of the two possible isomers (XVIII) is formed; the proportions of the latter depend also on the concentration of the base[43–45]. Rearrangement of the isomeric chloro-ketone (XIX: R = CH_3) yields approximately equal quantities of the isomeric acids (XVIII: R = CH_3) in both protic and aprotic solvents[40].

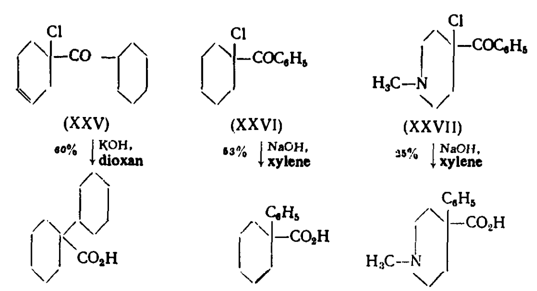
Rearrangement of the ketones (XVII) and XIX) is of interest primarily as a method for synthesising angularly methylated tertiary acids. Such structures are present in abietic, marrianolic, and allenolic acids, and therefore the Favorskii rearrangement may prove useful for their synthesis. An example of its application to marrianolic acids is the rearrangement of the chloro-ketone (XX).[46] The resulting diester on Dieckmann cyclisation gave an isomer of oestrone ("oestrone-c"). Application of the Favorskii rearrangement to the synthesis of allenolic acids is illustrated by the conversion of the bromo-ketone (XXI) into the methyl ester (XXII).[47]



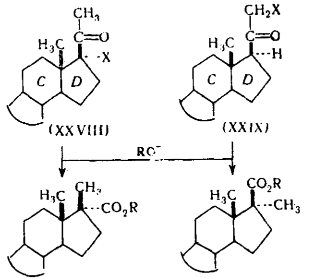
On rearrangement of the bromo-ketone (XXIII) in which the carbonyl group is labelled, in the presence of diethylamine as base, the tracer passes into the carbamoyl group, which demonstrates unambiguously that the carbon skeleton has undergone rearrangement[48]. These results are especially valuable, since only skeletal changes should be included in the range of Favorskii rearrangements. Therefore numerous examples of the reactions of α-halogeno-aldehydes with bases, for example should not be termed Favorskii rearrangements, since the carbon skeleton is not reorganised in this case, the analogy being purely formal. A tracer technique has shown that the carbon skeleton undergoes no rearrangement when the dibromo-ketone (XXIV) is converted into the corresponding hydroxy-acid[49]. Hence caution must be exercised in including reactions of dibromo-ketones of the types (XXXVII) and (XLV) in the range of the Favorskii rearrangement.



Ketones containing cyclohexyl groups (XXV)[50–52] and aryl groups (XXVI and XXVII)[53–57] undergo Favorskii rearrangement when boiled with alkalis in aprotic solvents, to form cyclic acids which are difficult to obtain by other methods. The reaction of piperidine chloro-ketones of the type (XXVII) has found application for the synthesis of the analgesics demerol and β-pethidine[54,56,58]. In optically active compounds of the types (XXVI) and (XXVII) the Favorskii rearrangement is accompanied by racemisation[54-57]. Replacement of chlorine by bromine in the ketone (XXVI) lowers the yield of the corresponding acid[59].

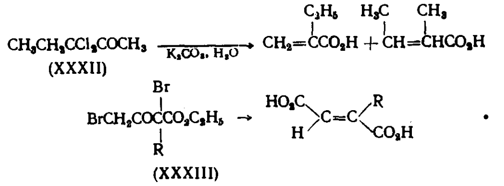


The keto-group is present in the side-chain also in 20-oxosteroids containing a halogen atom at $C_{(17)}$ (XXVIII) and $C_{(21)}$ (XXIX). In conformity with the principle of the equivalence of α- and α'-positions, rearrangement of both ketones gave good yields of a mixture of the epimeric 17ξ-methyletianic acids (XXX) and (XXXI).[60-63] The composition of the mixture depends on the structure of the initial steroid, the nature of the halogen, and the conditions of reaction. In most cases the isomer (XXXI) is formed predominantly, with maintenance of the configuration at $C_{(17)}$, both from (XXVIII: X = Br)[64-66] and from (XXIX: X = F, Cl, Br)[64,67-70]. The nature of the solvent is probably the decisive factor in the stereochemistry of the rearrangement. For example, 17α-bromopregnenolone acetate forms almost pure isomer (XXX) with sodium methoxide in dimethoxyethane, but almost pure isomer (XXXI) in aqueous potash[71].



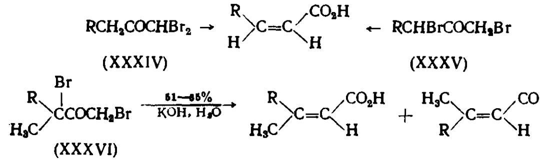
By using the product (XXXI) of the Favorskii rearrangement as starting material it was possible to accomplish a transition to highly active analogues of gestagens[63,72] and corticosteroids[70,73,74] containing a 17α-methyl group.

Di- and poly-halogeno-ketones, as well as monohalogeno-ketones, can undergo the Favorskii rearrangement. Derivatives of acrylic acids are formed from dihalogenoketones, an example being provided by the reactions of compounds (XXXII)[2,75,76] and (XXXIII: R = H, $CH_2COOC_2H_5$)[4,6,77]:



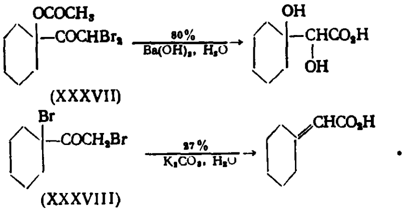
The same acids are formed in 50–90% yields by the action of bases on $\alpha\alpha$- and $\alpha\alpha'$-dihalogeno-ketones (XXXIV and XXXV: R = Alk, cycloalkyl): i.e. the equivalence of α- and α'-positions is observed here[78-82].

Therefore dibromination of ketones followed by Favorskii rearrangement (without separation of the isomers) provides a method for synthesising $\alpha\beta$-unsaturated acids[83]. The rearrangement of ketones of the type (XXXIV) and (XXXV) usually proceeds stereospecifically to yield *cis*-isomers of substituted acrylic acids. In the presence of bases, however, they readily isomerise to the more stable *trans*-isomers, which may distort the stereochemical picture of the reaction[78,80].

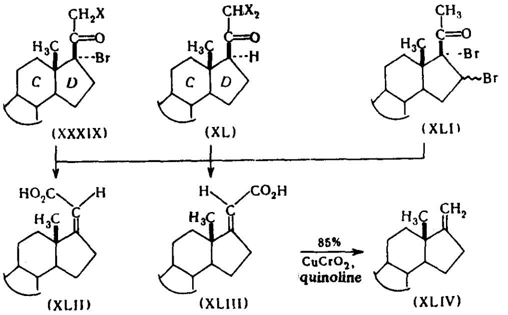


With branched dibromo-ketones of the type (XXXVI: R = Alk) the stereospecificity of the rearrangement disappears, and approximately equal quantities of the two possible isomers are formed[84,85].

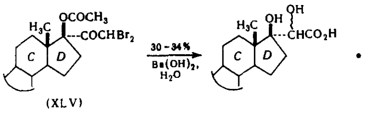
Dibromo-ketones involving a side-chain attached to a six-membered ring have also been subjected to the Favorskii rearrangement. Examples are given below for $\alpha\alpha$-dibromo-ketones of type (XXXVII)[86,87] and $\alpha\alpha'$-dibromo-ketones of type (XXXVIII)[85,88,89]:



Examples of dihalogeno-ketones in which the side-chain is attached to a five-membered ring are the steroid $\alpha\alpha'$-, $\alpha\alpha$-, and $\alpha\beta$-disubstituted ketones—(XXXIX: X = Br, I)[62,68,88,90-93], (XL: X = F, Br)[67,94], and (XLI)[95] respectively—all three types giving high yields (up to theoretical) of mixtures of the isomeric acids (XLII) and (XLIII), in which the latter isomer probably predominates[96]. These acids are used to build up a corticoid side-chain[97,98], and their decarboxylation yields a 17-methylene-steroid (XLIV)[93]. Compounds similar to (XLIV) can be obtained also by the Favorskii rearrangement of 17α-bromo-20-oxo-steroids (XXVIII) under oxidising conditions capable of detaching the carbonyl group from the intermediate cyclopropanone derivative[99].

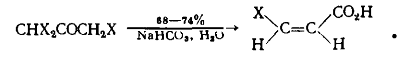


Dibromo-ketones like (XLV) containing a 17α-side-chain yield on rearrangement mixtures of diastereoisomeric 17β,20ξ-dihydroxy-acids[100,101], which are readily interconvertible under mild conditions:



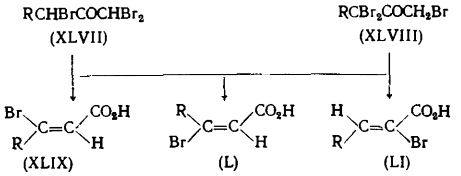
(XLV)

The Favorskii rearrangement of trihalogeno-ketones produces halogenated acrylic acids. With the simplest example, a 1,1,3-trihalogenoacetone (XLVI: X = Cl, Br), the only product is the *cis*-β-halogenoacrylic acid[102]:

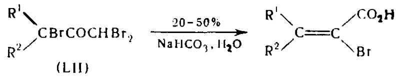


(XLVI)

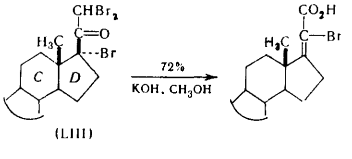
With the higher homologues—e.g. the ketones (XLVII) and (XLVIII)—structural and steric specificity is usually lost, a mixture of β- and α-halogenoacrylic acids (XLIX)–(LI) being formed, the proportions of which depend both on the bulk of the alkyl radical R and on the reaction conditions[103,104]. Replacement of one or two bromine atoms in (XLVII) or (XLVIII) by chlorine yields predominantly β-chloro-analogues of the acids (XLIX) and (L), which indicates that bromine is more readily eliminated than chlorine under the conditions of the Favorskii rearrangement[104,105].



Only α-halogenoacrylic acids are formed by rearrangement of tribromo-ketones of type (LII) containing a branched carbon chain. When $R^1 \neq R^2$, a mixture of roughly equal quantities of geometric isomers is formed[103,106]. The analogous steroid tribromo-ketones of type (LIII) yield α-bromo-acids on treatment with alkalis[96,106-108].

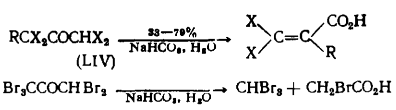


(LII)



(LIII)

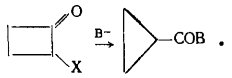
Tetrahalogeno-ketones (LIV: R = H, Alk; X = Cl, Br) undergo a Favorskii rearrangement with the formation of ββ-dihalogenated acrylic acids[109,110]. Under the conditions of the rearrangement penta- and hexa-halogenoketones are cleaved by a halogenoform reaction, as indicated below for pentabromoacetone[111,112].



2. Monocyclic Halogeno-ketones

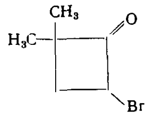
The Favorskii rearrangement has been widely applied to monocyclic halogeno-ketones to prepare compounds containing one less atom in the ring. The reaction is applicable to alicyclic and heterocyclic compounds containing 4–13 atoms in the ring.

Rearrangement of cyclobutane derivatives yields cyclopropanecarboxylic acids. An example is the reaction of the 2-halogenocyclobutanones (LV), which occurs extremely readily when X = Br and rather less readily when X = Cl[113-116]:

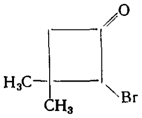


(LV)

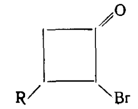
The substituted cyclobutanones (LVI), (LVII), (LVIII: R = CH_3, OC_6H_5), and (LIX) react similarly to (LV)[115,117-119]. The reactions of the disubstituted ketones (LVIII) and (LIX) occur stereospecifically with formation of the *cis*-isomers of the monosubstituted cyclopropanecarboxylic acids. The αα'-disubstituted ketone (LIX) undergoes a Favorskii rearrangement, whereas αα-substituted ketones (LX) and (LXI) undergo ring cleavage in the presence of bases with the formation of γγ-di- and ααγγ-tetra-bromobutyric acids[115]. It has not proved possible to obtain benzocyclopropene derivatives by a Favorskii type of rearrangement[120].



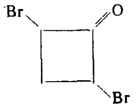
(LVI)



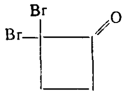
(LVII)



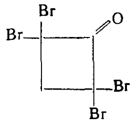
(LVIII)



(LIX)

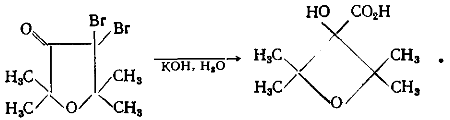


(LX)



(LXI)

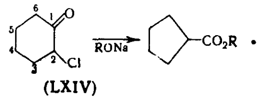
α-Halogenated cyclopentanones do not undergo the Favorskii rearrangement, but form products of polycondensation, substitution, or dehalogenation depending on the conditions[121-126]. However, condensed bromo-ketones of the type (CIX) (see below) yield the cubane system: i.e. five-membered rings are converted into four-membered rings. A similar transformation may occur when the dibromo-oxofuran (LXII) is treated with alkalis[126]:



(LXII) (LXIII)

However, the structure of the product (LXIII) cannot be regarded as completely proved.

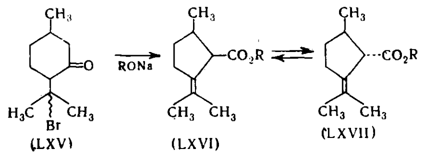
The Favorskii rearrangement of α-halogeno-ketones containing a six-membered ring has been the most thoroughly studied. A typical representative, 2-chlorocyclohexanone (LXIV), forms derivatives of cyclopentanecarboxylic acid:



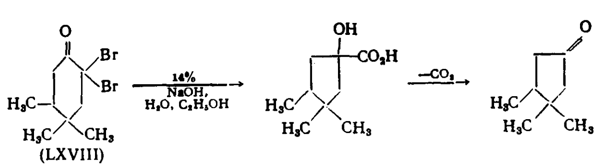
(LXIV)

A comparative study of the activity of various bases (alkalis[121,124], alkoxides[127–133], and alkyl sulphides[131,132,134–136]) has shown aliphatic branched-chain alkoxides to be the most efficient. The 2-bromo- and 2-fluoro-analogues of (LXIV) give smaller yields of the reaction products[67,137]. Alkyl homologues of (LXIV) containing substituents in positions 3–6 also undergo the Favorskii rearrangement[34,124,138–144], whereas 2-chloro-2-methylcyclohexanone does not undergo rearrangement[42,145].

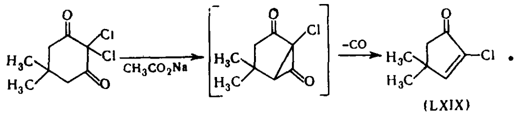
Dibromo-ketones containing a six-membered ring have been studied in especial detail in the case of pulegone dibromide (LXV)[146–153]. The pulegenic acid formed by its rearrangement can be used as a valuable intermediate for the synthesis of cyclopentanoid terpenes, which occur widely in plants and in insects. Both *cis*- and *trans*-isomers of pulegenic acid (LXVI) and (LXVII) can be obtained[154]. An attempt was made to use the stereospecificity of the reaction to establish the mechanism of the Favorskii rearrangement[155]. However, it was shown that the ratio of the isomeric pulegenic acids (LXVI and LXVII: R = H) is not a result of the rearrangement itself but depends on their ease of mutual isomerisation under the influence of bases (the equilibrium mixture contains 26% of the *cis*- and 74% of the *trans*-isomer) and on the slower rate of hydrolysis of the sterically hindered *cis*-ester (LXVI: R = CH_3, C_2H_5) in comparison with the *trans*-ester (LXVII: R = CH_3, C_2H_5). In several cases, therefore, the *trans*-acid, corresponding to the more readily hydrolysed ester (LXVII), is formed exclusively[156,157].



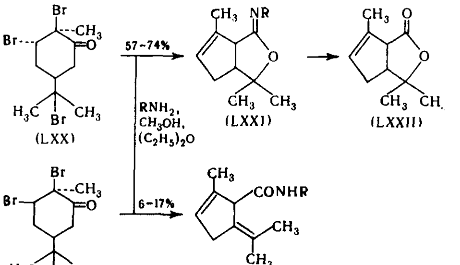
2,2-Dibromocyclohexanones of type (LXVIII) react with alkalis to form 2-hydroxy-acids, decarboxylation of which provides an easy route to the corresponding cyclopentanones[158,159]. Here, as with the ketones (LXII), (LXXVIII), and (LXXXI), it is entirely possible that the reaction may not be a Favorskii rearrangement but involve hydrolysis of (LXVIII) with formation of the 1,2-dione, which then undergoes a benzilic acid rearrangement.



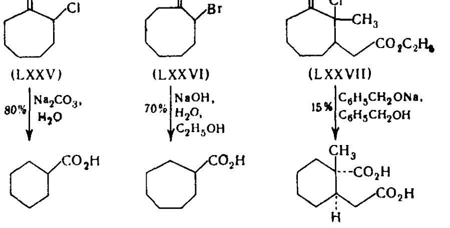
Ring contraction occurs also in the reaction of 2,2-dichlorodimedone with sodium acetate. Formation of the unsaturated chloro-ketone (LXIX) was explained by decarbonylation of the intermediate cyclopropanone derivative[160]:



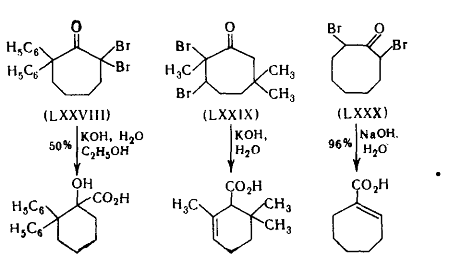
The individual tribromo-ketone isomers (LXX) and (LXXIII) or their mixtures undergo the Favorskii rearrangement under the influence of ammonia or an amine to form an iminolactone (LXXI) contaminated with an unsaturated amide (LXXIV). Hydrolysis of (LXXI) yields carvenolide (LXXII), which is the starting material for the synthesis of various iridolactones[161,162].



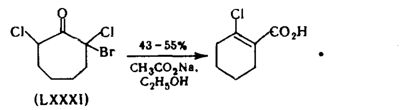
α-Halogeno-ketones containing a seven- or an eight-membered ring react with bases similarly to their six-membered analogues, forming in the Favorskii rearrangement acids containing respectively a six-membered or a seven-membered ring. Examples are the reactions of 2-chlorocycloheptanone (LXXV)[121,163,164] and of 2-bromocyclo-octanone (LXXVI)[165,166]. The α-chloro-ketones (LXXVII) gave a low yield of a compound which was a fragment of the structure of marrianolic acids[42].



Dibromo-ketones containing the halogen atoms in the αα-, αδ-, and αα′-positions—(LXXVIII)[167,168], (LXXIX)[169,170], and (LXXX)[166]—react with bases to form the corresponding unsaturated acids or hydroxy-acids containing contracted rings:



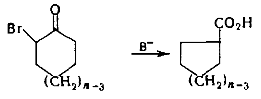
Rearrangement of the trihalogeno-ketone (LXXXI) gives a chlorinated unsaturated acid:



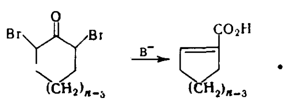
which indicates that bromine is more easily detached than is chlorine[171]. Tribromocyclo-octanone reacts similarly[166].

The Favorskii rearrangement has found application also for contracting rings of moderate size, examples being the reactions with bases of monobromo-ketones of the type

(LXXXII: $n = 10, 12$)[172,173] and dibromo-ketones of the type (LXXXIII: $n = 10$–12)[172–174]:



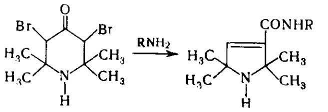
(LXXXII)



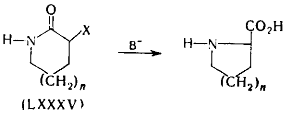
(LXXXIII)

the yields of the acids reaching 65–75%.

The Favorskii rearrangement has been accomplished also with heterocyclic α-halogeno-ketones. Thus the reaction of dibromopiperidone (LXXXIV) with ammonia or an amine yields the corresponding amide[175,176]. Analogues of proline are formed by the reaction of α-halogeno-lactams of the type (LXXXV: X = Cl, Br; n = 3, 7–11) with barium hydroxide[177–179] or with potassium t-butoxide[180]. In this case the resulting α-imino-acids may be formed by hydrolysis of (LXXXV) followed by recyclisation.



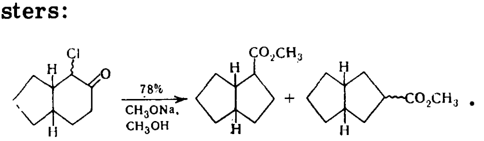
(LXXXIV)



(LXXXV)

3. Dicyclic and Polycyclic Halogeno-ketones

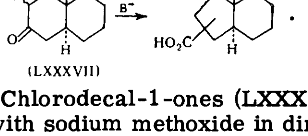
α-Halogeno-ketones containing the oxo-group in a fused carbocyclic system also undergo the Favorskii rearrangement, which provides a method for obtaining fused systems containing a smaller number of carbon atoms in the ring. The simplest example is the chloro-derivative of *cis*-perhydroindanone (LXXXVI), which under the influence of bases forms a mixture of *cis*-bicyclo[3,3,0]octanecarboxylic esters:



(LXXXVI)

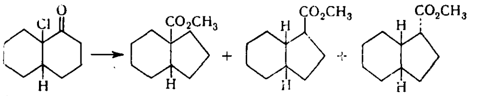
The corresponding *trans*-derivative does not undergo Favorskii rearrangement, perhaps owing to the steric strain in the *trans*-bicyclo[3,3,0]octane system[181–184].

The most widely investigated dicyclic halogeno-ketones are *trans*-decal-2-one derivatives of the type (LXXXVII: X = Cl, Br; R = H, CH_3), rearrangement of which yields a mixture of isomeric perhydroindanecarboxylic acids[142,185–189]:

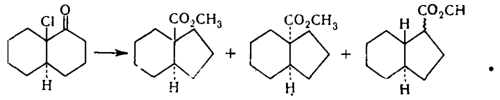


(LXXXVII)

cis- and *trans*-9-Chlorodecal-1-ones (LXXXVIII) and (LXXXIX) react with sodium methoxide in dimethoxyethane to form products which almost completely retain the initial configuration at $C_{(9)}$:



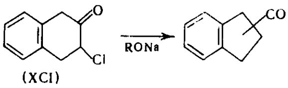
(LXXXVIII) 32% 57% 11%



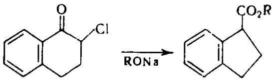
(LXXXIX) (XC) 88% 2% 10%

The yields of the products are indicated below the formulae. Especially interesting is the stereospecific synthesis of the *trans*-perhydroindane derivative (XC) with a methoxycarbonyl group between the rings[190].

The chlorotetralone (XCI) reacts with alkoxides to form the corresponding esters[140,191]. Its isomer (XCII) also forms products of the Favorskii rearrangement according to some results[140,191], but only alkoxy-oxides of type (V) according to other results[192].

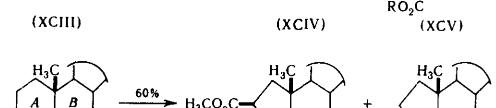


(XCI)

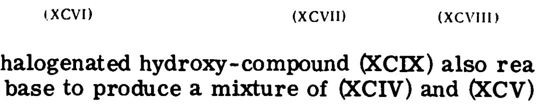


(XCII)

Application of the Favorskii reaction to halogenated steroid ketones, which are structurally related to decalone derivatives, enables modified steroids to be obtained in which A or B is a five-membered ring. The reactions of bases with halogenated cholestan-3-ones have been studied in greatest detail. Compounds in which the relative orientation of rings A and B is *trans* (XCIII) form a mixture of 2- and 3-alkoxycarbonyl isomers (XCIV) and (XCV). Some results[193,194] indicate that the former isomer (XCIV) predominates strongly, whereas others[195–198] show approximately equal quantities of the two isomers. The rate of the reaction depends on the nature of the halogen, decreasing in the sequence I > Br > Cl[143,144,199]. Compounds in which the orientation of rings A and B is *cis* (XCVI) also form a mixture of isomeric esters (XCVII) and (XCVIII)[194,200].



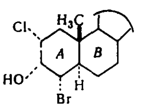
(XCIII) (XCIV) (XCV)

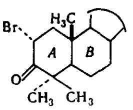


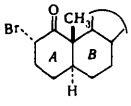
(XCVI) (XCVII) (XCVIII)

The dihalogenated hydroxy-compound (XCIX) also reacts with a base to produce a mixture of (XCIV) and (XCV)[201]. This probably involves initial dehydrohalogenation with formation of the ketone (XCIII). Yet the bromo-ketones

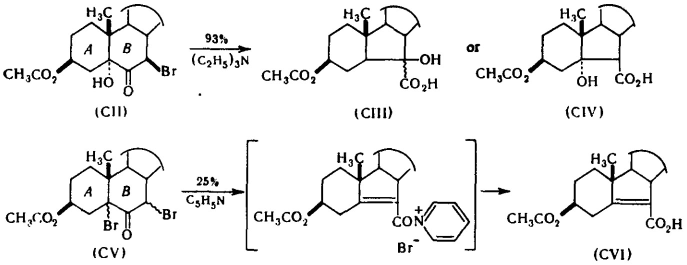
(C) and CI) do not undergo Favorskii rearrangement, but form only hydrolysis or substitution products with bases[202].


(XCIX)

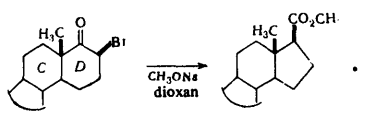

(C)


(CI)

Examples of the contraction of ring B are provided by Favorskii rearrangement involving cholestane derivatives (CII) and (CV). The structure (CIII) was ascribed to the product in the former case[203]. It has been pointed out[204] that the structure (CIV), in which the hydroxyl remains at its previous position, must be regarded as more probable. When the dibromocholestanone (CV) was boiled with pyridine, dehydrobromination products were accompanied by the B-nor-acid (CVI), probably formed via the corresponding acylpyridinium bromide[205,206].

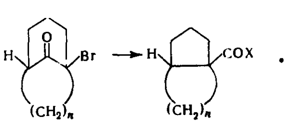


Contraction of the six-membered ring D by rearrangement of the D-homoandrostane derivative (CVII) could be accomplished only in very low yield[194,200,207]:

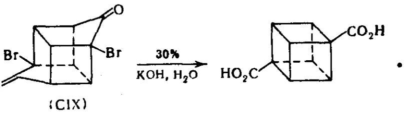


(CVII)

An interesting example of the Favorskii rearrangement involving bridged bicyclic systems is provided by the reactions of bromo-ketones of the type (CVIII: n = 5–8) with alkoxides, sodamide, silver nitrate, and mercury(II) acetate, when *cis*-isomers of derivatives of the corresponding acids (X = OH, OR, NH_2) are formed in 70–94% yield[35,208,209]:

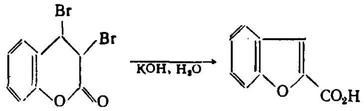

(CVIII)

The Favorskii rearrangement is applied also in the synthesis of cubane derivatives[210-212]. An example is the reaction of the dibromo-dione (CIX) with boiling aqueous alkali[213]:



(CIX)

The only example known of the Favorskii rearrangement of a bicyclic heterocycle is the reaction of mono- and di-bromocoumarins with alkalis to give acids of the type (CX)[214-218]:



(CX)

The formation of these acids can equally well be explained by opening of the pyran ring followed by recyclisation.

The results surveyed in this Section enable us to discuss the part played by the conformation of the halogen in the Favorskii rearrangement. Conformationally rigid structures (LXXXVII), (XCIII), and (XCVI), containing equatorial halogen, readily undergo rearrangement in good yield. Nevertheless, derivatives of the ketone (LXXXVII) and the chloro-ketone (LXXXIX)[219] (in protic solvents), containing axial halogen, did not undergo Favorskii rearrangement. It was therefore concluded[188] that an equatorial conformation of the halogen is necessary for this reaction to occur. However, this conclusion is disproved by other results[220], according to which the ketone (LXXXIX) containing an axial chlorine atom rearranges in aprotic solvents in high yield. Monocyclic tribromo-ketones (LXX) and (LXXIII)[162], as well as *cis*-2-chloro-4-t-butylcyclohexanone[143], also undergo Favorskii rearrangement. The presence in these compounds of a bulky 1-bromo-1-methylethyl or t-butyl substituent confers great rigidity on the axial conformation of their α-halogeno-substituents. All this indicates that the conformation of the halogen can have no significant effect on the possibility or the course of the Favorskii rearrangement.

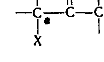
III. MECHANISM OF THE FAVORSKII REARRANGEMENT

A considerable number of papers on the mechanism of the Favorskii rearrangement have been summarised in several reviews[11,204,221-223]. Nevertheless, no mechanism has yet been suggested which would be suitable for all structural types of α-halogeno-ketones and would explain unambiguously the features of the reaction. Most workers therefore assume that the rearrangement may occur by different mechanisms depending on the structure of the initial ketone and even on the conditions.

The α-halogeno-ketones undergoing the Favorskii rearrangement, which have been discussed in the preceding sections, can be divided into four structural types (A–D) distinguished by the presence or absence of hydrogen atoms in the α- and α'-positions:

Hydrogen atoms attached to α- and α'-carbon atoms—(XI), (XIX)–(XXI), (XXIII), (XXIX), (XXXIV), (XXXV), (XL), (XLVI), (XLVII), (LV), (LVII)–(LIX), (LXIV), (LXXV), (LXXVI), (LXXX), (LXXXII)–(LXXXIV), (LXXXVI), (LXXXVII), (XCI), (XCIII), (XCVI)

A


$-\overset{H}{\underset{X}{C_\alpha}}-\overset{O}{\overset{\|}{C}}-\overset{H}{C_{\alpha'}}-$.

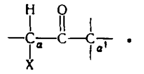
Hydrogen attached only to α'-carbon atom–(VIII), (IX), (XIV), (XVII), (XXV), (XXVIII), (XXXII), (XXXIII), (XXXVI), (XXXVIII), (XXXIX), (XLI), (XLVIII), (LII)–(LIV), (LXV), (LXX), (LXXIII), (LXXVII), (LXXIX), (LXXXI), (LXXXVIII), (LXXXIX), (CVIII), (CIX)

B


$-\underset{X}{C_\alpha}-\overset{O}{\overset{\|}{C}}-\overset{H}{C_{\alpha'}}-$.

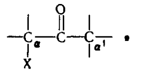
Hydrogen attached only to α-carbon atom—(XXXVII), (XLV), (LVI), (LXVIII), (XCII), (CII), (CV), (CVII)

C



No hydrogen attached to α- and α'-carbon atoms—(XIII), (XXVI), (XXVII), (LXIII), (LXXXVIII),

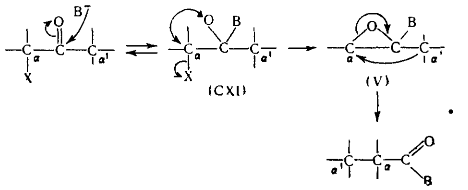
D



The equivalence of the α- and α'-positions in the Favorskii rearrangement, many examples of which have been quoted for the different structural types of ketones in subsections 1–3 of Section II, is extremely significant for the mechanism. It is convenient to divide the mechanisms which have been suggested into two groups according to whether they are able to explain this equivalence ("symmetrical" mechanisms) or require additional postulates for such explanation ("unsymmetrical" mechanisms).

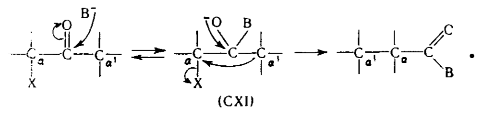
1. "Unsymmetrical" Mechanisms

The first unsymmetrical mechanism to be considered is the oxide–ester mechanism suggested by Favorskii in 1894[2,13,224], according to which the base attacks the carbonyl group to form as the first step the anion (CXI), which is converted with loss of halogen into the intermediate oxide (V), further rearrangement of which yields the final product:



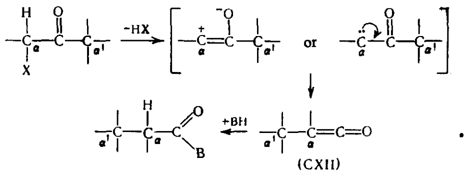
The Favorskii mechanism is applicable to all structural types of halogeno-ketones. It was considered to be supported by the isolation of oxide–ethers of the type (V: B = OR) in certain rearrangements[225,226]. However, these oxide–ethers could not be converted into the final products[227,228], and their formation is therefore a secondary process, unrelated to the main reaction.

The semibenzilic mechanism[53], so called from its resemblance to the mechanism of the benzilic rearrangement, is more soundly based. It also involves initial formation of the anion (CXI), but this then undergoes direct rearrangement with migration of the α'-atom, the oxide stage being bypassed:



The semibenzilic mechanism is also applicable to ketones of types A–D. A modified (push–pull) form of this mechanism was suggested[35] for rearrangements occurring under the influence of silver(I) and mercury(II) salts. It is noteworthy that these cations are electrophilic—not nucleophilic—reagents, and therefore cannot be regarded as usual catalysts for the Favorskii rearrangement. The semibenzilic mechanism and its push–pull modification are normally applied to ketones with which the formation of symmetrical intermediates is impossible or difficult for structural reasons. The limits of the possible applicability of the semibenzilic mechanism will be examined later in discussing symmetrical mechanisms.

According to the keten mechanism, suggested by Richard in 1938[229], the first stage in the rearrangement is the elimination of hydrogen halide from the α-atom of the initial ketone[48] (or detachment of a proton from the enolic form followed by removal of halogen[229]). The resulting dipolar or diradical (carbene) intermediates undergo direct rearrangement into a keten (CXII), which reacts with the base to form the final product:

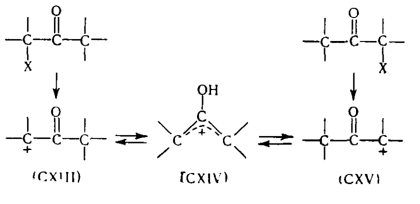


The keten mechanism is obviously applicable only to ketones of types A and C, containing hydrogen attached to the α-carbon atom. This mechanism is considered[118,119] to be inconsistent with data on the stereochemistry of the Favorskii rearrangement.

In all unsymmetrical mechanisms the carboxyl in the product should be attached to the α-carbon atom (with which the halogen was combined in the initial ketone). This leads to the conclusion that the α- and α'-positions are not equivalent with respect to the structure of the products, which is inconsistent with numerous experimental results. In order to avoid this difficulty, it was suggested that halogen migrated from α- to α'-positions, which would have explained the observed equivalence of these positions[64,65,230]. When this hypothesis was tested on acyclic[25,231] and cyclic[48] ketones, it was found that such migration of the halogen does not take place under the conditions of the Favorskii rearrangement. Therefore some "symmetrising" stage in the reaction must be postulated to explain the equivalence of α- and α'-positions.

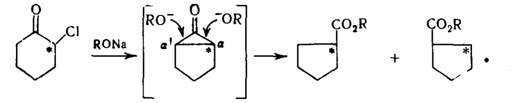
2. "Symmetrical" Mechanisms

The first "symmetrical" mechanism was put forward by McPhee and Klingsberg in 1944[22]. The symmetrising stage in this mechanism is tautomeric equilibrium between the carbonium ions (CXIII) and (CXV) formed in the first stage, through a common enolic form (CXIV), which undergoes rearrangement into the final products:



The principal defect of the above mechanism is that it does not explain the part played by the base in the reaction. According to this mechanism the rate of elimination of halogen should be independent of the concentration of the base, whereas experiment indicates kinetics of the first order with respect to B^-.[23,144] A somewhat modified form of this mechanism suggested recently is also inconsistent with experimental results[25].

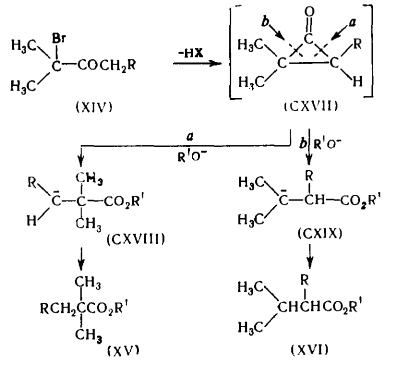
The cyclopropanone mechanism put forward by Loftfield in 1950[48,232] is free from these defects†. The rearrangement of 2-chlorocyclohexanone labelled with carbon-14 at the point of chlorination yielded a mixture of cyclopentanecarboxylic esters in which the tracer was equally distributed between the α- and β-carbon atoms (relative to the carboxyl). This was explained by the intermediate formation of a substituted cyclopropanone (CXVI), in which the α- and α′-carbon atoms were formally equivalent as a consequence of symmetry, and cleavage of the three-membered ring could occur with equal probability at the two bonds:



(CXVI)

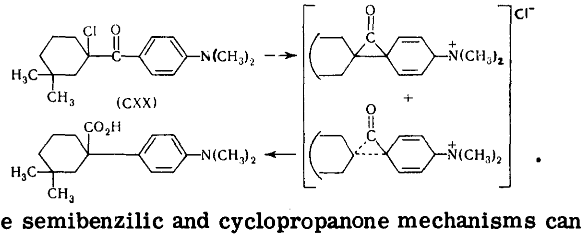
At the present time the cyclopropanone mechanism is generally accepted for the Favorskii rearrangement. It is supported by the isolation of cyclopropanone intermediate products in the reactions of monohalogeno-ketones with bases[238] and of cyclopropenone derivatives in those of αα′-dihalogeno-ketones[239,240]. Direct evidence has also been obtained that already formed cyclopropanones[241,242] and cyclopropenones[243,244] react with strong bases in conformity with the Favorskii rearrangement to form acid derivatives. Compounds in which the cyclopropane ring is separated from the keto-group by a double bond also react in similar fashion[245]. Cyclopropanone intermediates have also been isolated and identified in reactions with dienes and with methanol[246-250].

The cyclopropanone mechanism explains quite well the structural selectivity of the reaction. It is supposed that cleavage of the intermediate cyclopropanone yields the more stable of the two possible carbanions. The stability of non-conjugated carbanions increases in the sequence: tertiary < secondary < primary < benzyl[11]. In conformity with this the intermediate dimethylcyclopropanone (CXVII: R = H) formed from halogeno-ketones of the type (XIV: R = H), for example, is cleaved with the formation of derivatives of αα-dimethylpropionic acid (XV: R = H)—not of β-methylbutyric acid (XVI: R = H)—since the former are produced via the primary anion (CXVIII: R = H), and the latter via the less stable tertiary anion (CXIX: R = H). It is interesting that fission of the specially prepared dimethylcyclopropanone (CXVII: R = H) occurs in the same way under the influence of bases[242].

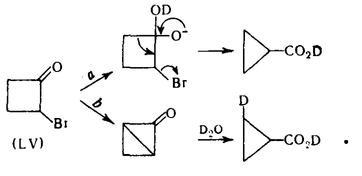


The above considerations are sufficient to explain the structural selectivity in the large majority of examples of the Favorskii rearrangement which have been studied. Recently however, results have been obtained which require more detailed account to be taken of possible operative factors[36]. Rearrangement of ketones of the type (XIV: R = Alk) is found to yield a mixture of the two possible products in which the proportion of (XVI), which is formed via the less stable tertiary carbanion (CXIX), increases with increase in the bulk of the alkyl radical R. This indicates that the course of the reaction is controlled not only by the stability of the intermediate carbanions but also by steric factors. With the ketone (XIV: R = H) these two factors act in the same direction: the intermediate product (CXVII: R = H) is attacked on the sterically less hindered side to form the more stable primary carbanion (CXVIII). In the case of ketones (XIV: R = Alk), however, these factors oppose one another, which results in the formation of a mixture of isomers. It should also be noted that the proportion of (XV: R = CH_3) in the reaction products is smaller when rearrangement is effected by sodium methoxide than with sodium ethoxide, and especially with potassium t-butoxide. This indicates that the part played by steric factors involving the base must be taken into account in addition to the influence of the bulk of the alkyl group of the alkoxide[36].

In its classic form the cyclopropanone mechanism is applicable only to ketones of types A and B, which contain the α′-hydrogen atom necessary for closure of the three-membered ring. With ketones of type C and D the semibenzilic mechanism is usually assumed without proof, their reactions being combined under the name Favorskii quasi-rearrangement, which emphasises this difference in mechanism. For several examples of the rearrangement of ketones of type D containing aryl substituents, however, the cyclopropanone mechanism can be applied in a somewhat modified form. Thus rearrangement of the ketone (CXX) and its heterocyclic analogues, which is accompanied by racemisation at the reactive centre, cannot be explained by a semibenzilic mechanism, but requires the acceptance of a "racemising" stage—assumed to be the formation of cyclopropanone intermediates[54-57]:



The semibenzilic and cyclopropanone mechanisms can be more reliably distinguished by investigating the incorporation of deuterium into the final product when the reaction is conducted in a deuteriated solvent. The difference between these mechanisms can be conveniently explained with the rearrangement of 2-bromocyclobutanone (LV) in heavy water as example:



According to the semibenzilic mechanism (*a*) the resulting cyclopropanecarboxylic acid should not contain deuterium

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† A mechanism involving cyclopropanone intermediates was suggested as early as the 1890s[2,77,233,234]. It unites the Favorskii rearrangement with similar rearrangements of α-halogeno-sulphones[235], α-halogeno-amides[236], halogenated diazoethers[237], etc.

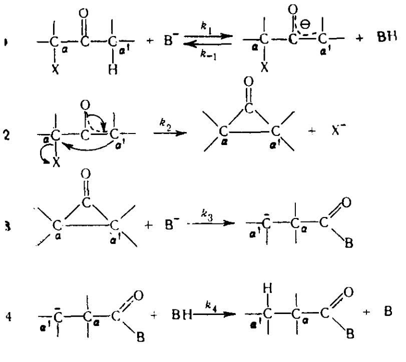
in the ring, whereas the cyclopropanone mechanism (*b*) leads to a deuteriated product. The undeuteriated acid obtained experimentally indicated that this reaction had a semibenzilic mechanism[119,251]. A more exact interpretation of the process requires that the exchange of deuterium between ketone and heavy water, unconnected with the Favorskii rearrangement, should be taken into account. According to the unsymmetrical scheme (*a*) the *α*- and *β*-carbon atoms (with respect to the carboxyl) should have different degrees of deuteriation, but according to the symmetrical scheme (*b*) they should be the same. Investigations on this basis confirmed the semibenzilic mechanism of the Favorskii rearrangement for the ketone (LV)[252].

Nevertheless, the rearrangement of 17*α*-bromo-20-oxo-steroids of the type (XXVIII) in deuteriated solvents (D_2O, CH_3OD) yielded predominantly the products (XXX) and (XXXI) containing one deuterium atom in the 17-methyl group. This is evidence of the cyclopropanone mechanism of this reaction (exchange of deuterium between the ketone and the medium is negligible here)[66].

As a third example we can consider the mechanism of the Favorskii rearrangement of ketones of the type (CVIII: $n = 6-8$), determined from the entry of deuterium into the reaction products[209]. When $n = 6$, the ketone (CVIII) reacts by the semibenzilic mechanism both with NaOD–C_2H_5OD and with t-C_4H_9OK–t-C_4H_9OD. When $n = 7$, the semibenzilic mechanism operates with NaOD, but the cyclopropanone mechanism with t-C_4H_9OK. Finally, when $n = 8$, the Favorskii rearrangement takes place by the cyclopropanone mechanism in both cases, as is confirmed by the racemisation of the optically active ketone (CVIII: $n = 8$) during the reaction. Thus with compounds of type (CVIII) the mechanism of the rearrangement may depend not only on the structure of the initial ketone but also on the reaction conditions.

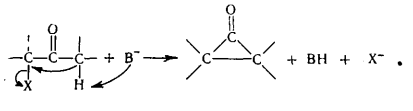
The kinetics and stereochemistry of the Favorskii rearrangement are usually explained in terms of the cyclopropanone mechanism. The elementary form of this mechanism outlined above becomes inadequate to explain all the kinetic and stereochemical results. We must therefore examine in detail existing views on the sequence of stages in the rearrangement, the significance of each of them, and also the nature of the transition state. The most probable variant of the cyclopropanone mechanism can be represented in its complete form by the four-stage scheme 1.

Scheme 1



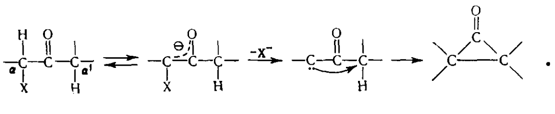
The first stage in the Favorskii rearrangement according to this scheme consists in enolisation of the ketone with loss of the *α*'-proton. In the second stage the resulting enolate splits off halogen as the anion and gives a cyclopropanone intermediate. This is followed by opening of the cyclopropanone by the anion of the base (third stage) and reaction of the resulting carbanion with the base to yield the final product (fourth stage). Stages 3 and 4 are supposed to occur so rapidly that they have no effect on the overall rate of the process.

The above scheme of the Favorskii rearrangement has been partly modified by many authors. Thus it has been suggested that stages 1 and 2 occur synchronously and that 1,3-elimination of the hydrogen halide to form the cyclopropanone[39] takes place in a single step:



This hypothesis, however, sharply contradicts the stereochemistry of many cases of the Favorskii rearrangement which have been studied, especially among the steroids[223].

As an alternative to the above four-stage mechanism it has been suggested also that formation of the anion may involve the *α*-hydrogen atom—not the *α*'-atom—after which chlorine is detached from the same atom and the resulting carbene is converted into a cyclopropanone[221]. An argument in favour of this possibility was the ease of enolisation of the initial halogeno-ketone at the *α*-atom. This peculiar combination of carbene and cyclopropanone mechanisms imposes additional structural limitations on the initial ketone, and is applicable only to halogeno-ketones of type A, containing hydrogen on both *α*- and *α*'-carbon atoms:



Neither of the above modifications of the main scheme is consistent with the kinetic and stereochemical data[23,25], and is therefore rejected by most authors at the present time. The kinetics and the stereochemistry of the Favorskii rearrangement are usually interpreted in terms of a four-stage scheme. The rate-determining stage in the reaction is established by study of deuterium exchange between the ketone and the medium and of the effect of the nature of the halogen.

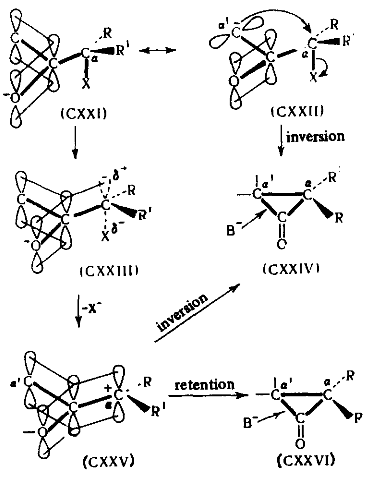
Enolisation at the *α*'-atom as the first stage in the Favorskii rearrangement is proved by the occurrence of deuterium exchange between this position in the halogeno-ketone and the medium or by conducting the reaction in a deuteriated solvent or with a deuteriated halogeno-ketone. Such exchange is observed to some extent with most halogeno-ketones—both acyclic ketones of types (IX), (XI), and (XVII)[23,25,40,253-255] and 2-halogenocyclohexanones and their derivatives[144,256]—and also with 2*α*-halogeno-3-oxo-steroids[143,144,199]. Yet it is negligible with 17*α*-bromo-20-oxo-steroids (XXVIII)[66] and 9-chloro-*trans*-decal-1-one (LXXXIX)[219]. The occurrence of stage 1 explains also the catalytic effect of certain salts (lithium chloride, lithium iodide, sodium iodide) on the Favorskii rearrangement[25,38,44]. It was assumed that these salts associate with the base formed in stage 1 (BH—methanol in the present example), thereby shifting the equilibrium in this stage to the right and increasing the concentration of the enolate.

The degree of deuterium exchange, which depends primarily on the structure of the halogeno-ketone, is of fundamental importance for comparing stages 1 and 2. We can cite as example ketones of the types $ArCH_2COCH_2X$ and $ArCH_2COCHXCH_3$, which differ only in the presence of a methyl group in the latter[25,38]. Whereas ketones of the first type exchange ~ 80% of the α′-hydrogen for deuterium before the reaction, the degree of deuterium exchange in ketones of the second type does not exceed 5%. Hence stage 1 is rapid ($k_{-1} > k_2$) in the first case: i.e. the rate of rearrangement is determined by the stage in which halogen is eliminated. In the second case, however, the presence of the methyl group increases the rate of solvolysis of the enolate and makes $k_2 > k_{-1}$. Deuterium exchange is therefore poor, and the reaction velocity is determined by the first stage—enolisation of the initial ketone.

With 4,4-disubstituted 2-halogenocyclohexanones and steroid ketones of the type (XCIII) deuterium exchange depends on the nature of the halogen[143,144,199]. In the α′-position deuterium exchange is considerably more facile with chloro-ketones than with bromo-ketones. In the first case, therefore, the rate of the reaction is determined by stage 2 ($k_2 < k_1$) and in the second case by stage 1 ($k_1 < k_2$). The group which is eliminated also has quite considerable effects in these examples: $k_{Br}/k_{Cl} = 6-116$ (according to various results). Thus, depending on the structure of the initial halogeno-ketone, the rate of the Favorskii rearrangement may be determined by either stage 1, stage 2, or both.

The electronic interpretation of the second stage in the Favorskii rearrangement, which is associated with the explanation of its stereochemistry, has also been the subject of prolonged controversy. Scheme 2 shows the chief possibilities for the occurrence of this stage.

Scheme 2



The anion produced in stage 1 in the form (CXXI) or (CXXII) can be further converted into cyclopropanone in two ways. Intramolecular substitution of S_N2 type—(CXXII) → (CXXIV)—involves inversion of configuration at the reaction centre (the α-carbon atom). This results in stereospecific formation of the cyclopropanone (CXXIV), which is opened by the base at stages 3 and 4 to give a final product having a configuration at the α-atom‡ which is the inverse of the initial configuration.

Attainment of the configuration necessary for S_N2 substitution requires considerable distortion of the normal geometry of the enolate anion (CXXI) on passing to the carbanion (CXXII), which should result in a considerable energy barrier. It was therefore suggested[257-259] that a halogeno-enolate (CXXI) first loses the anion X^- to form the delocalised intermediate (CXXIII), which gives rise to the zwitterion (CXXV). Calculations by the LCAO-MO method indicate that the change (CXXI) → (CXXV) is accompanied by an increase in the delocalisation energy, this increase being regarded as the driving force of the process. The zwitterion (CXXV) can undergo direct cyclisation of the disrotatory type into the cyclopropanone[260]. In the transition state (CXXIII) during detachment of the X^- anion the C–X bond is highly ionic in character. A considerable positive charge appears on the α-carbon atom, which can be balanced by the supply of electrons from substituents attached to the α′-atom and especially from those on the α-atom. Therefore the stage of detachment of X^- is accelerated on α′-substitution by electron-donor groups (this is reflected in the high negative value of the Hammett ρ-coefficient, from −2.4 to −5.0, in halogeno-ketones of the type $ArCHClCOCH_3$ and $ArCH_2COCH_2Cl$[23,25]) and especially by the introduction of a donor methyl group in the α-position[255]. All these results support the possibility that the reaction may occur via the zwitterion (CXXV). The planar intermediate state (CXXV), in which the centre of asymmetry has disappeared, can obviously yield on cyclisation both the cyclopropanone (CXXIV) and the cyclopropanone (CXXVI), ring-opening of which will give final products with inversion and retention of the initial configuration at the α-centre (Scheme 2).

It is now accepted that the Favorskii rearrangement may occur by both the routes considered—through (CXXII) and through (CXXV)—and the stereochemistry of the reaction is interpreted on this basis. As shown in Section II, the Favorskii rearrangement is not characterised by any definite stereochemical requirements: depending on the structure of the halogeno-ketone, the type of base, and even the concentration of the latter, it occurs with either complete retention or complete inversion of configuration, or even with formation of a mixture of isomers. However, the most thoroughly studied examples of the rearrangement of ketones of type (XVII) and (XVIII) indicate that in aprotic solvents (ether, dimethoxyethane) the reaction involves inversion of configuration, whereas in protic solvents (methanol, water) either a mixture of isomers or one isomer with retention of the initial configuration is formed. The influence of the solvent on the fate of the anion formed in stage 1 has been discussed[43,45,241]. In aprotic solvents this anion is slightly if at all solvated, and therefore its "free" negative charge may enter the reaction as the carbanion (CXXII), forming products with inversion of configuration (CXXIV). Solvation of the anion in protic solvents confers on it an enolic structure and directs the reaction through the zwitterion (CXXV) to the product (CXXIV) or (CXXVI). The relative proportions of these isomers are determined primarily by steric factors. With 17α-bromo-20-oxo-steroids (XXVIII), for example, it has been shown that, in the detachment of Br^- from the intermediate enolate (CXXVII), steric hindrance

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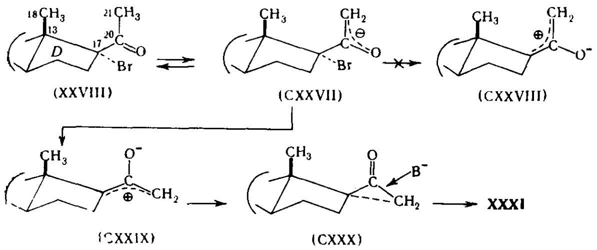
‡ The same stereochemical course of the reaction should be characteristic also of the concerted 1,3-elimination mentioned above.

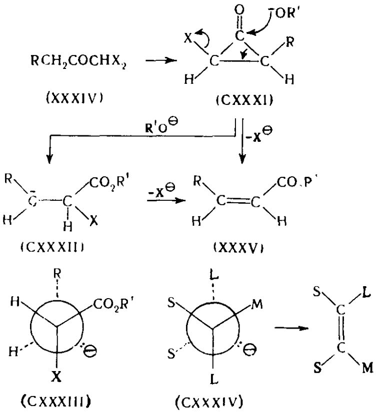
by the angular methyl group $C_{(18)}$, tending to prevent rotation about the $C_{(17)}$–$C_{(20)}$ bond, will ensure formation predominantly of the zwitterion (CXXIX), not of (CXXVIII). Cyclisation of (CXXIX) will lead to the corresponding cyclopropanone (CXXX), ring-opening of which by bases should yield a reaction product in which the initial configuration at the α-atom is retained (XXXI). Such stereochemistry is observed in protic solvents[66,71,223].



Various explanations of the stereochemistry of the Favorskii rearrangement have also been based on the intermediate formation of the cyclopropanones (stages 3 and 4)[42,43], but they are not so generally applicable, and are to some extent inconsistent with kinetic data.

The stereospecific formation of *cis*-acids of acrylic type in the Favorskii rearrangement of di- and tri-halogeno-ketones, e.g. (XXXIV), is explained on a different basis. The formation of *cis*-acids (XXXV) can be regarded[80,81] as resulting from concerted *trans*-antiparallel 1,3-elimination with formation of a *cis*-2-alkyl-3-halogenocyclopropanone (CXXXI). This product is then opened by the base into the acid (XXXV), also by a concerted process of elimination of the halide anion with preservation of the configuration.

Scheme 3



A more probable form of explanation is that the stereochemistry of the reaction is determined at the stage of elimination of halogen from the anion (CXXXII) formed when the cyclopropanone (CXXXI) is opened by the base[261]. Analysis of possible conformations of this anion indicates that the most probable type of conformation will be (CXXXIII), detachment of X^- from which will give the *cis*-acid (XXXV) stereospecifically. This conformation can be written more generally as (CXXXIV), where L denotes a large substituent, M a medium substituent, and S a small substituent (the sizes of the substituents are arbitrarily assumed to form the sequence $X > R \gg COOR > H$). This hypothesis explains most of the known facts on the stereochemistry of the rearrangement of acyclic polyhalogeno-ketones[261] (Scheme 3).

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Zelinskii Institute of Organic Chemistry,
USSR Academy of Sciences,
Moscow

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Polyphosphoric Acid in Cyclisation and Polycyclisation Reactions

E.S.Krongauz, A.L.Rusanov, and T.L.Renard

The literature data on the structure of polyphosphoric acid (PPA) and cyclisation and polycyclisation reactions in polyphosphoric acid whereby thermally stable polyheteroarylenes of various structures may be obtained are reviewed and the possible mechanisms of these reactions are discussed.
The bibliography includes 235 references.

CONTENTS

I. INTRODUCTION

Syntheses in polyphosphoric acid (PPA) are nowadays so widely employed that it is difficult to point to a branch of organic chemistry where it has not found an application.

Polyphosphoric acid was first recognised as a cyclising agent and was then extensively employed in a wide variety of reactions catalysed by acids such as condensation, esterification, hydrolysis, and acylation; polyphosphoric acid is an excellent reagent for many rearrangements, etc. The great importance which this acid has acquired in synthetic organic chemistry is shown also by numerous original papers on the subject. A number of reviews published during the period 1954–1963 give a complete bibliography on this question[1-8].

In subsequent years polyphosphoric acid found application in macromolecular synthetic chemistry. This was facilitated by a unique combination of properties in polyphosphoric acid: it is at the same time a good solvent for organic compounds, including macromolecular compounds, a proton donor which favours condensation reactions, and a cyclodehydrating agent which ensures slow intramolecular cyclisation over a wide range of temperatures. In many cases this makes it possible to carry out simultaneously two or three stages without isolating the intermediates, which is particularly important in the synthesis of polymers.

The use of polyphosphoric acid instead of other acid reagents (aluminium chloride, phosphorus pentoxide, hydrofluoric acid, and concentrated sulphuric acid) is frequently preferable, since it does not usually give rise to side reactions, in particular oxidation processes; reactions in polyphosphoric acid can be readily carried out without the need for special precautions; as a rule higher yields of the final products are obtained. Certain reactions cannot be achieved at all with other acid reagents.

This review deals with one aspect of the application of polyphosphoric acid where it has particular advantages: the cyclisation and polycyclisation reactions, which lead to the formation of low-molecular and polymeric heterocyclic compounds and which evidently take place via the same mechanism.

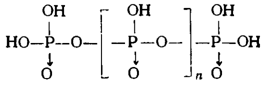
Since cyclisation processes have already been dealt with to some extent in earlier publications, this review does not quote an exhaustive bibliography on this problem. Attention was concentrated on the syntheses of heterocycles in polyphosphoric acid which have already found or may find applications in macromolecular chemistry for the synthesis of polyheteroarylenes.

II. PREPARATION AND PROPERTIES OF POLYPHOSPHORIC ACID

In the early studies phosphorus pentoxide was added to a solution of an organic compound in phosphoric acid[9,10]. Subsequently this method was improved and nowadays polyphosphoric acid is usually obtained by dissolving phosphorus pentoxide in orthophosphoric acid with heating until a homogeneous mixture is produced[10-14]. Polyphosphoric acid can also be prepared by the thermal dehydration of phosphoric acid or by treating the latter with phosphorus trioxide, but regardless of the method of preparation, polyphosphoric acid has a composition and properties which are determined by its P_2O_5 and water content[15].

Polyphosphoric acid is a complex mixture of polymeric phosphoric acid species with different degrees of condensation. A large number of studies have been made on the structure of polyphosphoric acid, among which mention should be made in the first place of the work of Thilo and Sauer[15], Bell[16], and Huhti and Gartaganis[17]. The use of β-naphthylamine and benzidine, which are capable of precipitating chains of particular length, and also paper chromatography, ion-exchange chromatography, and nuclear magnetic resonance (NMR) led to the determination of the approximate composition and structure of the complex mixture referred to as polyphosphoric acid[18-22].

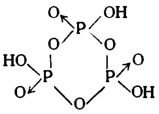
It has been shown that mixtures with 82–86% P_2O_5 contain, apart from orthophosphoric and pyrophosphoric acid, linear polyphosphoric acid with the following general structure:

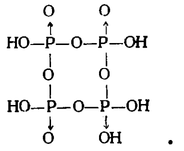


$$HO-\overset{OH}{\underset{\downarrow\atop O}{P}}-O-\left[-\overset{OH}{\underset{\downarrow\atop O}{P}}-O-\right]_n-\overset{OH}{\underset{\downarrow\atop O}{P}}-OH .$$

The Table presents the compositions of these mixtures referred to as polyphosphoric acid, since it cannot be obtained with a uniform degree of polymerisation and is always polydisperse.

When the content of phosphorus pentoxide in the mixture is higher, cyclic compounds and compounds with a three-dimensional structure are present; as a result of reaction with water, these again give rise to linear acids:





Composition of polyphosphoric acids with different contents of phosphorus pentoxide.

Mixture component	Mixture compositions with different P_2O_5 contents, wt.%		
	80.5[33]	81.6[17]	84.2[17]
Orthophosphoric acid	14	8	4
Pyrophosphoric acid ($n = 0$)	38	27	11
Triphosphoric acid ($n = 1$)	23	22	11
Tetraphosphoric acid ($n = 2$)	13	17	13
Pentaphosphoric acid ($n = 3$)	7	11	12
Hexaphosphoric acid ($n = 4$)	2	6	10
Heptaphosphoric acid ($n = 5$)	1	4	8
Octaphosphoric acid ($n = 6$)	0.2	2	6
Nonaphosphoric acid ($n = 7$)	—	2	5
Acids with higher values of n	—	1	20

The structure of these acids has been the subject of recent studies, which led to more accurate values of the angles between different bonds and also of the bond length[24,25].

Using a flexible linear acid model, Parks and van Wazer[26,27] found the theoretical distribution of acid species in PPA; their results agree with the experimental data[24]. Pearson and coworkers[28,29] investigated the specific gravity, viscosity, refractive index, and the rate of rearrangement as a function of the concentration of phosphorus pentoxide in various PPA mixtures. The measurements of the refractive index are less accurate than those of viscosity but they are simpler and may be used to determine the concentration of phosphorus pentoxide in PPA.[28]

The dissociation constants of various phosphoric acids are quoted by Quimby[30]. The ionisation constants of ortho- and pyrophosphoric acids have not been determined with adequate accuracy and the published data do not agree[31-33].

Polyphosphoric acid exhibits simultaneously the properties of an acid and an anhydride, since it contains both the acid and the anhydride groups of the initial compound used in its preparation. The anhydride groups bind the water evolved in the process, preserving thereby the effectiveness of the reagent for some time. They are then converted into acid groups, with splitting off of orthophosphoric acid molecules.

The mechanism of the hydrolysis of polyphosphoric acid was represented by van Wazer[34] in the following way: the simultaneous rupture of several P–O–P bonds in one molecular ion is impossible; the rupture takes place exclusively at the end of the chain. Thus triphosphoric, pyrophosphoric, and orthophosphoric acids are formed in succession from tetraphosphoric acid. At room temperature and at neutral pH the time required for the hydrolysis of the P–O–P linkage is several years. A decrease of the pH and an increase of temperature appreciably accelerate the hydrolysis; for example, for each 5 deg of temperature rise, the rate of hydrolysis increases by a factor of 2.

The removal of water, which is a stronger base than many organic compounds reacting under the influence of PPA, from the reaction sphere is important for the preservation of the effective acidity of the reaction medium.

The dehydrating action of polyphosphoric acid is much milder than that of phosphorus pentoxide, which makes it possible to carry out reactions at a higher temperature. Reactions in polyphosphoric acid are much more rarely accompanied by a rearrangement with a change in the carbon skeleton than in other acid agents, although they are sometimes possible[35].

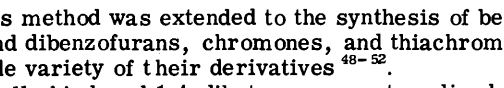
Usually polyphosphoric acid is employed in amounts such that it serves at the same time as a solvent and a reactant. However, the application of solvents in reactions with polyphosphoric acids, for example glacial acetic acid in chloroform[36], have been described. The reaction products are usually isolated by decomposing the reaction mixture with water or ice. In experiments with basic substances, it may be necessary to neutralise the dilute phosphoric acid before isolating the reaction products. Koo[37,38], Uhlig[5], and others[39,40] investigated cyclisation in polyphosphoric acid as a function of the nature of the products formed and the reactivity of the starting materials and established that the higher the melting points of the latter the more severe are the reaction conditions.

III. SYNTHESIS OF HETEROCYCLIC COMPOUNDS IN POLYPHOSPHORIC ACID

Polyphosphoric acid proved to be an effective cyclising (condensing) agent in the synthesis of a wide variety of heterocyclic systems. Numerous derivatives of indole, quinoline, isoquinoline, and others have been obtained using polyphosphoric acid; polyphosphoric acid is important in the synthesis of intermediates for many alkaloids[41], medicinal preparations[42], steroids, and other heterocyclic compounds containing nitrogen, oxygen, and sulphur[43-45].

I. Oxygen-Containing Heterocycles

Polyphosphoric acid was used for the first time in the syntheses of oxygen-containing heterocycles by Nowlin[46], who obtained diarylfurans from the corresponding 1,4-diketones in almost quantitative yields:



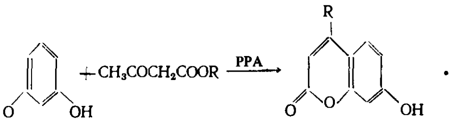
Later this method was extended to the synthesis of benzofurans and dibenzofurans, chromones, and thiachromones, and a wide variety of their derivatives[48-52].

Sterically hindered 1,4-diketones are not cyclised with formation of the furan ring; an aromatic hydrocarbon and an acid are formed under these conditions. A similar phenomenon has been observed earlier by Lutz et al.[47] in other systems.

Chromanone and 6-phenylchromanone[53] and 7-methoxychromanone and 6-nitrochromanone[52] were obtained by the cyclisation of β-phenoxypropionic acid and its derivatives in polyphosphoric acid.

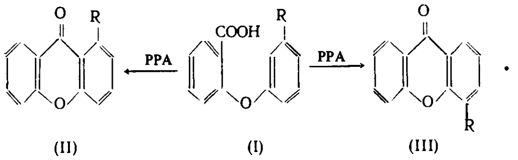
A number of substituted 1,2,3,4-tetrahydrodibenzofurans were synthesised by treating the corresponding 2-phenoxycyclohexanones with polyphosphoric acid[50].

The use of polyphosphoric acid as a condensing agent in the synthesis of coumarins by Pechmann's method[51] has been described. Thus, 4,7-dimethylcoumarin was obtained in 76% yield from m-cresol and acetoacetic ester[54] and the condensation of resorcinol with acetoacetic, α-methylacetoacetic, and benzoylacetic esters led to the synthesis of the corresponding hydroxycoumarins in very high yields[38]:



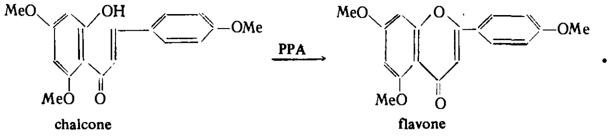
The mechanism of the formation of chromones and coumarins by Pechmann's method involving the interaction of β-arylcrotonic acids and β-ketoesters with phenols in the presence of polyphosphoric acid, has been investigated[55]. However, it is noteworthy that cyclisation does not always take place[56].

Xanthones have been synthesised with the aid of polyphosphoric acid[57]:



It has been shown that in the cyclisation of 3-substituted 2-carboxydiphenyl ethers (I) the mode of ring closure [(II) or (III)] depends on the nature of the substituent in the 3-position. For substituents with powerful-I and $-M$ effects (NO_2, COOH, CN), the ratio of products of cyclisation in the 2-position (II) and 6-position (III) is about 4 : 1, for substituents with powerful-I and $+M$ effects (NHAc, MeO), the ratio is approximately 1 : 3, and for Me or Cl as substituents the ratio is 1 : 1. The authors note that these ratios are independent of the choice of cyclising agent.

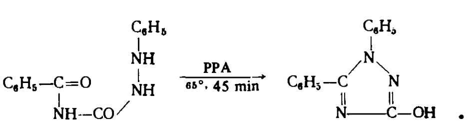
Mention should also be made of the synthesis of flavone from the corresponding chalcone in polyphosphoric acid[58]:



2. Nitrogen-containing Heterocycles

Among heterocyclic systems, the most widespread are nitrogen-containing heterocycles and, apart from other methods, their syntheses with the aid of polyphosphoric acid play an important role.

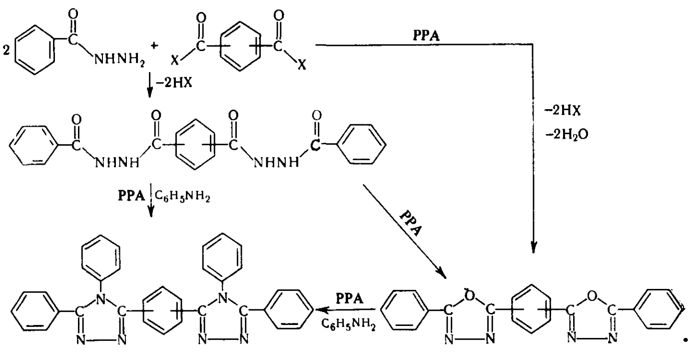
The simplest heterocycle obtained by the action of polyphosphoric acid on semicarbazide derivatives is substituted triazole:



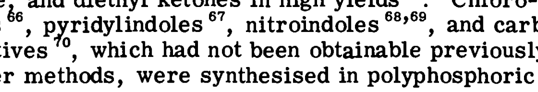
3-Hydroxy-1,5-diphenyl-1,2,4-triazole was obtained in 76% yield[59]. When the benzoyl group in the initial semicarbazide is replaced by the p-nitrobenzoyl group, 3-hydroxy-5-p-nitrophenyl-1-phenyl-1,2,4-triazole, which is unobtainable by other methods, is produced, but in the case of the 2,4-dinitrobenzoyl derivative the reaction could not be achieved[59].

3,4,5-Triphenyl-1,2,4-triazole was obtained in two ways: by treating 2,5-diphenyl-1,3,4-oxadiazole with aniline in polyphosphoric acid and by the cyclocondensation of dibenzoylhydrazine with aniline in polyphosphoric acid[60].

Holsten and Lilyquist[61] synthesised phenyl-substituted bis-1,2,4-triazoles via the following mechanism:



The Fischer synthesis of indoles, improved by the use of polyphosphoric acid, is carried out both by the cyclisation of arylhydrazones and in one stage—by the interaction of phenylhydrazine with α-ketoesters, ketones, and aldehydes[62–65]:

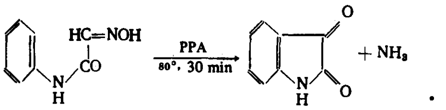


The single-stage synthesis is a general method whereby it is possible to prepare and investigate the entire series of alkyl- and aryl-substituted indoles. Thus 2-phenylindole, 3-methyl-2-phenylindole, 2-methylindole, and 3-ethyl-2-methylindole were obtained respectively from derivatives of hydrazine and acetophenone, propiophenone, acetone, and diethyl ketones in high yields[62]. Chloroindoles[66], pyridylindoles[67], nitroindoles[68,69], and carboline derivatives[70], which had not been obtainable previously by other methods, were synthesised in polyphosphoric acid.

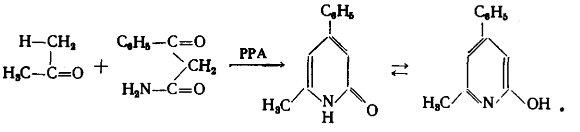
It has also been noted that polyphosphate esters are effective in the synthesis of indoles by the Fischer method, which makes it possible to carry out the reaction in boiling chloroform[71]. There exists a patent[74] for the synthesis of 2,3-dimethylindole from N-butenylaniline.

However, in many cases cyclisation to indoles does not occur[73]. Frasca and coworkers[74,75] showed that, when t-nitrophenyl hydrazones of certain acetophenones, benzaldehydes, and benzophenones are heated in polyphosphoric acid, indazoles are formed and not the expected indole derivatives; in addition, rearrangement products are isolated. Attention has been drawn to the fact that[76] polyphosphoric acid is relatively ineffective in the synthesis of indoles unsubstituted in the 2-position.

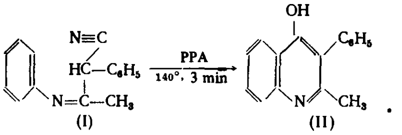
The action of polyphosphoric acid on isonitrosoacetanilide and its derivatives leads to the formation of isatin and substituted isatins in 50–60% yields via the mechanism[77]



Hauser and Eby[78] used polyphosphoric acid in the synthesis of substituted pyridones formed when β-ketoamides or β-ketonitriles reaction with ketones:



The syntheses of many derivatives of six-membered heterocyclic systems have been achieved in polyphosphoric acid. The formation of 4-hydroxyquinolines by the reaction of arylamines on β-ketoesters or β-ketonitriles (the Conrad–Limpach method) takes place smoothly in polyphosphoric acid in a single stage[79]. The anils of β-ketonitriles and β-ketoamides are also smoothly converted under the action of polyphosphoric acid into 4-hydroxyquinolines in high yields. Thus 4-hydroxy-2-methyl-3-phenylquinoline (II) was obtained from the anil (I) or directly from aniline and α-aceto-α-tolunitrile in 56% yield (instead of 4% when the usual catalysts are employed in the Conrad–Limpach method)[79]:

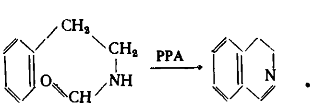


Similarly 4-hydroxy-2,3-diphenylquinoline was obtained in 34% yield.

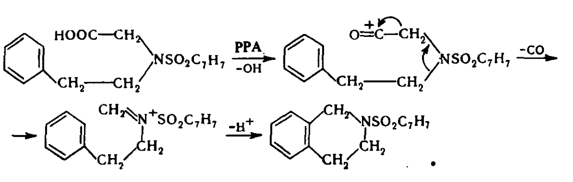
The use of polyphosphoric acid as a catalyst in the Skraup reaction was not successful[80].

6,7-Dimethoxyisoquinoline[81] and 7,8-dimethoxyisoquinoline[82,83] were synthesised in polyphosphoric acid by a modified Pomeranz–Fritsch reaction; the aminoacetyl derivatives of furfural were not cyclised under the action of polyphosphoric acid[82].

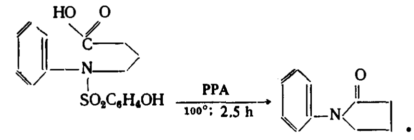
A complete study of polyphosphoric acid as a cyclodehydrating agent in syntheses of dihydroisoquinolines by the Bischler–Napieralski reaction demonstrated its high effectiveness[84]; in all cases the yields of dihydroisoquinolines in polyphosphoric acid were much higher than with other acid reagents[86–89]:



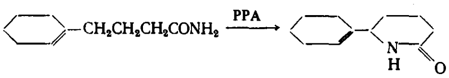
Proctor and Thompson[89] described a new method for the synthesis of tetrahydroisoquinoline derivatives. When toluenesulphonamide of N-β-phenylethylalanine is heated with polyphosphoric acid, the toluenesulphonamide of tetrahydroisoquinoline is formed instead of the expected product, probably by the following mechanism[89]:



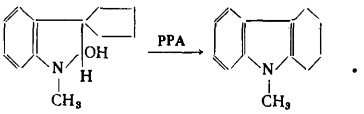
However, 1-phenyl-2-pyrrolidinone was obtained in 94% yield from the toluenesulphonamide of N-phenyl-γ-aminobutyric[90]:



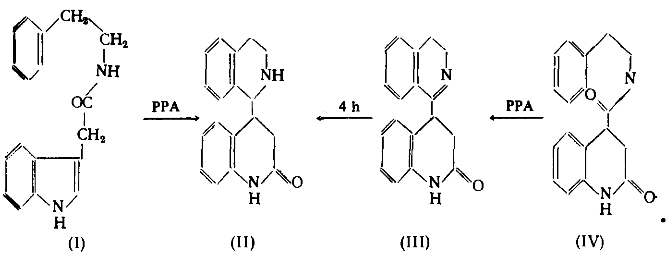
In the presence of polyphosphoric acid it proved possible to synthesise perhydro-1,4,6,9-tetraoxopyridazo-[1,2-*a*]pyridazine from succinic acid and hydrazine hydrate[91] and spiropiperidinone from γ-cyclohexen-1-ylbutyric acid amide[92,93]:



A new method has been developed for the synthesis of benz[*a*]-acridines[94]. An interesting ring expansion reaction under the action of polyphosphoric acid, consisting in the conversion of spirooxindole into 9-methyltetrahydrocarbazole and accompanied by a rearrangement of the Wagner–Meerwein type, was achieved by Witkop and Patrick[95]:

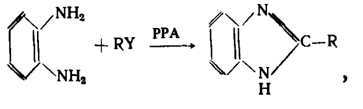


Other polynuclear heterocyclic systems synthesised in polyphosphoric acid include phenanthridine[96], 3,4-benzophenanthridine[97], 3,4-dihydro-4-phenylcarbostyril and 3,4-dihydro-4-phenylisocarbostyril[98], 2,4-dimethylindeno-[3′,2′:6,7]quinoline obtained from the anil of acetophenone and 2-aminofluorene[99], and 4-(1,2,3,4-tetrahydro-1-isoquinolyl)hydrocarbostyril, which is obtained by the rearrangement of the β-phenylethylamide of heteroauxin with subsequent cyclisation[100] according to the mechanism:



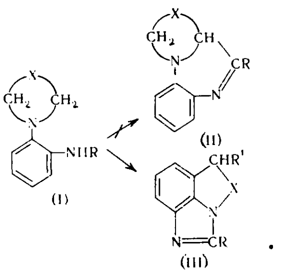
The conversion of the β-phenylethylamide (I) into the carbostyril derivative (II) can be explained only by the migration of the indoline component, which permits the formation of a six-membered ring. Structure (II) was confirmed by synthesising compounds (III) and (IV).[100] It was shown that in certain cases a mixture of polyphosphoric acid and $POCl_3$ is more effective than each component separately. In some cases the heterocycles formed were alkylated in the cyclisation process[101,102].

Polyphosphoric acid was successfully employed in the synthesis of heterocycles containing more than one nitrogen atom. 2-Substituted benzimidazoles were obtained by the following general reaction of o-diamines with carboxylic acids and their derivatives[103,104]:



where Y = COOH, COOR, $CONH_2$, or CN and R = alkyl, aryl, or substituted aryl. Similarly, using tetramines in reactions with carboxylic acids or *o*-diamines in reactions with dicarboxylic acids, bisbenzimidazoles of different structures were obtained[105,106].

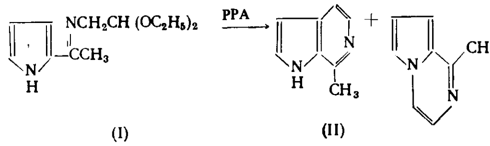
Suschitzky[83] observed an interesting and unexpected reaction involving the formation of the benzimidazole ring when *N*-2-acylaminophenyl heterocycles were treated with hot polyphosphoric acid:



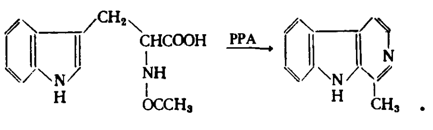
Instead of the expected 1,2-dihydroquinoxalines [(II), X = $(CH_2)_3$, $(CH_2)_4$, or $CH_2)_5$],[107] benzimidazoles (III) were obtained from the acylated amines. The authors believe that, under the action of polyphosphoric acid, the heterocyclic ring in the initial compound (I) is opened and the next stage is cyclic dehydration involving the tautomeric form of the amide N: C(OH)R, which leads to imidazole. Further alkylation of the benzene ring gives a product of type (III).

Polyphosphoric acid has found application in the synthesis of six-membered heterocycles[108-110], which could not be obtained by the Pomeranz–Fritsch and Bischler–Napieralski reactions using sulphuric acid.

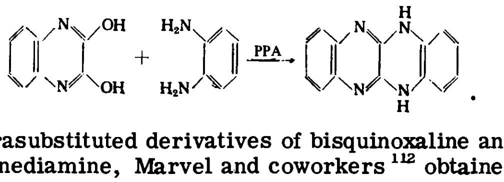
The cyclisation of Schiff bases derived from pyrrole frequently leads to a mixture of pyrazine and pyridine derivatives; for example, the aminoacetyl derivative of 2-acetylpyrrole gives a mixture of apogarmine (II) and 1-methylpyrrolo[1,2-*a*]pyrazine[108]:



Under the action of polyphosphoric acid, *N*-formyltryptophan and *N*-acetyltryptophan gave the corresponding harmans[87]:

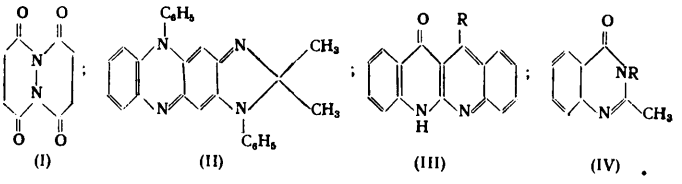


Badger and Nelson[111] obtained a new heterocycle containing four nitrogen atoms (fluoflavine) by the reaction of 2,3-dihydroxyquinoxaline with *o*-phenylenediamine in polyphosphoric acid:



From tetrasubstituted derivatives of bisquinoxaline and *o*-phenylenediamine, Marvel and coworkers[112] obtained 2,2-bisfluoflavine.

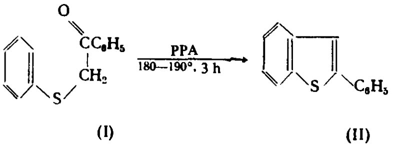
New syntheses in polyphosphoric acid of bicyclic and polycyclic nitrogen-containing systems of the following type have been developed: perhydro-1,4,6,9-tetraoxopyridazo[1,2-*a*]pyridazine (I),[113] 5,2'-dihydro-2',2'-dimethyl-5,1'-diphenylquinoxalino[5',4' : 2,3]phenazine (II),[114] 4-hydroxy-1,4-quinolono[2,3 : 2',3']quinoline (III),[115] quinazolones (IV),[116] and others[117-119]:



3. Heterocycles Containing Sulphur and Arsenic

Only a limited number of such compounds are known and the application of polyphosphoric acid in their synthesis has been investigated in much less detail than in the reactions discussed in the preceding section.

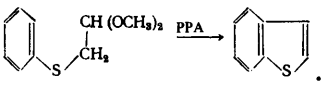
The cyclisation of α-arylthioketones of the type $AR-S-CH_2COR$, where R = aryl, is accompanied by a rearrangement and leads to the formation of 2-arylthionaphthene instead of the expected 3-arylthionaphthene[120]:



When, instead of the benzoyl derivative the acetyl derivative is employed, 3-alkylthionaphthenes are formed without rearrangement[121]. In the presence of hydrofluoric acid, compound (I) also rearranges to compound (II).[55]

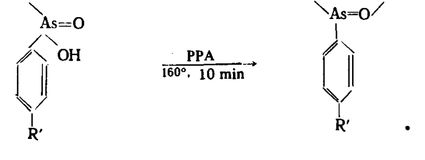
According to the data of Davies and Middleton[121], phenyl phenacyl ether undergoes an analogous rearrangement to 2-phenylbenzofuran in the presence of polyphosphoric acid. When sulphur or oxygen in the above compounds are placed by the methylene group, ring closure takes place without rearrangement[37,121].

A number of thionaphthenes were obtained in polyphosphoric acid in high yields from arylthioaldehyde acetals[122,123]:



Under the action of polyphosphoric acid, arylthiophenoxyacids also form cyclic products[124,125].

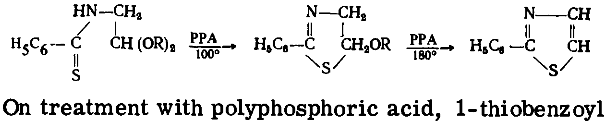
Using polyphosphoric acid, Campbell and Poller[126] synthesised arsafluorene oxide in 70% yield in one stage, while in the usual three-stage method the yield did not exceed 55%:



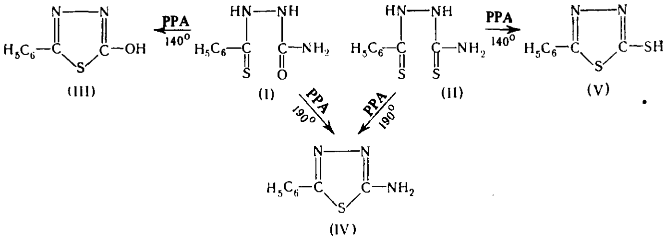
4. Mixed Heterocycles

The use of polyphosphoric acid as a condensing agent greatly extended the scope of the syntheses of a wide variety of heterocycles, including some of practical importance[127].

2-Phenylthiazoline was obtained by the cyclisation of a 2-thiobenzamidoacetal under the action of polyphosphoric acid. 5-Ethoxy-2-phenylthiazoline is formed similarly at 100°C; at a higher temperature (180°) 2-phenylthiazole is formed[128]:

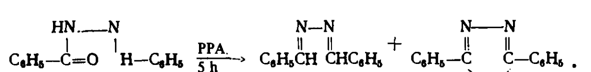


On treatment with polyphosphoric acid, 1-thiobenzoylsemicarbazide gives thiadiazole derivatives in high yields. The reaction conditions are very important for cyclisation in polyphosphoric acid; the temperature and duration of the reaction frequently determine the nature of the compound obtained. Thus in the cyclisation of thiobenzoylsemicarbazide (I) and thiobenzoylthiosemicarbazide (II) at different temperatures, various substituted 1,3,4-thiadiazoles are formed[228]:

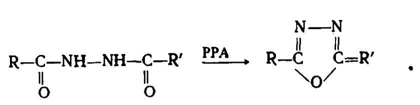


After isolation and purification, the yields were 88% of 2-hydroxy-5-phenyl-1,3,4-thiadiazole (III), 65% of 2-amino-5-phenyl-1,3,4-thiadiazole (IV), and 83% of 2-mercapto-5-phenyl-1,3,4-thiadiazole (V).

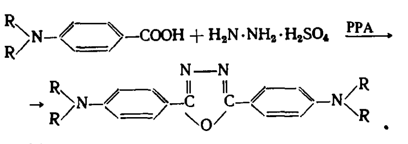
When 1-benzoyl-2-benzylidenehydrazine was treated with polyphosphoric acid under mild conditions (reaction temperature below 100°C), a mixture of benzaldazine and 2,5-diphenyl-1,3,4-oxadiazole was obtained[129]:



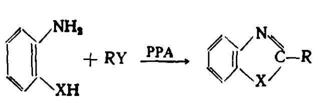
Cyclisation of hydrazine derivatives under more severe conditions (180–205°C) gives rise to derivatives of 1,3,4-oxadiazoles in quantitative yields[130,131]:



2,5-Di-(*p*-aminophenyl)-1,3,4-oxadiazole was obtained by treating *p*-aminobenzoic acid with hydrazine sulphate in polyphosphoric acid[132,133]:



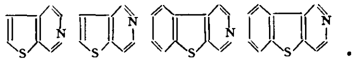
Hein et al.[104] achieved the synthesis of benzimidazoles, benzoxazoles, and benzothiazoles substituted in the 2-position by the condensation of carboxylic acids, their esters, amides, and nitriles with *o*-amino-, *o*-hydroxy-, and *o*-mercapto-anilines in polyphosphoric acid:



where X = NH, O, or S, Y = COOH, COOR, $CONH_2$, or CN, and R = alkyl or aryl.

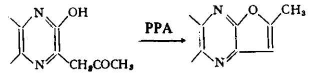
Advances have been achieved in the synthesis of bisazoles and bisbenzazoles in polyphosphoric acid[134,135].

Thieno[2,3-*c*]pyridine (I) and thieno[3,2-*c*]pyridine (II) were synthesised by the cyclisation of the Schiff bases (Pomeranz–Fritsch reaction) obtained by the reaction of formylthiophencarboxylic acids and aminoacetals in polyphosphoric acid. Thianaphtheno[2,3-*c*]pyridine (III) and thianaphtheno[3,2-*c*]pyridine (IV) were obtained in low yields. A mixture of polyphosphoric acid and phosphorus oxychloride is recommended for these syntheses[108]:

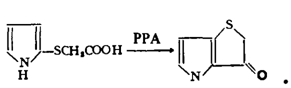


(I) (II) (III) (IV)

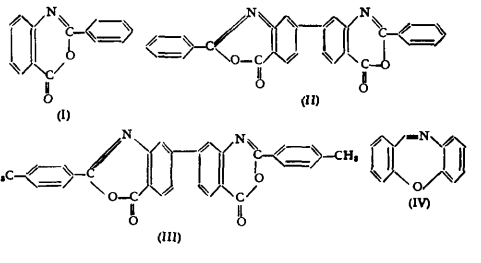
On treatment with polyphosphoric acid, xanthopterin derivatives are cyclised with formation of natural dyes—pteridines[136,137]:



A convenient method has been described for the synthesis of thieno[3,2-*b*]pyrrole, the first stage of which is the formation of 2*H*,3*H*-thieno[3,2-*b*]pyrrol-3-one as a result of the rearrangement and cyclisation of 2-pyrrolylthioacetic acid under the action of polyphosphoric acid[138–140]:

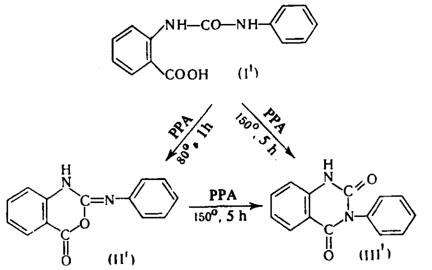


New syntheses in polyphosphoric acid of 2-phenyl-4*H*-3,1-benzoxazin-4-one (I) 2,2′-diphenyl-(6,6′-bi-4*H*-3,1-benzoxazyl)-4,4′-dione (II), 2,2′-di-*p*-tolyl-(6,6′-bi-4*H*-benzoxazyl)-4,4′-dione (III),[141,142] and a seven-membered cyclic compound (IV) containing nitrogen and oxygen as heteroatoms[143] have been developed:



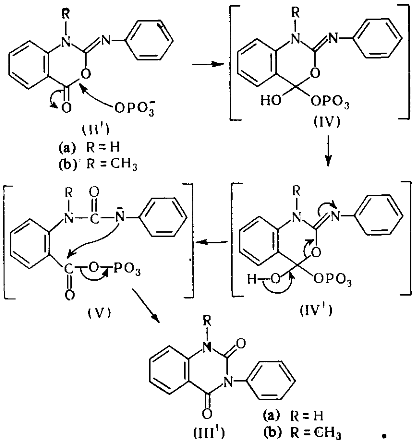
Compound (I) was obtained from benzoylanthranilic acid and compounds (II) and (III) from benzidinedicarboxylic acid and benzoyl chloride or *p*-toluoyl chloride.

The formation of the heterocycles (III′) is accompanied by an intramolecular rearrangement[141]. Thus, when *N*-phenylcarbamoylanthranilic acid (I′) is heated for 1 h at 80–100°C, 1,2-dihydro-2-phenylimino-4*H*-3,1-benzoxazin-4-one (II′) is formed (yield 95%, m.p. 193°C). Heat treatment of this acid at 150°C for 5 h leads to 3-phenyl-2,4-(1*H*)-quinazolinedione (III') (quantitative yield, m.p. 280°C):



When compound (II') is treated with polyphosphoric acid at 150°C, compound (III') is formed in 70% yield, which can only be accounted for by the migration of the ureide group.

Kurihara and Yoda[144] suggest the following mechanism for this rearrangement: on further heating of compound (II') in polyphosphoric acid, the carbonyl group of benzoxazinone is phosphorylated with formation of an intermediate (IV and IV'); subsequent ring opening leads to a mixed anhydride of a carboxylic and phosphoric acid (V). The negatively charged ureide nitrogen attacks the carbonyl group of the mixed anhydride displacing phosphoric acid. Recyclisation gives the quinazolinedione ring (II):



IV. SYNTHESIS OF POLYHETEROARYLENES IN POLYPHOSPHORIC ACID

The synthesis of thermostable polymers which can be worked constitutes one of the most urgent problems in the modern chemistry of macromolecular compounds. Considerable advances in this field have been achieved using the polyheterocyclisation reaction, whereby it is possible to obtain aromatic polymers with alternating carbocycles and heterocycles—the so called polyheteroarylenes[145]. In recent years considerable attention has been devoted to the development of new methods for polyheterocyclisation processes, among which high temperature polycyclisation in solution occupies a special place. This method has been successfully used in the first place for the synthesis of polyheteroarylenes (for example, polyimides[146]) soluble in the reaction mixture.

Naturally in reactions of this kind the correct choice of solvent is of exceptional importance. It is most useful to employ compounds with a high solvent power and a high boiling point or decomposition temperature which catalyse the reaction and bind the side products liberated (the usual side product in polyheterocyclisation reactions is water). Polyphosphoric acid meets all these requirements to a considerable degree.

Since 1960 polyphosphoric acid has been fairly extensively employed to prepare various polyheteroarylenes[147,148]. As shown above, polyphosphoric acid is an exceptionally effective condensing and cyclising agent; among the specific features of the syntheses of polyheteroarylenes in polyphosphoric acid, we shall mention the following.

1. As a rule, polycyclisation in polyphosphoric acid yields polymers with higher molecular weights than those obtained by other methods.

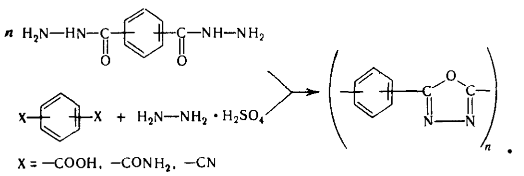
2. One of the most important problems in the synthesis of polyheteroarylenes is the attainment of the highest possible degree of cyclisation, since this parameter determines to a considerable extent the thermal and other characteristics of polymers. In solid-phase polycyclisation, macromolecular chains become increasingly rigid as the reaction proceeds, which hinders to a considerable degree the completion of the polycyclisation reaction, since the activation energy for the cyclisation process rises continuously[149] and free rotation about the bonds in the ring-forming fragments becomes more difficult.

Polyphosphoric acid behaves as a plasticiser, which is responsible to a considerable degree for the possibility of attaining a higher extent of cyclisation compared with other methods.

3. In many cases the polymers obtained in polyphosphoric acid differ significantly in their properties from polymers with similar structures prepared by other procedures. Thus poly-(1,3,4-oxadiazole-2,5-diyl-1,4-phenyleneoxy-1,4-phenylene) obtained in polyphosphoric acid[150] is more soluble than the similar polymer synthesised by a multistage process[151], which may be attributed both to only a weak development in polyphosphoric acid of intermolecular "cross-linking" reactions and to the difference in the phase states of these polymers. This finding has attracted particular interest, since the synthesis of soluble and hence workable polyheteroarylenes in one stage is technologically and economically more convenient compared with a two-stage process.

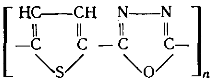
4. The use of polyphosphoric acid solves to a considerable degree the problems associated with the raw material base for the synthesis of polyheteroarylenes. For example, in the synthesis of various polybenzazoles polyfunctional nucleophilic agents are employed—bis-(*o*-phenylenediamines), bis-(*o*-aminophenols), bis-(*o*-aminothiophenols), etc., which are extremely unstable in the form of free bases and are readily oxidised. When the reaction is carried out in polyphosphoric acid, these compounds may be introduced in the form of much more stable salts—hydrochlorides, sulphates, phosphates, etc. Moreover, instead of employing the halides or anhydrides of the acids as the acid component of the reaction, it is possible to employ the more readily available free polycarboxylic acids.

The above advantages of the synthesis of polyheteroarylenes in polyphosphoric acid led to the wide employment of the polyheterocyclisation reaction for the synthesis of a wide variety of different classes of polymers. The principal classes of polyheteroarylenes containing five-membered heterocycles are polyazoles and polybenzazoles. The characteristics of the synthesis of polyazoles in polyphosphoric acid have been investigated in greatest detail for poly-1,3,4-oxadiazoles. Aromatic poly-1,3,4-oxadiazoles were obtained for the first time by Iwakura et al.[152] in a reaction of hydrazine sulphate with aromatic dicarboxylic acids, their amides, and nitriles, and also in the homocondensation of the dihydrazides of aromatic dicarboxylic acids:



Together with poly-1,3,4-oxadiazoles, the same investigators synthesised on the basis of isophthalic and terephthalic acids polymers containing alternating 1,3,4-oxadiazole and pyridine rings by the homocondensation of the dihydrazides of isomeric pyridinedicarboxylic acids—isocinchomeronic, dinicotinic, 2,6-dimethyldinicotinic, and dipicolinic[153].

Yet another type of polymer, containing only heterocycles—poly[2,3-thienylene-1,3,4-oxadiazole]—corresponding to the structural formula



was obtained by Manecke and coworkers[154] on heating the polyhydrazide of thiophendicarboxylic acid in polyphosphoric acid at 150°C for 5 h.

All the polymers synthesised exhibited high thermal stability and poly-1,3,4-oxadiazoles based on isophthalic and terephthalic acids also had high molecular weights: however, these polymers are soluble only in concentrated sulphuric acid and it is difficult to work them.

In order to obtain soluble polymers, Iwakura and coworkers[155] attempted to synthesise poly-1,3,4-oxadiazoles from the dihydrazides of aliphatic acids with the general formula

$$H_2NHNCO(CH_2)_mCONHNH_2\,,$$

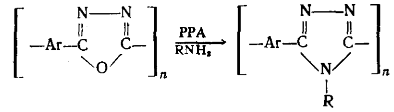
where m = 0, 1–10, 12, 15, and 20,[155] and alicyclic dicarboxylic acids[156]; poly-1,3,4-oxadiazole containing cyclohexane, cyclopropane, and spiro[3,4]heptane rings were obtained in the latter case[208].

In a number of cases the polymers were soluble in organic solvents but their thermal stability and resistance to heat were considerably inferior to those of aromatic poly-1,3,4-oxadiazoles.

A successful combination of useful thermal properties with solubility was achieved for poly-1,3,4-oxadiazoles by Korshak and coworkers, who synthesised these polymers on the basis of derivatives of di-(4-carboxyphenyl) ether[150] and diphenylphthalide-4′,4″-dicarboxylic acid[157,158].

The study of certain characteristics of the polyheterocyclisation reaction in polyphosphoric acid by Korshak, Krongauz, and coworkers[159] showed that the following factors favour the formation of high molecular-weight poly-1,3,4-oxadiazoles: (1) the absence of sulphuric acid from the reaction medium, which can be conveniently achieved by using hydrazinium phosphate instead of hydrazinium sulphate; (2) the binding of the water evolved in the condensation process by adding to the reaction mixture an additional amount of P_2O_5; (3) a high reaction temperature and short duration of the process.

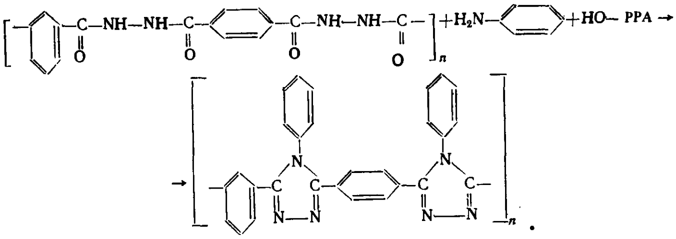
The relative ease of the opening of the 1,3,4-oxadiazole ring in polyphosphoric acid under the influence of different reagents permitted a series of polymer-analogue conversions of poly-1,3,4-oxadiazoles into other polyazole systems. Thus in a reaction of poly-1,3,4-oxadiazoles with various amines in polyphosphoric acid, Korshak and coworkers obtained a series of poly-(4-substituted)-1,2,4-triazoles[102,160–163]:



The amines employed were aniline, α-naphthylamine, cyclohexylamine, etc. Amines form stable complexes with polyphosphoric acid[164]. The reaction involving substitution of the oxygen in the oxadiazole ring by the N–R residue occurs only when the reaction medium contains a free amine, formed as a result of the dissociation of the amine–PPA complex at the reaction temperature. Therefore the successful occurrence of the substitution reaction depends on the basicity of the amines, which determines, on the one hand, the ease of dissociation of the amine–PPA complex and, on the other, the ease of substitution[162].

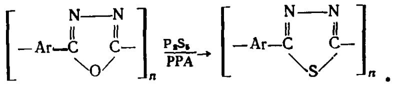
Poly(4-aryl)-1,2,4-triazoles contain bulky aryl substituents which weaken the interaction between the macromolecules; consequently these polymers are readily soluble in strong organic and inorganic acids. For this reason, the conversion of the insoluble aromatic poly-1,3,4-oxadiazoles into soluble poly(4-aryl)-1,2,4-triazoles, which can be carried out in a single reaction system without isolating the intermediate poly-1,3,4-oxadiazole[165], is of definite practical interest.

Holsten and Lilyquist showed[166,167] that analogous polymers may be obtained by heating polyhydrazides with aromatic amines in polyphosphoric acid:

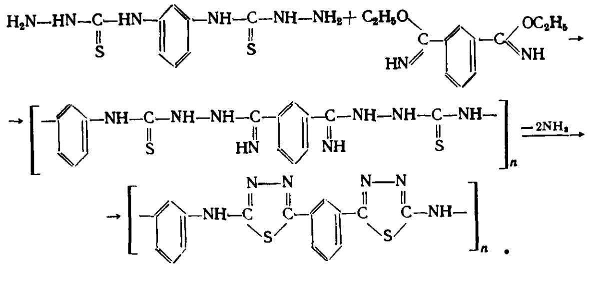


This method is more complex than direct substitution of oxygen in the 1,3,4-oxadiazole ring, but it yields products with higher molecular weights.

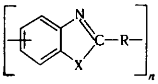
When P_2S_5 in polyphosphoric acid acts on poly-1,3,4-oxadiazoles, the latter undergo a polymer-analogue conversion into poly-1,3,4-thiadiazoles[168,169]:



Poly-1,3,4-thiadiazole with a somewhat different structure were obtained by the reaction of m-phenylenedithiosemicarbazide with diethyl isophthalimidate in polyphosphoric acid at 100–180°C:[170]

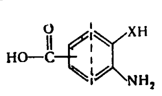


Another class of polyheteroarylenes in the synthesis of which polyphosphoric acid is widely employed are polybenzazoles. The principal representatives of this class of polyheteroarylenes are polybenzimidazoles, polybenzoxazoles, and polybenzothiazoles, corresponding to the general formula

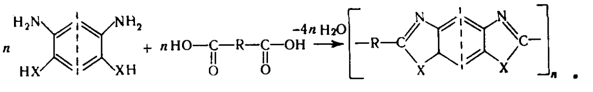


where X = NH, O, or S.

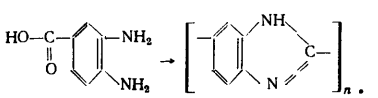
These polymers were obtained by the homocondensation of compounds with the general formula



or by the polycondensation of tetrafunctional nucleophilic agents with dicarboxylic acids or their derivatives:



Polybenzimidazoles have been investigated in greatest detail among polybenzazoles; this is probably because the majority of them dissolve in strong acid and certain amide solvents, even when the degree of cyclisation is high, and therefore by carrying out the process in one stage in polyphosphoric acid one does not preclude the formation of a workable polymer. Iwakura and coworkers[171,172] synthesised in polyphosphoric acid aromatic polybenzimidazoles by the homocondensation of 3,4-diaminobenzoic acid, its hydrochloride, sulphate, phosphate, and the potassium salt at 160°C, for 1–5 h:

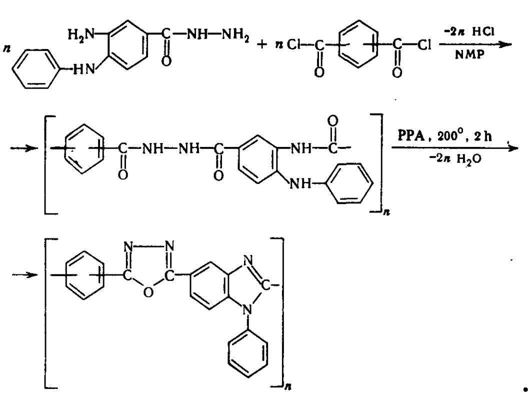


Apart from 3,4-diaminobenzoic acid, 3,4-diamino-3′-carboxybiphenyl, 3,4-diamino-4′-carboxybiphenyl, and 2,3-diamino-6-carboxynaphthalene have been employed as starting materials[171].

The same workers[173-177] synthesised polybenzimidazoles from the tetrachloride of 3,3′-diaminobenzidine and isophthalic, terephthalic, fumaric, and certain saturated aliphatic and alicyclic dicarboxylic acids. Both the acids themselves and their chlorides, nitriles, hydrazides, and esters were introduced into the reaction.

Koton and coworkers[178] employed di-(4-carboxyphenyl) ether and di(4-carboxyphenyl) sulphone as the acid components. In almost all cases high-molecular-weight polymers were obtained ($\eta_{\log}$† = 0.8–2.6), the syntheses of aromatic polybenzimidazoles being carried out under fairly severe conditions.

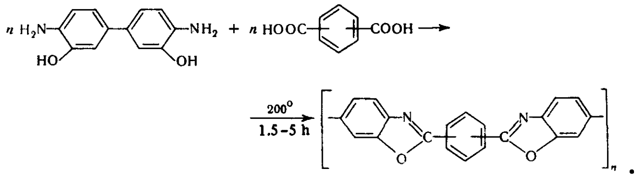
At the present time there are very few literature data on the application of polyphosphoric acid in the syntheses of poly-(*N*-aryl)benzimidazoles—polymers distinguished by enhanced solubility and resistance to thermo-oxidative degradation, compared with unsubstituted polybenzimidazoles[179]. We may note the work of Culbertson and Dietz[180], where polyaminohydrazides—the products of the low-temperature polycondensation of the hydrazide of 3-amino-4-anilinobenzoic acid with the dichlorides of isophthalic and terephthalic acid in *N*-methylpyrrolidinone—were subjected to cyclodehydration in polyphosphoric acid:



The poly-[2-(*mp*-phenylene)-5-(1,3,4-oxadiazolyl)-1-phenylbenzimidazoles] obtained in this way began to decompose only above 440°C both in nitrogen and air.

Considerable attention has been devoted to the synthesis in polyphosphoric acid of polybenzoxazoles and polybenzothiazoles. Aromatic polybenzoxazoles were obtained by the homocondensation at 160–200°C of isomeric aminohydroxybenzoic acids: 4-amino-3-hydroxybenzoic and 3-amino-4-hydroxybenzoic acids or their hydrochlorides[172]; the polymers had $\eta_{\log}$ = 0.7–2.2.

Aromatic polybenzoxazones with a somewhat different structure were synthesised by the reaction of bis-(*o*-aminophenols) or their hydrochlorides with aromatic dicarboxylic acids[181]; 3,3′-dihydroxybenzidine has been most often employed as the bis-(*o*-aminophenol):



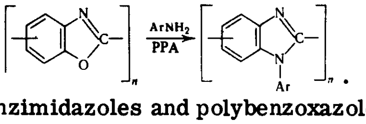
Aromatic polybenzoxazoles are obtained under very severe conditions; when the reaction is carried out at 200°C and lasts 1.5–5 h, their molecular weights reach high values ($\eta_{\log}$ = 1.36–2.1).

The reaction of bis-(*o*-aminophenols) with aliphatic dicarboxylic acids takes place, as in the synthesis of polybenzimidazoles[176], under milder conditions—at 100 to 120°C.[181]

The study of the thermal stability of polybenzoxazoles showed that the aromatic polymers decompose in air at about 450°C and those containing aliphatic units at about 300°C.

Polybenzoxazoles based on alicyclic dicarboxylic acids have also been synthesised[177].

Although the benzoxazole ring exhibits higher thermal and chemical stability compared with the 1,3,4-oxadiazole ring, under the action of primary aromatic amines in polyphosphoric acid, polybenzoxazoles are converted into the corresponding poly-(*N*-aryl)benzimidazoles[182]:



Like polybenzimidazoles and polybenzoxazoles, polybenzothiazoles may be synthesised in polyphosphoric acid both by the homocondensation of compounds containing

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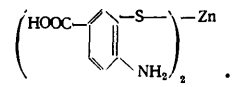
†Inherent viscosity or logarithmic viscosity number (Ed. of Translation).

nucleophilic and carboxy-groups and by the reaction of polyfunctional nucleophilic agents with dicarboxylic acids or their derivatives.

Iwakura and coworkers [172] synthesised aromatic polybenzothiazoles by the homocondensation of 4-amino-3-mercaptobenzoic acid as the hydrochloride and as the zinc thiophenoxide derivative:

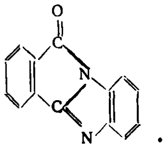


At a reaction temperature of 160–200°C for a process duration of 4 h, polymers with high molecular weights were obtained ($\eta_{\log} = 0.43-2.03$). Later investigations [183] showed that 4-amino-3-mercaptobenzoic and 3-amino-4-mercaptobenzoic acids, 3-amino-4-mercaptobenzamide, and 2,2-dimethylbenzothiazole-5-carboxamide may be employed as the initial compounds. The polycondensation was carried out at 250°C for 3 h; the molecular weights of the polymers thus obtained ($\eta_{\log} = 0.91-1.33$) greatly exceeded those of analogous polymers obtained in the melt and in solution in *m*-cresol and dimethylacetamide.

The syntheses of polybenzothiazoles in polyphosphoric acid on the basis of the dihydrochloride of 3,3′-dimercaptobenzidine were carried out at 200°C for 5–10 h in the case of isophthalic and terephthalic acids and at 120°C for 2 h in the case of sebacic acid [181]. The polymers had fairly high molecular weights ($\eta_{\log} = 0.31-1.02$).

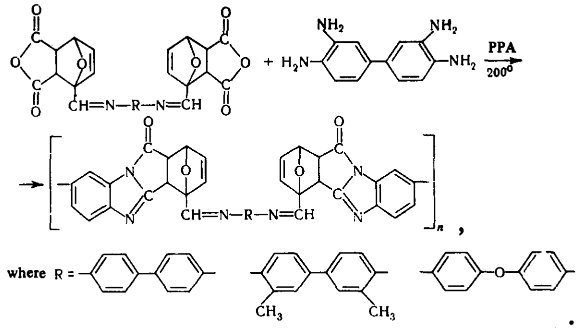
Hergenrother and coworkers [184] synthesised polybenzothiazoles from the dihydrochloride of 3,3′-dimercaptobenzidine and the following acid components: isophthalic acid, the diamide of isophthalic acid, di-(4-carboxyphenyl) ether, and the dimethyl ester of 4,4′-dicarboxybenzophenone. They succeeded in obtaining products with even higher molecular weights ($\eta_{\log} = 0.36-1.51$).

Yet another class of polybenzazoles which were synthesised in polyphosphoric acid is polybenzoylenebenzimidazoles containing 1,2-benzoylenebenzimidazole as the characteristic structural fragment of the condensed system:



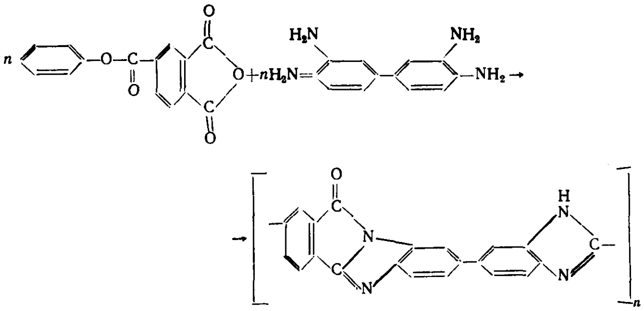
Polybenzoylenebenzimidazoles have been recently attracting particularly close attention of investigators in connection with the search for new types of so called "ladder" and "block-ladder" polymers, which, according to Tessler's theoretical postulates [185], should exhibit higher thermal stability and heat resistance than the usual polyheteroarylenes.

Dawans and Marvel [186] synthesised polybenzoylenebenzimidazoles in polyphosphoric acid from pyromellitic dianhydride and the tetrahydrochlorides of 1,2,4,5-tetraaminobenzene, 3,3′-diaminobenzidine, and di-(3,4-diaminophenyl) ether. The polycyclisation reactions were carried out at 200–220°C and yielded polybenzoylenebenzimidazoles with $\eta_{\log} = 1.91-1.81$‡. Berlin and coworkers [187] obtained polybenzoylenebenzimidazoles by the reaction in polyphosphoric acid of the dianhydrides of tetracarboxylic acids obtained as the bisadducts of the Diels–Alders reaction of furans and maleic anhydride derivatives with 3,3′-diaminobenzidine at 200°C for 8 h:

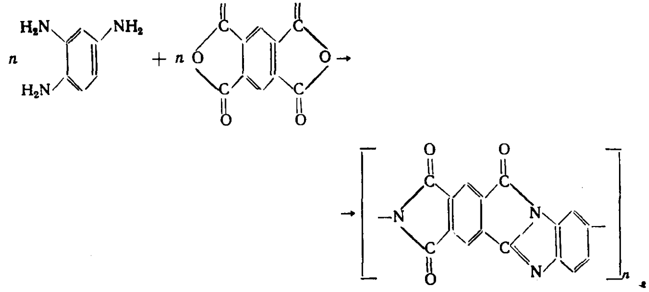


The polymers proved to be stable in air up to 350 to 450°C and dissolved in polyphosphoric acid and sulphuric acid; the reduced viscosity of their 1% solutions in concentrated sulphuric acid did not exceed 0.25.

Culbertson and Murphy [188], who carried out the reaction of the anhydride of 4-phenyltrimellitate with the tetrahydrochloride of 3,3′-diaminobenzidine in polyphosphoric acid at 200–210°C for 2 h, obtained an aromatic polymer containing alternating benzimidazole and benzolyenebenzimidazole rings and soluble in concentrated sulphuric acid only ($\eta_{\log} = 0.22$):



The polymer exhibited high thermal stability—intense decomposition in nitrogen and in air began at 550°C; in nitrogen the polymer retained 70 wt.% of its weight at 1000°C. A polymer with an analogous structure but a higher molecular weight ($\eta_{\log} = 0.513$) was obtained by the reaction of trimellitic anhydride with 3,3′-diaminobenzidine [189]. In addition the reaction of 1,2,4-triaminobenzene with pyromellitic dianhydride gave poly(imidobenzoylenebenzimidazole) with $\eta_{\log} = 0.63$: [189]



All the polymers containing benzoylenebenzimidazole rings and obtained in polyphosphoric acid are very insoluble. This may be a consequence both of the nature of the macromolecules themselves, and the presence of

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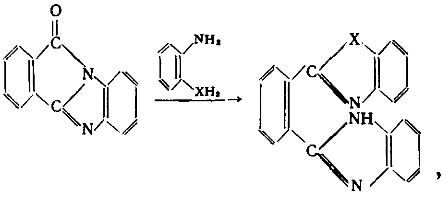
‡Intrinsic viscosity = 1.1–1.8 according to the original paper (Ed. of Translation).

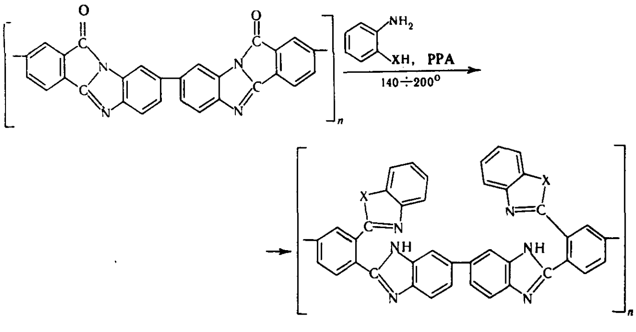
"cross-links" between them. "Cross-linked" structures may be formed as a result of the reaction of 1,2-benzoylenebenzimidazole with aromatic nucleophilic agents in polyphosphoric acid, analogous to the reaction of these compounds in nitrobenzene[190]:



where X = NH, O, or S.

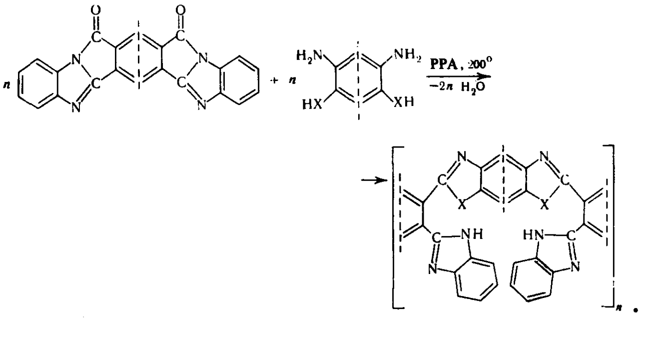
According to this reaction, one may expect that the terminal *o*-phenylenediamine groups of these macromolecules may react with the benzoylenebenzimidazole rings in their centre giving rise to "branching" of the bibenzimidazole type, which subsequently leads to "cross-linking". This reaction of the benzoylenebenzimidazole ring has been used to prepare various polybenzazoles containing attached benzazole groups.

Thus, by treating polybenzoylenebenzimidazoles with *o*-phenylenediamine, *o*-aminophenol, and *o*-aminothiophenol in polyphosphoric acid at 140–200°C, polybenzimidazoles were obtained with attached benzimidazole, benzoxazole, and benzothiazole groups in the *o*-position relative to the benzimidazole rings of the main macromolecular chains[191,192]:



where X = O, S, or NH.

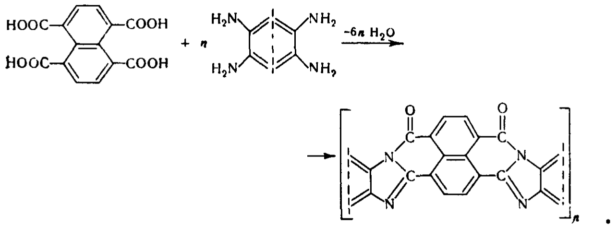
When this reaction was extended to bisbenzoylenebenzimidazoles, which are the products of the reaction of aromatic tetracarboxylic acids or their anhydrides with *o*-phenylenediamine, various polybenzazoles containing attached benzimidazole groups were obtained[193,194]:



Polymers of this kind show a combination of high thermal stability with high solubility in polar solvents.

Polyphosphoric acid has been used successfully in syntheses of polymers containing five- and six-membered condensed heterocycles, typical representatives of these polymers being polynaphthoylenebenzimidazoles—the products of the reaction of naphthalene-1,4,5,8-tetracarboxylic acid or its derivatives with bis-(*o*-phenylenediamines).

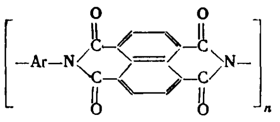
Van Deusen and coworkers[195,196] carried out the reaction of naphthalene-1,4,5,8-tetracarboxylic acid with 1,2,4,5-tetra-aminobenzene tetrahydrochloride and 3,3′-diaminobenzidine in polyphosphoric acid at 180–190°C for 20–24 h:



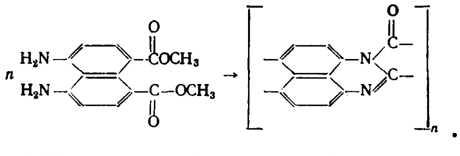
In the first case the product was a polymer entirely of the "ladder" type and in the second a polymer containing "ladder" blocks comprising eight condensed rings. The polymers dissolved in polyphosphoric and sulphuric acids had a high viscosity ($\eta_{\log} = 0.9–1.5$).

Berlin and coworkers[197,198] synthesised polymers of a similar structure from the dianhydride of naphthalene-1,4,5,8-tetracarboxylic acid and 3,3′-diaminobenzidine. The same investigators obtained polynaphthoylenebenzimidazoles based on di-(3,4-diaminophenyl)methane and di-(3,4-diaminophenyl) ether[199,200]. When the dianhydride of naphthalene-1,4,5,8-tetracarboxylic acid was replaced by the dianhydride of perylene-3,4,9,10-tetracarboxylic acid, the polymers had a relatively low molecular weight but exhibited high thermal stability[200,201].

When aromatic diamines (benzidine and others) were introduced into these reactions instead of bis-(*o*-phenylene diamines), polymers containing six-membered imide rings were obtained[198,200]:



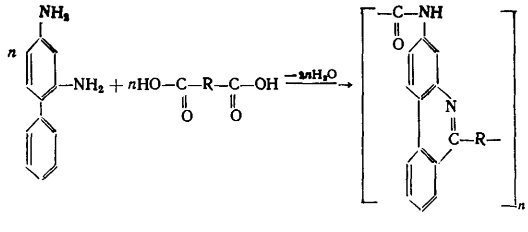
Van Deusen and coworkers[202] showed that the homypolycondensation of dimethyl 4,5-diaminonaphthalene-1,8-dicarboxylate and the anhydride of 4,5-diaminonaphthalene-1,8-dicarboxylic acid in polyphosphoric acid at 100 to 250°C results in the formation of a polymer with a "ladder" structure-poly(perimidine-6,7 : 1,2-tetrayl-1-carbonyl):



Polymers of this type are distinguished by high thermal stability: they are stable in air up to 450°C and in argon up to 600°C.

A number of studies have been made on the synthesis in polyphosphoric acid of other polyheteroarylenes incorporating six-membered nitrogen-containing heterocycles.

Thus Kolesnikov and coworkers[203] synthesised polyphenanthridinylamides from 2,4-diaminobiphenyl and aliphatic and aromatic dicarboxylic acids:



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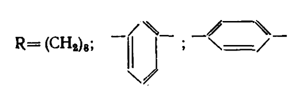
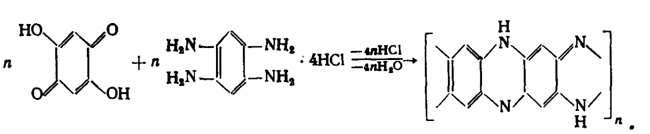
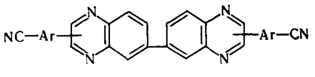


Stille and coworkers[204-207] employed polyphosphoric acid as a reaction medium in the synthesis of "ladder-type" polyquinoxalines. Thus, in the polycondensation of 2,5-dihydroxy-*p*-benzoquinone with 1,2,4,5-tetra-aminobenzene tetrahydrochloride in polyphosphoric acid at 150°C for 6–12 h, a hydrogenated aromatic "ladder-type" polyquinoxaline soluble in hexamethylphosphoramide and having $\eta_{\log} = 1.4$ was obtained[204,206,207]:



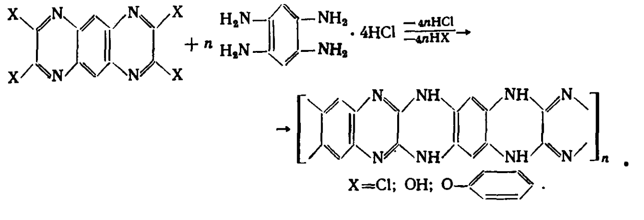
At an elevated temperature the polymer was dehydrogenated and acquired a stable fully aromatic structure. Other starting materials employed were 1,2,6,7-tetraoxopyrene and 1,2,5,6-tetraoxoanthracene[205,207] and also 2,3,6,7-tetra-aminodibenzo-*p*-dioxin and 3,3′-diaminobenzidine[207].

Copolymers containing in the main chain quinoxaline and benzimidazole rings were obtained by the reaction of phenoxycarbonylphenylglyoxals with bis-(*o*-phenylene diamines)[208]. The same polymers were also formed by the reaction of biscyanoarylquinoxalines having the general formula

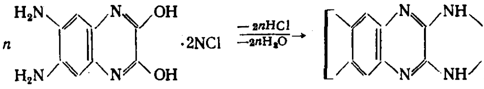


with 3,3′-diaminobenzidine tetrahydrochloride in polyphosphoric acid.

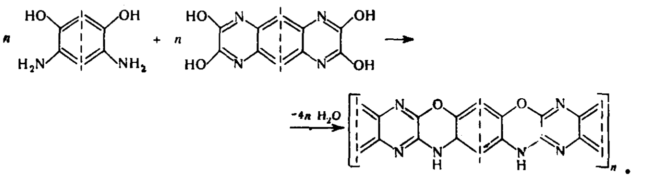
Marvel and coworkers[112,209-211] condensed substituted derivatives of quinoxaline with bis-(*o*-phenylenediamines), bis-(*o*-aminophenols), and bis-(*o*-aminothiophenols) to synthesise quinoxaline-containing polymers. Thus the reaction of tetra-aza-anthracene derivatives with 1,2,4,5-tetra-aminobenzene tetrahydrochloride in polyphosphoric acid at 250°C for 24 h gave "ladder-type" polymers containing quinoxaline and diazine rings[209]:



A polymer with a similar structure was obtained in the homopolycondensation of a diaminodihydroxy-compound containing a quinoxaline ring[209]:

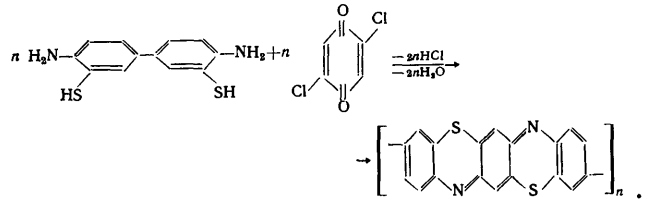


The reaction of diaminodihydroxy-compounds (2,5-diamino-1,4-dihydroxybenzene and 3,3′-dihydroxybenzidine) with tetrasubstituted quinoxalines [2,3,7,8-tetrahydroxy-1,4,6,9-tetra-aza-anthracene, 2,2′,3,3′-tetrahydroxy-6,6′-bisquinoxaline, and bis-(2,3-dihydroxy-6-quinoxalyl) ether] in polyphosphoric acid at 230–250°C for 24 h resulted in the formation of polymers containing quinoxaline and oxazine rings, which were partially soluble in concentrated sulphuric and methanesulphonic acids[210,211]:

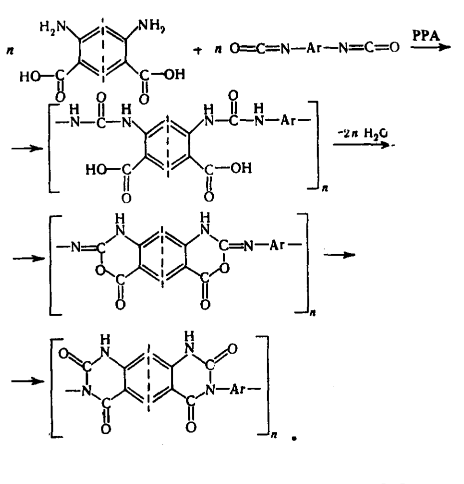


Tetrachloro-substituted quinoxalines have also been employed as the quinoxaline component[211].

Polytriphenodithiazine was obtained similarly by the reaction of 3,3′-dimercaptobenzidine with 2,5-dichloro-*p*-benzoquinone in polyphosphoric acid[212]:

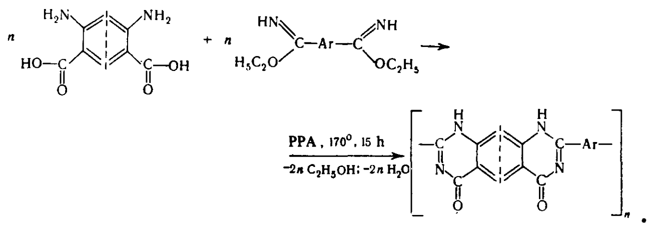


A number of cyclochain polymers with a set of valuable properties were synthesised on the basis of certain diaminodicarboxylic acids. In particular, a detailed study was made of the products of the bisanthranilic interaction in polyphosphoric acid of bisanthranilic acids [4,4′-diamino-3,3′-biphenylenedicarboxylic acids (Ed. of Translation)] with di-isocyanates—the so called polyquinazolinediones[141,142,213,214]:



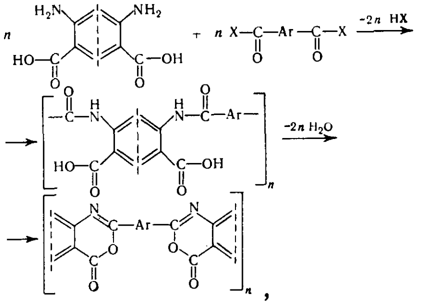
3,3′-Dicarboxybenzidine is the most widely employed bisanthranilic acid. [Inorganic] isocyanate, 3,3′-dimethyl-4,4′-diphenylene di-isocyanate, 3,3′-dimethoxy-4,4′-phenylmethane, etc. have been employed together with this compound. *p*-Phenylene di-isocyanate, *p,p'*-diphenylmethylene di-isocyanate, 1,5-naphthylene di-isocyanate, 3,3'-dimethyl-4,4'-diphenylene di-isocyanate, 3,3'-dimethoxy-4,4'-diphenylene di-isocyanate, 2,4-toluylene di-isocyanate, etc. have been used as the di-isocyanate component.

Eda and coworkers synthesised polyquinazolones by the reaction of bisanthranilic acids with bisimino ethers[215]:



The polyquinazalones had a comparatively low molecular weight—the characteristic§ viscosities of 0.5% solutions of these polymers in sulphuric acid did not exceed 0.15.

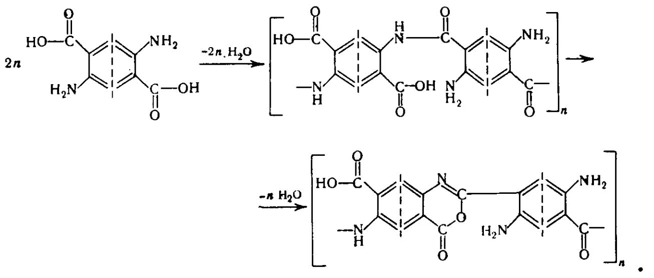
Products with much higher molecular weights were obtained by the reaction of bisanthranilic acids with aromatic dicarboxylic acids and their derivatives[216-220]. Here the first stage involves the formation of poly-*o*-carboxyamides, which on further increase of temperature are cyclised to the corresponding polybenzoxazinones:



where X = COOH, COCl, COBr, $CONH_2$, CN, or $COOCH_3$.

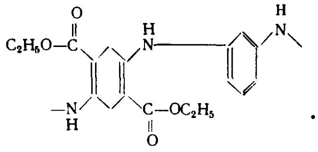
Polybenzoxazinones as well as polyquinazolinediones are very insoluble—they dissolve only in sulphuric and nitric acids; therefore it is desirable to convert them into finished products at the stage of poly-*o*-carboxyamides, which are soluble in organic solvents. The temperature of the onset of the decomposition of the fully aromatic polymers reaches 550°C.

Polymers containing benzoxazine fragments were obtained by the homopolycondensation of bisanthranilic acids (2,5-diaminoterephthalic, benzidine-3,3'-dicarboxylic, and others) in polyphosphoric acid[221,222]:

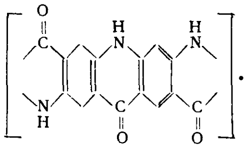


These polymers showed somewhat lower thermal stability compared with polyquinazolinediones and polybenzoxazinones: they proved to be stable in an inert atmosphere up to 450°C and began to decompose under the conditions of thermo-oxidative degradation at 350°C.

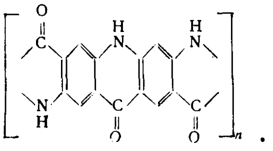
Kimura[223] developed a synthesis of polyquinolones—a new class of polyheteroarylenes. The reaction in polyphosphoric acid of diethyl succinosuccinate with aromatic diamines [m-phenylenediamine and di-(4-aminophenyl) ether] gave polyamines of the following type:



Their cyclisation in polyphosphoric acid (in an inert atmosphere) yielded insoluble polydihydroquinolones infusible up to 400°C and having a "ladder" structure:



The same polyamines may be oxidised by chloranil in dimethylformamide to aromatic polyamines, whose cyclisation in polyphosphoric acid gives infusible and insoluble polyquinolones:



V. THE MECHANISM OF CYCLISATION REACTIONS IN POLYPHOSPHORIC ACID

The complex composition of polyphosphoric acid makes it extremely difficult to investigate the mechanism of reactions occurring in it and for this reason very little has been done in this field. The high viscosity of polyphosphoric acid, which prevents the isolation of intermediates by crystallisation, and the impossibility of employing cyroscopic methods made it very difficult to carry out the necessary kinetic measurements and therefore in the interpretation of the mechanisms there remains a considerable element of guesswork.

Among the reactions in polyphosphoric acid, the cyclisation of substituted aromatic acids, the conversion of γ-lactones into cyclopentanones, and the Beckmann and Lossen rearrangements have been investigated in greatest detail.

According to the literature, polyphosphoric acid functions simultaneously as a protic acid, a Lewis acid, and a phosphorylating agent[224]. Thus in the cyclisation of γ-phenylbutyric acid protonation or the formation of a

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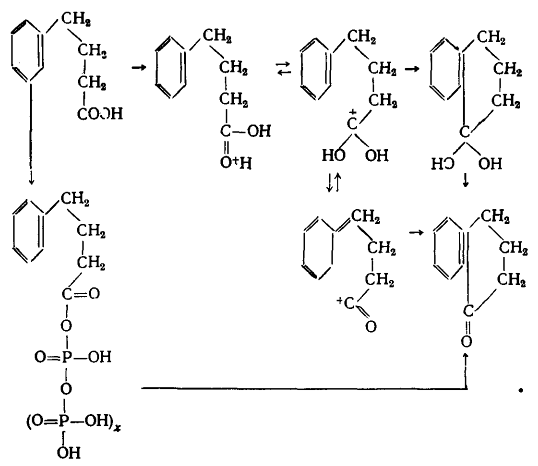
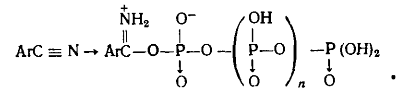
§Probably inherent (Ed. of Translation).

mixed anhydride is postulated as the initial stage, as shown below:



In the conversion of γ-lactones into cyclopentanones the intermediate formation of a ketocarbonium ion is suggested[225]. In the cyclisation of nitriles and also in the conversion of γ-lactones into cyclopentanones, phosphate esters may be formed and in the first case this is probably preceded by the addition of elements of polyphosphoric acid to the triple bond[5]:



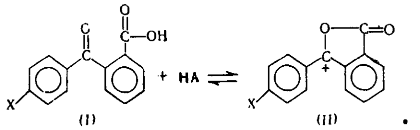
$$\mathrm{ArC\equiv N\rightarrow Ar\overset{\overset{+}{N}H_2}{C}{-}O{-}\underset{\downarrow\atop O}{\overset{O^-}{P}}{-}O{-}\left(\underset{\downarrow\atop O}{\overset{OH}{P}}{-}O\right)_n{-}\underset{\downarrow\atop O}{P}(OH)_2}\ .$$

The presence of the intermediate carbonium ion has been confirmed only indirectly[226].

Since the majority of the latest communications on the applications of polyphosphoric acid are related to cyclodehydration or more specific intermolecular acylation, kinetic study of this type of reaction is of the greatest practical and theoretical interest. The elucidation of the mechanism of these reactions was preceded by a detailed study of the acid properties of polyphosphoric acid itself treated as the $P_2O_5-H_2O$ system.

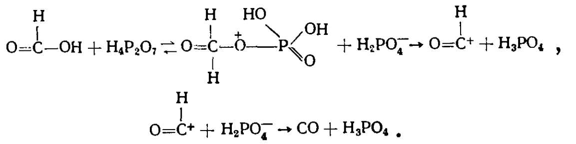
In an early investigation by Downing and Pearson[29] it was shown that the acidity of the $P_2O_5-H_2O$ system (from 65 to 85.7 wt.% P_2O_5 at 25–27°C) increases monotonically with increasing P_2O_5 content. The data obtained by Gel'bshtein et al.[227] in a study of the acid properties of the $P_2O_5-H_2O$ system between 2.7 and 83.5 wt.% P_2O_5 at 25°C with 2,4-dichloro-6-nitroaniline and 2-bromo-4,6-dinitroaniline as indicators also confirm the absence of an acidity maximum in the $P_2O_5-H_2O$ system in the region corresponding to polyphosphoric acid.

In this connection it is noteworthy that, when polyphosphoric acid is employed as a catalyst in a number of reactions, its catalytic activity passes through a maximum. For example, the rate of heterolytic decomposition of formic acid is a maximum at 80 wt.% P_2O_5.[228] This was also reported by Downing and Pearson[229], who established that the rate of intermolecular acylation of *o*-benzoylbenzoic acids [*o*-benzoyl-, *o*-(*p*-chlorobenzoyl)- and *o*-(*p*-tolyl)-benzoic acids] passes through a maximum in the range of compositions corresponding to 78–83 wt.% P_2O_5. The authors found it difficult to explain this observation, since they postulated that the mechanism of the cyclisation of *o*-benzoylbenzoic acids in polyphosphoric acid is in general analogous to the mechanism proposed by Newman[230] for sulphuric acid, i.e. that the reaction takes place via an intermediate cyclic carbonium ion (II):



Thus in the above reactions there is no correspondence between the acidity of the medium and their rate. This is also reflected in the fact that for certain heterolytic reactions, a given rate is observed in polyphosphoric acid with a much lower acidity than in sulphuric acid, for example. Thus the rate constants for the reaction $HCOOH = CO + H_2O$ at 50°C in polyphosphoric acid containing 80.5 wt.% P_2O_5 and in 90% sulphuric acid are virtually identical ($2.4 \times 10^{-3}\ s^{-1}$ and $2.7 \times 10^{-3}\ s^{-1}$ respectively). Nevertheless the acidity function of polyphosphoric acid of the above composition is $H_0 = -5.80$ at 25°C and that of 90% sulphuric acid is $H_0 = -8.44$ at 20°C.[228] Analogous relations have been observed for the Beckmann rearrangement of acetophenone oximes[231] and also for intramolecular cyclisation[229]. According to many investigators, the above findings may be explained by rejecting the hypothesis of purely proton-dependent mechanisms of the above reactions in polyphosphoric acid, adopting instead a mechanism including acid-catalysed phosphorylation. Probably polyphosphoric acid transfers to the substrate the $(H_2PO_3)^+$ ion, and not H^+, with formation of the corresponding anion, for example: $H_4P_2O_7 = [H_2PO_3]^+ + H_2PO_4^-$.

In the decomposition of formic acid in polyphosphoric acid this will correspond to the following mechanism:



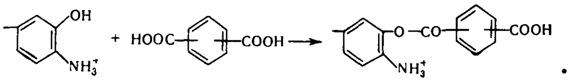
$$\mathrm{O{=}\overset{H}{C}{-}OH+H_4P_2O_7\rightleftarrows O{=}\underset{H}{\overset{H}{C}}{-}\overset{+}{O}{-}\overset{HO}{P}\begin{smallmatrix}OH\\O\end{smallmatrix}+H_2PO_4^-\rightarrow O{=}\overset{H}{C}{}^+ + H_3PO_4}\ ,$$

$$\mathrm{O{=}\overset{H}{C}{}^+ + H_2PO_4^-\rightarrow CO+H_3PO_4}\ .$$

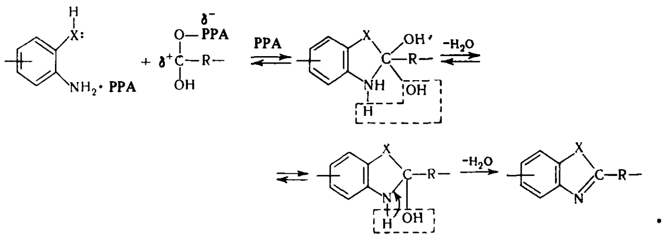
It is known that H_3PO_4 and polymeric metaphosphoric acid $(HPO_3)_n$ are incapable of phosphorylation, while acids such as $H_4P_2O_7$ and $H_5P_3O_{10}$ behave as phosphorylating agents. The content of these acids in the $P_2O_5-H_2O$ system is a maximum in the range of P_2O_5 concentrations where there are maxima in the rates of the reactions considered. Thus the existence of reaction rate maxima in polyphosphoric acid has been explained. In media incapable of phosphorylation, the reactions take place via a proton mechanism which corresponds to a lower rate at the same acidity[227].

The results of kinetic studies on the ring closure of 2-carboxy-2′-deuterobiphenyl to fluorenone by Donney and Klemchuk[232] and the data of Goldberg and Wragg[233], who determined the rate constants for the cyclisation of *o*-phenoxybenzoic acid to xanthone in polyphosphoric acid containing 81.6% P_2O_5, can also be explained from this standpoint.

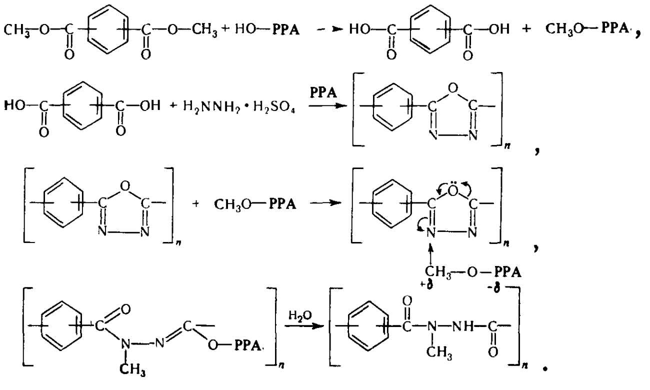
Problems associated with the changes in the reactivity of various compounds in polyphosphoric acid are of considerable interest[181]. It has been shown that polyphosphoric acid, which is a strong Lewis acid, increases the positive charge at the carbon atom of the carbonyl group and thereby leads to an increase of its electrophilic reactivity. It is also interesting to note that in reactions in polyphosphoric acid the basicity of the hydroxy-group is higher than that of the amino-group; therefore in the reaction of bis-(*o*-aminophenols) with dicarboxylic acids in polyphosphoric acid, there is initially selective formation of a polyester[181]:



Taking into account these facts, Iwakura and coworkers[181] proposed the following general mechanism for the formation of polybenzazoles:

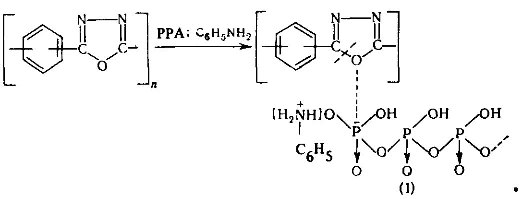


Probably the mechanism of the formation of poly-1,3,4-oxadiazoles from dicarboxylic acids and hydrazine derivatives is similar. However, in the presence of alkylating agents the 1,3,4-oxadiazole ring is opened. Thus, when dimethyl and diethyl esters of isophthalic and terephthalic acids were employed as starting materials, poly-(*N*-alkyl)-hydrazides were obtained[147]. The reaction probably takes place via the following mechanism:



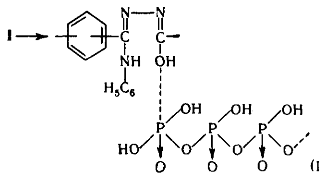
This mechanism is supported by the finding that in the interaction of poly-1,3,4-oxadiazole (obtained separately) with alkylating agents in polyphosphoric acid, the oxadiazole ring is opened with subsequent *N*-alkylation and formation of a poly-(*N*-alkyl)hydrazide.

Substitution of one of the heteroatoms in the heterocycle by another also takes place with opening of the oxadiazole ring. The mechanism of the substitution reaction was examined in the synthesis of poly-(4-phenyl-1,2,4-triazoles)[161]. According to the mechanism proposed, a molecule of the polyphosphoric acid salt and a molecule of aniline add to the oxygen atom of the oxadiazole ring, forming an unstable intermediate complex (I), in which the C–O bond in the ring is weakened:



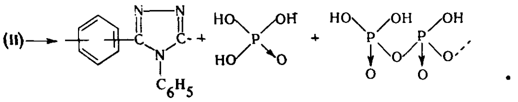
(I)

Under the influence of high temperature, the complex (I) dissociates with liberation of free aniline, which attacks the weakened C–O bond. The ring is then opened and the aniline residue adds to the carbon atom in the 5-position and the proton adds to the oxygen atom [compound (II)]:

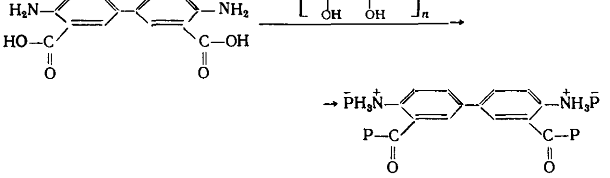


(II)

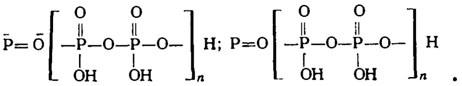
Then the polyphosphoric acid molecule is split off together with the hydroxy-group and the mobile hydrogen atom at the nitrogen acts on the O–P bond and facilitates the dissociation of an orthophosphoric acid molecule from polyphosphoric acid; at the same time the ring is closed and a polytriazole is formed:



The mechanism of the homocondensation and co-condensation reactions of bisanthranilic acid in polyphosphoric acid[234,235], which takes place via the formation of a phosphorylated intermediate, was examined in somewhat greater detail:

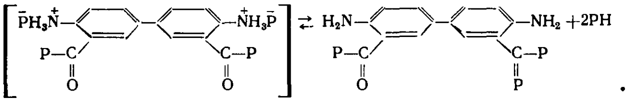


where



$$\bar{P}=\bar{O}\left[\begin{matrix} & \overset{O}{\overset{\|}{}} & & \overset{O}{\overset{\|}{}} & \\ - & P & -O- & P & -O- \\ & \underset{OH}{|} & & \underset{OH}{|} & \end{matrix}\right]_n H;\quad P{=}O\left[\begin{matrix} & \overset{O}{\overset{\|}{}} & & \overset{O}{\overset{\|}{}} & \\ - & P & -O- & P & -O- \\ & \underset{OH}{|} & & \underset{OH}{|} & \end{matrix}\right]_n H .$$

When the temperature is raised, the phosphorylated product dissociates:



The products thus formed contain free amino-groups and mixed anhydride groups, which facilitates the amidation reaction and is responsible for the possibility of both the homocondensation of bisanthranilic acids and their copolycondensation with dicarboxylic acids.

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The cyclisation and polycyclisation reactions in polyphosphoric acid constitute a comparatively new and rapidly developing field, which will undoubtedly enrich organic chemistry in new valuable experimental and theoretical data in the immediate future.

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Institute of Organic Derivatives
of the Elements, USSR Academy
of Sciences, Moscow

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Differentiating Effect of Amphiprotic Solvents in Relation to Phenol and Benzoic Acid Derivatives

L.N.Bykova and S.I.Petrov

The review deals with the methods of estimating the differentiating effect of amphiprotic solvents on the acid strengths of phenol and benzoic acid derivatives. New literature data are presented for the dissociation constants and half-neutralisation potentials of electrolytes of the above classes. The possibility of using the Hammett equation to characterise the differentiating effect of solvents is discussed. The available literature values of the autoprotolysis constants of amphiprotic solvents are analysed critically. The problem of the relation between the parameters characterising the differentiating effect of amphiprotic solvents is considered particularly as regards individual groups of electrolytes and the autoprotolysis constant. The causes of the different differentiating capacities of amphiprotic solvents in relation to phenols and benzoic acids are discussed.
The bibliography includes 119 references.

CONTENTS

I. INTRODUCTION

The problem of the differentiating effect of solvents on the strengths of electrolytes has been attracting the attention of specialists in various branches of chemistry in connection with wide employment of non-aqueous solvents in physical, organic, and analytical chemistry[1-4]. According to Brönsted's proton theory of acids and bases[5], the differentiating effect of solvents, i.e. their capacity to alter the relative strengths of electrolytes, is shown only in relation to electrolytes of different charge types: cationic, neutral, and anionic acids. When the p*K* values for the dissociation of electrolytes in two solvents are compared, they are found to fit on three parallel lines with a slope of unity according to the particular charge type to which the acids belong.

The reviews of data for the dissociation constants of acids and bases in various solvents, in the monographs of Shatenshtein[6] and Izmailov[1] showed that there are linear relations between the p*K* values for the dissociation of acids or bases in water and a non-aqueous solvent or between the values in two non-aqueous solvents. However, as a refinement of Brönsted's theory, it was established that in many solvents uncharged acids exhibit relations associated with various natural groups to which they belong. A detailed study of the charges of the relative strengths of acids and bases under the influence of solvents enabled Izmailov[1] to find the limits of applicability of Brönsted's theory and to establish the differentiating effect of solvents on the strengths of acids and bases.

Izmailov[1] showed that the differentiating effect of solvents is related to their solvating capacity. The relative dissociation constants of different acids in the same solvent depend on their relative intrinsic acidities and the differences between the solvation energies of the acid anions and molecules. The change in the strength of the electrolyte on passing from one solvent to another is due to the change in the relative solvation energies of the ions and molecules of the acid in the two solvents.

Numerous studies have been made on the nature of the solvating effect of solvents[7-14], which showed that the solvation of ions and molecules of electrolytes in solution depends on a number of factors. Apart from the proton affinity of the molecules and lyate ions of solvents (the basicity and acidity of solvents), solvation is determined by the donor–acceptor interaction between the solvent molecules and the molecules and anions of the acid, the formation of hydrogen bonds, electrostatic forces, dipole–dipole and ion–dipole interactions, dispersion interaction, and changes in the structure of the solvent.

Various methods are available for estimating the differentiating effect of solvents. The principal method consists in the measurement and comparison of the dissociation constants of electrolytes (K_{diss}).[1] Recently the half-neutralisation potentials of electrolytes ($E_{1/2}$) have also been measured and compared[4,15-20]. This simple method is widely used in analytical chemistry, since it makes it possible to predict the optimum conditions for the separate titration of acids or bases in mixtures. The differentiating effect of solvents can also be estimated on the basis of the Hammett and Taft equations by comparing the reaction constants ρ and ρ^*, since they depend not only on the type of reaction but also on its conditions, i.e. primarily on the nature of the solvent[21-25].

The present review deals with the differentiating effect of amphiprotic solvents in relation to compounds which exhibit acid properties in solutions, mainly in relation to phenol and benzoic acid derivatives—the most thoroughly investigated classes of electrolytes. Amphiprotic solvents include those whose acidic and basic properties are not more pronounced than the corresponding properties of water: alcohol, ketones; acetonitrile, and dimethylformamide; an exception is dimethyl sulphoxide, whose basic properties are somewhat more marked than those of water.

The differentiating effect of solvents may be characterised in terms of the following parameters: (1) the slope of the relation $pK_A(ns)^† = \alpha pK_A(H_2O) + \beta$, i.e. the parameter α, which is equal to the difference between the pK_A values of two electrolytes in a non-aqueous solution when their $pK_A(H_2O)$ differ by unity; (2) the slope of the relation $\Delta E_{1/2} = A pK_A(H_2O) + B$, i.e. the parameter A, which is equal to the difference between the half-neutralisation potentials of two electrolytes in a non-aqueous solution when their $pK_A(H_2O)$ values differ by unity; (3) the slope of the relation $\Delta E_{1/2} + A'\Sigma\sigma + B'$, i.e. the parameter A', which is equal to the difference between the half-neutralisation potentials of two electrolytes in a non-aqueous solution when their $\Sigma\sigma$ values differ by unity (the σ are the constants of the substituents); (4) the reaction constant ρ in the Hammett equation $pK_{rel} = \rho\Sigma\sigma$.

2. STUDY OF THE DIFFERENTIATING EFFECT OF SOLVENTS BY MEASURING THE DISSOCIATION CONSTANTS OF ELECTROLYTES

The dissociation of acids in non-aqueous solutions takes place in a much more complex manner than in an aqueous medium. Izmailov[1] showed that the interaction of an acid with a solvent includes a number of interrelated processes involving the formation of addition products of solvent molecules with the electrolyte molecules and the formation of solvated ions and ion pairs. The study of acid–base interaction in solvents with weak acidic properties, which are therefore incapable of forming hydrogen bonds via the hydrogen atoms in solvent molecules, showed that the mechanisms of the dissociation of acids and bases must be supplemented by the following equilibria[26-31]:

$$A^- + HA \rightleftarrows HA_2^-,$$
$$BH^+ + B \rightleftarrows B_2H^+.$$

These processes, called homoconjugation, take place to a particularly high degree in solvents which Parker[8,9,32] called "aprotic dipolar", since they are incapable of forming hydrogen bonds with the anions of acids and the molecules of bases. Such solvents include in the first place acetonitrile whose basic and acidic properties are both weak. In dimethylformamide and dimethyl sulphoxide homoconjugation processes are weaker because of the higher basicity of these solvents (SH), whose molecules enter into the following competitive reaction with the anion A^-:[33]

$$A^- + HS \ldots HA \rightleftarrows A^- \ldots HA + SH.$$

The studies of Yasinskii's and coworkers[34] showed that in acetone as well as in acetonitrile homoconjugation processes occur to a considerable extent.

As a result of the complexity of the dissociation of acids in non-aqueous solutions, the use of different methods for the determination of K_{diss} in such media produces greater discrepancies than in water. Thus in acetonitrile the range of pK_A values for 2,4,6-trinitrophenol is between 4.34 and 11.0.[30,31,35-38] In solvents with high dielectric constants ($\epsilon < 20$) a considerable proportion of ions are bound in ion pairs which behave as free ions in spectrophotometric and indicator methods for the measurement of pK_A. Therefore in such solvents the K_A values determined by optical methods prove to be higher than those found by electrometric methods. In "aprotic dipolar" solvents homoconjugation processes complicate the calculation of the pK_A values from conductimetric and potentiometric measurements. Reliable pK_A values for acids in such solvents may be obtained by employing a group of methods for measurement (potentiometric, conductimetric, and spectrophotometric).[30,31] For a quantitative interpretation of the acid–base interaction in acetonitrile, it is necessary to take into account more than 10 equilibria[39].

In order to characterise the differentiating effect of solvents, we interpreted the literature pK_A data for phenols and benzoic acids in alcohols, ketones, acetonitrile, dimethylformamide, and dimethyl sulphoxide. The pK_A values for phenols and benzoic acids in non-aqueous solvents are listed in Tables 1 and 2 respectively. For alcohols, their mixtures with water, and acetone, the pK_A values were measured largely by electrometric methods, while for acetonitrile, dimethyl sulphoxide and dimethylformamide the chosen values were obtained by both electrometric and spectrophotometric methods.

The greatest scatter of experimental pK_A data occurs in the case of 2,4,6-trinitrophenol in all the solvents examined. Even in water the pK_A values for 2,4,6-trinitrophenol range from 0.4 to 2.3.[48,60] For 2,4,6-trinitrophenol, we employed $pK_A(H_2O) = 0.71$ obtained conductimetrically[40]. In methanol we adopted $pK_A = 3.67$ taken from Juillard[44] instead of 4.80 which Izmailov[1] quoted without indicating the method of measurement. Examination of the pK_A data for 2,4,6-trinitrophenol in acetone and dimethylformamide showed that it is difficult to give preference to any one value and therefore we employed the average of the data quoted in Table 1.

It follows from Brönsted's theory[5] that the pK_A values for acids in a non-aqueous solvent and in water are related as follows:

$$pK_A(\text{ns}) = pK_A(H_2O) + \text{const.} \qquad (1)$$

On the basis of the literature and his own data, Izmailov[1,46] showed that, for acids of the same natural group in two solvents, Eqn. (1) is of the following form:

$$pK_A(\text{ns}) = \alpha pK_A(H_2O) + \beta, \qquad (2)$$

where α and β are quantities which depend on the natural group of acids and the chemical nature of the solvent.

Fig. 1 presents examples of the relations for the pK_A of phenols in non-aqueous solvents as a function of $pK_A(H_2O)$. The numbers of the points in Fig. 1 correspond to those in Table 1. In plotting the above relations, use was made of the average values of the concordant data quoted in Table 1. The straight lines referring to acetone, dimethylformamide, and acetonitrile are almost parallel and have a much higher slope than the lines for methanol.

Fig. 2 presents examples of the relations between the pK_A for benzoic acids in non-aqueous solvents and the $pK_A(H_2O)$; in plotting these functions, use was made largely of the $pK_A(ns)$ values for benzoic acids determined potentiometrically. The numbers of the points in Fig. 2 corresponds to those in Table 2. The variation of pK_A in ethanol with $pK_A(H_2O)$ shows different changes in the $pK_A(ns)$ values for the *m*- and *p*-derivatives of benzoic acid on passing from an aqueous to a non-aqueous solution compared with the *o*-derivatives, which are weaker in non-aqueous solutions than would be expected from their

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† ns = non-aqueous solvent.

Table 1. The negative exponents of the dissociation constants of phenols at 25°C in certain solvents measured potentiometrically (P), conductimetrically (C), spectrophotometrically (SP), and by an indicator method (I).

No.	Compound	Solvents											
		water ref. 40–42	methyl alcohol ref 43,44	water–isopropyl alcohol (P) (Ref.45); isopropyl alcohol, %						acetone refs. 2, 35 & 46	acetonitrile refs.30,31, 33,35,37 & 38	dimethyl formamide refs 47–50	dimethylsulphoxide refs. 33,51 &52
				16.0	42.4	62.7	73.8	86,6	93.5				
1	Phenol	9.98	14.46 (SP)	—	—	—	—	—	—	—	26.6 (P,SP)	—	16.4 (P,C,SP)
		—	—	—	—	—	—	—	—	—	—	—	16.9 (P)
2	*m*-Nitrophenol	8.40	—	8.74	9.30	9.65	10.05	10.70	—	—	22.6 (P)	13.85(P)	—
3	*o*-Nitrophenol	7.23	—	7.38	7.93	8.43	8.74	9.15	9 92	13.82 (P)	22.0 (P,SP)	12.14(P)	11.0 (P,C,SP)
		—	—	—	—	—	—	—	—	—	22.0 (P)	12.9 (P)	—
		—	—	—	—	—	—	—	—	—	21.2 (P)	—	—
4	*p*-Nitrophenol	7.15	11.09(P)	7.30	7.82	8.25	8.55	9.08	9.75	13.52 (P)	20.7 (P,SP)	11.84 (P)	9.9 (I)
		—	11.50(SP)	—	—	—	—	—	—	—	20.9 (P,SP,C)	12.18 (P)	11.0 (P,C,SP)
		—	—	—	—	—	—	—	—	—	20.0 (P)	—	—
5	2,4-Dinitrophenol	3.96	7.85 (P)	3.87	3.88	4.28	4.53	5.06	5.70	8.76 (P)	16.0 (P,SP)	6.36 (P)	5.2 (I)
		—	—	—	—	—	—	—	—	—	16.0 (P)	6.33 (P)	—
		—	—	—	—	—	—	—	—	—	15.3 (P)	—	—
6	2,5-Dinitrophenol	5.16	8.98 (P)	5.14	5.33	5.70	6.03	6.55	7.21	10.3 (P)	17.5 (P)	8.78 (P)	—
		—	—	—	—	—	—	—	—	—	—	8.61 (P)	—
7	2,6-Dinitrophenol	3.70	7.63 (P)	3.64	3.82	4.21	4.51	5.07	5.56	8.76 (P)	16.0 (P.SP)	6.07 (P)	4.9 (P,C,SP)
		—	—	—	—	—	—	—	—	—	16.45(P)	—	—
8	2,4,6-Trinitrophenol	0.71	3.67 (P)	—	—	—	—	—	—	3.17 (P)	11.0 (SP,P)	3.67 (P)	−1.9 (I)
		—	—	—	—	—	—	—	—	4.73(SP)	11.0 (P)	1.20 (P)	−1.0 (P,C,SP)
		—	—	—	—	—	—	—	—	4.14 (I)	11.0 (P)	—	—
9	3,5-Dinitrophenol	6.7	—	—	—	—	—	—	—	—	20.7 (P,C,SP)	—	10.6 (P,C,SP)
10	4-Chloro,2,6-dinitrophenol	2.97	—	—	—	—	—	—	—	—	15.3 (P,C,SP)	—	3.5 (P,C,SP)
11	2,6-Dichloro-4-nitrophenol	3.55	7.40 (P)	—	—	—	—	—	—	—	14.3 (P)	5.71 (P)	—
12	2,6-Dibromo-4-nitrophenol	3.38	7.31 (P)	—	—	—	—	—	—	—	14.0 (P)	5.7 (P)	—
13	4-Bromo-2,6-di-t-butyl phenol	10.83	15.91 (P)	—	—	—	—	—	—	—	—	—	—
14	*p*-Chlorophenol	9.38	—	—	—	—	—	—	—	—	—	—	16.1 (P)

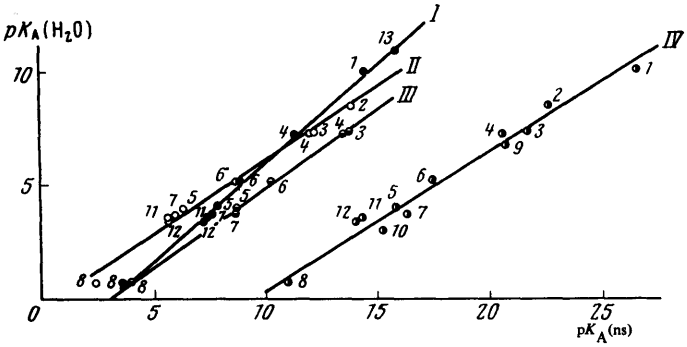

Figure 1. Variation of the pK_A (negative exponent of the dissociation constant) of phenol derivatives in non-aqueous solvents with the pK_A in water: I) methyl alcohol; II) dimethylformamide; III) acetone; IV) acetonitrile.

p$K_A(H_2O)$. Owing to the small number of points, individual relations for the *m*- and *p*-derivatives on the one hand and the *o*-derivatives on the other could not be obtained in other solvents. In the derivation of Eqns. (2), the pK_A values for the *m*- and *p*-derivatives only were employed.

Eqns. (2) were derived by least squares on a "Promin" computer. The equations obtained, the number of experimental points used in their derivation (*n*), the correlation coefficients (*r*), and the standard deviations (*s*) are listed in Table 3.

The empirical Eqns. (2) were compared with the thermodynamic equation derived by Izmailov[1] and Grunwald and Berkowitz[7]:

$$pK_{A(ns)} = \overbrace{pK_A(H_2O) + \lg\frac{\gamma_{0A^-}}{\gamma_{0HA}}}^{a pK_A(H_2O)} + \overbrace{\lg\gamma_{0H^+}}^{\beta}. \qquad (3)$$

If on passing from water to a non-aqueous solvent the quantity $\lg(\gamma_{0A^-}/\gamma_{0HA})$ for a given reaction series varies in proportion to p$K_A(H_2O)$:

$$\lg\frac{\gamma_{0A^-}}{\gamma_{0HA}} = b pK_A(H_2O), \qquad (4)$$

then the coefficient α in Eqn. (2) will differ from unity owing to the effect of the term $\lg(\gamma_{0A^-}/\gamma_{0HA})$ and is equal to $1 + b$. In this case the constant term should be equal to $\lg\gamma_{0H^+}$ for the given solvent. If on passing from water to a non-aqueous solvent the relation

$$\lg\frac{\gamma_{0A^-}}{\gamma_{0HA}} = b pK_A(H_2O) + c, \qquad (5)$$

holds, the constant term β will differ from $\lg\gamma_{0H^+}$ by an amount c.

It follows from Table 3 that β is indeed close to $\lg\gamma_{0H^+}$ for phenol and *m*- and *p*-derivatives of benzoic acid in alcohols and acetone[61]. The value of $\lg\gamma_{0H^+}$ for dimethylformamide is unknown, but comparison of the relative positions of the relative acidity scales for dimethylformamide and water shows that the value of $\lg\gamma_{0H^+}$ should be close to zero[62]. The $\lg\gamma_{0H^+}$ literature data for acetonitrile differ somewhat among themselves[33,61]. Possibly Eqn. (5) holds for acetonitrile. Fig. 2 shows that for

Table 2. The negative exponents of the dissociation constants of benzoic acids at 25°C in various solvents measured potentiometrically (P), conductimetrically (C), spectrophotometrically (SP) and by an indicator method (I).

No.	Acid	Solvents										
		Water refs. 40–42	methyl alcohol refs.44,53–55	water–ethyl alcohol (P) (ref.56); alcohol, %				ethyl alcohol refs. 55–57	acetone ref.46	acetonitrile refs.27, 33	dimethylformamide refs.47–49, and 52	dimethyl sulphoxide refs.33, 51, 58, & 59
				33.2	52.0	73.4	84.5					
1	Benzoic	4.20	9.38(P)	5.16	5.76	6.57	7,25	10.40(I)	11,95(P)	20.1(C)	12.27(P)	10.9(P)
		—	9.25(P)	—	—	—	—	10.15(P)	—	20.7(P)	12.20(P)	11.1(P,C)
		—	9,27(P)	—	—	—	—	10,22(P)	—	—	—	11.0(P)
		—	—	—	—	—	—	—	—	—	—	10.0(P)
		—	—	—	—	—	—	—	—	—	—	10,0(I)
2	o-Hydroxybenzoic	2,99	7.85(P)	—	—	—	—	8.4(I)	9.57(P)	16.7(P)	8,23(P)	6.9(P)
		—	7.9(I)	—	—	—	—	—	—	16.9(C)	7.85(P)	6.8(P,C,SP)
		—	—	—	—	—	—	—	—	—	—	6.6(P)
3	p-Hydroxybenzoic	4.54	—	—	—	—	—	—	12,68(P)	20.8(P)	—	11.8(P)
		—	—	—	—	—	—	—	—	20,3(C)	—	—
4	m-Hydroxybenzoic	4.08	—	—	—	—	—	—	—	—	—	11.1(P)
5	m-Nitrobenzoic	3,46	8.22(P)	4.14	4.67	5.37	6.03	8.82(P)	10.66(P)	—	—	8.2(P)
		—	8.4(I)	—	—	—	—	9.15(P)	—	—	—	—
		—	—	—	—	—	—	9.2(I)	—	—	—	—
6	p-Nitrobenzoic	3.40	8.22(P)	4,06	4.58	5.27	5.93	8.90(P)	10.59(P)	18.7(P)	10.62(P)	8.9(P)
		—	—	—	—	—	—	9.04(P)	—	19.0(C)	—	8.05(P)
7	o-Nitrobenzoic	2.20	7.6(I)	3.51	3.99	4.76	5,47	8.21(P)	—	—	10.05(P)	—
		—	—	—	—	—	—	8,58(P)	—	—	9.60(P)	—
		—	—	—	—	—	—	8.6(I)	—	—	—	—
8	m-Bromobenzoic	3.81	8,71(P)	4.71	5.27	5.96	6.77	9,46(P)	—	19.5(P)	—	—
		—	—	—	—	—	—	9.65(P)	—	19.1(C)	—	—
9	p-Bromobenzoic	3.97	8.83(P)	4.83	5.34	6.04	6.74	9.79(P)	—	—	—	9.45(P)
		—	8.7(I)	—	—	—	—	9.93(P)	—	—	—	—
		—	—	—	—	—	—	9.6(I)	—	—	—	—
10	o-Bromobenzoic	2,85	—	4.07	4.71	5,44	6.13	8.85(P)	—	—	—	—
		—	—	—	—	—	—	9.26(P)	—	—	—	—
11	m-Chlorobenzoic	3.81	8.70(P)	4.78	5.37	6.03	6.67	9.61(P)	—	—	—	—
		—	8.6(I)	—	—	—	—	9.75(P)	—	—	—	—
12	p-Chlorobenzoic	4.03	8.93(P)	4.83	5.38	6.10	6.62	9.75(P)	—	—	—	10.1(P)
		—	—	—	—	—	—	9.85(P)	—	—	—	—
13	o-Chlorobenzoic	2.89	—	4.14	4.78	5.53	6.17	9.01(P)	—	—	11.17(P)	—
		—	—	—	—	—	—	9.31(P)	—	—	—	—
14	m-Fluorobenzoic	3.85	—	4.74	5.36	6.07	6.70	9.71(P)	—	—	—	—
15	p-Fluorobenzoic	4.14	—	4.95	5.55	6.27	6.98	9.90(P)	—	—	—	—
16	o-Fluorobenzoic	3.27	—	4.54	5.25	5.99	6.69	9.69(P)	—	—	—	—
17	m-Toluic	4.25	9.37(P)	5.29	5.92	6.62	7.32	10.37(P)	—	—	—	11.0(P)
		—	9.29(P)	—	—	—	—	10.5 (P)	—	—	—	11.0(P)
18	p-Toluic	4.37	9,45(P)	5.37	6.00	6.80	7.46	10.48(P)	—	—	—	11.9(P)
		—	9.46(P)	—	—	—	—	10.65(P)	—	—	—	—
								10.3 (I)	—	—	—	—
19	o-Toluic	3.90	9.00(P)	5.16	5.82	6.58	7,26	10.16(P)	—	—	—	11.0(P)
		—	—	—	—	—	—	10,24(P)	—	—	—	—
20	m-Methoxybenzoic	4.09	—	5.06	5.72	6.48	7.14	10.13(P)	—	—	—	—
21	p-Methoxybenzoic	4.47	—	5.45	6.09	6.88	7.59	10.55(P)	—	—	—	—
22	o-Methoxybenzoic	4.09	—	5.19	5,83	6.58	7.21	10.09(P)	—	—	—	—
23	3,5-Dinitrobenzoic	2.80	7.4(I)	—	—	—	—	8.1 (I)	—	16.9(P)	8,48(P)	—
		—	—	—	—	—	—	—	—	17,2(C)	—	—
24	2,4-Dinitrobenzoic	1.43	6.5(I)	—	—	—	—	7.3 (I)	—	—	—	—
25	p-Aminobenzoic	4.92	—	—	—	—	—	—	13.46(P)	—	—	12.7(P)
26	2,6-Dihydroxybenzoic	1.30	—	—	—	—	—	—	—	12.6(P,C,SP)	—	3.1(P,C,SP)
27	2,4-Dihydroxybenzoic	3.29	—	—	—	—	—	—	—	—	—	7.5(P)
28	2,5-Dihydroxybenzoic	2.97	—	—	—	—	—	—	—	—	—	7.1(P)
29	m-Aminobenzoic	4.79	—	—	—	—	—	—	—	—	—	11.6(P)
								—	—	—	—	10.4(P)

o-derivatives of benzoic acid the constant term β in Eqn. (2) is not equal to $\lg \gamma_{0\mathrm{H}^+}$ for the given solvent. This can be accounted for by the specific effect of substituents in the *o*-position on the changes in the relative solvation energies of the anions and molecules of the acids on passing from water to a non-aqueous solvent.

The data presented in Table 3 show that, in terms of the coefficient α in Eqns. (2), which reflect the differentiating effect of the solvent in relation to a single reaction series of electrolytes, the solvents examined can be arranged in the following series, which is common to both phenol derivatives and *m*- and *p*-derivatives of benzoic acid:

$$(CH_3)_2SO > CH_3CN > (CH_3)_2NCHO > CH_3COCH_3 > C_2H_5OH > CH_3OH > H_2O.$$

When water is added to a non-aqueous solvent, the differentiating effect of the latter falls, as can be seen for aqueous ethanol mixtures with respect to benzoic acids

Table 3. Equations relating the negative exponents of the dissociation constants of phenols and benzoic acids in non-aqueous solutions to the corresponding values in water: $pK_A(ns) = \alpha pK_A(H_2O) + \beta$.

№	Solvent	Phenol derivatives					*m*- and *p*-derivatives of benzoic acid					lg $\gamma^{\bullet}_{H^+}$
		α	β	*n*	*r*	*s*	α	β	*n*	*r*	*s*	
1	Methyl alcohol	1.17	+3.1	9	0.999	0.13	1.34	+3.6	9	0.995	0.07	+3.1
2	Ethyl alcohol	1.26	+3.4	4	—	—	1.67	+3.1	13	0.970	0.13	+3.9
3	33.2% ethyl alcohol	—	—	—	—	—	1.29	−0.3	13	0.987	0.07	—
4	52% ethyl alcohol	—	—	—	—	—	1.40	−0.1	13	0.978	0.10	—
5	73.4% ethyl alcohol	—	—	—	—	—	1.49	+0.2	13	0.974	0.12	—
6	85.4% ethyl alcohol	—	—	—	—	—	1.52	+0.8	13	0.973	0.12	—
7	16% isopropyl alcohol	1.08	−0.4	6	0.999	0.10	—	—	—	—	—	—
8	42.4% isopropyl alcohol	1.09	−0.8	6	0.999	0.13	—	—	—	—	—	—
9	62.7% isopropyl alcohol	1.20	−0.4	6	0.999	0.06	—	—	—	—	—	—
10	73.8% isopropyl alcohol	1.22	−0.2	6	0.999	0.09	—	—	—	—	—	—
11	86.6% isopropyl alcohol	1.23	+0.3	6	0.999	0.08	—	—	—	—	—	—
12	93.5% isopropyl alcohol	1.25	+0.8	6	0.999	0.08	—	—	—	—	—	—
13	Dimethylformamide	1.57	+0.6	9	0.995	0.39	2.67	+1.2	3	0.989	0.40	—
14	Acetonitrile	1.64	+9.4	12	0.987	0.74	2.65	+9.5	4	0.992	0.39	+5.5; +7.9
15	Acetone	1.48	+3.0	6	0.998	0.25	1.88	+4.2	5	0.996	0.14	+3.3; +4.7
16	Dimethyl sulphoxide	1.90	−2.3	9	0.999	0.27	3.00	−1.9	10	0.969	0.37	−1.5

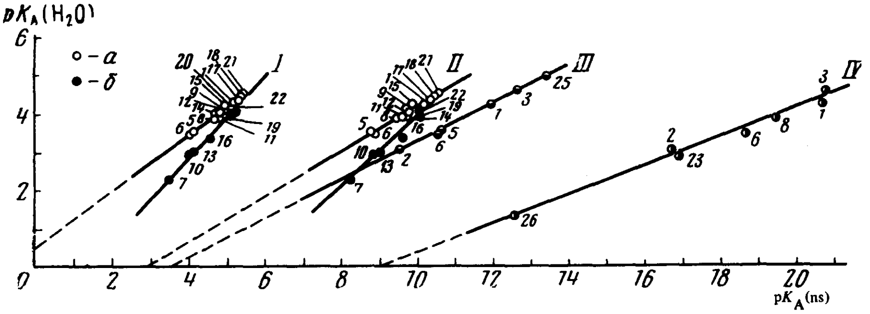

Figure 2. Variation of the pK_A (negative exponent of the dissociation constant) of benzoic acid derivatives in non-aqueous solvents with the pK_A in water (the numbers of the points correspond to those in Table 2): I) 33.2% ethyl alcohol; II) ethyl alcohol; III) acetone; IV) acetonitrile [*a*) *m*- and *p*-derivatives; *b*) *o*-derivatives].

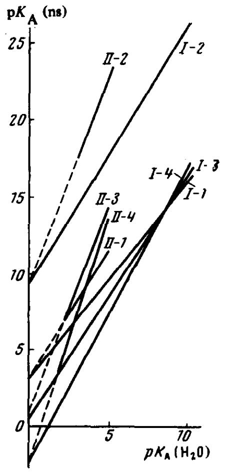

Figure 3. Variation of the pK_A (negative exponent of the dissociation constant) of phenol (I) and benzoic acid (II) derivatives in non-aqueous solvents with the pK_A in water: 1) ethyl alcohol; 2) acetonitrile; 3) dimethylformamide; 4) dimethyl sulphoxide.

and water–isopropyl alcohol mixtures with respect to phenols.

The differentiating effect of solvents in relation to electrolytes of different classes is various: the acid strength of benzoic acids is different in amphiprotic solvents compared with water and to a greater extent than for phenols. As a result, the difference $\Delta pK_A(ns)$ between benzoic acid and phenol derivatives depends on the $pK_A(H_2O)$ values for the electrolytes compared and is greater the higher is $pK_A(H_2O)$ (Fig. 3). For this reason ΔpK_A is not always constant for two different groups of electrolytes and in such cases does not characterise the differentiating effect of the non-aqueous solvent relative to water, as was assumed in a number of investigations[47,48,63,64]. The similarity of the slopes of the plots of $pK_A(ns)$ against $pK_A(H_2O)$ for phenols and carboxylic acids is a consequence of the fact that the group of carboxylic acids includes electrolytes of different reaction series (aromatic and aliphatic carboxylic acids). To establish the laws governing the variation of the relative strengths of acid on passing from solvent to solvent, i.e. the differentiating effect of solvents, it is necessary to examine narrow series of electrolytes[22,60,65].

3. STUDY OF THE DIFFERENTIATING EFFECT OF SOLVENTS BY MEASURING THE HALF-NEUTRALISATION POTENTIALS OF ELECTROLYTES

This method of measuring the relative strengths of electrolytes has proved fruitful not only in the determination of acid strengths in aprotic solvents, where it is possible to determine only relative constants, but also in protolytic solvents, where it is possible to avoid many difficulties associated with the determination of the usual dissociation constants.

The relative strengths of acids and bases in non-aqueous solvents are characterised in three ways, which differ only in the scale of the measurements employed: by the value of pK_{rel} and the pH or potential at the half-neutralisation point—$pH_{1/2}$ and $E_{1/2}$.[4,66-71] In the potentiometric measurement of the relative dissociation constants of acids the pK_{rel} are related to $pH_{1/2}$ and $E_{1/2}$ by the following equations: $pK_{rel} = pH^{x}_{1/2} - pH^{st}_{1/2}$ or $pK_{rel} = (E^{x}_{1/2} - E^{st}_{1/2})/59$, where $pK^{x}_{1/2}$ and $E^{x}_{1/2}$ are the half-neutralisation pH or potentials (mV) for the test compound and $pH^{st}_{1/2}$ and $E^{st}_{1/2}$ are the corresponding values for a standard compound.

To characterise the relative acidities of electrolytes, one employs absolute values of $pH_{1/2}$ and $E_{1/2}$ as well as values referred to a standard ($\Delta pH_{1/2}$ and $\Delta E_{1/2}$), which reduces the effect of variations in the diffusion-potential. In non-aqueous solvents $pH_{1/2}$ and $E_{1/2}$ or $\Delta pH_{1/2}$ and $\Delta E_{1/2}$ are not always functions of the dissociation constants of the electrolytes only but also reflect the effect of factors on which the form of the titration curves depends (the degree of dissociation of the salt formed, its solubility, homoconjugation phenomena, etc.). An increase in the slope of the titration curve in the buffer region results in a displacement of the half-neutralisation potential of the acid to a more basic region; this is facilitated by homoconjugation phenomena[34,39]. A decrease of the slope of the titration curve in the buffer region results in a displacement of the half-neutralisation potential of the acid to a more acidic region; this is favoured by the formation of ion pairs of the salt and its precipitation. However, for acids of a single natural group, the change in $E_{1/2}$ basically correctly reflects the variation of the dissociation constants of the electrolytes in the same solvent.

The half-neutralisation potentials of phenol derivatives were measured in alcohol (methyl, ethyl, propyl, isopropyl, butyl, isobutyl, and t-butyl), ketones (acetone, ethyl methyl ketone, and isobutyl methyl ketone), acetonitrile, dimethylformamide, dimethyl sulphoxide, and other solvents[4,17-19,59,71-76]. Comparison of the half-neutralisation potentials with the $pK_A(H_2O)$ values yields relations described by the equation

$$\Delta E_{1/2}(\text{HP}) = ApK_A(H_2O) + B, \tag{6}$$

where $\Delta E_{1/2}$ is the half-neutralisation potential of phenol measured relative to the half-neutralisation potential of benzoic acid. Measurements for halogeno- and nitro-derivatives of phenol with substituents in the *m*- and *p*-positions showed that the sequence of acidities characteristic of the aqueous solutions is retained[18,72,73]. In a study of halogeno- and nitro-derivatives of phenol containing only *o*-substituents or *o*-substituents together with *m*- and *p*-substituents, it was established that in alcohols phenols with *o*-substituents behave as weaker electrolytes than the *m*- and *p*-derivatives which have the same values of $pK_A(H_2O)$ (Fig. 4). The weaker acid strength of *o*-derivatives of phenol compared with the *m*- and *p*-derivatives may be accounted for by the effect of the intramolecular hydrogen bond between the hydrogen of the phenolic hydroxyl and the substituent in the *o*-position. In ketones, acetonitrile, and dimethylformamide, the effect of the formation of an intramolecular hydrogen bond in *o*-derivatives of phenol cannot be detected, since the titration curves have high slopes in the buffer region owing to homoconjugation, which leads to a displacement of $E_{1/2}$ to a more basic region (Fig. 5). This has a particularly

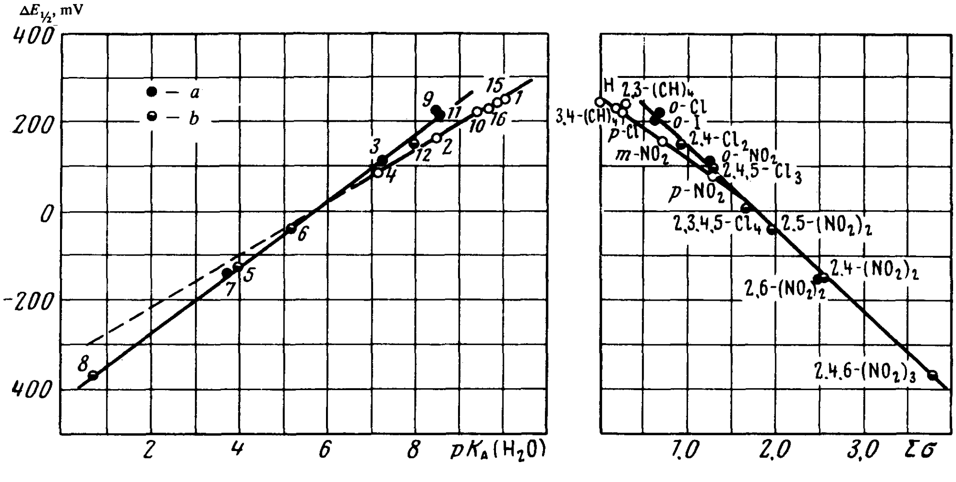

Figure 4. Variation of the half-neutralisation potentials of phenol derivatives in propyl alcohol with $pK_A(H_2O)$ and σ constants: 1) phenol; 2) *m*-nitrophenol; 3) *o*-nitrophenol; 4) *p*-nitrophenol; 5) 2,4-dinitrophenol; 6) 2,5-dinitrophenol; 7) 2,6-dinitrophenol; 8) 2,4,6-trinitrophenol; 9) *o*-chlorophenol; 10) *p*-chlorophenol; 11) *o*-iodophenol; 12) 2,4-dichlorophenol; 13) 2,4,5-trichlorophenol; 14) 2,3,4,5-tetrachlorophenol; 15) α-naphthol; 16) β-naphthol [*a*) *o*-derivatives; *b*) *o*-derivatives containing *m*- and *p*-substituents].

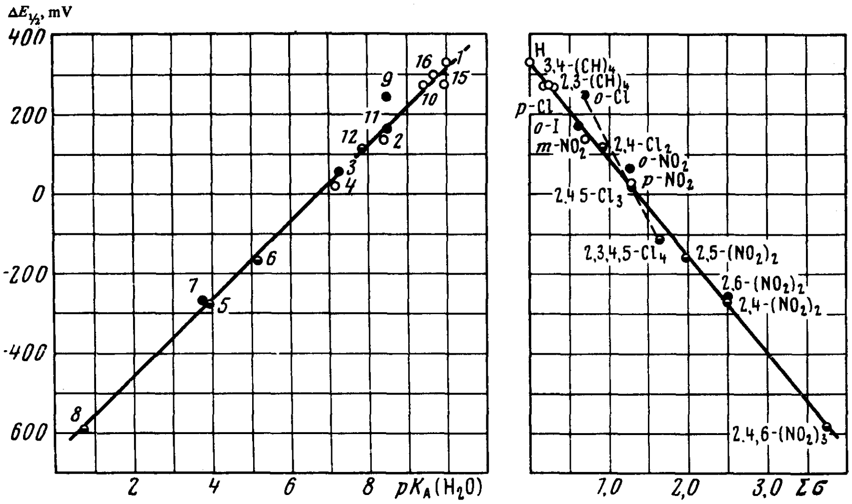

Figure 5. Variation of the half-neutralisation potentials of phenol in acetone with $pK_A(H_2O)$ and σ constants (the numbers and designations of the points are the same as in Fig. 4).

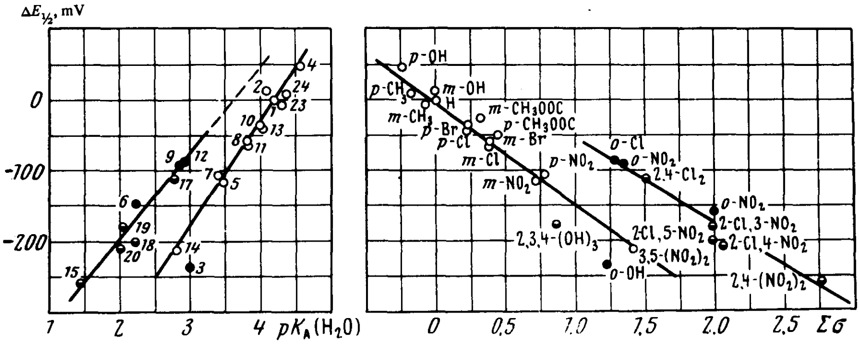

Figure 6. Variation of the half-neutralisation potentials of benzoic acid derivatives in dimethylformamide with $pK_A(H_2O)$ and σ constants; 1) benzoic acid; 2) *m*-hydroxybenzoic acid; 3) *o*-hydroxybenzoic acid; 4) *p*-hydroxybenzoic acid; 5) *m*-nitrobenzoic acid; 6) *o*-nitrobenzoic acid; 7) *p*-nitrobenzoic acid; 8) *m*-bromobenzoic acid; 9) *o*-bromobenzoic acid; 10) *p*-bromobenzoic acid; 11) *m*-chlorobenzoic acid; 12) *o*-chlorobenzoic acid; 13) *p*-chlorobenzoic acid; 14) 3,5-dinitrobenzoic acid; 15) 2,4-dinitrobenzoic acid; 16) 3,4-dihydroxybenzoic acid; 17) 2,4-dichlorobenzoic acid; 18) 2-chloro-5-nitrobenzoic acid; 19) 2-chloro-3-nitrobenzoic acid; 20) 2-chloro-4-nitrobenzoic acid; 23) *m*-toluic acid; 24) *p*-toluic acid.

marked effect on *m*- and *p*-derivatives and therefore *o*-, *m*-, and *p*-derivatives of phenol have a common relation between $\Delta E_{1/2}$ and $pK_A(H_2O)$ in ketones, acetonitrile, and dimethylformamide.

Pearce and Simkins[60] investigated the differentiating effect of ethyl alcohol and acetone with respect to various phenol derivatives: nitrophenols, derivatives of picric acid, and derivatives of styphnic acid. Comparison of $\Delta E_{1/2}$ with $pK_A(H_2O)$ showed that there is no single relation between these quantities for all the electrolytes investigated; instead, there is a family of straight lines: one relation refers to derivatives of picric acid, dinitrophenols give rise to another straight line with a smaller slope relative to the $pK_A(H_2O)$ axis, and it is possible that styphnic acids also have a specific relation with a steeper slope. The authors showed that, when a small number of species are investigated, apparent relations may be obtained between $E_{1/2}$ and $pK_A(H_2O)$, which hold only for a strictly limited group of compounds. Thus an apparent relation for picric acid derivatives, including also styphnic acid, was obtained by Elder and Mariella[74].

The half-neutralisation potentials of benzoic acids have been measured in methyl, ethyl, and isopropyl alcohols, acetone, ethyl methyl ketone, isobutyl methyl ketone, acetonitrile, dimethylformamide, and other solvents[4,16,18,59,60,77,78]. Separate relations corresponding to Eqn. (6) for

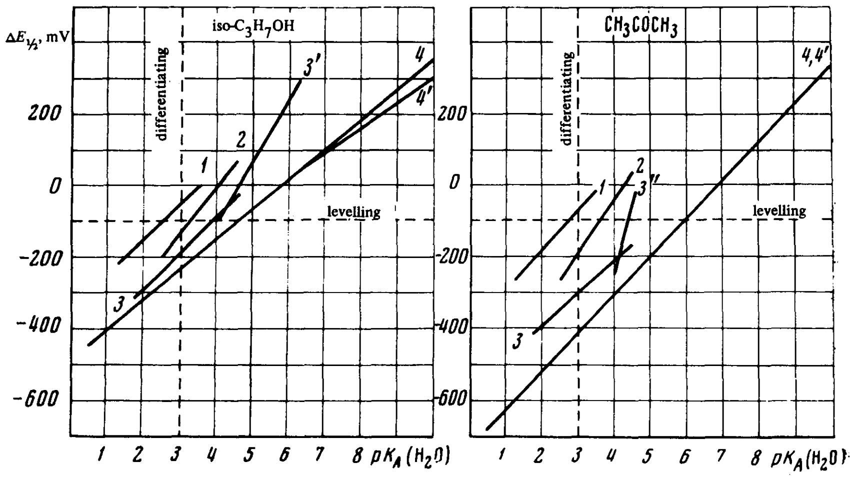

Figure 7. Variation of the half-neutralisation potentials of electrolytes in non-aqueous solvents with $pK_A(H_2O)$: 1) *o*-derivatives of benzoic acid; 2) *m*- and *p*-derivatives of benzoic acid; 3) and 3″) dicarboxylic acids (first dissociation); 3′) dicarboxylic acids (second dissociation); 4) *o*-derivatives of phenol; 4′) *m*- and *p*-derivatives of phenol.

m- and *p*-derivatives and for *o*-derivatives were obtained for all the solvents (Fig. 6). In the case of benzoic acids, on passing from water to non-aqueous solvents, a more pronounced weakening is observed for the *o*-derivatives compared with the *m*- and *p*-derivatives than in the case of phenol. This can probably be accounted for by the steric factors operating in the formation of the intramolecular hydrogen bond (in particular the formation of six-membered rings by *o*-derivatives of benzoic acid). The weakening of the acid strengths of the *o*-derivatives of benzoic acid is so pronounced that homoconjugation even in acetonitrile does not eliminate the difference between the behaviour of *m*- and *p*-derivatives on the one hand and *o*-derivatives on the other, although in acetonitrile $E_{1/2}$ for the *m*- and *p*-derivatives of benzoic acid approaches the value of $E_{1/2}$ for the *o*-derivatives with the same acid strength in water.

Benzoic acid derivatives containing in the same molecule *m*- or *p*-substituents together with *o*-substituents lie on the plot for *o*-derivatives. An appreciable deviation from linearity in all the solvents is shown by *o*-hydroxy derivatives which, owing to the stabilisation of the anion by the intramolecular hydrogen bond, become stronger acids in non-aqueous solvents compared with other acids with the same values of $pK_A(H_2O)$. A deviation from linearity is also shown by acids which on titration give rise to the formation of salt precipitates.

The measurements of the half-neutralisation potentials of phenol and benzoic acid derivatives permit a comparison of the differentiating effects of solvents relative to these groups of electrolytes. On passing from water to amphiprotic solvents, the points for phenols and benzoic acids lie on different straight lines, i.e. there is a differentiating effect of the solvent. Fig. 7 shows as an example the relations between $\Delta E_{1/2}$ in non-aqueous solutions and $pK_A(H_2O)$ for isopropyl alcohol and ethyl methyl ketone. It is evident that the strengths of electrolytes of different groups with the same $pK_A(H_2O)$ values are differentiated to varying extents depending on the value of $pK_A(H_2O)$. For example, in isopropyl alcohol for $pK_A(H_2O) = 2.5$, the half-neutralisation potentials of phenol and any *m*- or *p*-benzoic acid differ by 80 mV and for $pK_A(H_2O) = 4$ by 150 mV. As a result, in relation to some electrolytes the non-aqueous solvents exhibit a differentiating effect while in relation to others they have a levelling effect. Thus on passing from water to isopropyl alcohol or ethyl methyl ketone, the non-aqueous solvents have a differentiating effect with respect to the electrolytes located on the vertical line in Fig. 7 and a levelling effect in relation to the electrolytes located on the horizontal line.

The coefficient *A* in Eqns. (6) represents the slope of the straight lines, i.e. the differentiating effects of the solvents with respect to electrolytes of the same group. The constant term in the equation makes it possible to arrange the groups of electrolytes in a sequence relative to one another. The physical significance of the coefficient *A* is that it represents the difference between the half-neutralisation potentials in a non-aqueous solution between two electrolytes whose $pK_A(H_2O)$ values differ by unity. The differentiating effects of non-aqueous solvents in terms of the coefficient *A*, i.e. in terms of the number of millivolts per unit $pK_A(H_2O)$ value, are compared in Table 4, which shows that alcohols can be arranged in the following sequence in terms of their differentiating effects in relation to phenols and benzoic acids:

$$\text{iso-}C_3H_7OH > \text{iso-}C_4H_9OH > \text{n-}C_4H_9OH > \text{n-}C_3H_7OH,\ C_2H_5OH > CH_3OH\ .$$

Comparison of the differentiating effects of alcohols in relation to phenol and benzoic acid derivatives containing only *m*- and *p*-substituents and derivatives with *o*-substituents shows that alcohols behave differently in relation to phenols and benzoic acids. Thus the differentiating effect of alcohols is greater in relation to phenols containing *o*-substituents than in relation to phenols with only *m*- and *p*-substituents. On the other hand, in relation to benzoic acids, alcohols show a greater differentiating effect for *m*- and *p*-derivatives than for *o*-derivatives. The greater differentiating effect of alcohols with respect to *o*-derivatives compared with *m*- and *p*-derivatives is evidence of a greater difference between the solvation energies of the molecules and ions of *o*-derivatives of phenols compared with the *m*- and *p*-derivatives. In the case of benzoic acids the lower differentiating effect with respect to *o*-derivatives shows that the differences between the solvation energies of the molecules and ions of *m*- and *p*-derivatives of benzoic acid are greater than for the *o*-derivatives. The explanation is probably that the effect of the *o*-substituents diminishes as the polarity of the solvent is reduced owing to a greater non-coplanarity of the carboxy group with respect to the benzene ring, as shown by Charton and Charton[79].

Table 4. Differentiating effects of non-aqueous solvents in relation to phenol and benzoic acid derivatives[72,73,78,81].

Solvent	Phenol derivatives		Benzoic acid derivatives	
	m- and *p*-derivatives	derivatives containing *o*-substituents	*m*- and *p*-derivatives	derivatives containing *o*-substituents
I. Slopes of $\Delta E_{1/2}$ -pK_A(H$_2$O) plots in mV per pK_A(H$_2$O) unit				
Methyl alcohol	—	64	90	68
Ethyl alcohol	61	73	104	78
Propyl alcohol	58	74	—	—
Isopropyl alcohol	80	85	125	95
Butyl alcohol	65	78	—	—
Isobutyl alcohol	67	78	—	—
Acetone	97	97	140	121
Ethyl methyl ketone	105	105	149	109
Acetonitrile	88	88	115	123
Dimethylformamide	108	108	150	120
II. Slopes of $\Delta E_{1/2}$-$\Sigma\sigma$ plots in mV per $\Sigma\sigma$ unit				
Methyl alcohol	—	161	84	70
Ethyl alcohol	135	185	100	81
Propyl alcohol	136	187	—	—
Isopropyl alcohol	186	213	122	97
Butyl alcohol	153	195	—	—
Isobutyl alcohol	157	198	—	—
Acetone	242	242	139	125
Ethyl methyl ketone	264	264	147	111
Acetonitrile	219	219	113	127
Dimethylformamide	267	267	149	125

The differentiating effects of acetone and ethyl methyl ketone with respect to acids are almost the same. The differentiating effect of acetonitrile is less marked than that of ketones, probably due to homoconjugation in the electrolyte solutions, which is particularly pronounced in the titration process. The differentiating effect of dimethylformamide with respect to phenols and benzoic acids is similar to that of ethyl methyl ketone. Thus, ketones, acetonitrile, and dimethylformamide can be arranged in the following series in order of their differentiating effects:

$$(CH_3)_2NCHO > CH_3COC_2H_5,\ CH_3COCH_3 > CH_3CN\ .$$

Gur'ev[76] gave a systematic account of data for the coefficients of pK_A(H$_2$O) in the relation between $\Delta E_{1/2}$ in non-aqueous solutions and pK_A(H$_2$O); he took these coefficients from studies dealing with relations of this kind, calculated them from the pK_{rel} for electrolytes determined by non-electrometric methods, or determined them from potentiometric titration curves. In relation to all groups of acids, pyridine showed the greatest differentiating effect, and was followed in this respect by dimethylformamide, ketones, acetonitriles, and aprotic solvents and their mixtures with protolytic solvents. Compared with water, all the solvents differentiate the acid strengths of benzoic acids to a greater extent than those of phenols.

Hitherto, we have considered changes in the differentiating effect on passing from water to a non-aqueous solvent. In turn, water as a solvent has varied differentiating effects on different groups of electrolytes depending on their molecular structure. Thus the differentiating effect of water with respect to phenol derivatives is shown to a much greater extent than with respect to benzoic acids, owing to the closer location of the substituent in the phenol molecule to the reaction centre than in the benzoic acid molecule. Thus in the Hammett equation the reaction constant ρ for the dissociation of benzoic acids in aqueous solution is unity and for the dissociation of phenols 2.23.[80] Therefore, apart from a comparison of $\Delta E_{1/2}$ with pK_A(H$_2$O), it is of considerable interest to compare $\Delta E_{1/2}$ with the σ constants for the substituents[18,78,81].

Comparison of the differentiating effects of solvents in terms of the slope of the plots of $\Delta E_{1/2}$ against σ or $\Sigma\sigma$ in the presence of several substituents in the same molecule (Table 4) makes it possible to follow the changes in the differentiating effect of solvents with respect to electrolytes belonging to different reaction series as a function of the structural differences between the molecules. Figs. 4–6 present examples of the relations between $\Delta E_{1/2}$ in non-aqueous solutions and $\Sigma\sigma$ for phenol and benzoic acid derivatives. These relations are characterised by an equation of the form

$$\Delta E_{1/2} = A'\Sigma\sigma + B'. \tag{7}$$

The coefficient A' is equal to the difference between the half-neutralisation potentials of two electrolytes whose $\Sigma\sigma$ values differ by unity.

In the first place mention should be made of the fact that the number of millivolts per pK_A(H$_2$O) unit and the number of millivolts per σ unit are very similar for benzoic acids, since the reaction constant ρ for the dissociation of benzoic acids in aqueous solution is unity. The slight discrepancies between these values are a consequence of the deviation from unity of the correlation coefficient for the relation between pK_A(H$_2$O) and $\Sigma\sigma$ and also of the fact that, as a result of the different degrees of dissociation of the salts formed, the formation of ion pairs, and homoconjugation, the half-neutralisation potentials are not always functions of the acid dissociation constants alone. Comparison of the differentiating effects of the solvents on the basis of the number of millivolts per $\Sigma\sigma$ unit shows that the differentiating effect on non-aqueous solvents, like that of water, is much greater for phenol derivatives than for benzoic acid derivatives.

The relative E_S acidity scale, the extent of which determines the possibility of the differential titration of mixtures of electrolytes, is an analytical chemical characteristic of solvents in acid–base potentiometric titrations[4,62,82]. The E_S scale for solvents is measured under the same conditions as the half-neutralisation potentials of electrolytes. It is therefore of interest to compare quantities characterising the differentiating effects of solvents with respect to individual groups of electrolytes with the extents of the relative acidity scales of the solvents. It is to be expected that the correlation between these quantities will be most clear cut within the limits of a single chemical group of solvents. Fig. 8 shows a comparison of the extents of the E_S scales for solvents with the coefficients A and A' in Eqns. (6) and (7). It is seen from the Figure that there is a linear relation between the extents of the relative acidity scales for alcohols and the coefficients A and A' characterising the differential effects of the alcohols not only in relation to phenols and benzoic acids but also in relation to dicarboxylic acids[83]. The differentiating effects of non-aqueous solvents in relation to phenols and benzoic acid can also be compared in terms of the relative dissociation constants of these electrolytes in different solvents, which are calculated from the half-neutralisation potentials of phenols and benzoic acids[78,81] by the formula (at 20°C)

$$pK^{x}_{\mathrm{rel}} = pK^{x}_{\mathrm{A}} - pK_{\mathrm{A}}^{C_6H_5COOH} = \frac{\Delta E_{1/2}}{58} \quad . \qquad (8)$$

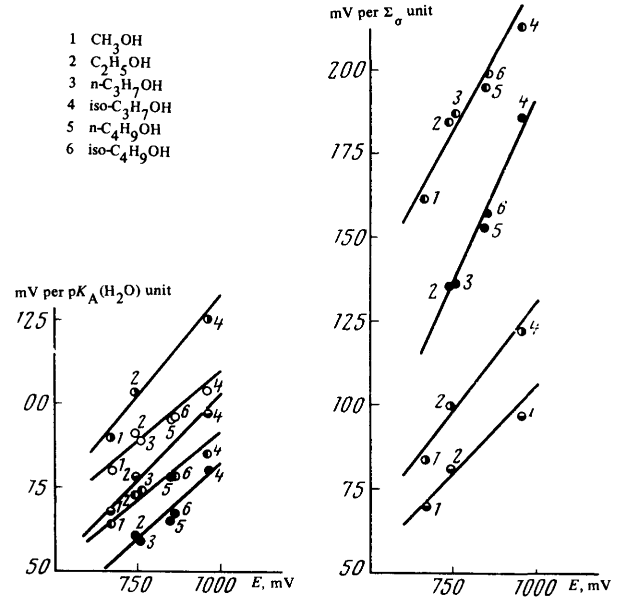

Figure 8. Relation between the slopes of plots of $\Delta E_{1/2}$(ns) against $pK_A(H_2O)$ and $\Delta E_{1/2}$(ns) against $\Sigma\sigma$ and the range of the relative acidity scale of the solvent: ●—*m*- and *p*-derivatives of phenol; ◐—*o*-derivatives of phenol; ◑—*m*- and *p*-derivatives of benzoic acid; ⊖—*o*-derivatives of benzoic acid; ○—dicarboxylic acids (first dissociation).

The pK_{rel} values for phenols and benzoic acids in various solvents are compared in Figs. 9–12. On passing from water to alcohols, the acid strength of phenols increases relative to that of benzoic acids (Fig. 9). The same also happens on passing from water to other non-aqueous solvents. Consequently, on passing from water to alcohols, the solvation of phenoxide ions compared with that of phenol molecules increases more than the solvation of benzoate ions compared with that of benzoic acid molecules. In solvents belonging to the same natural group (ethyl and isopropyl alcohols) differentiation of the acid strengths of phenols and benzoic acids is not observed. According to Brönsted's theory, the points for all electrolytes lie on a single straight line with a slope of unity (Fig. 10). The same happens on passing from acetone to ethyl methyl ketone.

On passing from ketones to alcohols, i.e. solvents of another natural group, the acid strengths of phenols and benzoic acids are differentiated. However, whereas on

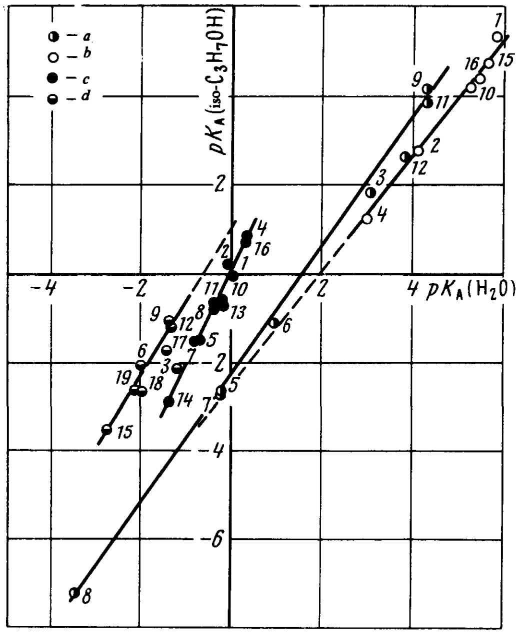

Figure 9. Relation between the pK_{rel} of phenol and benzoic acid derivatives in water and isopropyl alcohol (the numbers of the points for the phenols are the same as in Fig. 4 and those for benzoic acid are the same as in Fig. 6): *a*) phenol derivatives containing *o*-substituents; *b*) *m*- and *p*-derivatives of phenol; *c*) *m*- and *p*-derivatives of benzoic acid; *d*) derivatives of benzoic acid containing *o*-substituents.

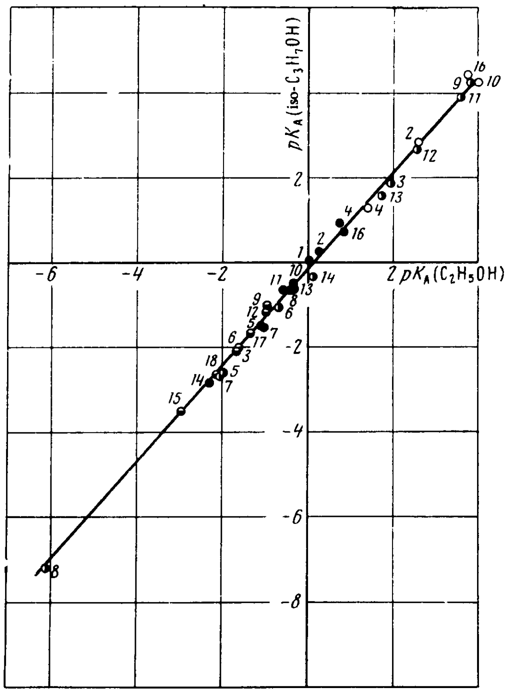

Figure 10. Relation between the pK_{rel} of phenol and benzoic acid derivatives in ethyl and isopropyl alcohols (the numbers and designations of the points correspond to those in Fig. 9).

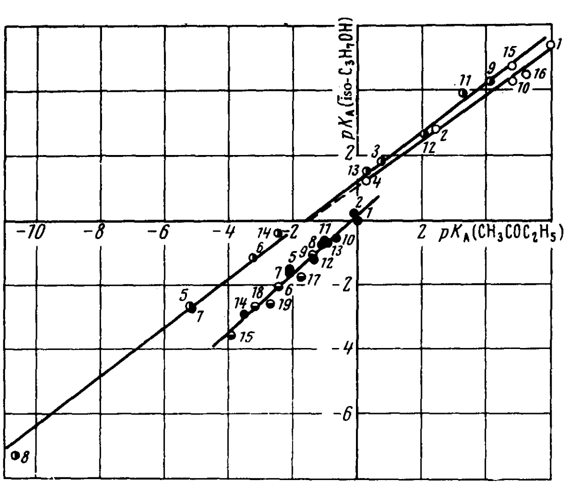

Figure 11. Relation between the pK_{rel} of phenol and benzoic acid derivatives in ethyl methyl ketone and isopropyl alcohol (the numbers and designations of the points correspond to those in Fig. 9).

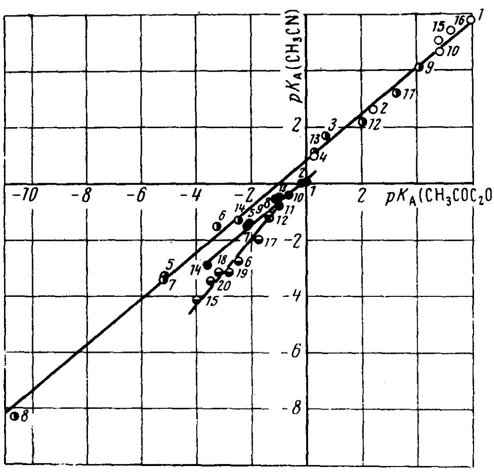

Figure 12. Relation between the pK_{rel} of phenol and benzoic acid derivatives in ethyl methyl ketone and acetonitrile (the numbers and designations of the points correspond to those in Fig. 9).

passing from water to alcohols there is an increase in the acid strength of phenols compared with benzoic acids, on passing from ketones to alcohols the opposite phenomenon is observed: phenols become weaker than benzoic acids (Fig. 11). Within a single class of electrolytes, the differentiating effect changes on passing from ketones to alcohols only among phenols. The points for all the benzoic acids lie on a single straight line with a slope close to unity, which is evidence that the solvation energies of the ions and molecules of benzoic acids change to the same extent on passing from ketones to alcohols. On going from ketones to acetonitrile, the acid strengths of phenols and benzoic acids are also differentiated (Fig. 12). In contrast to the effect on passing from ketones to alcohols, the acid strengths are differentiated within the class of benzoic acids but not within the class of phenols. As stated above, *m*- and *p*-derivatives of benzoic acid become weaker in acetonitrile compared with *o*-derivatives than in ethyl methyl ketone, in consequence of homoconjugation, which is particularly pronounced in acetonitrile.

The results of the above comparison of the relative acid strengths of phenols and benzoic acids in various solvents are consistent with the data presented in the monographs of Izmailov[1] and Shatenshtein[6] for solvents of the same and different natures. Shatenshtein's latest data on the differentiating effects of solvents in relation to C–H acids obtained by an isotope exchange method also confirmed the conclusion that the differentiating effect is due to a change in the solvation of ions and molecules of acids in the solvents compared[10].

4. STUDY OF THE DIFFERENTIATING EFFECT OF SOLVENTS BASED ON THE HAMMETT EQUATION

Acid strengths, particularly of benzoic acid and phenol derivatives, in aqueous solutions can be successfully predicted on the basis of the Hammett equation[80,84]. If the σ constants did not change on passing from water to non-aqueous solvents, the effect of the latter on the dissociation of substituted acids might be taken into account using the constant ρ:

$$\lg \frac{K}{K^0} = \rho\sigma \quad , \tag{9}$$

where K and K^0 are the dissociation constants of the substituted and unsubstituted acids.

It has been stated[21,22,85-94] that the σ constants vary on passing from water to non-aqueous solvents owing to changes in the solvation of the polar groups of the substituents, in particular the type of hydrogen bond between the substituent and the solvent molecules; under the influence of the solvent, the capacity of the substituent for polar conjugation with the reaction centre may alter, etc. As a rule, the effect of the solvent on the σ constant is small[21]. Only certain substituents (for example OH groups) show an appreciable variation of the σ constants on changing the solvent[21,23,90].

The effect of the solvent on the σ constant cannot be taken into account with the aid of the dielectric constant ϵ of the medium, as suggested by Hammett[22,84]. For example, it is known that the relation

$$\rho = \left(1.87 + \frac{67}{\varepsilon}\right) \cdot \frac{1.09}{2.8^n},$$

(where n is the number of atoms separating the reaction centre from the phenyl carbon atom) holds satisfactorily for benzoic acids in water, ethylene glycol, and methyl and ethyl alcohols, but not in n-propyl and n-butyl alcohols and aqueous dioxan mixtures[93].

The use in Eqn. (9) of known Hammett's σ constants for aqueous solutions does not yield a constant ρ which would reflect the influence of the solvent on the transmission of only the inductive effect of the substituents. In this connection, the method of estimation of the constant ρ proposed by Palm[22] and based on the use of Taft's universal σ^* induction constants for aliphatic substituents and the ρ^* universal interaction constant is of interest. However, the lack of adequate literature data for the K_A of aliphatic carboxylic acids in non-aqueous solvents precludes the use of this method for the estimation of the effect of the solvent on the ρ^* constant. Therefore one may assume, as emphasised in a number of monographs[21,22] and papers[23,24,94], that at the present time the weakest point of all quantitative theories of the effect of substituents is the little investigated effect of solvents.

In earlier reviews[23,24] the ρ constants for the dissociation of benzoic acid in certain alcohols, aqueous alcoholic, and aqueous dioxan mixtures were given. In contrast to Jaffe[23], Wells[24] quotes in his review also the values of ρ obtained by the method described in the paper of van Bekkum et al.[95], who used a reaction series involving only *m*-derivatives of benzoic acid to exclude the effect of polar conjugation between the substituent and the reaction centre; this leads to an increase of ρ. The values of ρ quoted in the reviews[23,24] were obtained on the basis of the K_A constants for benzoic acid measured largely by indicator methods.

The data for the dissociation constants of *m*- and *p*-derivatives of benzoic acid obtained by electrometric methods permitted the calculation of new values of the constant ρ.[44,56,58,89,96,97] These values of ρ, calculated by ourselves and taken from papers by other investigators are listed in Table 5. The reaction constants ρ, the correlation coefficients r, and the standard deviations s were calculated by least squares on a "Promin'" computer. Table 5 also lists the numbers of correlated quantities n.

Table 5. Reaction constants ρ in the Hammett equation for the dissociation of *m*- and *p*-derivatives of benzoic acid in non-aqueous solutions.

Solvent	Calc. from pK_A (25°)					Calc. from $\Delta E_{1/2}$ (20° ± 2°)				
	ρ	n	r	s	from Refs. 44, 56, 58, and 96	ρ	n	r	s	from Refs. 59 and 60
Methyl alcohol	1.38	9	0.995	0.05	1.38; 1.54; 1.55	1.42	16	0.969	0.18	—
Ethyl alcohol	1.67	13	0.984	0.09	1.65; 1.67	1.68	15	0.955	0.25	1.3
33.2% ethyl alcohol	—	13	—	—	1.28	—	—	—	—	—
52% ethyl alcohol	—	13	—	—	1.40	—	—	—	—	—
73.4% ethyl alcohol	—	13	—	—	1.52	—	—	—	—	—
85.4% ethyl alcohol	—	13	—	—	1.53	—	—	—	—	—
Isopropyl alcohol	—	—	—	—	—	2.01	15	0.988	0.15	—
Acetone	1.96	5	0.997	0.09	—	2.30	14	0.970	0.27	—
Ethyl methyl ketone	—	—	—	—	—	2.41	13	0.987	0.18	—
Acetonitrile	2.65	4	0.998	0.09	2.8	1.91	14	0.990	0.13	—
Dimethylformamide	2.65	3	0.991	0.35	—	2.42	14	0.986	0.19	—
Dimethylsulphoxide	3.13	11	0.982	0.27	2.6	—	6	—	—	2.5

In examining the data in Table 5, it is necessary to bear in mind that the values of ρ quoted were obtained on the basis of K_A data for *m*- and *p*-derivatives of benzoic acid and therefore they reflect the influence of the solvent on the inductive and resonance effects and the effect of polar conjugation of substituents with the reaction centre.

As in the calculation of α in Eqn. (2), the most reliable values of ρ refer to methyl and ethyl alcohol, water–ethyl alcohol mixtures, and dimethyl sulphoxide, since a large number of experimental points ($n = 9 - 13$) were employed in these calculations. For acetonitrile, ρ was obtained without taking into account *p*-hydroxybenzoic acid, since the latter shows a marked deviation from linearity, which is probably due to the change in the ρ constant of the OH group on passing from water to acetonitrile.

The lack of data or their inadequacy for solvents such as isopropyl alcohol, acetone, ethyl methyl ketone, dimethylformamide, and acetonitrile led to the necessity for the determination of the constant ρ also on the basis of the relative concentration dissociation constants of *m*- and *p*-derivatives of benzoic acids obtained from half-neutralisation potentials (see Section 3).

Table 5 shows that the values of ρ for methyl and ethyl alcohols obtained by the two methods agree well. The constants ρ for ketones, acetonitrile, and dimethylformamide obtained from the pK_{rel} data should of course be lower than the true values owing to the distortion of the potentiometric titration curves. The value of ρ for acetone obtained from pK_{rel} is higher than ρ calculated from pK_A. In all probability this suggests that the available literature values of pK_A of benzoic acid in acetone are not sufficiently valid characteristics of the differentiating effect of this solvent. The values of ρ for isopropyl alcohol, acetone, and ethyl methyl ketone indicate a higher differentiating effect of these solvents for benzoic acid compared with ethyl and methyl alcohols.

There is a limited amount of ρ data[23,24] for the dissociation of phenol derivatives in water–ethyl alcohol mixtures. The constant ρ has also been determined for 45 vol. % isopropyl alcohol in water ($\rho = 2.80$).[98]

It follows from the data in Table 1 that the experimental dissociation constants of phenol derivatives refer predominantly to nitro-derivatives containing *o*-substituents together with *m*- and *p*-substituents. Even in aqueous solutions *o*-substituents do not have invariant values of the σ constants[80]. Therefore there is all the more reason to expect a change in σ_{ortho} on passing from water to non-aqueous solvents. Consequently the data in Table 1 were not used to calculate the constants ρ for the dissociation of phenol derivatives in non-aqueous solvents.

Table 6. Reaction constants ρ in the Hammett equation for the dissociation of phenol derivatives in non-aqueous solutions calculated from half-neutralisation potentials (20° ± 2°).

Solvent	ρ	n	r	s
Propyl alcohol	2.25	6	0.997	0.08
Butyl alcohol	2.59	6	0.993	0.16
Isobutyl alcohol	2.67	6	0.986	0.24
Isopropyl alcohol	3.17	6	0.993	0.20
Acetonitrile	3.72	16	0.998	0.29
Acetone	4.11	16	0.999	0.22
Ethyl methyl ketone	4.48	16	0.999	0.21
Dimethylformamide	4.57	16	0.995	0.39

Mention should be made of an investigation[25] where the relative acidities of 4-substituted derivatives of 2,6-dichloro and 2,6-dimethylphenols in water, methyl and isopropyl alcohols, acetone, and water–dioxan mixtures were determined from measurements of half-neutralisation potentials. The differentiating effect of non-aqueous solvents increases with decrease in the polarity of the solvent. Thus ρ for 4-substituted 2,6-dichlorophenols is 2.55 in water, 2.99 in methyl alcohol, 4.13 in isopropyl alcohol, and 5.39 in acetone. On addition of water to dioxan there is a sharp decrease of ρ, which is 5.15 in 99.8% dioxan containing 0.2 vol. % of isopropyl alcohol, 4.00 in 98% dioxan, 3.66 in 95% dioxan, 3.43 in 91% dioxan, and 2.72 in 71% dioxan.

An attempt has been made to investigate the ρ constant for the dissociation of phenols in non-aqueous solutions by measuring the half-neutralisation potentials, from which the pK_{rel} for phenols in alcohols, acetone, ethyl methyl ketone, dimethylformamide, and acetonitrile were calculated[81]; the constants ρ for these solvents are listed in Table 6. It is noteworthy that in alcohols the reaction series contains only *m*- and *p*-derivatives of phenol and in ketones, dimethylformamide, and acetonitrile also derivatives with *o*-substituents, since (as already mentioned in section 3) in these solvents there is a common relation between $E_{1/2}$ and the σ constants adopted for the substituents in aqueous solutions.

Table 6 shows that, on passing from solvent to solvent, the differentiating effect of solvents determined from measurements of the pK_{rel} values for phenols varies in the same sequence as in relation to *m*- and *p*-derivatives of benzoic acid. The values of ρ for isopropyl alcohol and acetone listed in Table 6 are lower than those obtained by Fischer et al.[25] (3.46 and 4.93 respectively), which can be accounted for by the effect of the titrant solvent employed in the determination of pK_{rel}; the data in Table 6 were obtained with about 1% methyl alcohol in the solvent and those of Fischer et al.[25] with about 0.2% of isopropyl alcohol.

The data on the differentiating effect of amphiprotic solvents obtained from the ρ constants in Hammett's equation and those found by comparing $pK_A(ns)$ or $\Delta E_{1/2}$ with $pK_A(H_2O)$, quoted in Sections 2 and 3, agree well with one another if account is taken of the difference between the values of ρ in water for the corresponding reaction series. The change in the differentiating effect of solvents for a given reaction series may be expressed by the ratio ρ_{ns}/ρ_{H_2O}, the physical significance of which is equivalent to that of the quantity α in Eqn. (2).

5. THE AUTOPROTOLYSIS CONSTANT AS A CHARACTERISTIC OF THE DIFFERENTIATING EFFECT OF A SOLVENT

The autoprotolysis of a solvent is accompanied by the formation of lyonium and lyate ions which in a given solvent are the strongest acid and the strongest base respectively. Therefore the autoprotolysis constant of the solvent,

$$K_s = a_{SH_2^+} a_{S^-} ,$$

is a measure of its differentiating effect on the strengths of acids and bases. The negative exponent of the autoprotolysis constant defines the extent of the acidity scale of the solvent. The more pronounced are the acidic and basic properties of the solvent, the higher is the autoprotolysis constant, and the smaller the extent of its acidity scale. With decrease of the acidic and basic properties of the solvent, the extent of the acidity scale increases together with the differentiating effect of the solvent in relation to acids and bases.

If the acidic and basic properties of the solvent are less pronounced than those of water, its differentiating effect relative to water is greater for all classes of electrolytes. On the other hand, if the acidic or basic properties of the solvent exceed those of water, then in comparing their differentiating effects it is necessary to take into account also the relative positions of the acidity scales of the solvents in terms of a single acidity scale. The displacement of the acid limit of the acidity scale of the solvent relative to that of the water scale is unambiguously characterised by the transolvation energy of the proton on passing from an infinitely dilute aqueous solution to the given solvent[61]. With decrease in the acidity of the solvent, which leads to a displacement of the basic limit of its acidity scale towards lower proton activities, the differentiating effect of the solvent in relation to weak acids and strong bases increases; with decrease of the basicity of the solvent (shift of the acid limit of the scale towards higher proton activities), its differentiating effect in relation to weak bases and strong acids increases. Thus, the differentiating effect of the solvent is different for electrolytes of different strengths and is characterised by its autoprotolysis constant and the position of its acidity scale in terms of a single acidity scale. Moreover, according to Izmailov's theory of solvation[1], the differentiating effect of solvents is different for electrolytes belonging to different reaction series.

Table 7. Negative exponents of the autoprotolysis constants of certain solvents.

Solvent	pK_s		
	calc. from Eqn.(10)	measured values (25°)	obtained by methods of comparative calculations
Methyl alcohol	15.9	16.7[99–101]	16.3[115] 16.7[117]
Ethyl alcohol	—	16.8[102]; 17.9[100]; 18.9[103]; 19.1[99,104]; 19.5[105,106]	17.1[115] 18.8[117]
Propyl alcohol	—	19.4[103]	20.8[115] 19.4[117]
Isopropyl alcohol	22.0	20.8[100,103]	21.3[115]
Butyl alcohol	—	—	21.1[115] 19.6[116]; 21.6[117]
t-Butyl alcohol	26.8	22.2[100]	21.1[115]
Acetone	32.5	—	22.3[115] 22.8[118]
Ethyl methyl ketone	—	25.7[107]	21.5[115] 21.0[118]
Acetonitrile	33.2	19.5[108]; 26.5[109] 28.5[30]; 33.3[110]	25.5[117]
Dimethylformamide	29.4	18.0[111]	17.0[117]
Dimethylsulphoxide	31.8	17.3[112]; 33.3[51]	—

The autoprotolysis constants of by no means all amphiprotic solvents have now been measured and their reliability in many cases is not great, since the range of pH values which may be used in acid–base titration frequently correspond to a higher value of pK_S than indicated by the available literature data[82]. Table 7 lists the pK_S values for certain amphiprotic solvents measured by different methods[30,51,99–112]. The Table shows that the values quoted by various authors for a series of solvents differ appreciably among one another. Thus the discrepancy for ethyl alcohol is about 3 pH units, for acetonitrile 6.8 pH units, and for dimethyl sulphoxide up to 16 pH units. In the first place this discrepancy is evidence of the experimental difficulties in the determination of autoprotolysis constants, particularly for solvents with low values of K_S and is a consequence for the errors associated with the different methods for the determination of the dissociation constants of a base and its conjugate acid, the indeterminancy of the diffusion junction potential in cells with transport, incomplete dissociation of electrolytes, etc.[82,110] One of the most important causes of unduly high values of K_S is also the presence of water in solvents, the ionisation of which is responsible for protolysis in the given solvent[113].

The values of pK_S for solvents may be estimated by measuring the relative acidity scale values for solvents from the approximate equation[82]

$$pK_s = \frac{E_s}{59} + \lg c_{HClO_4}c_{R_4NOH}, \tag{10}$$

where E_S is the relative acidity scale value (mV) for the solvent, equal to the difference between the half-neutralisation potentials of $HClO_4$ and R_4NOH in the given solvent, and c_{HClO_4} and c_{R_4NOH} are the concentrations of the acid and base at the instant of half neutralisation.

The measurements of the E_S scale values for solvents are usually made under conditions where the solvent contains 1–1.5% of water and methanol; the E_S for pure solvents may be found by extrapolation using equations describing the variation of the limits of the scale with the composition of the mixed solvents[114]. It must be emphasised that the values of pK_S for solvents calculated in this way are low because the activities of H^+ and OH^- ions are not equal to the concentrations of $HClO_4$ and R_4NOH and in consequence of the use of a base not containing the lyate ions of the solvent, the inadequate sensitivity of the glass electrode in strongly acidic and strongly basic media, and other causes. However, the values of pK_S calculated from the E_S for pure acetonitrile and dimethyl sulphoxide are close to the latest literature data, which is evidence of the adequate reliability of the pK_S obtained from measurements of the relative acidity scale values. They may be regarded as the lower limits of the true values.

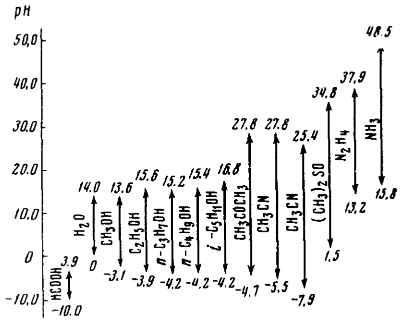

Figure 13. Izmailov's unique acidity scale for solvents.

Comparison of the pK_S calculated by Eqn. (10) for amphiprotic solvents with the literature data (Table 7) shows that the literature values of the pK_S for isopropyl and t-butyl alcohols, ethyl methyl ketone, and dimethylformamide are too low. It also follows from Table 7 that the methods of comparative calculation are suitable only for the estimation of the pK_S of lower alcohols[115,117,118]. Fig. 13 shows a single pA solvent acidity scale[1,61] obtained using the most reliable values of pK_S for amphiprotic solvents (printed bold in Table 7) as well as certain others on the basis of the primary effects of the medium ($\lg\gamma_{0H^+}$) determined by Izmailov[61] and other workers[33]. It follows from Fig. 13 and Table 7 that amphiprotic solvents are characterised by a wide range of acidity scales.

On the basis of data for the relative basicities and acidities of solvents, one may assume the decrease of the K_S values for alcohols with increase of the size of the alkyl group and the degree of its branching is largely due to the decrease of the contributions to acidity which depend on the electron-donating properties of the alkyl group in the alcohol molecule. The low autoprotolysis constants of ketones, dimethylformamide, acetonitrile, and dimethyl sulphoxide are related to their extremely weak acid properties as C–H acids; ketones and acetonitrile are also extremely weak bases[119].

The differentiating effects of amphiprotic solvents can be arranged in the following sequence on the basis of the autoprotolysis constants:

$$(CH_3)_2SO,\ CH_3CN > CH_3COC_2H_5,\ CH_3COCH_3 > (CH_3)_2NCHO >$$
$$> t\text{-}C_4H_9OH > iso\text{-}C_3H_7OH > n\text{-}C_4H_9OH,\ n\text{-}C_3H_7OH,$$
$$n\text{-}C_2H_5OH > CH_3OH > H_2O,$$

which, within the limits of the reliability of the K_S values, is the same as the sequence of the differentiating capacities of the solvents established on the basis of the dissociation constants and the half-neutralisation potentials of the electrolytes.

It was of interest to follow the relation between the pK_S for amphiprotic solvents and α in Eqn. (2), since these are parameters characterising the differentiating effects of solvents. According to Eqn. (2), for a reaction series of n electrolytes arranged in order of increasing pK_A values, the difference between the pK_A values of two consecutive electrolytes is

$$\Delta pK_A^i\,(\mathrm{ns}) = \alpha\Delta pK_A\,(H_2O), \text{where } i = 1, 2, 3, \ldots, n-1$$

and

$$\sum_{i=1}^{n-1} \Delta pK_A^i\,(\mathrm{ns}) = \alpha \sum_{i=1}^{n-1} \Delta pK_A^i\,(H_2O) \quad . \tag{11}$$

The positions of the reaction series on the acidity scales of water and the non-aqueous solvent may be represented as follows:

$$pK_s\,(H_2O) = \sum_{i=1}^{n-1} \Delta pK_A^i\,(H_2O) + a + b \tag{12}$$

and

$$pK_s\,(\mathrm{ns}) = \sum_{i=1}^{n-1} \Delta pK_A^i\,(\mathrm{ns}) + c + d \quad , \tag{13}$$

where a, b, c, and d are the sections of the acidity scales of the solvents in the acid and alkaline regions unoccupied by the given reaction series.

Eqn. (11) suggests that Eqn. (13) is a first-degree polynomial in α. Then it is possible to obtain from Eqns. (12) and (13) a relation between pK_S and α:

$$pK_s\,(\mathrm{ns}) = \mathrm{const}_1\,\alpha + \mathrm{const}_2\ , \tag{14}$$

where const_1 and const_2 are constants for each reaction series.

Tests of Eqn. (14) for phenol and benzoic acid derivatives showed that there is indeed a linear relation between the negative exponents of the autoprotolysis constants of amphiprotic solvents and the values of α in Eqn. (2) for the corresponding reaction series (Fig. 14). It follows from Fig. 14 that benzoic acid and phenol derivatives give rise to separate relations characterised by different slopes. It is also seen that, compared with water, the differentiating effect of amphiprotic solvents is greater with respect to benzoic acids. The ratio of the slopes of lines I and II is close to the ratio of the ρ_{H_2O} constants for the reaction series considered (about 2.5). This suggests that the effect of substituents on passing from solvent to solvent is constant and the effect of the solvent may be taken into account by the change of the constant ρ. Since $\alpha = \rho_{ns}/\rho_{H_2O}$, there should be a linear relation between the pK_S and ρ for amphiprotic solvents. Fig. 14 shows the presence of such a linear relation for *m*- and *p*-derivatives of benzoic acid (line III). In plotting the relation between pK_S and ρ, use was made also of the values of ρ obtained from measurements of the half-neutralisation potentials.

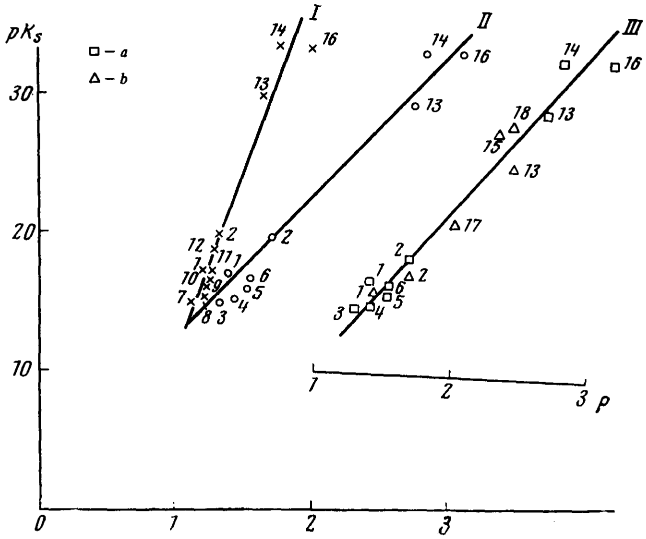

Figure 14. Correlation between the pK_S of solvents and the coefficients α in Eqn. (2) or the constants ρ in Hammett's equation: I) phenol derivatives; II) and III) benzoic acid derivatives [*a*) on the basis of pK_A; *b*) on the basis of $E_{1/2}$; the numbers of points *1* to *16* correspond to those in Table 3; *17*) isopropyl alcohol; *18*) ethyl methyl ketone].

Bearing in mind that at the instant of the measurement of $E_{1/2}$ for benzoic acids the solvents contained about 1–1.5% of water and methyl alcohol, the ρ values were compared with the pK_S of solvents containing the same amounts of water and methanol. These pK_S were calculated from Eqn. (10) on the basis of the values scale $\dot{E}_S$ measured under the same conditions as $E_{1/2}$.

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The above examination of the differentiating effects of amphiprotic solvents with respect to *m*- and *p*-benzoic acids and phenol derivatives on the basis of the pK_A and $E_{1/2}$ values for electrolytes and the ρ constants in the Hammett equation showed that the autoprotolysis constant of an amphiprotic solvent is a quantitative characteristic of its differentiating effect. The lower is the value of K_S, the greater the differentiating effect of the amphiprotic solvent.

According to Izmailov's solvation theory[1], the differentiating effects of solvents are related to changes in the ratio of the solvation energies of the anions and molecules of the acids, the transolvation of anions making the greatest contribution to this change. In hydroxylated solvents hydrogen bonds play a considerable role in the solvation of anions, which reduces the difference between the anion solvation energies on passing from one solvent to another. In aprotic dipolar solvents, incapable of forming hydrogen bonds with anions, the difference between the anion solvation energies are much greater. This is because electrostatic and dispersion interaction forces, which are related, on the one hand, to properties of the solvents such as their dielectric constant, dipole moment, and polarisability of their molecules and on the other hand to the charge, radius, and polarisability of the anions, play the greatest role in the solvation of anions. As a result of all these factors, in aprotic dipolar solvents, the solvation of ions and electrolyte molecules is largely determined by the specific characteristics of the electrolyte.

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Mendeleev Moscow Institute
of Chemical Engineering

Moscow Technological Institute
of the Food Industry

U. D. C. 546.26-162

Epitaxial Synthesis of Diamond in the Metastable Region

B.V.Deryagin and D.V.Fedoseev

Recent trends in the preparation of synthetic diamonds, relying on the influence of surface forces exerted by the diamond seed crystal on the carbon deposition processes, are discussed. Epitaxial synthesis can occur from carbon-containing gases or from molten metals. Foreign publications and patents are discussed as well as the work of Soviet scientists.
The preparation and properties of filamentary and of isometric diamond crystals, prepared at low pressures for the first time, are also discussed. 22 references.

CONTENTS

I. INTRODUCTION

Leipusnkii's theoretical work[1], published in 1939, showed that diamond can be prepared from graphite, in principle, at high temperatures and pressures. A more accurate phase diagram for carbon has since become available[2].

A team led by L. F. Vereshchagin at the USSR Academy of Sciences successfully solved the problem of the synthesis of diamonds at high temperatures and pressures in 1960. The Institute of Super-hard Materials played an important role in the development of industrial methods of production of diamonds.

The high-pressure method for the synthesis of diamond adopted in many countries, characterised by a high reaction rate, has some well-defined regions of application whose boundaries are determined by the specific crystallisation conditions. Under certain conditions the main advantage of the method—its high speed—may become a drawback by making the synthesis uncontrollable and by preventing the formation of crystals of appreciable size.

The principle of an alternative method of synthesis of diamond, briefly mentioned in Leipunskii's paper, is closely bound up with the physicochemical study of surface phenomena. In principle, if a diamond crystal is already present in the system, it can be made to grow even in the region of metastable existence of this allotropic modification (for example, under atmospheric or reduced pressure) if the flux of carbon atoms to the diamond surface is not too large.

Research on the epitaxial synthesis of diamonds began in the Surface Phenomena section of the USSR Academy of Sciences (Institute of Physical Chemistry) in 1956.

2. GENERAL THEORY OF THE NUCLEATION OF DIAMOND IN THE METASTABLE REGION

The epitaxial method for the synthesis of diamond from carbon-containing gases is based on the heterogeneous decomposition reactions

$$CH_4 \rightleftarrows \underset{\text{diamond}}{C} + 2H_2$$

$$C_2H_2 \rightleftarrows \underset{\text{diamond}}{2C} + H_2$$

The epitaxial synthesis can be explained either from the standpoint of the molecular mechanism of crystal growth or in terms of the general theory of the formation of a new phase (nucleation). If the concentration of carbon atoms (either in the form of vapour or chemically bound as methane or ethylene molecules) in the neighbourhood of a diamond crystal face is higher than the corresponding equilibrium value, the excess of carbon atoms will be deposited on the surface. These atoms will experience the force field of the crystal lattice, tending to extend the array of "building blocks" which had initially given rise to the substrate. In other words, the substrate compels new carbon atoms to take up the predetermined positions. The process by which a substrate influences the growth of a crystal modification isomorphous with or similar in structure to itself is known as epitaxy. The present example can be termed autoepitaxy (homoepitaxy). However, if the supersaturation with respect to diamond is too large, and the deposition process is too fast, the influence of surface forces may cease to control the process, and nuclei of the thermodynamically preferred modification (graphite) may be formed and grow. Initially, graphite and diamond can grow simultaneously on different parts of the surface, but if the supersaturation of carbon remains high the graphite modification will cover the entire surface and the autoepitaxial growth of diamond will stop.

The conditions under which this situation can be avoided are implied in the general theory of crystal nucleation and growth developed by Gibbs, Volmer, Kaishev, and others. It is shown that the probability of formation of a stable (critical) nucleus of a new phase decreases as the work of formation of the new phase increases. The work of formation is proportional to the surface energy of the nucleus of "critical" size: this size increases as the supersaturation decreases. Hence the probability of formation of graphite can be minimised by controlling the supersaturation at a level just sufficient to allow growth of the diamond crystal to proceed. However, if we approach too closely the boundary below which the diamond seed cannot grow, the linear velocity of crystallisation will be unacceptably low. Under these conditions, and in spite of the presence of the seed crystal, some of the stages involved in the deposition of a new layer of atoms may be rate-limited by the work of formation of a two-dimensional critical nucleus. At very low supersaturations the probability of formation of such a nucleus is low, and the growth of the diamond crystal becomes "hesitant". However, growth may be continuous on some areas of the crystal surface, either because the work of formation of the two-dimensional nucleus is locally zero (e.g. on a (100) diamond face), or (e.g. at the outcrop of a screw dislocation) because two-dimensional nucleation is unnecessary and growth can proceed uniformly and continuously as when ascending a spiral ramp.

Thermodynamic calculations show that the equilibrium pressure of carbon-containing gas, of vapour, or of solution over diamond is approximately twice as large as over graphite. This is the basic reason for the difficulty of growing diamond epitaxially from carbon-containing gases.

The theory of the epitaxial synthesis of diamond by chemical decomposition of carbon-containing gases has not yet been developed. On the one hand, a sufficiently general theory of nucleation is not available, and on the other hand the chemical crystallisation of two competing phases (diamond and graphite) is too complex a situation. A few theoretical propositions relating to the low-pressure epitaxial synthesis of diamond have been put forward[3], and also discussed at the 22nd International Congress on Theoretical and Applied Chemistry[4].

We shall compare the rates of formation of critical nuclei of diamond and graphite on the surface of a seed crystal of diamond†. Since the (111) is both the equilibrium and the most commonly encountered face of diamond, we shall confine the discussion to this face. It consists of two layers of atoms in a puckered hexagonal configuration. The projection of the elementary edge of the hexagonal network on a (111) plane is 1.44 Å long, i.e. is not very different from the lattice constant of the graphite basal plane (1.42 Å). Hence, we shall assume that a graphite nucleus on a (111) diamond face is oriented as though the substrate were a basal plane of graphite.

The work of formation ΔG of a two-dimensional nucleus of perimeter l and thickness h can be expressed in the general form

$$\Delta G = l\varepsilon + \gamma l^2 h \Delta G_V + \gamma l^2 (\sigma_{C-X} - \sigma_{X-V} + \sigma_{C-V}) \qquad (1)$$

where γl^2 is the area of the nucleus; σ_{C-X}, σ_{X-V}, and σ_{C-V} are the specific interfacial free energies at the boundaries between the nucleus (C), the crystal (X), and the medium (V); ϵ is the specific free energy of the edge. We can write

$$\Delta G_V = -\frac{kT}{\Omega} \ln \frac{p}{p_e} \quad ,$$

where p is the partial pressure of carbon-containing gas, p_e is the equilibrium pressure of this gas, Ω is the volume occupied by one atom in the crystalline state, and T is the absolute temperature.

Since the distance between the graphite layers (3.35 Å) is much greater than the bond length in the diamond crystal (1.55 Å), we can equate the energy of the bond between the crystal and the graphite nucleus to the binding energy between graphite layers:

$$\sigma_{C-X} = \sigma_{X-V} - \sigma_{C-V} \qquad (2)$$

In this case the last term in the right-hand side of Eqn. (1) vanishes. By maximising ΔG_V with respect to l we obtain the work of formation of the critical nucleus (ΔG^*) and the perimeter of the critical nucleus (l^*):

$$\Delta G^* = -\frac{\varepsilon^2}{4\gamma h \Delta G_V} \qquad (3)$$

$$l^* = -\frac{\varepsilon}{2\gamma h \Delta G_V} = \frac{2\Delta G^*}{\varepsilon}$$

According to the Volmer–Weber–Becker–Dering theory[5], the rate of formation of nuclei of critical size is given by

$$I = l^* a \exp\left(-\frac{\Delta G^*}{kT}\right). \qquad (5)$$

The factor a depends on the molecular collision frequency and on the pressure, and is the same for diamond and graphite.

Using the subscripts α and β to denote quantities relating to diamond and graphite respectively, and introducing Eqn. (4), we obtain

$$\frac{I_\alpha}{I_\beta} = \frac{\varepsilon_\beta \Delta G_\alpha^*}{\varepsilon_\alpha \Delta G_\beta^*} \exp\left[-\frac{\Delta G_\alpha^*}{kT}\left(1 - \frac{\Delta G_\beta^*}{\Delta G_\alpha^*}\right)\right] \qquad (6)$$

The equilibrium form of the two-dimensional nuclei, calculated by means of Wulff's theorem, is a regular hexagon for graphite ($\gamma_\beta = \frac{1}{\gamma\sqrt{3}}$) and a triangle with [110], [011], and [101] sides for diamond ($\gamma_\alpha = \frac{1}{\gamma\sqrt{3}}$) as shown in Fig. 1. The specific free energies of the edges are

$$\varepsilon_\alpha = \frac{\varphi_\alpha}{3d\sqrt{3}}, \quad \varepsilon_\beta = \frac{\varphi_\beta}{2d\sqrt{3}},$$

where φ_α and φ_β are the bond energies between nearest neighbours in the diamond and the graphite lattice, and d is the lattice constant of the basal graphite plane.

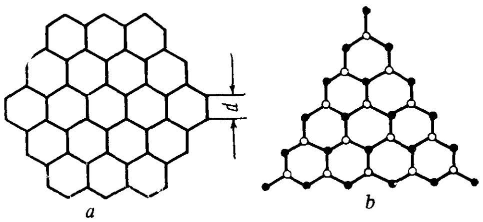

Figure 1. Nuclei of (*a*) graphite and (*b*) diamond on the (111) face of a diamond seed crystal.

The ratio of the energies of formation of the critical nuclei is

$$\frac{\Delta G_\beta^*}{\Delta G_\alpha^*} = 2.5 \frac{\ln p/p_{e\alpha}}{\ln p/p_{e\beta}}. \qquad (7)$$

As stated above, thermodynamic calculations indicate that between 1000 and 2000°K (i.e. in the region of spontaneous graphitisation of diamond)

$$p_{e\alpha} = 2p_{e\beta} \qquad (8)$$

Introducing the symbol

$$\frac{\ln \frac{p}{p_{e\beta}}}{\ln 2} = x,$$

we can readily show that

$$\frac{I_\alpha}{I_\beta} = 0.8 \frac{x}{x-1} \exp\left[-0.9 \left(\frac{\varphi}{kT}\right)^2 \frac{1-0.6x}{x(x-1)}\right]. \qquad (9)$$

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† We acknowledge V. P. Varnin's assistance in the calculation which follows.

The maximum of this expression corresponds to $x = 2.7$. For $x \to 0$, $I_\alpha/I_\beta \to 0$; for $x \to \infty$, $I_\alpha/I_\beta \to 0.8$. For $x = 1.67$, the exponent vanishes and $I_\alpha/I_\beta = 2.00$.

Fig. 2 shows a plot of the function (9).

In this way, classical nucleation theory can identify the most favourable region $(p/p_{e\beta})$ for the epitaxial growth of diamond. However, the present calculation, given as an example, assumes that the rates of nucleation of diamond and graphite are mutually independent, whereas under real conditions the two processes are competitive.

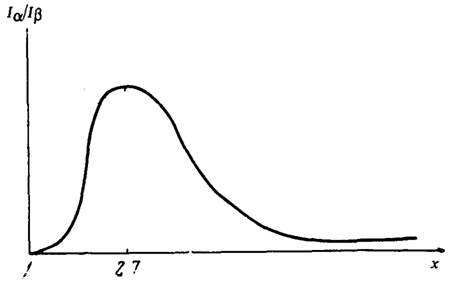

Figure 2. Variation with supersaturation of the ratio of the nucleation rates of diamond and graphite.

It should also be noted that the equilibrium pressure of methane decreases on raising the temperature, whereas that of the other carbon-containing gases (e.g. acetylene) over diamond and graphite changes in the opposite sense. Hence, the methane supersaturation (at constant total pressure) increases rapidly, whereas in an acetylene atmosphere the supersaturation changes much less rapidly with temperature.

3. MAIN METHODS OF PRODUCTION OF DIAMOND IN THE METASTABLE REGION

We shall review the most important patents and papers dealing with the epitaxial synthesis of diamond in the metastable region (between 10^{-3} mmHg and 1000 atm). In 1962 Eversole filed two patents[6]. In the first, the carbon-containing gas is passed over the diamond seed crystal held at a controlled temperature. The temperature range quoted in the patent is 600–1600°, but the best results are obtained at 900–1100°. The partial pressure of carbon-containing gases (with methyl groups) must not exceed 75 mmHg, and should preferably be in the range 0.1–1 mmHg When carbon monoxide (or a mixture of the monoxide and dioxide) is used, the pressure can be as high as 2500 atm. The preferred pressure range is 70–140 atm. Diamond grows on the seed crystal until the formation of other modifications of carbon arrests the growth. The seed can be freed from graphite, and exposed to further diamond growth. The time for the whole cycle of operations (growth and reactivation) varies from a few minutes to 100–200 h, depending on conditions. The reactant can be methane, ethane, propane, chloromethane, methanethiol, or acetone. No growth was observed with benzene, carbon disulphide, dichloromethane, and other hydrocarbons not containing methyl groups. Argon and nitrogen do not inhibit the reaction.

Most of the experiments described[6] were made with diamond powders of 0.1 μm average size, and crystals up to 0.1 carat in weight were obtained. The use of powders offers the advantage of a large specific surface area (up to 20 m^2 g^{-1}).

Non-diamond carbon was removed either by boiling in a mixture of sulphuric and chromic acids, or in hydrogen at pressures up to 50 atm and temperatures between 1000 and 1100°. The latter method relies on the different kinetic activities of diamond and graphite.

The growths of diamond were identified by density measurements and by lattice parameter determinations using electron diffraction.

The maximum increase in weight of the starting powder was 59.5%. This required 85 successive cycles of growth (1.79 h) and graphite removal (4.5 h).

Eversole's second patent is an extension of the first, and essentially consists in the use of gases which can dissociate with formation of free methyl radicals. Angus and coworkers[7] repeated and checked Eversole's work in 1968. They subjected the processed diamond powders to density measurements, to spectroscopic, X-ray diffraction, and electron diffraction analysis, and they studied their microwave absorption and ESR behaviour. The starting and the grown material were identical in every respect. These workers also compared the reaction rates of diamond and of graphite with hydrogen. The activation energy of the diamond–hydrogen reaction was found to be 125 kcal $mole^{-1}$, with an approximately fifth-power pressure dependence, as compared with 85.5 kcal $mole^{-1}$ and a linear pressure dependence for graphite. However, these results were obtained over a narrow pressure range (50–70 atm).

The West German firm of Siemens und Halske filed a French patent in 1962 entitled[8] "Method of Production of Carbon in the Diamond Form at Low Pressures". The invention consists in admitting to the hot reaction zone a carbon compound whose structure is a complete or partial replica of that of the diamond lattice. One of the recommended starting materials is cyclopentane, whose five-membered ring of carbon atoms is practically unstrained (angular deformation less than 1°). In addition to cyclopentane and cyclohexane, other carbon compounds can be used if their thermal decomposition gives rise to products in which the carbon chains are a replica of the diamond lattice structure. Inert gases, hydrogen, or gaseous hydrocarbons at room temperature can be used as carrier gases for the starting material.

To assist the formation of seeds of the diamond form in the reaction zone, catalysts are used. These include substances capable of forming carbides with a cubic structure, e.g. silicon, titanium, Group V elements such as niobium and tantalum, and also a tungsten–cobalt alloy. The catalyst is introduced into the reaction zone either in the form of a solid substrate (for the preparation of crystalline layers) or as metal-containing vapours (for the preparation of carbon powders with the diamond structure). The preferred reaction temperature is between 800 and 1200°. The reaction mixture is activated by some form of electrical gas discharge.

Another patent[9] by the same firm claims every method of preparation of diamonds by means of chemical transport reactions. The pressure of carbon-containing gas must not be allowed to depart too significantly from the equilibrium value for diamond, otherwise carbon may be deposited in a non-diamond form. The theory of the transport process has been discussed by the present writers[10] from the standpoint of non-equilibrium thermodynamics.

The patent[11] "Method and Apparatus for the Replication of Crystal Structures" has interesting possibilities in microelectronics technology. The diamond seed crystal is heated by a controlled electron beam, and a carbon-containing gas is led through the reaction zone without interrupting the electron beam. According to the patent, diamond is deposited on the area where the electron beam is focussed. Gases mentioned in the patent include carbon tetrachloride, carbon tetrabromide, carbon disulphide, and some others. The diamond substrate is heated between 1000 and 3000°: the preferred temperature range is 1800–2500°. Silicon layers can be grown by the same method over the diamond layers from silicon tetrachloride, and these can in turn be overgrown with diamond layers.

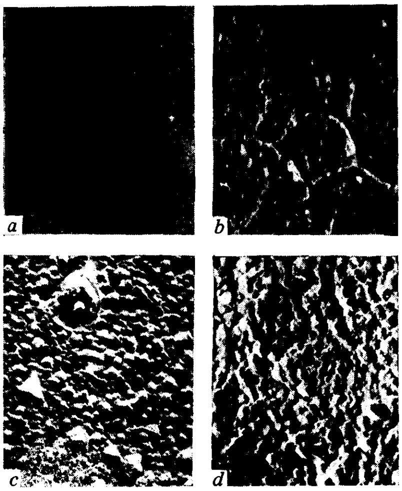

Figure 3. Successive stages in the growth of a (111) diamond face, × 10 000: *a*) initial surface, *b*) and *c*) successive growth stages, *d*) stage corresponding to the formation of a continuous crystallisation front.

In 1964, Brinkman and coworkers[12] extended their earlier work (1957) by disclosing a method for the epitaxial growth of diamond from solutions of carbon in metals. The source of carbon is a sample of graphite held at a higher temperature than the diamond seed crystal. The method can be reduced in practice to two forms: the flow method and the static method. In the flow method, liquid metal is continuously pumped through the system, and carbon atoms are transported from the graphite to the diamond. In the static method the liquid metal is saturated with carbon from the walls of a graphite crucible, the temperature is decreased by an amount corresponding to the desired supersaturation with respect to diamond, and the seed crystal is immersed in the solution. Another patent by the same workers[13] discloses a method for the production of diamond from carbon atoms emitted by a carbon source at high temperature (up to 4000°).

Litvin and Butuzov[14] published a very interesting paper on the growth kinetics of diamond from a solution of carbon in molten metal at 1150° and pressures of the order of 40 000 atm. The planar metal–graphite interface was oriented parallel to the (100) face of the diamond seed crystal. The distance between the two surfaces was of the order of 0.5 mm, and the temperature difference was not allowed to exceed 15°. The kinetic data obtained in this work are of fundamental importance for the development of a theory of crystallisation in the metastable region.

We have recently described[15] the autoepitaxial growth of diamond layers from the gas phase (methane) on natural diamond powder and also on the (111) face of a natural diamond seed crystal. Electron micrographs of successive stages of growth of the same layer are shown in Fig. 3. Fig. 3*a* shows the initial surface, Fig. 3*b* and 3*c* show intermediate stages, and Fig. 3*d* corresponds to the formation of a continuous layer.

4. FILAMENTARY DIAMOND CRYSTALS

The growth of filamentary diamond crystals is of the utmost importance. Such crystals have been obtained by the present writers in collaboration with Luk'yanovich, Ryabov, Spitsyn, Lavrent'ev, and Builov[16-19]. Filamentary crystals (or "whiskers") have a number of unique properties and have attracted a great deal of interest: they have a perfect crystal structure, they retain their elasticity and strength at high temperatures, they show complete strain recovery on subsequent heating, and they have an exceptionally high strength, close to the theoretical value. For example, whereas the tensile strength of ordinary iron is 18–23 kg mm^{-2}, iron whiskers 2 μm in diameter and ~ 2 mm long have a tensile strength of 1200–1300 kg mm^{-2}. The use of sapphire whiskers in niobium composites (50 wt. %) increases the strength of mechanical components by a factor of 4 as compared with pure niobium whilst at the same time reducing their weight: the importance of these properties in aerospace technology is evident.

Filamentary crystals had previously been grown only in the region of thermodynamic stability. Our discovery of filamentary diamond crystals has a twofold significance: on the one hand, it has demonstrated the possibility of growing whiskers under metastable conditions, and on the other hand it has shown that diamond crystals can be grown at low pressures from carbon-containing gases at appreciable linear velocities of crystallisation (at least, in principle). These velocities are many orders of magnitude higher than the linear growth rate of diamond powders (from a few to a few tens of Ångstroms per hour).

The experiments were carried out in a radiation furnace based on a super-high-pressure xenon lamp (type DKSR-6000). The apparatus has already been described in detail[20,21]. The diamond seed crystal was secured by pointed rhenium supports, and located at the focal spot of the apparatus, whose diameter was greater than the largest dimension of the seed crystal. The temperature of the crystal was measured with an optical pyrometer.

The surface of the seed crystal could be observed in a microscope during the experiment. The formation and subsequent growth of filamentary diamond crystals was established in this way. The growth rate is a function of temperature, pressure, and some other parameters. Since the parameters of the radiant flux at the focal spot are not uniform, conditions at the apex of the growing whisker are not the same as at the substrate surface. Thus, the illumination could vary by a factor of two as between the apex and the base of a whisker 400 μm long. The mean growth rate of the whiskers was 50–250 μm h^{-1}: this was genuinely a mean linear velocity, and it is reasonable to assume that much higher linear growth velocities are possible and did indeed obtain at some stage in the growth of these whiskers.

Fig. 4 shows a filamentary diamond crystal approximately 1.00 mm long, grown on the (111) face of a diamond seed crystal. The pointed rhenium seed holder is visible in the photograph.

Diamond whiskers grown on a (111) face are inclined at an angle of 50–60° to this face: their growth is probably normal to a (110) face, as in the case of silicon and germanium whiskers, which crystallise in the diamond lattice.

Figure 4. Filamentary diamond crystal, 1.0 mm long.

The cathodoluminescence of the diamond whiskers has been found to be similar to that of the substrate. After one experiment, the formations were identified unequivocally as diamond by examining the powdered whisker in an electron microscope in the electron diffraction mode. Using platinum as a standard, the interplanar spacings were calculated from the diffraction pattern and compared with tabulated values.

d_{tab}, Å	2,05	1,26	1.072	0,885	0.813	0.721
d_{calc}, Å	2,07	1,24	1.068	0,920	0.825	0.740

The electron diffraction patterns show that the whiskers are single crystals. Kikuchi lines are clearly visible in some of the patterns.

The apex of the diamond whiskers was occasionally found to be covered by a dark, spherical formation. One possible explanation is metallic contamination of the substrate surface before growth. A special series of experiments was therefore devised to study the growth of filamentary diamond crystals under droplets of molten metal by the VLS (vapour–liquid–solid) method[19]. Transparent filamentary crystals supporting a droplet of solidified metal were produced. The best results were obtained with metals in which the solubility of carbon is high and which can wet diamond (nickel, iron, manganese). No formations were observed under molten gold droplets. Evidently, the VLS method must be considered among the possible methods of growing diamond crystals. The role of the intermediate liquid metal phase in the growth of diamond has been discussed by one of us[3]. The energy of formation of a two-dimensional diamond nucleus under the layer of metal can be very much lower than the energy of formation of a three-dimensional critical nucleus of graphite. This is because surface energies at the graphite–metal interface are usually much higher than the surface energy at the graphite–air interface, and therefore the work of formation of graphite nuclei is increased and the generation of such nuclei is suppressed.

The recently observed conversion of filamentary crystals into isometric crystals is also worth noting. We were able to follow, using a microscope, the growth of a diamond whisker. When growth stopped, the crystal began to thicken until an isometric crystal of diamond with 0.1 mm average cross-section and very weakly developed facets was obtained. This crystal was examined by X-ray micro-diffraction (beam diameter 12 μm) at the top, the side, and the bottom of the crystal as grown, and it was found to be a single crystal.

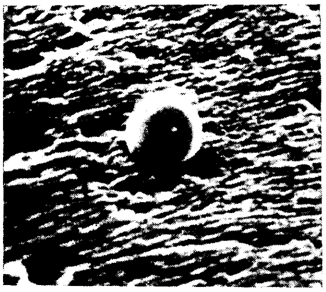

Figure 5. Isometric diamond crystal grown on a (111) face, photographed in a scanning electron microscope. Crystal diameter 20 μm.

Scanning electron microscopy is a particularly revealing technique for examining isometric crystals. A scanning electron micrograph of an isometric crystal 20 μm in diameter, taken in V. G. Spivak's laboratory at the Moscow State University, is shown in Fig. 5.

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Institute of Physical Chemistry
of the USSR Academy of Sciences,
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Metal-Metal Bonds and Covalent Atomic Radii of Transition Metals in Their π-Complexes and Polynuclear Carbonyls

B.P.Biryukov and Yu.T.Struchkov

The review presents a compilation of recent results in one of the most important fields of structural chemistry at the present time—compounds with metal-metal bonds.
The bibliography includes 56 references.

CONTENTS

I. INTRODUCTION

The rapid development of the chemistry of the π-complexes of transition metals has already led to the synthesis of numerous groups of compounds the molecules of which contain two or several metal atoms linked either directly or via additional bridging ligands. The considerable interest in this unusual class of compounds is due to the fact that metal–metal bonds in many respects determine the chemistry of transition metal compounds.

The problem of the interaction between metal atoms in complexes has attracted attention for a long time. The accumulation of extensive experimental data led to many attempts at reviews, primarily those listed in Refs. 1–12.

The present review deals with the metal–metal interaction in the π-complexes of transition metals and is based on the experimental interatomic distances and valence angles in their molecules.

The most successful classification of compounds on the basis of metal–metal bond types has been proposed by Nyholm[2,5] and is partially applicable also to π-complexes and polynuclear carbonyls. In the first place, it is necessary to distinguish a group of compounds with covalent bonds between metal atoms, including both molecules with covalent bonds between transition metal atoms—for example, $Mn_2(CO)_{10}[(\pi\text{-}C_5H_5)Mo(CO)_3]_2$, $(\pi\text{-}C_5H_5)Mo(CO)_3\text{-}Mn(CO)_5$—and molecules with covalent bonds between elements in Groups IB–IVB and transition metals—for example, $(C_6H_5)_3PAuMn(CO)_5$, $Hg[Co(CO)_4]_2$, and $[(C_6H_5)_3SnMn(CO)_5]$. The first group may be subdivided into homopolymetallic complexes with identical electronic configurations of the transition metal atoms—for example, $Mn_2(CO)_{10}$ and $[(\pi\text{-}C_5H_5)Mo(CO)_3]_2$—and heteropolymetallic complexes, i.e. with different electronic configurations of the transition metal atoms—for example, $(\pi\text{-}C_5H_5)Mo(CO)_3\text{-}Mn(CO)_5$.

It is possible to distinguish further a group of π-complexes with metal–donor bonds, the molecules of which are combined in the crystal into polymeric chains owing to metal–metal interaction.

II. π-COMPLEXES WITH COVALENT METAL–METAL BONDS

In their reviews Lewis and Nyholm[2-6] attempted to estimate the factors which determine the nature of the interaction between covalently linked metal atoms. Most important among these factors are the effective charge of the metal atom, its electronic configuration, and also the electronic properties of ligands and their steric characteristics. However, these factors probably do not exhaust the entire set of influences on the type of metal–metal bonds, since, as will be shown in the discussion of interatomic distances, these bonds are fairly variable in their strength, length, and number of electrons involved in them. The effect of bridging groups, which in many complexes to a considerable degree determine the nature of the metal–metal interaction, is also undoubtedly important.

A. COMPOUNDS WITH COVALENT BONDS BETWEEN TRANSITION METALS

1. Homopolymetallic Complexes

The lengths of the metal–metal bonds in homopolymetallic complexes (Table 1) vary within fairly wide limits (up to about 0.5 Å for Fe–Fe bonds). As pointed out by Poray-Koshits and Gilinskaya[11], this means that the curve relating the metal–metal interaction energy to the interatomic distance has a fairly gently sloping profile with a diffuse minimum or a series of several closely spaced minima.

Therefore the problem arises of the validity of the application of a widely used criterion—the sum of single bond covalent radii—to characterise the metal—metal interaction forces. The problem of the values of the single bond covalent radii of transition metal atoms in their π-complexes has been frequently discussed (see, for

Table 1. Lengths (Å) of metal–metal bonds in molecules of homopolymetallic π-complexes.

Bond	Range of variation of metal-metal bond lengths		Twice the single bond covalent radius	Bond	Range of variation of metal-metal bond lengths		Twice the single bond covalent radius	Bond	Range of variation of metal-metal bond lengths		Twice the single bond covalent radius
	with bridging ligands	without bridging ligands			with bridging ligands	without bridging ligands			with bridging ligands	without bridging ligands	
Ti—Ti	—	3.11	3.1_2	Zr—Zr	—	—	3.52	Hf—Hf	—	—	3.5_4
V—V	—	—	2.98	Nb—Nb	2.73—2.74	—	3.1_2	Ta—Ta	—	—	3.1_2
Cr—Cr	2.67—2.94	3.40 *	2.92	Mo—Mo	2.89—3.26	3.22—3.27	3.1_6	W—W	—	3.24	3.1_8
Mn—Mn	2.50—2.94	2.91—2.97	2.76	Tc—Tc	—	3.94	3.0_6	Re—Re	—	2.96—3.18; 3.39*	3.02
Fe—Fe	2.37—2,88	2.67—2.88	2.6_8	Ru—Ru	2.74; 2.95	2.85	2.9_8	Os—Os	2.74	2.88	3.00
Co—Co	2.37—2,64	2.66	2.58	Rh—Rh	2.62—2.73	2.66—2.73	2.92	Ir—Ir	2.73	2.68—2.73	2.9_4
Ni—Ni	2.33—2,80	—	2.7_0	Pd—Pd	2.58	—	2.9_8	Pt—Pt	2,75—2,79	—	2.8_8

*Three-centre metal–hydrogen–metal bond.

Table 2. Single bond covalent radii of transition metals in their π-complexes.

Ti 1.5_6* (1.36; 1.46)**	V 1.49 (1.22; 1.34)	Cr 1.46 (1.19; 1.28)	Mn 1.38 (1.18; 1.27)	Fe 1.3_4 (1.17; 1.26)	Co 1.29 (1.16; 1.25)	Ni 1.3_5 (1.15; 1.24)
Zr 1.76 (1.51; 1.60)	Nb 1.6_8 (1.34; 1.46)	Mo 1.5_8 (1.30; 1.39)	Tc 1.5_3 (1.27; 1.36)	Ru 1.4_9 (1.25; 1.34)	Rh 1.46 (1.25; 1.34)	Pd 1.4_9 (1.28; 1.37)
Hf 1.7_7 (1.50; 1.59)	Ta 1.6_8 (1.34; 1.46)	W 1.5_9 (1.30; 1.39)	Re 1.51 (1.28; 1.37)	Os 1.50 (1.26; 1.35)	Ir 1.4_7 (1.27; 1.36)	Pt 1.4_3 (1.30; 1.39)

*According to Andrianov et al.[13]

**Single bond covalent radii according to Pauling[14]: the first for a coordination number of 6 and the second for a coordination number of 12.

example, Andrianov et al.[13]), since theoretical and experimental results have shown that the single bond transition metal radii proposed by Pauling[14] cannot be used to analyse the interatomic distances in their π-complexes. Incidentally, we may note that the revision of the atomic radii of transition metals was in fact stimulated by the study of compounds with metal–metal bonds. Indeed the Mn–Mn bond length (2.926 Å) in the dimanganesetetracarbonyl molecule[15] $Mn_2(CO)_{10}$ is greater by about 0.4 Å than twice the value of Pauling's atomic radius of manganese (2.54 Å). However, Cotton[16] found a contradiction between the fairly high energy of this bond (34 kcal $mole^{-1}$)† and its very marked extension, which clearly indicated that the value of 1.27 Å for the atomic radius of manganese is too low.

The single bond covalent radii of transition metals in their π-complexes[13], which will be employed‡ in the analysis of the metal–metal interatomic distances, are compared in Table 2 with the values proposed by Pauling[14]. In the analysis of the interatomic metal–metal distances in homopolymetallic π-complexes (Table 1) the fact that the shortest of them are observed in molecules with bridging ligands attracts attention. This suggests that such ligands draw the metal atoms together by virtue of the rigidity of their geometry.

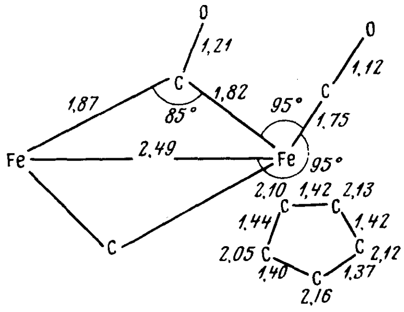

Figure 1. Geometry of the $[(\pi\text{-}C_5H_5)Fe(CO)_2]_2$ molecule.

The most widespread and the most readily available molecules for a simple geometrical examination are those in which the bridging ligands are linked to only two metal atoms (the so called "edge" bridges) and form MXM groups (X = C, N, S, etc.) via only one of their atoms, for example in bis(dicarbonyl-π-cyclopentadienyl-iron) $[(\pi\text{-}C_2H_5)Fe(CO)_2]_2$ (Fig. 1).[20] In the formation of the FeCFe group in this molecule the bridging carbon atom is in the sp^2-hybridised state and therefore the most favourable angle is probably 120°. However, examination of the geometry of the planar fragment Fe_2C_2 (Fig. 1) shows that in this case the distance between the bridging carbon atoms not linked by valence bonds is 1.9–2.0 Å (while twice the van der Waals radius is 3.6 Å), i.e. is unexpectedly small. This factor probably in fact forces the bridging carbon (nitrogen, sulphur) atoms to move apart to acceptable distances with a decrease of the real

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† See the footnote on p. 791.

‡ It must be specially emphasised that, according to one view[17], the very concept of atomic radius is inapplicable to complex (three-dimensional) cluster systems (see p. 791) and this undoubtedly true owing to the many-centre nature of all the bonding orbitals responsible for the metal–metal interaction[8,18,19]. Therefore the system of radii proposed by Andrianov et al.[13] is applicable to complexes in which the bonds are largely localised and collective groups of atoms are absent.

$MX_{bridge}M$ angles to 67–86°C (instead of the "ideal" value 120°C). Thus if the FeCFe angle in the molecule under discussion is assumed to be 90°C and the length of the Fe–C bond is taken to be 1.9 Å, the C... C distance between bridging carbon atoms not linked by valence bonds increases to the now admissible value of 2.7 Å. Then the Fe–Fe distance also becomes close to 2.7 Å, i.e. it is virtually equal to twice the single bond radius of the iron atom (2.68 Å). Thus it appears that the FeCFe angle close to 90°C corresponds to the optimum configuration of the Fe_2C_2 fragment.

However the problem then arises of the cause of the decrease of the Fe–Fe distance to 2.49 Å and the decrease of the FeCFe angle to 85°C in the $[(\pi\text{-}C_5H_5)Fe(CO)_2]_2$ molecule compared with the optimum values 2.7 Å and 90°C, and in the more general case of the cause of the considerable variability of the metal–metal distance and of the bridging angle in the range 67–86°C§. An attempt may be made to answer these questions in the following way. By virtue of the rigidity of their geometry, the bridging ligands exert a purely geometrical influence on the metal–metal distance; then the difference between the geometrical requirements of the bridging groups (and in particular the dimensions of the bridging atom) are responsible for certain differences in the metal–metal distances. This is combined also with effects which determine the nature of the direct interaction between the metal atoms, namely their electronic configuration, effective charge, the repulsion of the non-bonding electrons, and the steric effects of the ligands. All these factors give rise to variations in the metal–metal distances, which in turn lead to a change in the bridging angles. Thus it becomes quite evident that the variability of the metal–metal distances over a wide range in π-complexes in the presence of bridging ligands is reasonable.

All that has been said refers also to molecules containing bridging ligands linking three metal atoms (the so called "face" bridges); in this case the geometrical requirements of the ligands also give rise to an appreciable variation in the metal–metal distances but now in trigonal systems comprising metal atoms.

It is clear from these facts that, in the presence of bridging or pseudo-bridging groups, a widely used criterion of bond types, such as the sum of single bond covalent radii, cannot be applied because the metal–metal distance does not reflect the true nature of the interaction. Moreover, magnetic measurements have shown[10] in many cases that in some molecules the bridging groups may bring appreciably more closely together the non-bonded metal atoms, while in others the marked overlapping of the orbitals of the metal atoms can occur over a large distance. The problem arises of the characterisation of the force of the metal–metal interaction in molecules with bridging groups. In many cases the magnetic properties of the compound may serve as a criterion of this kind but, as pointed out by Lewis[4], it is often difficult to distinguish direct interaction between two metal atoms from interaction via a bridging group and there is no doubt that sometimes interactions of both types occur.

In a comparison of metal–metal bond lengths in molecules (not containing bridging ligands) with twice the values of single bond radii (Table 1) it is important to note that, for elements of the first series, the bond lengths are appreciably increased. This indicates some weakening of the bonds between the metal atoms of the first transition series compared with ordinary covalent bonds. However, with increasing atomic number of the metal within the limits of a given transition series, a tendency is observed for the experimental interatomic metal–metal distances to approach twice the values of the single bond covalent radii, i.e. in the first transition series the force of the metal–metal interaction increases from vanadium to nickel. This tendency is maintained also in the second and third series and the metal–metal bonds actually become shorter than twice the single bond radii (Table 1), which according to Lewis and Nyholm[2–6] is due to a change in the dimensions of the atomic orbitals participating in the formation of the metal–metal bond.

Thus metals in the second and third transition series form stronger bonds than their analogues in the first transition series, which is clearly illustrated by an examination of similar $M_2(CO)_{10}$ (M = Mn, Tc, or Re) molecules with the same structures (Fig. 2). Comparison of the Mn–Mn bond length (2.923 Å) in the dimanganesedecacarbonyl $Mn_2(CO)_{10}$ molecule[15], the Tc–Tc bond length (3.036 Å) in the ditechnetiumdecacarbonyl $Tc_2(CO)_{10}$ molecule[22], and the Re–Re bond length (3.02 Å) in the dirheniumdecacarbonyl $Re_2(CO)_{10}$ molecule[23] with twice the single bond covalent radii (2.76, 3.0_6, and 3.02 Å respectively) indicates a significant difference between the metal–metal bonds in these molecules with identical structures: the Mn–Mn length is increased by about 0.16 Å (i.e. is weakened compared with the ordinary covalent bond), while the Tc–Tc and Re–Re bond lengths are virtually equal to twice the radii (i.e. these bonds are essentially of the ordinary covalent type).

This conclusion is fully consistent with the relative anionic nucleophilicities $[Mn(CO)_5^- \ll Re(CO)_5^-]$,[24] the dissociation energies[25] of the Mn–Mn (0.96 eV or 22 kcal)¶ and Re–Re (2.22 eV or 51.1 kcal) bonds and force constants (Mn–Mn < Re–Re).[25] The strengthening (or more precisely the lack of weakening) of the Tc–Tc and Re–Re bonds compared with the Mn–Mn bond cannot be due to steric effects: the molecules have the same structures and the distances in them between valence non-bonded atoms are similar. Probably the causes of the difference in the behaviour of transition metals of the same Group should be sought also in the variation of the dimensions of their atomic orbitals.

In the case of homopolymetallic complexes where metals of the same Group but different series are combined, their "additive" interaction is observed. Thus in the $(CO)_5Mn–Re(CO)_5$ molecule the Mn–Re bond (length 2.96 Å)[26] is intermediate in strength between the Mn–Mn and Re–Re bonds in the decacarbonyls of the two metals: the Mn–Mn bond length increases by about 0.16 Å, Mn–Re by about 0.07 Å, and the Re–Re bond length is the same as the length of the ordinary covalent bond.

The work of Dahl and coworkers on structural studies of homopolymetallic complexes is outstanding; they investigated the dinuclear carbonyls of iron in which the sulphur

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§ As pointed out by Wei and Dahl[21], who analysed structures with bonds between metal atoms of the first transition series and with symmetrical CO bridging groups, in these molecules, with the exception of $C_8H_8Fe_2(CO)_5$ and $[C_8H_4(CH_3)_4]Fe_2(CO)_5$, the metal–metal distances do not exceed 2.58 Å, the $M–C_{bridge}$ bond lengths are in the range 1.82–1.96 Å, and the MCM angles are in the range 78–86°C. A direct correlation between these quantities has not been observed.

¶ We may note that clearly contradictory data are quoted in the literature for the energy of the Mn–Mn bond: 34 ± 13 kcal $mole^{-1}$ (kinetic data[16]) and 18.9 ± 1.4 and 22.1 kcal $mole^{-1}$ (mass-spectrometric data[24]).

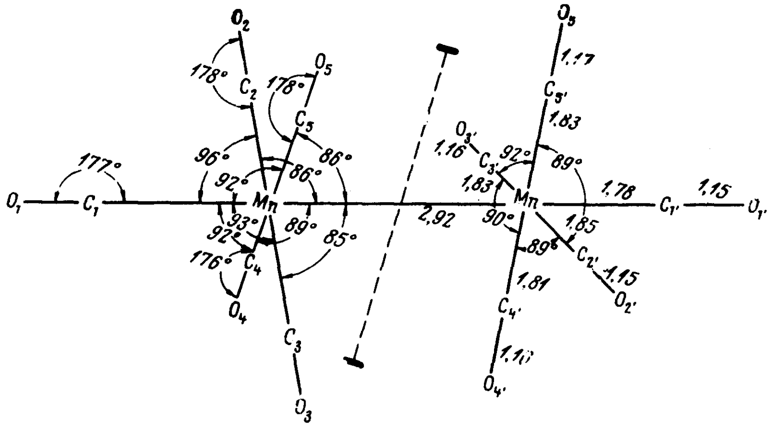

Figure 2. Molecules of the series $M_2(CO)_{10}$(M = Mn, Tc, or Re).

or selenium atom plays the role of the bridge. This group of molecules with the general formula $[XFe(CO)_3]_2$ (where X = S, RS, or RSe and R is an organic group), a typical example of which is $[C_2H_5SFe(CO)_3]_2$ (Fig. 3)[27], has attracted attention because here the concept of so called bent bonds was introduced to describe the metal–metal interactions. Indeed, in molecules of this group the formation of covalent bonds between metal atoms via a colinear overlapping of their atomic orbitals is impossible without a significant distortion from octahedral symmetry. Consequently Dahl[28] postulated an almost undistorted octahedral configuration of the metal atom, which forms a bond with another metal atom via a non-colinear overlapping of a pair of their axial orbitals, i.e. the bond is bent (Fig. 3).

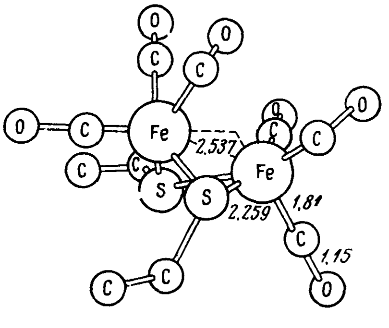

Figure 3. Geometry of the $[C_2H_5SFe(CO)_3]_2$ molecule.

The most interesting of the fields, developed by Dahl and coworkers, comprises work on the elucidation of the effect of the unpaired electrons on the molecular geometry of the complex. This is illustrated by the isomorphous complexes $Co_3(CO)_9S$ and $FeCo_2(CO)_9S$. The paramagnetic molecule of tricobaltenneacarbonyl sulphide[29] $Co_3(CO)_9S$ contains a triangle of Co atoms (Fig. 4) whose side has an average length of 2.64 Å; the S atom is a triple bridge and is located at equal distances (2.14 Å) from all the CO atoms. In the isomorphous complex $FeCo_2(CO)_9S$, which differs from $Co_3(CO)_9S$ by the replacement of a Co atom by an Fe atom, the average metal–metal bond length is 2.554 ± 0.007 Å,[30] i.e. it is shorter by 0.08 Å, although the covalent radius of iron is greater by 0.05 Å than the radius of cobalt. According to Dahl[30], this shortening is evidence of the effect of the unpaired electron on the molecular geometry of the complex. Indeed the replacement of one of the cobalt atoms in the paramagnetic $Co_3(CO)_9S$ molecule by an iron atom leads to a diamagnetic complex $FeCo_2(CO)_9S$ and strengthening of the metal–metal bonds; this shows that the unpaired electron in $Co_3(CO)_9S$ must be located in an antibonding molecular orbital.

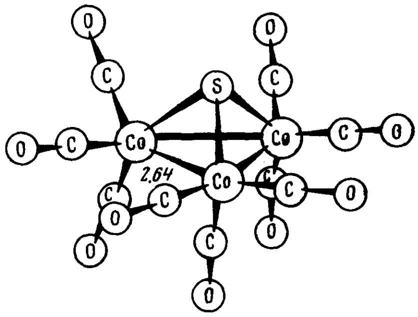

Figure 4. Geometry of the $Co_3(CO)_9$ molecule.

Finally, mention must be made of the structural work of Dahl and coworkers on organocobalt sulphur-containing complexes in which an attempt was made to determine the Co–Co bond order on the basis of quantum-chemical concepts used to analyse the structure of the anion $[Re_3Cl_{12}]^{-3}$ (see, for example, Wei and Dahl[31]).

Nowadays many workers are vigorously investigating the so called cluster compounds, which contain groups of a finite number of metal atoms. According to Cotton[8], the term "cluster" is usually understood as comprising compounds with finite closed groups of metal atoms, forming triangles, for example $(\pi\text{-}C_5H_5Ni)_3(CO)_2$ (Fig. 5)[32], tetrahedra, for example $Rh_4(CO)_{12}$(Fig. 6)[33], pentameric groups, for example $Fe_5(CO)_{15}C$ (Fig. 7)[34], and even octahedra, for example $Rh_6(CO)_{16}$ (Fig. 8)[35]. The wide interest in cluster compounds can be explained in the first place by their very unusual properties; one deals not with an individual transition metal atom but with a group, for which such firmly established concepts as, for example, the coordination number and atomic radius† are sometimes inapplicable, since instead of individual atoms one has to consider a fairly complicated collective electron system of a group of metal atoms. This factor permits the inclusion among complexes with covalent bonds only some of the cluster compounds; some of these, for reasons indicated above, can be treated only within the framework of the molecular orbital method, the application of which to such systems is valid and fruitful.

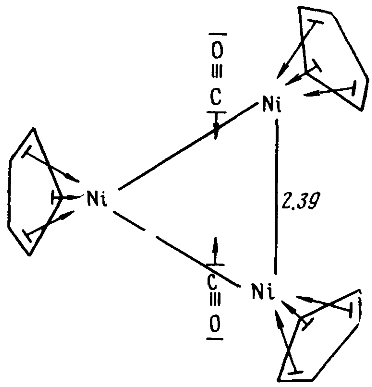

Figure 5. Trigonal group of metal atoms in the $(\pi\text{-}C_5H_5Ni)_3(CO)_2$ molecule.

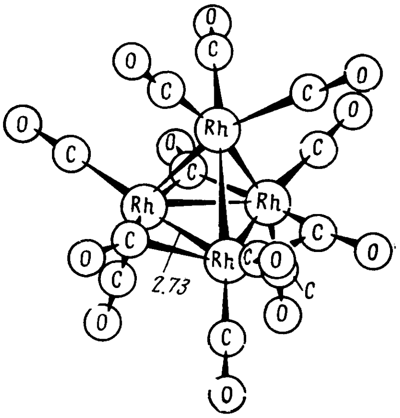

Figure 6. Tetrahedral grouping of metal atoms in the $Rh_4(CO)_{12}$ molecule.

2. Heteropolymetallic Complexes

The number of π-complexes with bonds between transition metals belonging to different Groups‡, whose structures have been investigated, is small (Table 3) and studies of this kind have not been systematic.

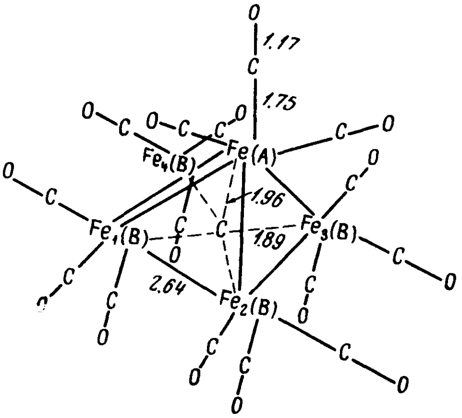

Figure 7. Pentameric grouping of metal atoms in the $Fe_5(CO)_{15}C$ molecule.

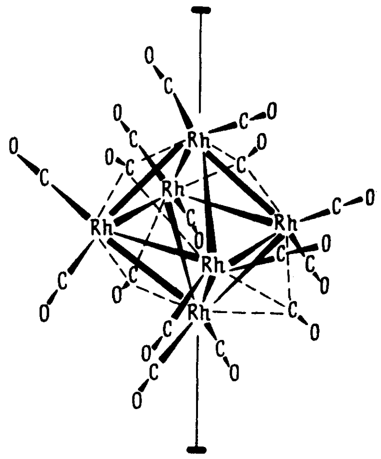

Figure 8. Octahedral grouping of metal atoms in the $Rh_6(CO)_{16}$ molecule.

The results of the investigations of heterodimetallic molecules such as $(\pi\text{-}C_5H_5)Mo(CO)_3\text{-}Mn(CO)_5$ (Fig. 9)[36], which are a combination of the monomeric fragments of dimeric homodimetallic molecules {in this case $[(\pi\text{-}C_5H_5)Mo(CO)_3]_2$ [37] and $Mn_2(CO)_{10}$ [15]} via a metal–metal

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† See the footnote on p. 791.

‡ Heteropolymetallic π-complexes of course include also compounds containing the same metal atoms with different electron configurations, but the metal–metal bond lengths in them are close to those found in homopolymetallic complexes.

bond. The equality of the Mo–Mn bond length (3.08 Å) in this molecule to half the sums of the Mo–Mo and Mn–Mn distances in dimeric molecules [(3.222 + 2.923)/2 = 3.072] indicates that in the formation of heterodimetallic complexes the interaction of monomeric fragments is "additive", i.e. takes place without appreciable changes in the nature of the orbitals of the metal atoms participating in the formation of the metal–metal bonds.

Table 3. Metal–metal bond lengths in heteropolymetallic π-complexes.

Bond	Bond length, Å	Sum of single bond covalent radii	Absolute change in bond length	Relative change in bond length, %
Fe—Mn	2.82	2.7_2	+0.10	+3.7
Fe—Pd*	2.59	2.8_3	−0.24	−8.5
Mo—Mn	3.08	2.9_6	+0.12	+4.1
Mo—Re	3.12	3.0_9	+0.03	+1.0
W—Mn	3.16	2.9_7	+0.19	+6.4
Pt—Co	2.61	2.7_2	−0.11	−4.0
Pt—Mn	2.74	2.8_1	−0.07	−2.5

*Bond "strengthened" by a bridging group.

Thus the type of interaction between covalently linked metal atoms in heteropolymetallic complexes is determined by the same factors as in the previously discussed homopolymetallic complexes.

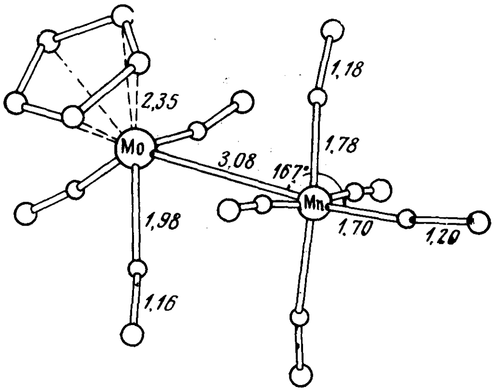

Figure 9. Geometry of the $(\pi\text{-}C_5H_5)Mo(CO)_3Mn(CO)_5$ molecule.

To illustrate this conclusion, we shall consider the pairs of compounds $(\pi\text{-}C_5H_5)Mo(CO)_3\text{–}M(CO)_5$ (M = Mn or Re) and $(\pi\text{-}C_5H_5)M(CO)_3Mn(CO)_5$ (M = Mo or W). Comparison of the metal–metal bond lengths (3.08 Å[36] and 3.12 Å[26]) with the sums of the single bond covalent radii (2.96 and 3.09 Å) for the first pair of compounds shows that the Mo–Mn bond (relative bond elongation Δ_{rel} = +4.1%, see Table 3) is somehwat weaker than the Mo–Re bond (Δ_{rel} = +1.0%). Comparison of the second pair of compounds shows that the W–Mn bond is somewhat weaker than Mo–Mn (Δ_{rel} = 6.4 and 4.1% respectively). Thus in the case of heteropolymetallic complexes too the metals of the second and third transition series from stronger bonds and the maximum tendency of this kind is shown by metals of the second transition series.

It is noteworthy that, although the molecules with metal–metal bonds discussed are not overcrowded in the usual sense of this term, certain details of their real conformations are in fact due to the interaction of the valence non-bonded atoms. Thus in the $(\pi\text{-}C_5H_5)Mo(CO)_3\text{–}Mn(CO)_5$ molecule[36] already discussed (Fig. 9) there is a considerable number of brief contacts between the carbonyl groups at the Mo and Mn atoms, i.e. the $(\pi\text{-}C_5H_5)Mo(CO)_3$ and $Mn(CO)_5$ fragments undergo mutual steric repulsion, which leads to a weakening of the metal–metal interaction.

B. COMPOUNDS WITH COVALENT BONDS BETWEEN TRANSITION METALS AND ELEMENTS OF GROUPS IB–IVB

The number of structural studies on compounds of this type has been small and they have been systematic only for compounds with direct bonds between transition metals and non-transition elements of Group IVB.

A characteristic feature of compounds with direct bonds between Group IB elements (copper, silver, and gold) and transition metals, for example $(C_6H_5)_3PAu\text{–}Mn(CO)_5$,[38] is the presence of phosphine or arsine ligands attached to the

Table 4. Covalent bonds between transition metal atoms and those of elements in Groups IB–IVB.

Bond	Metal-metal bond length, Å	Sum of single bond covalent radii, Å	Absolute change in bond length, Å	Relative change in bond length, %
Group IB element-transition metal				
Au—Mn	2.52—2.57	2.82	— (0.25—0.30)	8,9—10.6
Au—Co	2.50	2.73	—0.23	8,4
Au—W	2.69	3.0_3	-0.3_4	11.2
Cu—Mn	2.56	2.66	—0.10	3.8
Group IIB element-transition metal				
Hg—Fe	2.44—2.59	2.8_6	— (0.27—0.42)	9.4—14.7
Hg—Co	2.50—2.58	2.81	— (0.23—0.31)	8.2—11.0
Zn—Co	2.30	2.63	—0.33	12.5
Group IIIB element-transition metal				
In—Co	2.53—2.63	2.73	— (0.10—0.20)	3.7— 7.2
Group IVB element-transition metal				
Sn—Cr	2.85	2.86	—0.01	0.3
Sn—Mo	2.75	2.9_8	-0.2_3	7.7
Pb—Mo	2.90	3.0_4	-0.1_4	4.6
Sn—W	2.76—2.81	2.9_9	$-(0.1_8-0.2_3)$	6.0— 7.7
Ge—Mn	2.53—2.60	2.60	— (0—0.07)	0—3.0
Ge—Re	2.69	2.73	—0.04	0.2
Sn—Mn	2.63—2.74	2.78	— (0.04—0.15)	1.0— 5.3
Sn—Re	2.74	2.91	—0.17	5.8
Pb—Re	2.77	2.97	—0.20	6.7
Ge—Fe	2.36—2.40	2.5_6	$-(0.1_6-0.2_0)$	6.2— 7.8
Sn—Fe	2.46—2.75	2.7_4	— (0.01—0.28)	0.4—10.2
Sn—Ru	2.56—2.69	2.8_9	— (0.20—0.33)	6.9—11.4
Pb—Fe	2.71	2.8_0	-0.0_9	3.2
Si—Co	2.25—2.38	2.46	— (0.08—0.21)	3.2— 8.5
Sn—Co	2.66	2.69	—0.03	1.1
Sn—Jr	2.64	2.8_7	-0.2_3	8.0
Sn—Pd	2.56	2.8_9	-0.3_3	11.4
Sn—Pt	2.80	2.8_3	-0.0_3	10.6

*Pauling's radii[14] corresponding to a coordination number of 12 were employed for elements in Group IB–IIIB; the values for Group IVB elements were taken from Bokii and Struchkov[55] and those for transition metals from Andrianov et al.[13] see Table 2.

non-transition element. Groups such as $(C_6H_5)_3PAu$ and $(C_6H_5)_3SbCu$ have electronegativities similar to those of halogens[2]. This suggests[39] the possibility of an electronic d_π–d_π interaction between these groups and transition metals. As a result there is a transfer of non-bonding *d* electrons of the transition metal atom to the vacant *d* orbitals of the IB Group element and the stability of derivatives of the type $R_3P \rightarrow Au{-}Mn(CO)_5$ increases[40] as the electron-acceptor properties of the R substituents become more pronounced.

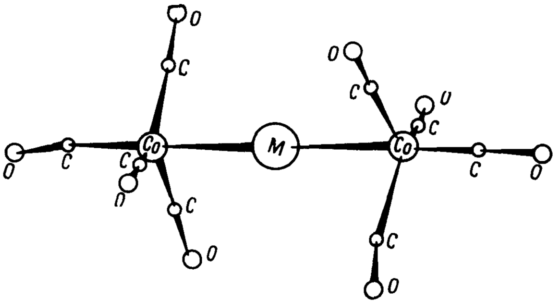

Figure 10. Molecules of the series $M[Co(CO)_4]_2$ (M = Hg or Zn).

The occurrence of d_π–d_π interaction is supported also by the fact that substitution reactions in derivatives of this kind involve carbonyl groups. Finally, comparison of the bond lengths between Group IB elements and transition metals with the sums of the single bond covalent radii (Table 4) shows that the bond lengths are appreciably shorter (by about 0.1–0.3 Å), which is evidence of an increase in the multiplicity of these bonds compared with ordinary covalent bonds.

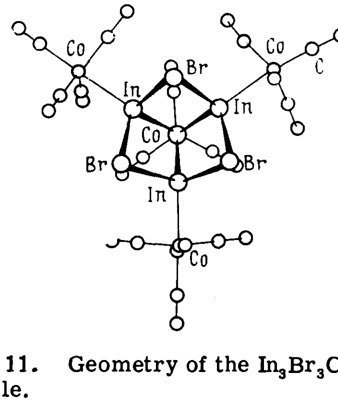

Figure 11. Geometry of the $In_3Br_3Co_4(CO)_{15}$ molecule.

An analogous situation is observed also for compounds with direct bonds between elements of Group IIB and transition metals, for example $M[Co(CO)_4]_2$ (M = Hg [41] or Zn,[42] Fig. 10). The significant shortening (by about 0.3–0.4 Å, Table 4) of these bonds also suggests their partial double bond character, caused[43] by the transfer of *d* electrons from the occupied orbitals of the transition metal to vacant orbitals of the IIB Group elements.

Amongst compounds with bonds between Group IIIB elements and transition metals, structural studies have been made[44] only on the product of the reaction of InBr and $Co_2(CO)_8$ having the composition $In_3Br_3Co_4(CO)_{15}$.

The molecule contains a buckled six-membered ring (Fig. 11) consisting of alternating In and Br atoms. Each indium atom is linked to a $Co(CO)_4$ group via a metal–metal bond with a length of 2.53–2.58 Å and the fourth cobalt atom (in a $Co(CO)_3$ group), which is different from the other cobalt atoms, forms bonds with all three indium atoms with a length of 2.57–2.63 Å. All these bonds are shorter than the sum of the single bond radii (2.73 Å).

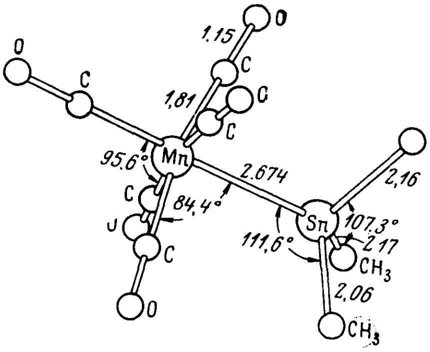

Figure 12. Bond lengths and valence angles in the $(CH_3)_3SnMn(CO)_5$ molecule.

We now come to the discussion of π-complexes with bonds between transition metals and non-transition Group IVB elements, a typical example of which is $(CH_3)_3Sn{-}Mn(CO)_5$ (Fig. 12);[45] this group of compounds has been most completely investigated. Examination of the metal–metal distances of these molecules reveals two striking facts: appreciable variability of the metal–metal bond lengths and a significant shortening of the bonds compared with the sums of the single bond covalent radii (Table 4). For example the Sn–Mn and Sn–Fe bond lengths vary in the ranges 2.63–2.74 and 2.47–2.75 respectively, while the sums of the radii are 2.78 and 2.74 Å.

Numerous studies of the infrared spectra of such series of compounds show that the stretching vibration frequencies of the carbonyl groups attached to the transition metal atoms are exceptionally sensitive to the nature of the substituent X at the atom of the non-transition Group IVB element. This effect has been treated in two different ways in the literature (see, for example, Refs. 46–48). According to the first treatment, the change in the nature of the σ bond between metal atoms on replacement of X (for example as a result of a change in the σ-donor properties of the ligands $X_3Sn{-}$, $X_2Sn\!<$, and $XSn\!\lessdot$) leads to a change in the effective charge at the transition metal atom, which is reflected in a variation of the stretching vibration frequencies of the CO groups. For example, an increase in these frequencies on replacement of $X = CH_3$ by the more electronegative X = Cl in the series $X_3Sn{-}Mn(CO)_5$ ($X = CH_3$, Fig. 12) can be due to the more positive nature of the Mn atom in the latter case (in other words a lower negative charge of the atom), which leads to a weakening of the dative $d_\pi - p_\pi$ Mn–C bond and an increase in the multiplicity of the C–O bond.

In the treatment of the second type of effect of the substituent X consists in a change of the affinity of the vacant *d* orbitals of the non-transition Group IVB element for the non-bonding *d* electrons of the transition metal atom if one postulates the occurrence of $d_\pi - d_\pi$ interaction in the metal–metal bond under consideration. Thus the two types of treatment are not mutually exclusive and require both σ-donor and π-acceptor properties of the ligands to be taken into account.

We are bound to admit that the problem of the occurrence of $d_\pi - d_\pi$ interaction in metal–metal bonds is at present controversial, particularly owing to the lack of quantum-chemical calculations for this group of compounds, but there is much indirect spectroscopic[48] and chemical evidence in favour of such interaction.

The experimental data for interatomic metal–metal distances also indicate some increase in the bond multiplicity. For example, the length of the Mn–Mn bond varies in the range 2.63–2.74 Å and is much shorter than the sum of the single bond covalent radii (2.78 Å).

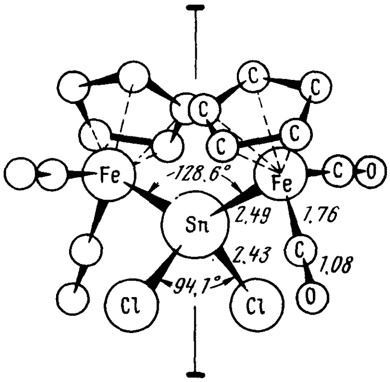

Figure 13. Bond lengths and valence angles in the $[(\pi\text{-}C_5H_5)Fe(CO)_2]_2SnCl_2$ molecule.

In another very fully investigated group of compounds with Sn–Fe bonds, it is possible to distinguish molecules of the series $[(\pi\text{-}C_5H_5Fe(CO)_2]_2SnX_2$, for example with X = Cl (Fig. 13).[49] Spectroscopic studies also show[50,51] a change in the stretching vibration frequencies of the CO group as a function of the properties of the substituent X. The Sn–Fe bonds gradually become shorter with increasing electronegativity of X, the length decreasing from 2.60 Å for X = CH_3 [52] to 2.49 Å for X = Cl,[49] while the sum of the single bond covalent radii is 2.75 Å. At the same time a gradual increase of the FeSnFe angle is observed: from 123.4° to 128.6°C on replacement of CH_3 by Cl. All these findings suggest that, with increase of the electronegativity of X, the multiplicity of the metal–metal bond also increases owing both to an enhancement of the $d_\pi - d_\pi$ interaction and the hybridisation ($sp^3 \rightarrow sp^2$) of the tetrahedral atomic orbitals of the non-transition element participating in the metal–metal bond, in accordance with Bent's rule[53].

The experimental interatomic distances permit a comparison of the molecules of the series under consideration, differing both in the transition metal atoms, for example $(C_6H_5)_3Ge-M(CO)_5$ (where M = Mn or Re), and the atom of the non-transition Group IVB element, for example $(C_6H_5)_3A-Re(CO)_5$ (where A = Ge, Sn, or Pb).

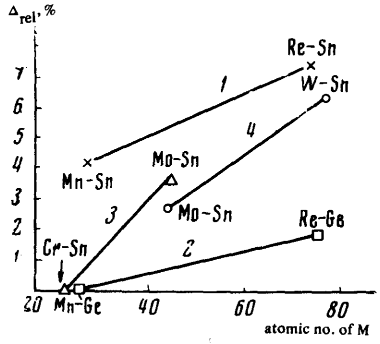

Figure 14. Variation of the relative shortening of metal–metal bonds with the atomic number of the transition metal in molecules with covalent bonds between transition metal atoms and those of a non-transition Group IVB element:
1) $(OC)_5MSn(C_6H_5)_3$; *2*) $(OC)_5M-Ge(C_6H_5)_3$;
3) $C_5H_5(CO)_3M-Sn(C_6H_5)_3$; *4*) $[C_5H_5M(CO)_3]_2Sn(C_6H_5)_2$.

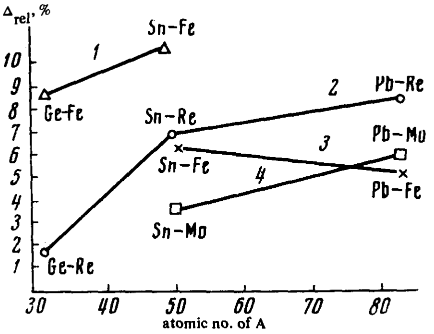

Figure 15. Variation of the relative shortening of metal–metal bonds with the atomic number of the transition metal in molecules with covalent bonds between transition metal atoms and those of a non-transition Group IVB element:
1) $[C_5H_5Fe(CO)_2]_2.ACl_2$; *2*) $(OC)_5Re-A(C_6H_5)_3$;
3) $[C_5H_5Fe(CO)_2]_2A(CH_3)_2$; *4*) $C_5H_5(CO)_3Mo-A(C_6H_5)_3$.

Fig. 14 presents plots of the relative shortening of the metal–metal bonds $\Delta_{rel} = \Delta_{abs}/\Sigma r$ with the atomic number of the transition metal showing that the overall tendency of the transition metal atoms of the second and third series to form more stable metal–metal bonds compared with their analogues in the first series is maintained also when they combine with a non-transition Group IVB element.

As regards molecules with different non-transition Group IVB elements, it is found that, within the limits of the available experimental data (Fig. 15), tin forms stronger bonds than germanium, while for lead no systematic trend has been observed.

III. COMPLEXES WITH METAL–DONOR BONDS

This group includes molecules with square planar coordination about the central metal atom, which has a d^8 valence configuration, for example $Rh(CO)_2[(CH_3CO)_2CH]$ [54] (Fig. 16). In crystals molecules of such compounds are distributed one on top of the other in parallel planes with metal–metal distances of 3.2–3.33 Å (while the distance equal to twice the covalent radius is 2.7–3.0 Å).

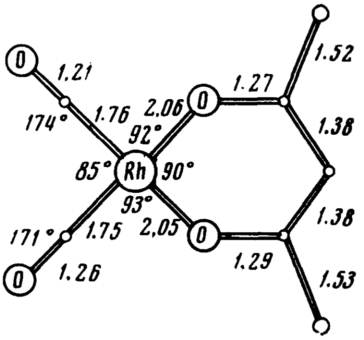

Figure 16. Geometry of the $Rh(CO)_2[(CH_3CO)_2CH]$ molecule.

Thus the coordination about the metal atom is increased to give a distorted octahedron as a result of the formation of the so called metal–donor or polymeric metal–metal bonds. It has been shown[3] that such metal–metal interaction, leading to the formation of an infinite one-dimensional polymetallic system, takes place as a result of the overlapping of the filled d_{z_2} orbital of one metal atom and the vacant p_z orbital of an adjacent atom. These bonds impart to the crystal certain properties of the metal, giving rise, in particular, to a sharp anisotropy of its electrical conduction and photoconduction. The metal–metal interaction of this type is probably not entirely covalent, so that crystals of compounds of this kind exhibit semiconductor properties to a greater extent than metallic properties.

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Institute of Organic Derivatives
of the Elements, USSR Academy
of Sciences, Moscow

Lomonosov Moscow
Institute of Fine Chemical
Engineering

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The Mechanism of the Action of Antioxidants and the Synergism of Mixed Antioxidants

P.I.Levin and V.V.Mikhailov

The review considers the mechanism by which various types of inhibitors act in the oxidation processes of carbochain polymers and also mixtures of inhibitors exhibiting a synergistic effect. In conclusion a new and promising class of stabilisers (polyfunctional inhibitors) is considered.
The bibliography includes 85 references.

CONTENTS

I. INTRODUCTION

The effective protection of polymers against thermo-oxidative degradation is an important theoretical and technical problem. The oxidation of organic compounds, including polymers, may be sharply inhibited by the introduction of small amounts of inhibitors or antioxidants. Antioxidants protect polymers from oxidative degradation during their processing at high temperatures and increase the useful life of articles made of polymers.

Mixtures of antioxidants have found application in recent years in the stabilisation of polymers and lubricating oils, since the effect of many mixtures proved to be much greater than would be expected from the additive effects of their components. Numerous studies have been devoted to this phenomenon, called synergism, and also to the search for effective inhibitor compositions.

A number of monographs[1-3] and reviews[4-6] published in recent years deal with the mechanism by which inhibitors of free-radical processes act but the problem of the mechanism of the action of phosphites and sulphur-containing compounds has been hardly touched upon. The mechanisms of the synergism of mixtures comprising inhibitors of free-radical processes and agents decomposing hydroperoxides have been very incompletely treated in the monographs and reviews published hitherto.

The present review deals with the mechanism by which inhibitors terminate kinetic oxidation chains (phenols and amines) and inhibitors suppressing chain branching (phosphites and sulphur-containing compounds); the possible mechanisms of the action of their mixtures, which exhibit synergistic effects, are also discussed.

II. THE MECHANISM OF THE ACTION OF INHIBITORS

1. Phenols and Amines

The oxidation of carbochain organic compounds and in particular of polymers involves a radical chain mechanism with degenerate branching[2], which can be described as follows[7]. Initiation takes place as a result of the reaction of oxygen with the hydrocarbon:

$$RH + O_2 \xrightarrow{w_u} \dot{R} + H\dot{O}_2$$

or

$$2RH + O_2 \xrightarrow{w_u} 2\dot{R} + H_2O_2 \,.$$

The kinetic chain is propagated and branches via the reactions

$$1.\ \dot{R} + O_2 \xrightarrow{k_1} R\dot{O}_2 \,,$$

$$2.\ R\dot{O}_2 + RH \xrightarrow{k_2} \dot{R} + ROOH \,,$$

$$3.\ ROOH \xrightarrow{k_3} R\dot{O} + H\dot{O} \,,$$

$$3'.\ ROOH + RH \xrightarrow{k_3'} \dot{R} + R\dot{O} + H_2O \,.$$

The chains are destroyed as a result of the recombination of the radicals $R\dot{O}_2$, since in the presence of oxygen $[\dot{R}] < [R\dot{O}_2]$:

$$4.\ R\dot{O}_2 + R\dot{O}_2 \xrightarrow{k_4} ROOR + O_2 \,.$$

In the presence of inhibitors of free-radical processes (phenols and amines), there is linear termination of the $R\dot{O}_2$ radicals by the inhibitor[8-10]:

$$5.\ R\dot{O}_2 + InH \xrightarrow{k_5} ROOH + I\dot{n} \,,$$

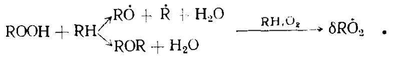
with formation of a hydroperoxide and a relatively inactive inhibitor radical, as shown in subsequent studies using ESR[11,12].

Semenov[7] showed that, when the above process mechanism operates, there should exist a critical inhibitor concentration defined by the equation

$$[InH]_{cr} = \frac{k_2[RH]}{k_5} \,. \qquad (1)$$

The presence of critical inhibitor concentrations has been established in a number of studies on the oxidation of liquid hydrocarbons[13,14] and polypropylene[15].

Eqn. (1) was derived on the assumption that reaction (5) yields stable products; nevertheless, the hydroperoxide formed is a branching agent in the chain process. When this is taken into account, then, as shown by Neiman[2], there should be no critical inhibitor concentration. Since the critical concentration is in fact observed experimentally and, within the framework of the oxidation process mechanism adopted by Semenov, Eqn. (1) is not entirely exact, it has been suggested[15] that the hydroperoxide reacts with the hydrocarbon[16] and ultimately the radicals $R\dot{O}_2$ are formed with a probability δ by the reaction



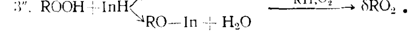
$$ROOH + RH \begin{cases} R\dot{O} + \dot{R} + H_2O \\ ROR + H_2O \end{cases} \xrightarrow{RH,O_2} \delta R\dot{O}_2 \; .$$

After this modification, the following expression was obtained[2,17] for the critical inhibitor concentration:

$$[InH]_{cr} = \frac{\delta}{(1-\delta)}\frac{k_2}{k_5}[RH] \; , \qquad (2)$$

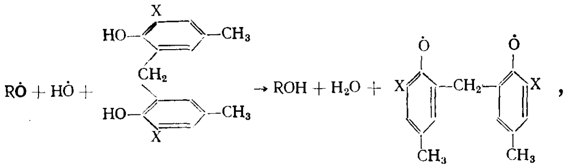
from which it follows that the critical concentration of the antioxidant can obtain only when $\delta < 1$. Up to the critical antioxidant concentration the oxidation reaction takes place under non-steady-state conditions and above it under steady-state conditions[13-15,17].

Hydroperoxides are known to react with phenols and amines at a higher rate than with hydrocarbons. Ingold showed that phenols and amines accelerate the decomposition of the hydroperoxides formed in the oxidation of mineral oil[18]. It has also been established[19,20] that amines sharply reduce the activation energy for the decomposition of polypropylene hydroperoxide: in the absence of amines the activation energy for the decomposition of the hydroperoxide is 25 kcal mole^{-1}, while in the presence of diphenylamine it is 17 kcal mole^{-1} and in the presence of *N*-cyclohexyl-*N*'-phenyl-*p*-phenylenediamine it is only 14 kcal mole^{-1}. Consequently, in the presence of such inhibitors the hydroperoxide reacts not with the hydrocarbon but with the inhibitor to form ultimately active $R\dot{O}_2$ radicals with a probability δ according to the mechanism



$$ROOH + InH \begin{cases} R\dot{O} + \dot{In} + H_2O \\ RO-In + H_2O \end{cases} \xrightarrow{RH,O_2} \delta R\dot{O}_2 \; .$$

It is easy to show that, when account is taken of this reaction, the preceding equation (2) is obtained for the critical antioxidant concentration. The antioxidants in whose presence $\delta \geqslant 1$ cannot at any concentration ensure a slow steady-state occurrence of the inhibited reaction. In their presence the reaction always takes place under non-steady-state conditions with appreciable acceleration. This acceleration cannot be detected from the absorption of oxygen, since it is too slight, but it can be observed from the decrease of the molecular weight of the polymer. If the antioxidant does not have a critical concentration, in its presence the molecular weight of the polymer falls sharply during the induction period. Thus in the presence of monohydric phenols, which do not have a critical concentration, the molecular weight of polypropylene falls much more appreciably than in the presence of bisphenols which do have a critical concentration[21]. Moreover, monophenols are much less effective than bisphenols (several times and not by a factor of two as would be expected on the basis of the number of hydroxy-groups). The different effectiveness of monophenols and bisphenols in the inhibited oxidation of polypropylene is probably associated with the participation of antioxidants in chain branching. It has been suggested[22] that effective antioxidants should have two active groups located close to one another in order to react simultaneously with the two radicals formed in the decomposition of the hydroperoxide, for example in a cage according to the mechanism



where X is a t-butyl group.

This process results in the formation of a single relatively inactive biradical. If the antioxidant has one active group, then in the cage it can react with only one radical. The second radical cannot recombine, which increases the probability of chain branching.

The dependence of the induction period (τ) in the oxidation of polypropylene on the concentration of 2,2'-methylenebis-(6-t-butyl-4-methylphenol) as an antioxidant in the presence and absence of 4-methyl-2,6-di-t-octylphenol has been investigated[23]. It was shown that in the presence of the monophenol τ for the bisphenol diminishes and the critical concentration increases. Other monophenols had a similar effect.

According to the authors, the increase of the critical concentration of the bisphenol in the presence of the monophenol is due to an enhanced probability of chain branching in the oxidation of polypropylene. However, the increase of the critical concentration and the decrease of τ for the bisphenol can also be caused by the reaction of the monophenoxy-radical with polypropylene:

$$\dot{In} + RH \rightarrow InH + \dot{R} \; .$$

If the monophenoxy-radical participates in chain propagation, then, as shown by Likhtenshtein and Urman[24,25], the critical concentration of the inhibitor increases. Possibly the inhibitor (monophenol) radicals are more active in the initiation of oxidation than the bisphenol radicals[12] and consequently increase the critical concentration of the latter. Under the conditions of identical reactivities of the monophenol and bisphenol inhibitor radicals, theoretical calculations show that the critical concentration is increased by the enhanced probability of branching. At low oxidation temperatures the inhibitor radicals are destroyed by recombination; at an elevated temperature there is a greater probability of their participation in chain propagation.

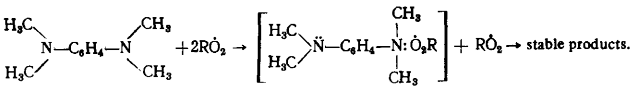
Thus it has been shown[26] that the critical concentration of an effective bisphenol increases both in the presence of an ineffective monophenol and an ineffective bisphenol (monohydroxybenzophenone and dihydroxybenzophenone). Probably chain transfer to the photostabiliser radicals plays an appreciable role.

Oxidation may be initiated also as a result of the direct oxidation by oxygen of an antioxidant molecule, for example, a monophenol, via the mechanism $InH + O_2 \rightarrow \dot{In} + H\dot{O}_2$ with formation of the relatively active radical $H\dot{O}_2$. On interaction with the hydrocarbon, the latter yields hydrogen peroxide, which breaks down into radicals and causes chain branching. As a result of this reaction, the critical concentration of the inhibitor should increase, as shown theoretically by Likhtenshtein and Urman[24]. Thus the increase of the critical concentration of the bisphenol in the presence of a monophenol can be caused both by the participation of the monophenol in degenerate branching and by the initiation of the oxidation process by the inhibitor radical and the inhibitor oxidation products.

It has been established in a number of investigations that the mechanism of inhibition by amines which contain a mobile hydrogen atom in the amino-group consists in linear termination of radicals:

$$R\dot{O}_2 + R''NHR' \rightarrow R'\dot{N}R'' + ROOH \; .$$

This mechanism of inhibition by amines is confirmed by the formation of inhibitor radicals[11,12] and the expected final oxidation products[1-6]. Thus in the oxidation of cumene in the presence of *NN*'-diphenyl-*p*-phenylenediamine, the latter is 80–95% converted into *NN*'-diphenyl-*p*-quinone-di-imine. However, it is known that tertiary amines also strongly inhibit the oxidation. It has been shown that in the oxidation of cumene in chlorobenzene solution each tetramethyl-*p*-phenylenediamine molecule terminates two oxidation chains:



This involves the intermediate formation of a radical complex[27]. Probably aromatic hydrazines which do not have mobile hydrogen atoms should fulfil a similar role. Further study of such compounds will undoubtedly be of great interest.

2. Sulphur-containing Compounds

Sulphur-containing compounds without amino- and phenolic groups inhibit the oxidation process by the decomposition of hydroperoxides with formation of stable molecules[28-31]:

$$6.\ \mathrm{ROOH} + \mathrm{R'_2S} \xrightarrow{k_4} \mathrm{ROH} + \mathrm{R'_2SO}\ .$$

In a study of the kinetics of the reaction of a hydroperoxide with sulphides, it was shown that the reaction is of first order with respect to the hydroperoxide[32]. Sulphides are oxidised further to sulphones[33-35]:

$$\mathrm{ROOH} + \mathrm{R'_2SO} \rightarrow \mathrm{ROH} + \mathrm{R'_2SO_2}\ .$$

Apart from the reactions mentioned above, sulphides are oxidised by peroxy-radicals without chain termination[28,30,31]:

$$\mathrm{R\dot{O}_2} + \mathrm{R'_2S} \rightarrow \mathrm{R\dot{O}} + \mathrm{R'_2SO}\ .$$

In this secondary reaction sulphides are consumed, which reduces their effectiveness.

Mercaptans inhibit oxidation via the mechanism

$$\mathrm{\dot{R}O_2} + \mathrm{R'SH} \rightarrow \mathrm{ROOH} + \mathrm{R'\dot{S}}\ .$$

Thiyl radicals can probably also interact with peroxy-radicals in the following way[36]:

$$\mathrm{R\dot{O}_2} + \mathrm{R'\dot{S}} \rightarrow \mathrm{R'\,(O)-S-O-R},$$

and can recombine with formation of disulphides. Aryl disulphides are as a rule more effective than aryl sulphides. However, in the presence of certain disulphides the molecular weight of polypropylene was found to diminish sharply during the induction period[37]. Probably at 200°C the aromatic disulphide breaks down into thiyl radicals which in the presence of oxygen cause the breakdown of the polymer.

In the first oxidation stage disulphides and hydroperoxides form intermediate thiosulphoxides:

$$\mathrm{R'S-SR''} + \mathrm{ROOH} \rightarrow \mathrm{R'S\,(O)\,SR''} + \mathrm{ROH},$$

which on further oxidation are converted into thiosulphones[35,38,39]. The sulphides themselves are rarely used to stabilise mineral oils and polymers, since their effectiveness is low but, when mixed with inhibitors of free-radical processes, they sharply increase the effectiveness of the latter. Among sulphur-containing compounds, sulphides, mercaptans, polysulphides, etc. are used in mixtures with phenols and amines. The most powerful synergistic effect is produced by esters of thiocarboxylic acids such as dilauryl and distearyl thiodipropionates and esters of thiovaleric acid. The synergistic effect of mixtures of free-radical process inhibitors with sulphides is widely used to stabilise various organic substances, including polymers.

3. Phosphites

Phosphite esters are widely used to stabilise polymers both in a pure form and in mixtures with phenols. In contrast to amines and phenols, phosphites do not colour polymers and therefore may be used in the manufacture of light-coloured articles. The mechanism of their action and the effectiveness of aromatic phosphites as a function of the structure of their phenoxy-residues have been little investigated.

It is known that aliphatic phosphites, like sulphides, break down hydroperoxides virtually without the formation of free radicals[40,41]:

$$7.\ \mathrm{ROOH} + (\mathrm{RO'})_3\mathrm{P} \rightarrow \mathrm{ROH} + (\mathrm{RO'})_3\mathrm{PO}\ .$$

Therefore it is suggested that phosphites inhibit oxidation only by suppressing chain branching. Furthermore, it has been shown[42] that at 130°C aliphatic phosphites are oxidised by peroxy- and oxy-radicals to phosphates without chain termination:

$$8.\ \begin{array}{l} \mathrm{R\dot{O}_2} + (\mathrm{\dot{R}'O})_3\mathrm{P} \rightarrow \mathrm{\dot{R}O} + (\mathrm{R'O})_3\mathrm{PO}\ , \\ \mathrm{R\dot{O}} + (\mathrm{\dot{R}'O})_3\mathrm{P} \rightarrow \mathrm{\dot{R}} + (\mathrm{R'O})_3\mathrm{PO}\ . \end{array}$$

Table 1. Effectiveness of phosphites in the oxidation of polypropylene at 200°C and an oxygen pressure of 200 mmHg [43].

No.	Phosphite	Induction period at a concn. of 0.05 mole kg^{-1} min
1	Tri(nonylphenyl) phosphite	30
2	Iso-octyl diphenyl phosphite	35
3	Phenyl *o*-phenylene phosphite	60
4	Tri-(4-t-butylphenyl) phosphite	90
5	α-Naphthyl *o*-phenylene phosphite	190
6	2,6-Di-t-butyl-4-methylphenyl *o*-phenylene phosphite	260
7	2,4,6-Tri-t-butylphenyl *o*-phenylene phosphite	400
8	2,6-Di-isobornyl-4-methylphenyl *o*-phenylene phosphite	1000

The effectiveness of action of the phosphites by this mechanism must be low. Indeed, it follows from the data in Table 1 [43-46] that aliphatic and aromatic phosphites without alkyl substituents in the phenoxy-residue have a low antioxidant activity.

Table 1 shows that the introduction of a t-butyl and particularly an isobornyl group into the *ortho*-position of phenol in *o*-phenylene phosphite sharply increases the induction period. A study of the kinetics of the absorption of oxygen in the oxidation of polypropylene in the presence of phosphites showed that relatively ineffective phosphites do not have a critical concentration (Fig. 1) [37]. Consequently they inhibit the oxidation, like sulphides, by breaking down the hydroperoxides without linear termination of peroxy-radicals[1,7]. On the other hand, effective phosphites have a critical concentration and therefore they inhibit the oxidation process by linear termination of radicals and possibly by breaking down the hydroperoxides (Fig. 2)[37].

The kinetics of the reactions of aromatic phosphites with the diphenylpicrylhydrazyl radical and with t-butyl hydroperoxide at room temperature have been investigated[47,48]. It was found that phosphites (6) and (7) (see Table 1) react rapidly, compound (4) much more slowly, and compound (3) and triphenyl phosphite hardly react at all with the diphenylpicrylhydrazyl radical[47]. Thus the reactivity towards radicals and the effectiveness of phosphites increase sharply on introduction of alkyl substituents into the phenoxy-residue. On the other hand, the reactivity of aromatic phosphites towards hydroperoxides bears an inverse relation, i.e. the lower the antioxidant activity of phosphites the faster they react with the hydroperoxide[48].

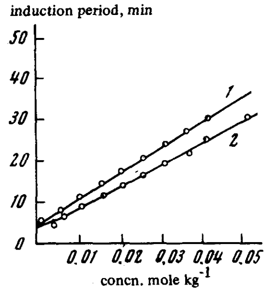


Figure 1. Variation of the induction period in the oxidation of polypropylene with the concentration of tri(nonylphenyl) phosphite (*1*) and iso-octyl diphenyl phosphite (*2*) at 200°C and P_{O_2} = 200 mmHg.

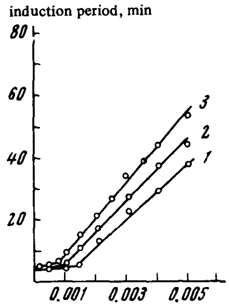


Figure 2. Variation of the induction period in the oxidation of polypropylene with the concentration of α-naphthyl *o*-phenylene phosphite (*1*), 2,6-di-t-butyl-4-methylphenyl *o*-phenylene phosphite (*2*), and 2,4,6-tri-t-butylphenyl *o*-phenylene phosphite (*3*) at 200°C and P_{O_2} = 200 mmHg.

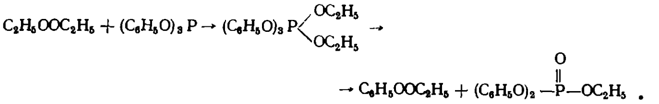
The reaction of peroxy- and oxy-radicals with aromatic phosphites has not been investigated at all. Walling and coworkers suggested[49] that in the reaction of aromatic phosphites with aliphatic RȮ radicals a double decomposition reaction is possible:

$$R\dot{O} + (R'O)_3P \rightarrow (R'O)_2POR + R'\dot{O}$$

in consequence of the formation of the more stable phenoxy-radical. Almost simultaneously it was shown[50] that in the reaction of diethyl peroxide with triphenyl phosphite at 130°C ethyl phenyl ether ($C_2H_5OC_6H_5$) and a phosphate with the probable structure $C_2H_5OP(O)(OC_6H_5)_2$ are formed. These products may be formed by the exchange of radicals via an intermediate quadrivalent phosphorus compound:

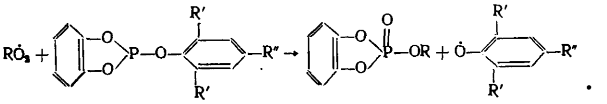
$$C_2H_5O + (C_6H_5O)_3P \rightarrow C_2H_5O\dot{P}(OC_6H_5)_3 \xrightarrow{C_2H_5\dot{O}}$$
$$\rightarrow (C_6H_5O)_2P(O)(OC_2H_5) + C_2H_5OC_6H_5$$

and probably in the reaction of the undecomposed diethyl peroxide with triphenylphosphite via an intermediate quinquevalent phosphorus compound:



$$C_2H_5OOC_2H_5 + (C_6H_5O)_3P \rightarrow (C_6H_5O)_3P\begin{matrix}\diagup OC_2H_5\\ \diagdown OC_2H_5\end{matrix} \rightarrow$$
$$\rightarrow C_6H_5OOC_2H_5 + (C_6H_5O)_2-\overset{\overset{\displaystyle O}{\|}}{P}-OC_2H_5\ .$$

Probably the reaction of pentoxy-radicals with aromatic *o*-phenylene phosphite esters with t-butyl groups in the phenoxy-residue can occur at an elevated temperature via a radical exchange mechanism with formation of a phosphate and a stable phenoxy-radical[43]:

9. 

This mechanism is consistent with the high reactivity of these phosphites towards diphenylhydrazyl radicals and their enhanced antioxidant effectiveness compared with other phosphites[37,43]. However, this mechanism is inconsistent with the experimental studies on the kinetics of the reaction of $R\dot{O}_2$ radicals with aromatic phosphites in ethylbenzene at 60°C using a chemiluminescence technique[51]. In these experiments it was shown that aromatic phosphites (5), (6), and (7) (Table 1) cause chain termination, but fifty phosphite molecules are required for the termination of a single $R\dot{O}_2$ radical. Possibly at the experimental temperature the phosphites only react slowly with peroxy-radicals and therefore do not affect the effectiveness of the luminescence. On the other hand, it would appear that the weak termination of peroxy-radicals in the presence of aromatic phosphites might be explained by the presence of hydrolysis products. On this basis, it was suggested that phosphites inhibit oxidation by the hydrolysis products formed in the oxidation process[5]. Nevertheless, this hypothesis is inconsistent with a number of observations. The hydrolysis products of *o*-phenylenephosphite esters do not have a critical concentration under the experimental conditions in the oxidation of polypropylene, like screened phenols, α-naphthols, and *o*-phenylene phosphorous acid, while the phosphite itself does have such a concentration (Fig. 2). Moreover, the effectiveness of phosphites (6), (7), and (8) (Table 1) would be almost the same if the oxidation of polypropylene were inhibited by the hydrolysis products, since the effectiveness of the latter differs little. It was further established that the effectiveness of phosphite (7) is much higher than that of any equimolar mixture of the hydrolysis products[37]. Probably at a high temperature phosphites enter into reactions (7), (8), and (9) with different probabilities (depending on the structure). Possibly aliphatic and aromatic phosphites with unscreened phenoxy-groups inhibit oxidation only by suppressing chain branching [reaction (7)] and are mainly consumed in reaction (8). On the other hand, aromatic phosphites with screened phenoxy-groups in the molecule may inhibit oxidation by radical termination via reaction (9). If the phenoxy-radicals formed propagate the oxidation chain via the reaction $\dot{\mathrm{In}} + \mathrm{RH} \rightarrow \mathrm{InH} + \dot{\mathrm{R}}$ with a lower probability, then the effectiveness of the phosphite will be high, and conversely. Moreover, at an elevated temperature effective aromatic phosphites, like aliphatic phosphites, probably react with hydroperoxides to form stable products. Experiments on the oxidation of polypropylene in the presence of a mixture of 2,6-di-t-butyl-4-methylphenyl-*o*-phenylene phosphite and dilauryl thiodipropionate showed that this mixture exhibits a synergistic effect, which, however, is much smaller than that of a mixture of phenols with the same sulphide[37]. Consequently, such sulphides inhibit chain branching to some extent as well. Moreover, effective phosphites can probably be partially consumed also by reaction (8).

The above mechanism of inhibition by screened phosphites is consistent with their high antioxidant activity and the critical concentrations observed in experiments on the oxidation of polypropylene.

III. THE MECHANISM OF THE SYNERGISM OF INHIBITOR COMPOSITIONS

When two or more inhibitors are introduced into the substance being oxidised, an antioxidant effect in excess of the additive value is frequently observed. Such an effect of the mixture is usually called synergism and is defined by the expression $\tau_{1,2} < \tau_1 + \tau_2$, where $\tau_{1,2}$, τ_1, and τ_2 are the induction periods for the mixture and the individual components respectively. Furthermore, the synergistic effect should be defined as one in which the antioxidant efficiency of the induction period for the mixture are higher than for any one component taken separately at a concentration equal to the overall concentration of the mixture (Fig. 3) [37,52]. On the other hand, strictly speaking, the phenomenon of synergism should be understood as the enhancement of the effectiveness of the active component by a completely inactive component.

With this definition of synergism, it is possible to establish both the magnitude of the effect and its maximum as a function of the molar ratio of the components. The synergistic effect for mixtures of inhibitors is observed in those cases where the mixture components inhibit oxidation by different mechanisms. Therefore we shall consider the possible mechanisms of the action of inhibitor compositions for which the synergistic effect is known to apply or may be postulated.

1. Mixtures of Inhibitors of Free-radical Processes with Sulphides.

The most powerful synergistic effect is usually shown by mixtures of two inhibitors one of which terminates the oxidation chain and the other breaks down hydroperoxides[15,32–34,36,37,52–55]. The considerable enhancement of the inhibiting effect can be explained in terms of this mechanism by the fact that one of the inhibitors reduces the yield of hydroperoxides, which, on decomposing into radicals cause chain branching, while the second breaks down the hydroperoxides and thereby both inhibitors protect one another from rapid consumption. However, hydroperoxide decomposing agents are evidently themselves oxidised by peroxy-radicals in the inhibition process.

This mechanism was confirmed[15] by kinetic data. Thus, when polypropylene is stabilised by a mixture of a chain terminating oxidant and a sulphide which decomposes hydroperoxide, the critical concentration of the antioxidant diminishes as that of the sulphide is increased, according to the equation

$$[\mathrm{InH}]_{\mathrm{cr}} = \frac{\delta k_2 k_4 [\mathrm{RH}]^2}{(1-\delta) k_4 k_5 [\mathrm{RH}] + k_6 [\mathrm{R_2S}]} \ . \qquad (3)$$

In the absence of the sulphide or another hydroperoxide decomposing agent, Eqn. (3) transforms into Eqn. (2) derived above.

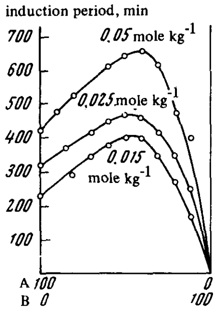


Figure 3. Variation of the induction period in the oxidation of polypropylene with the composition of a mixture of 2,2'-methylenebis-(6-t-butyl-4-methylphenol) (*A*) and dilauryl thiodipropionate (*B*) at different overall concentrations, 200°C, and P_{O_2} = 200 mmHg.

In the same investigation it was shown that 2,4,6-tri-t-butylphenol does not have a critical concentration in the oxidation of polypropylene (200°C, oxygen pressure 300 mmHg); in this case the induction period is short. However, in the presence of a sulphide[15] or a phosphite[46] (at a sufficiently high concentration) a critical concentration is observed and the effectiveness of the monophenol increases sharply. If the antioxidant has a critical concentration, then in the presence of a hydroperoxide decomposing agent it diminishes and the effectiveness of the antioxidant increases[15,46].

Mixtures of monophenols, bisphenols, and thiobisphenols with hydroperoxide decomposing agents show a marked synergistic effect[15,37,54,55–58]. Fig. 3 shows as an example the variation of the induction period of the oxidation of polypropylene as a function of the molar composition of a mixture of 2,2,-methylenebis-(6-t-butyl-4-methylphenol) and dilauryl thiodipropionate at different overall concentrations. It is seen that the induction period for the mixture is much longer than for the bisphenol at the concentration equal to the overall concentration of the mixture. It is interesting that the sulphur in the thiobisphenol molecule does not decompose the hydroperoxide, since thiobisphenols in a mixture with a sulphide exhibit an appreciable synergistic effect. The synergistic effect depends on the activity of the synergist. The most active synergist among the sulphides investigated proved to be dilauryl thiodipropionate[54], but, as shown by the present authors' experiments, thiovaleric esters are also active synergists; thioacetic esters are less active. The activity of thioacid esters increases with the number of carbon atoms in the aliphatic residue[58].

Synergistic mixtures of phenols with sulphur-containing compounds are widely used to stabilise polymers, largely polyolefins. There are more than 200 patents for the application of these synergistic mixtures. Certain mixtures effectively protect polyolefins during processing at a high temperature and under the conditions of their use[55-57]. Synergistic mixtures of phenols with thiophosphoric compounds and phosphites do not colour polymers or weaken them appreciably and they are very important in the manufacture of light-coloured high-quality articles.

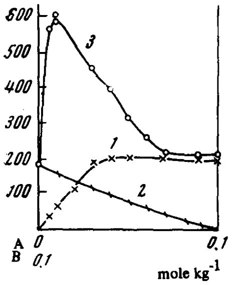


Figure 4. Variation of the induction period in the oxidation of polypropylene with the composition of a mixture of *p*-hydroxyphenyl-β-naphthylamine (*A*) and mercaptobenzimidazole (*B*) (*3*) and with the concentrations of the components (*1* and *2*) at 200°C and P_{O_2} = 200 mmHg.

Beside phenols, amines mixed with agents which decompose hydroperoxide exhibit a synergistic effect. For example (Fig. 4), the effectiveness of a mixture of *p*-hydroxyphenyl-β-naphthylamine with mercaptobenzimidazole (MBIA) is three times greater than the effectiveness of the most active component at the concentration equal to the overall mixture concentration[52]. It is interesting that the maximum effect is observed when MBIA is present in the mixture in an appreciable excess.

The synergistic effect is observed in different ways depending on the activity of the inhibitor of free-radical processes. Fig. 5 shows that a mixture of β-naphthylphenylamine with MBIA is not more effective than the initial amine[53]. A synergistic effect in respect of additivity is observed only at a low amine concentration. Probably at a high concentration the amine suppresses chain branching.

The different synergistic effects of the last two mixtures evidently depend also on the different rates of the direct oxidation of the amines employed according to the mechanism

$$\mathrm{InH} + \mathrm{O_2} \rightarrow \dot{\mathrm{In}} + \mathrm{H\dot{O}_2} \xrightarrow{\mathrm{RH}} \dot{\mathrm{In}} + \mathrm{H_2O_2} + \dot{\mathrm{R}} \ .$$

Indeed the curves relating τ to the antioxidant concentration (curves *1* in Figs. 4 and 5) show in the first place the attainment of a limiting induction period as the concentration is increased, while in the second case a limit is not reached. This shows that *p*-hydroxyphenyl-β-naphthylamine is vigorously oxidised by oxygen as the concentration increases[32]. The presence of an agent which decomposes hydroperoxide sharply decreases the yield of free radicals $\dot{\mathrm{R}}$, leading to an appreciable enhancement of the effectiveness of the mixture.

Thus certain mixtures consisting of a weak inhibitor and a synergist may be as effective as compositions comprising a strong inhibitor and the same synergist, i.e. the synergistic effect is greater the weaker is the inhibitor free radical process.

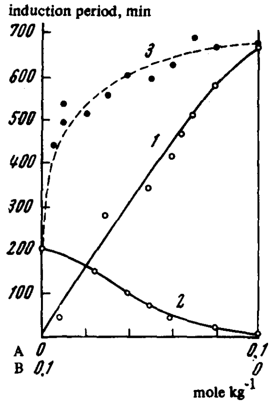


Figure 5. Variation of the induction period in the oxidation of polypropylene with the composition of a mixture of β-naphthylphenylamine (*A*) and mercaptobenzimidazole (*B*) (*3*) and with the concentrations of the components (*1* and *2*) at 200°C and P_{O_2} = 200 mmHg.

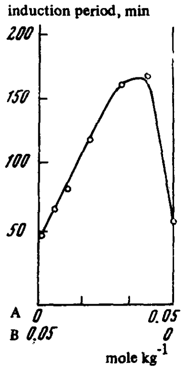


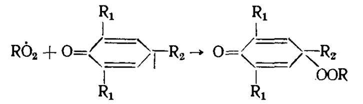
Figure 6. Variation of the induction period in the oxidation of polypropylene with the composition of a mixture of 2,4,6-tri-t-butylphenol (*B*) and dilauryl thiodipropionate (*A*) at 200°C and P_{O_2} = 200 mmHg.

If a strong inhibitor, for example a bisphenol or a diamine, binds both free radicals on interaction with the hydroperoxide in a cage, in the presence of a hydroperoxide decomposing agent the synergistic effect should be absent or small. However, Fig. 3 shows that a mixture of a bisphenol with dilauryl thiodipropionate exhibits an appreciable synergistic effect. Consequently bisphenols do not bind in a cage all the free radicals formed on decomposition of the hydroperoxide. Comparison of the synergistic effect of a mixture of a monophenol and a sulphide (Fig. 6) with that of a mixture of a bisphenol with the same sulphide (Fig. 3) shows that it is greater in the first mixture[15,37,46]. This finding evidently shows that in the presence of the bisphenol, the yield of radicals in the decomposition of the hydroperoxide is lower than in the presence of the monophenol. In principle, it is possible that polyphenols and polyamines which have either adjacent functional groups or well separated ones capable of approaching one another in space may completely suppress chain branching. Thus certain tetraphenols (for example Irganox 1010 produced by the Geigy Co., Switzerland) mixed with sulphides and oxides do not exhibit a synergistic effect, which probably shows that they suppress chain branching. Inhibitors capable of chain termination and suppression of chain branching should exhibit a high antioxidant activity provided that they are not oxidised by oxygen under these conditions. The search for such inhibitors is of considerable interest both from theoretical and practical points of view.

2. Mixtures of Phenols with Phosphites

It is known that aliphatic and aromatic esters of phosphorous acid, like sulphides, interact with hydroperoxides to form stable products[40,41]. Moreover, it has been shown[42] that phosphites react with peroxy-radicals without chain termination by reaction (8) and therefore are rapidly consumed. In the presence of inhibitors of free-radical reactions the consumption of phosphites by reaction with peroxy-radicals should diminish, which should increase the importance of phosphites in the suppression of chain branching. As a result of the above reactions, the effectiveness of the mixture components increases significantly and the mixture may exhibit a synergistic effect. However, this general inhibition mechanism probably depends on the structure of the alkoxy- and phenoxy-residues of the phosphite esters. Aliphatic phosphites mixed with phenols are relatively ineffective, although they rapidly decompose hydroperoxides with a low yield of free radicals[59]. Evidently this can be explained by the more rapid consumption of phosphites by reaction (8) so that they suppress chain branching only to a small extent. Nevertheless, mixtures of monophenols and bisphenols with iso-octyl diphenyl phosphite (Figs. 7 and 8) and with tri(nonnylphenyl) phosphite show a powerful synergistic effect[46], whose magnitude is greater for monophenols. Probably this is because bisphenols are more likely to suppress chain branching than monophenols. As mentioned above, this is also observed in mixtures of monophenols and bisphenols with dilauryl thiodipropionate.

The structure of phosphites has a very pronounced effect on the synergistic effect in mixtures of phenols with *o*-phenylene phosphite esters. Thus a mixture of a monophenol with 2,4,6-tri-t-butylphenyl *o*-phenylene phosphite does not show an appreciable additional effect[37], in contrast to the mixture of the same monophenol with iso-octyl diphenyl phosphite (Fig. 7). At the same time an appreciable synergistic effect is observed in mixtures of *o*-phenylene phosphite esters with bisphenols and thiobisphenols[37,44,60]. The absence of the synergistic effect from mixtures of monophenols with *o*-phenylene phosphite esters and conversely its occurrence in mixtures with bisphenols and thiobisphenols indicate a complex inhibition mechanism. In the inhibition of oxidation phosphite esters, like sulphides[15], do not exhibit a critical concentration[46]. Therefore both inhibit oxidation by suppressing chain branching and at the same time are oxidised by the peroxy-radicals with formation of stable products and an oxy-radical, i.e. without chain termination[31,42]. On the other hand, *o*-phenylene phosphite esters do have a critical concentration, which shows that they are responsible for linear termination of peroxy-radicals. The mechanism of the action of these phosphites was examined above and it was postulated that at a high temperature *o*-phenylene phosphite esters undergo reaction (9) with peroxy-radicals to form a phosphate and a phenoxy-radical. On the other hand, the phenoxy-radical can react with another peroxy-radical:



forming a peroxide, which, on decomposing at an elevated temperature into radicals, gives rise to chain branching.

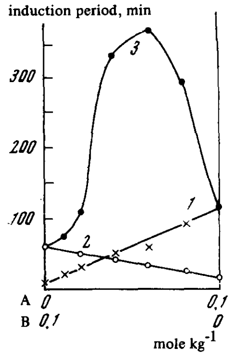


Figure 7. Variation of the induction period in the oxidation of polypropylene with the composition of a mixture of 2,4,6-tri-t-butylphenol (*A*) and iso-octyl diphenyl phosphite (*B*) (*3*) and with the concentrations of the components (*1* and *2*) at 200°C and P_{O_2} = 300 mmHg.

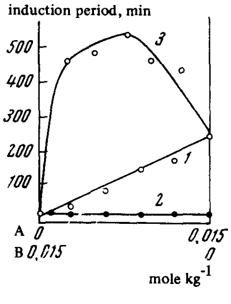


Figure 8. Variation of the induction period in the oxidation of polypropylene with the composition of a mixture of 2,2'-methylenebis-(6-t-butyl-4-methylphenol) (*A*) and iso-octyl diphenyl phosphite (*B*) (*3*) and with the concentrations of the components (*1* and *2*) at 200°C and P_{O_2} = 300 mmHg.

The different effects observed in the presence of bisphenols and monophenols can probably be explained by the different probabilities of the suppression of chain branching by these compounds. Bisphenols, which have two functional groups, are more likely to bind both radicals formed from the peroxide and thereby suppress chain branching, while monophenols can bind only one radical, the other continuing the chain propagation process.

This mechanism of the synergistic effect is consistent with the finding that it is a maximum at a high concentration of the bisphenol. However, for the final determination of the mechanism by which mixtures of screened *o*-phenylene phosphite esters with bisphenols act, it is necessary to investigate the elementary reactions of the peroxy-radical with these phosphites at an elevated temperature.

3. Mixtures of Inhibitors of Free Radical Processes

When mixtures of inhibitors of free radical processes inhibit only by linear termination of peroxy-radicals, they cannot exhibit a synergistic effect. However, such mixtures may have an antioxidant effect greater than the additive value in consequence of the hydrogen transfer reaction from the weaker inhibitor to the radical of the stronger inhibitor after the latter has given up its hydrogen to the peroxy-radical, according to the reaction

$$\dot{In}_1 + In_2H \rightarrow In_1H + \dot{In}_2 .$$

Such a reaction is possible, since even the least active inhibitor will then give rise to a resonance-stabilised radical. Reactions of this class have been observed between 2,4,6-tri-t-butylphenoxy-radicals and phenols, naphthols[61], and also 4-substituted phenols[62].

When the concentrations of both components are equal, the effectiveness of the mixture, which increases only by virtue of the hydrogen transfer reaction, cannot exceed the effectiveness of the strongest inhibitor at twice its concentration. Consequently this mechanism of the action of a mixture shows no synergistic effect. The mechanism shows that the concentration of the strong inhibitor component in the mixture should not alter in the oxidation process as long as the weaker inhibitor is not completely consumed.

Indeed, it has been shown[63] in the sensitised oxidation of ethylbenzene, that in the presence of β-naphthylphenylamine and 2,6-di-t-butylphenol at 60°C the concentration of the first compound remains constant and begins to fall only after the phenol has been completely consumed. It has also been shown[63] that the induction period is higher than the additive value, but does not exceed the value corresponding to the amine at the total inhibitor concentration.

Thus at a low oxidation temperature in the absence of chain branching, the interaction of inhibitors with the peroxide and of the inhibitor radicals with the hydrocarbon, i.e. in the absence of chain propagation reactions, the enhanced activity of the inhibitors is caused only by the transfer of hydrogen from the phenol to the amine.

In the oxidation of ethylbenzene at 120°C and in the presence of the same inhibitor, the authors observed a synergistic effect: the induction period for the mixture proved to be longer than that corresponding to the amine at the total inhibitor concentration[64]. At this temperature, the termination of peroxy-radicals by the inhibitor and the transfer of hydrogen from the phenol to the inhibitor radical may be accompanied by the decomposition of the hydroperoxide and chain propagation due to the reaction of the radical derived from the inhibitor (amine) with ethylbenzene: $\dot{In} + RH \rightarrow InH + \dot{R}$.

However, in the presence of the phenol, the chain propagation reaction is suppressed because of the lower activation energy for the reaction of the inhibitor radical with the phenol ($\dot{In} + PhOH \rightarrow InH + Ph\dot{O}$) than with ethylbenzene. Since chain propagation by the inhibitor radical sharply reduces the effectiveness of the inhibitor, suppression of this reaction does greatly enhance the effectiveness of the mixture. To establish the influence of the chain propagation reaction on the effectiveness of the mixture, a kinetic calculation was made on the branched chain mechanism of inhibited oxidation in the absence of the chain propagation reaction. The computer calculation showed that the suppression of the chain propagation reaction leads to the appearance of a synergistic effect. Nevertheless, it has been noted[6] that this effect can appear also due to the interaction of the hydroperoxide with the amine, evidently as a result of the suppression of chain branching.

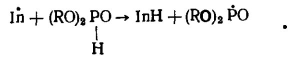
According to published work, many mixtures of free radical process inhibitors are more effective than would be expected from additivity, but until the publication of the studies described above a synergistic effect was not observed in any of the investigations.

The experimental observation of the synergistic effect and the theoretical explanation of its mechanism in mixtures of inhibitors of free radical processes opens up new prospects in the search for synergistic compositions.

The synergistic effect observed in the oxidation of alimentary fats and oils between phenols and certain organic and inorganic acids, which, while lacking antioxidant properties, nevertheless increased the effectiveness of the phenols, can also be accounted for by the hydrogen transfer reaction from the acid to the phenoxy-radical[65-67]. However, fairly strong acids such as phosphoric, succinic, and citric can decompose hydroperoxides catalytically without the formation of free radicals and thus suppress chain branching[68].

In a study of the combined action of phenols and dialkyl phosphites in the oxidation of a mineral oil it was shown that the effectiveness of phenols greatly increases although the activity of dialkyl phosphites is very low[69].

According to the authors, the enhancement of the activity of phenols is due to the reduction of the phenoxy-radical by the hydrogen of the phosphonic acid ester produced by the isomerisation of the dialkyl phosphite:



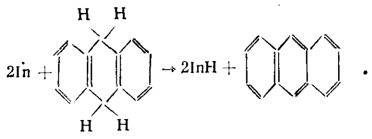
$$\dot{In} + (RO)_2\underset{\displaystyle H}{\underset{|}{P}}O \rightarrow InH + (RO)_2\dot{P}O .$$

This involves the formation of quadrivalent phosphorus. However, phosphites are known to decompose hydroperoxides and thereby suppress chain branching so that the synergistic effect of this mixture may be a consequence of both hydrogen transfer from the phosphonate ester to the phenoxy-radical and the suppression of chain branching. The reduction of the phenoxy-radical by the hydrogen of diethyl phosphite has been demonstrated using the ESR method[70]. It was also shown[70] that the concentration of phenoxy-radicals diminishes with increase in the concentration of diethyl phosphite. However, when the diethyl phosphite concentration is raised further, that of the radicals does not change, probably because of the formation of a phosphonate ester dimer.

A synergistic effect was also observed in the oxidation of a polyamide stabilised by naphthol and a diaryl phosphite[71] and in the oxidation of polypropylene in the presence of tri-t-butylphenol and *o*-phenylenephosphorous acid[37]. Thus, the synergistic effect observed in the oxidation of mineral oil, polyamide, and polypropylene in the presence of phenols and phosphonate esters is probably due to the hydrogen transfer reaction[70] and evidently the suppression of chain branching[46].

Apart from the mechanisms of the synergistic effect examined above, there can be yet another mechanism, which has been little investigated but which is important for the increased effectiveness of inhibitors and their mixtures at elevated temperatures.

The inhibitor radicals formed in the high-temperature inhibited oxidation initiate a new reaction chain by reacting with the substrate[64,72,73]; therefore, for example at temperatures above 250°C, inhibitors of free radical processes (phenols and amines) have only a weak inhibiting effect on the oxidation process. Initiation by the inhibitor radical may be sharply reduced, by adding to normal inhibitors or their synergistic compositions, compounds capable of combining with inhibitor free radicals, for example aromatic polymers with a system of conjugated bonds[24,74,75]. For this purpose, one can also use condensed aromatic compounds such as dihydroanthracene, which reacts with the inhibitor radical as follows:



The inhibitor radical is then reduced to the inhibitor molecule and dihydroanthracene is converted into anthracene, which is probably also capable of forming complexes with the radicals and thereby reducing their reactivity. However, dihydroanthracene may be oxidised by oxygen with formation of anthracene and $\dot{HO}_2$ radicals, which propagate the oxidation chain. Therefore the greatest effect should be shown by additives with a system of conjugated bonds, which do not initiate the oxidation reaction but are capable of inhibiting the chain propagation reaction. The study of inhibitors and their mixtures to which substances capable of binding inhibitor radicals have been added is probably important in solving the problem of stabilising polymers at a high temperature[74].

The effectiveness of a mixture of inhibitors changes when two components form a complex. Then the rate of reaction of the peroxy-radical with the complex may prove to be greater or smaller than that with any of the components. Moreover, in the reaction of the complex with the hydroperoxide there is a possibility of a decreased yield of free radicals. Thus the formation of complexes from the components may lead to either an increase and a decrease of their effectiveness. However, this mechanism of the action of mixtures has not been investigated. The effectiveness of inhibitor mixtures also changes when the components form a new chemical compound. It has been shown[76,77] that the oxidation of polyoxymethylene in the presence of α-naphthol and β-naphthylamine involves the interaction of the components with the formaldehyde formed, which leads to the formation of a new compound—1-(2-hydroxynaphthyl)-1-(2-aminonaphthyl)methane. It has been shown experimentally that this compound is more effective than any component present at the overall mixture concentration.

Table 2 lists the mechanisms of the action of inhibitor compositions examined together with their possible antioxidant effects. These effects of the mixtures evidently change when the components participate in processes other than the reactions quoted.

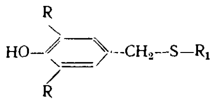
Table 2. Mechanism of the action of inhibitor compositions in the oxidation process in the presence of the reaction $In_1H + R\dot{O}_2 \rightarrow ROOH + \dot{In}_1$.

Type	Mechanism of action	Possible antioxidant effect	Refs.
Free-radical process inhibitor	$R\dot{O}_2 + In_2H \rightarrow \dot{In}_2 + ROOH$	additive effect	
Hydroperoxide decomposing agent	$ROOH + R'XR'' \rightarrow ROH + R'X(O)R''$	mutual enhancement of effectiveness by inhibitors (synergism)	15, 33, 46, 52, 53, 54
Hydrogen donor	$\dot{In}_1 + In_2H \rightarrow In_1H + \dot{In}_2$	enhancement of effectiveness (weak synergism)	63, 64
Radical acceptors. Polymers with conjugated bonds, condensed aromatic compounds	$\dot{In}_1 + A \rightarrow In_1 - A$	enhancement of effectiveness	24, 74
Complexones	$In_1H + In_2H \rightarrow In_1H - In_2H$	enhancement or decrease of effectiveness	
Chemical interaction between components	formation of a new compound	enhancement or decrease of effectiveness	76, 77

4. Polyfunctional Stabilisers (PFS)

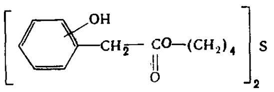
Polyfunctional stabilisers contain in their molecules several reactive groups capable of terminating chains and suppressing chain branching, i.e. capable of inhibiting individual elementary steps in a branched chain oxidation reaction. The application of polyfunctional stabilisers has a number of advantages compared with synergistic compositions, which usually consist of two components, one of which terminates the chain and the other decomposes the hydroperoxide with formation of stable molecules. Moreover, photostabilisers and deactivators of metals are introduced into these mixtures. In order to obtain the maximum synergistic effect, it is necessary to combine the components in appropriate proportions and mix them uniformly with the polymers, which requires complicated and laborious preliminary operations. Nor can one exclude the possibility of chemical interaction between the individual mixture components in the course of the high-temperature processing of the polymer, which may change their antioxidant activity.

All these disadvantages may be removed by employing universal polyfunctional stabilisers capable of inhibiting all the elementary steps in the oxidation and photodegradation. In recent years chemists have endeavoured to synthesise such ideal polyfunctional stabilisers. Among the known inhibitors, thiobisphenols should have polyfunctional properties (owing to the presence of the OH group and the sulphur atom), but their sulphur atoms are relatively inactive and therefore when they are mixed with sulphides they exhibit a synergistic effect[54]. Thioethers with the structure



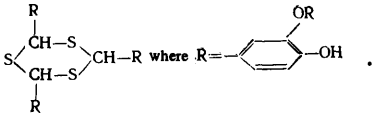
are regarded as the simplest polyfunctional stabilisers. Their effectiveness is higher than that of the corresponding phenols, but lower than that of the bisphenols[78,79].

Thioethers of aromatic hydroxy-carboxylic acids have a higher stabilising effect, for example:



and also mixed esters of two carboxylic acids containing sulphur or phosphorus atoms in the molecule[80].

Various heterocyclic compounds containing sulphur atoms in the ring are effective antioxidants for polyolefins, for example 2,4,6-tri(hydroxyphenyl)-1,3,5-trithianes[81-83]:



These compounds protect the polymer from oxidation and reduce the catalytic effect of multivalent metals. The effectiveness of aromatic derivatives of 1,3,5-trithianes is much higher than that of phenolic antioxidants and depends strongly on the substituents in the benzene ring. Trithianes with an alkoxy-group attached to the ring in the *ortho*-position relative to the hydroxyl show the best antioxidant properties. The addition of a sulphide is stated not to increase the antioxidant effectiveness of trithianes[83], but this needs to be verified.

In recent years reports have appeared on polyfunctional stabilisers which are active thermo- and photo-stabilisers. These data show that the most effective photo- and thermo-stabilisers are phosphorodithioic acid salts of various multivalent metals[84]. Complex chelate quinoxaline compounds appear to be particularly effective photostabilisers[85]. The study of the mechanism and effectiveness of the action of polyfunctional stabilisers constitutes a new field and, as shown by the first results, may lead to the discovery of more effective inhibitors than those known at present.

In conclusion we may note that the stabilisation of polymers at high temperatures still remains an unsolved problem. Possibly one of the ways for its solution will be the application of polyfunctional stabilisers resistant to oxidation by oxygen and capable of chain termination and suppression of chain branching.

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Institute of Chemical Physics,
USSR Academy of Sciences,
Moscow

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Frost Resistance of Polymers

V.I.Popov and V.A.Voskresenskii

Papers by Soviet and foreign authors on the problem of frost resistance are surveyed, and definitions are suggested for the concepts of the technical and the theoretical frost resistance of polymers. Existing qualitative methods for determining the frost resistance of various types of polymeric materials are discussed, together with quantitative methods proposed by Soviet authors, in particular those based on the thermomechanical method of investigation. Data are reported on the dependence of frost resistance on the previous history of the production and processing of polymers, the nature and duration of aging, the action of plasticisers, fillers, etc. The bibliography contains 91 references.

CONTENTS

1. History of Problem

The value of polymers in technology is continually increasing, and in the near future the volume of the production and consumption of polymers will exceed that of the manufacture and use of metals and alloys. In spite of their many valuable properties, however, polymers are not devoid of defects in several respects, one being the partial or complete loss of working properties at low temperatures, i.e. limited frost resistance. The experimental data show that the mechanical, dielectric, relaxation, and other properties of linear polymers vary substantially with temperature. Little work has been done on the behaviour of polymers at low temperatures, which is frequently an obstacle to their use in goods operating in the cold.

The tendency of polymers to crack when deformed below the brittle point is explained by the growth of stresses resulting from the retardation of processes in the macromolecular chains which lead to stress relaxation. It is therefore concluded that the frost resistance of polymers may be improved by the introduction of plasticisers[1] and by suitable chemical modification[2], since this enables the rate of relaxation processes to be increased and the development of cracks to be largely suppressed.

The ability of polymers themselves to retain their flexibility and elasticity at low temperatures is usually the main prerequisite for high frost resistance in polymeric materials based on them[2-5].

Aleksandrov[6] defines frost resistance as the ability of polymers to maintain their mechanical and other properties at low temperatures. A quantitative index of frost resistance is the temperature below which articles made of the given type of polymeric material disintegrate or suffer a sharp diminution in their physicomechanical properties under the influence of specified deforming forces. Brittle fracture of polymers thus begins with the finest inhomogeneities (microcracks), which are foci of considerable overstressing. When the overstresses become equal to the tensile strength of the material, a crack begins to grow at these sites, and leads to brittle fracture of the specimen at a specified frequency of deformation[7]. A roughly similar definition of the frost resistance of polymers is given in the relevant Soviet Standard[8].

Chernaya and Vol'chenko[9] and also Tager[10] regard the workability of a polymer at a definite low temperature limit of operation for a specified time as the main criterion of frost resistance. Sedlis[11] defines frost resistance as the ability of a polymer to retain flexibility and elasticity at low temperatures. Tinius[12] characterises frost resistance by the temperature at which specimens of the polymer become brittle with a given temperature–time operating schedule.

A provisional Soviet Standard for artificial leather and for film materials[13] notes that the temperature of frost resistance serves only for the comparison of these materials under given test conditions: it does not determine the lower temperature limit for goods to function, since this limit is determined by the actual conditions of operation.

In fact existing definitions of frost resistance are qualitative and applied in character, and to some extent serve merely as an indication of the technical (relative) frost resistance of a given polymeric material.

In addition to the concept of technical frost resistance it is useful to introduce that of the theoretical frost resistance, which should provide a more accurate measure of the true frost resistance of a polymer. The definition of frost resistance as the temperature threshold for the occurrence of segmental mobility in polymer chains, given by Kargin and Shteding[14], may correspond in considerable measure to the concept of theoretical frost resistance. In this case a thermomechanical method of investigation enabled the authors to find a boundary temperature between two zones—that in which segmental mobility appeared in practice and that in which it was absent—which was interpreted as the temperature of frost resistance.

The temperature of technical frost resistance of a polymer should obviously always lie somewhat above the level of theoretical frost resistance, since structural defects, foreign inclusions, internal and surface cracks, and residual stresses present in the material will promote the appearance of brittleness and disintegration of the material at higher temperatures than that at which segmental mobility disappears in the chain macromolecules. In view of the above, technical and theoretical frost resistance can obviously be defined as follows.

Technical frost resistance must be regarded as the ability of a polymeric material to maintain its operating properties at low temperatures for a certain length of time, i.e. to retain the ability to develop specified deformations or withstand disintegration.

Theoretical frost resistance is the lower temperature limit for the start of segmental mobility of the macromolecular chains, i.e. at which minute relaxation processes appear in the polymer for given rates of action of deforming forces of given magnitude, which prevent fracture of the polymer specimens.

2. Methods for Determination of Frost Resistance

Because of the very broad technical importance of frost resistance and the great difference in the conditions of operation of polymers a large number of test methods have been proposed. These methods differ significantly in the character, degree, and rate of deformation of the specimens, so that data on frost resistance obtained for the same material by different methods often differ considerably and are difficult to compare. The frost resistance of polymers is determined mainly from test results obtained by impact, single and multiple flexing, stretching, compression, torsion, etc.

Existing methods of testing polymers for frost resistance have been divided[15] into those based on determining the temperature at which a sample undergoes brittle fracture under the influence of a certain type of load (mostly impact) and those in which the temperature is determined at which a specimen under load acquires a predetermined deformation. The former type are most often used, and can usefully be further divided according to the type of load.

In an early form of apparatus proposed[16,17] for impact tests at low temperatures a weight of ~200 g fell on the frozen test specimen from different controlled heights. In an analogous instrument the weight was dropped from a constant height, but there were separate chambers for cooling and for testing the specimen. The limiting frost resistance of the polymer specimen was assessed from the appearance of cracks.

In test methods for rubbers[18] the brittle point is determined by bending the cooled specimen, fixed horizontally at one end, by the application of an impulsive load to the free end. The temperature at which cracks become visible to the naked eye or at which the specimen fractures is regarded as the brittle point.

In a study of the plasticising action on poly(vinyl chloride) of certain low-molecular-weight substances the frost resistance was determined[19] in a pendulum instrument by the impact on the frozen specimen of a weight of 500 g falling from a height of 300 mm. Specimens were regarded as withstanding the test if after impact no cracks were visible under a lens giving tenfold magnification.

In England polymeric film-forming materials are tested for frost resistance at low temperatures by Williams' method[20], in which a specimen 0.58 mm thick, made up of two halves, is frozen and then subjected to impact from a hammer driven by a spring.

A review[21] of existing methods and equipment for testing polymers for frost resistance divides the methods into those in which specimens may undergo disintegration and those in which the modulus of elasticity is measured. Such tests of films for frost resistance are made in a special impact apparatus.

The frost resistance of a new modification of polypropylene (poprolin), obtained by plasticising with dioctyl sebacate and applying a cross-linking agent to the polymer, was determined[22] from the brittle point at which 50% of the test specimens break down. A specimen was cooled to a definite temperature, and bent to a specified deflection by application of an impact load.

An impact method of loading has been used[23] to determine the frost resistance of films at temperatures from −73°C and above. In a test specimens were mounted on a frame, brought to the specified temperature, and punctured by a loaded rod moving at different speeds (from 14 to 38100 cm min^{-1}) depending on the test conditions. The load necessary to pierce the film, the corresponding deformation, the critical speed, and the brittleness of the specimens were determined. The results were rather high compared with values obtained by other methods.

Standards adopted in several countries for measuring frost resistance are based on determining impact strength at low temperatures: i.e. tests are made in which a specimen is subjected under standard conditions to the action of a falling weight of definite size. This technique is described, for example, in a Dutch Standard[24] for cables having poly(vinyl chloride) insulation and in other standards[25,26]. Turner[27] suggested a method for determining the frost resistance of polymers which had several advantages over the standard method[25]. A rapid method for determining the brittleness of rubber at low temperatures has also been suggested[28].

A German patent[29] proposed a special method for testing cable insulation. A piece of wire 1.5 m long is covered with the insulation and slowly cooled. After every 5 deg the wire is swung sharply (to imitate a whiplash). The frost-resistance temperature of the polymeric coating is then determined from the appearance of cracks.

Sorokobatkina[30] suggested apparatus for determining frost resistance from the brittle point in which the main variables—temperature and rate and magnitude of deformation—could be controlled.

There are several methods other than those involving impact for testing the frost resistance of polymers. For example, a Soviet standard[31] uses two ways—bending a specimen (fixed horizontally at one end) a specified amount, and compressing a loop of a polymer film 0.5 mm thick—for determining the brittle point. The frost resistance is taken to be the temperature at which 50% of the specimens tested yield cracks or break down at the specified deformation.

The principle of flexing a film through 180° is used also in testing cable rubber and resin on an ergometer[32] and in a small bath[33].

In the test for leathercloth[8] the specimen is not only bent through 180° but also smoothed out by weights totalling 1 kg. In another method[8] a loop of the film is pulled through a slit (1 mm wider than twice the thickness of the film) at 100 mm min^{-1}. The frost resistance is found from the load required to draw the loop through the slit at a certain temperature without rupture of the specimen or the appearance of cracks.

Schulz and Mehnert[34] suggest that the frost resistance of a film can be measured by the temperature at which a specimen in the form of a loop of precisely defined dimensions can still be pulled without breaking, through a slit of standard size, by a sharp jerk.

A method of testing frost resistance is often used in which a sample of the polymeric film is wound in the form of a tape at a specified rate on a spindle of definite diameter, without the appearance of cracks or breaks. This method is known as "cold bending". A British standard[35] provides that a poly(vinyl chloride) plastic tape 1.27 mm thick should be wound on a 0.5-cm spindle at a rate of 1 rev/sec. This method is widely used for testing cable insulation. The diameter of the spindle can be varied according to the thickness of the specimen, which enables more or less comparable results to be obtained when different samples of the same material are tested. Another test method is also given: the specimen is cooled to the specified temperature, and subjected to a constant load (105.5 kg cm^{-2}) for 30 s, after which the elongation of the specimen is measured.

A method of testing rubber for frost resistance is also based on comparing the elongation of a specimen at normal and low temperatures[36]. In this case a coefficient of frost resistance is obtained by dividing the elongation at normal temperature under a definite load into the elongation of the working part of the specimen cooled to a particular temperature.

Sedlis and Lel'chuk[37,38] suggested that the frost resistance should be measured by the temperature at which a specimen of a polymer film extends by a definite amount under the influence of a load for a controlled period of time. These workers suggested both a method for determining frost resistance and empirical formulae for calculating this temperature.

In another method[39] a sample of artificial leather was kept in a cold chamber for 1 h, after which its bending strength was tested in a Herfeld apparatus. Hofman[40] pointed out that a single flexing of a sample of artificial leather will lead to erroneous conclusions on frost resistance, so that more prolonged bending tests are necessary.

The frost resistance of polymer films can be determined also from the number of double flexings required for the appearance of cracks or destruction of the specimen[41]. Tests by this method showed that the frost resistance of polymer films is increased by raising the plasticiser content and increasing the extent of gel formation.

Wormald[42] used a specially designed apparatus to determine the number of flexings (external diameter of curved specimen six times the thickness) leading to destruction of a poly(vinyl chloride) film at a specified temperature, as a function of the type and content of plasticiser. This method established that tritolyl phosphate was not effective in the production of frost-resistant plastics. It was concluded that the frost resistance is improved by partial replacement of dioctyl phthalate in the film by a linear plasticiser—dioctyl sebacate.

Several papers recommend the use of compressive forces for determining the frost resistance of plastics. For rubber under compression the method[43] consists in measuring the deformation of specimens in a special instrument at normal temperature and comparing the results with the deformation obtained under the same applied load at low temperatures. The temperature at which the frost-resistance coefficient of the rubber is 0.1 is adopted as the index of frost resistance. This method is applicable only to block specimens: to determine the frost resistance of film materials a specimen in the form of a cylinder (a roll of film 20–200 μm thick) can be deformed under a definite compressive load[44]. The deformed sample is removed from the chamber and inspected with the naked eye. The presence of cracks is the criterion from which the frost resistance of the material is assessed.

Several workers[45] recommend testing artificial leather for frost resistance in an attachment to a Schopper cold chamber. It is characterised by the load required to compress a cooled specimen of the film in the form of a tube (of diameter 65 mm and length 100 mm) fixed in special clamps in a deformometer.

Since fracture of a material is a more critical indication than a temporary increase in rigidity in the cold, tests of frost resistance in which the brittle point is determined are employed more often than methods involving determination of the limiting "temperature of cold twisting"[46]. The method consists in measuring the angle of rotation of the upper portion of a standard specimen, firmly attached to a movable upper clamp, under the action of a definite rotating moment about a fixed lower clamp, and hence calculating the modulus of elasticity at a specified temperature. These tests yield the temperature at which a standard modulus of rigidity is reached. When published results are considered, however, it must be remembered that in many cases different values are used for the standard modulus of rigidity. The frost resistance characterised by the torsional modulus is determined according to the standards.[47,48]

However, a modified method was used in several investigations[50]. Although the tests were made according to the standard[48], the frost resistance was measured by the temperature at which the specimen breaks down when twisted through 360°, not 200°. The frost resistance was shown to have considerably diminished in specimens which had aged under natural conditions.

Hayes and Lannon[51] proposed a method for determining the flexibility of plasticised poly(vinyl chloride) by measuring the angles through which specimens were twisted by a definite twisting moment (5.68×10^5 dyn cm). The frost resistance was characterised by the temperature which a specimen should have for the angle of twist produced by the given moment to be 200°.

Study of frost resistance from the increase in rigidity has established[52] that the thickness and linear dimensions of specimens influence the rigidity of film materials.

Since the flexibility of a polymer can be measured by the apparent modulus of elasticity in bending and twisting tests, and since a linear relation exists between the plasticiser concentration and the temperature at which a specified Young's modulus is reached, it is possible to find[53] the temperature at which a specified modulus will be achieved with a given plasticiser content: i.e. a qualitative determination of frost resistance can be made by this method.

Bartenev and Zuev[54] studied the relation between the frost-resistance coefficient and the maximum mechanical losses of rubberlike polymers during multiple deformations in the region of vitrification (the coefficient of frost resistance was defined[55,56] as the ratio of the amplitude of deformation at the specified temperature to the amplitude of vibration at +20°C).

It is evident from the above discussion that methods of determining frost resistance employed in various branches of technology are qualitative in character, insensitive, cumbersome, laborious, and applicable only to quite specific conditions of use of the articles made from polymers. The type of deforming force, its rate of application, and other test conditions are chosen purely empirically. The result produced by the deforming force—the appearance of cracks or other defects in the specimens—is usually determined visually. According to the above methods specimens are brought to destruction, which is not always possible or advisable.

Several new methods have recently been proposed for studying the frost resistance of polymers. Kanavets and Yartsev[57] have suggested adopting the reversible elastic deformation on stretching, characteristic of the intact internal structure of the material, as index of frost resistance. In this case the temperature of frost resistance is found from the plot of percentage elastic deformation against temperature.

Shteding and Kargin[14] have shown the theoretical possibility of determining the frost resistance of polymers by means of the thermomechanical deformation—temperature characteristics obtained by the uniaxial stretching of specimens in a special instrument, a deformometer[58]. As noted above, this method involves finding the temperature of the boundary between the zone in which segmental mobility of the chain macromolecules is absent and the zone in which it is present, an external indication of this being the observed appearance of a minimum deformation. This temperature was taken to be an index of the frost resistance of polymeric film materials. The proposed method represents a considerable advance in determining frost resistance, but it necessitates the construction of a special and quite complicated instrument—the deformometer.

Kargin and Shteding's suggested principle has been used[59,60] to determine the frost resistance of polymer films, but the instrument was a specially adapted version of apparatus used in industry to determine the frost resistance of rubbers[36], certain changes and additions being introduced into its design and especially into the method of measurement[59], which improved the accuracy and permitted the use of an existing manufactured instrument. With our proposed modifications[60] to the Kargin–Shteding method not only can the absolute frost resistance of polymeric films be determined more accurately but also the effect on polymers of various external factors (type and amount of plasticiser, processing schedule, aging, etc.) can be followed quantitatively. The experimental results correlate well with those obtained by other physical methods of investigation, e.g. thermomechanical and rheological.

3. Dependence of the Frost Resistance of Polymers on Various Factors

An early qualitative observation[11] was that the frost resistance of polymeric materials depends primarily on the physicomechanical parameters of the polymers themselves. The higher the flexibility and extensibility of the polymers at room temperature the higher is usually the frost resistance of materials based on them. A high degree of polymerisation and great uniformity of molecular weight, a low content of fractions of low molecular weight, and the necessary flexibility of the macromolecular chains also favour the production of frost-resistant polymeric materials.

The most important procedures for improving frost resistance are plasticisation with polymeric plasticisers and with low-molecular-weight plasticisers for amorphous polymers, and copolymerisation and modification for crystalline polymers, i.e. changing the properties of the polymers by chemical reaction with modifiers of low molecular weight[9], e.g. by processing mixtures together on rolls, in mixers, etc. Simultaneous enhancement of frost resistance and lowering of the glass point of crystalline polymers usually requires the introduction of mixtures of plasticisers and modifiers or the use of copolymerisation followed by plasticisation of the resulting copolymers. The frost resistance of polymers depends very substantially on the content of plasticisers[61] and obviously on their chemical structure.

Nevertheless, Bauer and Cox[62] who examined the main classes of plasticisers usually employed to increase the elasticity of vinyl polymers at low temperatures, detected no dependence of efficiency on the type of plasticiser (at contents below 50%), and suggested that plasticisers should be selected only on the basis of their compatibility with the polymer, incombustibility, low volatility, etc. These workers found that mixtures of plasticisers possess no synergic action, but this is disproved by later work: the frost resistance of poly(vinyl chloride) cable insulation can be improved appreciably[63] by the use of mixtures of plasticisers—a monoester of low molecular weight and a polyester of high molecular weight, obtained from phthalic anhydride, triethylene glycol, sebacic acid, and an aliphatic alcohol.

Experiments by other workers[19,64] have shown that the frost resistance of samples of plasticised poly(vinyl chloride) depends substantially on the chemical structure of the plasticisers. With equimolecular contents of tributyl phosphate and tritolyl phosphate in the polymer, for example, films with the former plasticiser, which has linear side-chains, are the more frost-resistant.

The use of a plasticiser having a low freezing point does not always guarantee improved frost resistance in a polymer[65]. For example, the frost resistance of a p.v.c. film plasticised with dioctyl adipate (f.p. −75°C) is lower than that of films having an equimolecular content of dioctyl sebacate (f.p. −48°C).

Forman[66] showed that non-volatile plasticisers of higher viscosity, higher boiling point, and low vapour pressure exert a greater plasticising effect on neoprene rubbers at low temperatures.

Fedotova and Karp[67] used a mixture of a gel-forming plasticiser and a grease to improve the frost resistance of plasticised p.v.c.

Kozlov et al.[68] discovered an interesting phenomenon in a study of the action of mixed plasticisers on polystyrene. A mixture of a plasticiser of low molecular weight (phenyltributoxysilane) and an oligomer (polydiphenyloxysilane) gives a significant synergic plasticising effect: a mixture of such plasticisers produces a considerably greater shift in the glass and flow points.

Plasticisers of different types are obtained depending on the presence of polarisable groups[69]: those containing polar and aliphatic groups (e.g. trioctyl phosphate) are not readily compatible with poly(vinyl chloride), but raise the frost resistance of the polymer substantially; those of polar–aromatic structure (tritolyl phosphate) form gels readily with p.v.c., but improve its frost resistance only very slightly. The frost-resistant plasticisers which are normally widely employed[15,70–73] are diesters of aliphatic dicarboxylic acids, such as adipic, sebacic, etc.

The quantity of frost-resistant plasticisers in a composition is determined by the elasticity which the plasticised material should possess at low temperatures. With a given total quantity of added plasticiser a linear relation exists between the quantity in the mixture and the softness of the poly(vinyl chloride) plastic, the limiting temperature of "cold twisting", and the logarithm of the bulk resistance.

Plasticisers prepared from linear alcohols[74] have recently become widely used, as also have epoxystearates[15], for the production of frost-resistant compositions. Polymers were shown[75] to acquire the greatest frost resistance when esters of organic acids containing 6–8 carbon atoms in the chain were used as plasticisers. Esters containing a larger number of carbon atoms in the chain are not so compatible with polymers and tend to freeze out of the compositions at low temperatures. The degree of branching in the structure of the initial alcohol also has a great effect on the frost resistance of the polymer material, lowering it substantially[76]. For example, the frost resistance of p.v.c. diminished in the sequence—*n*-octyl > isohexyl > 2-ethylhexyl > iso-octyl > 2-ethyl-2-methylpentyl—on the introduction of different esters of phthalic acid with alcohols containing eight carbon atoms. The presence of several aromatic rings or polar groups in phthalic esters has an adverse effect on the frost resistance of the plasticised polymer[77]. Isophthalic diesters confer high frost resistance on p.v.c.[78]. Although phthalates are widely used to plasticise p.v.c., they are not sufficiently frost-resistant, and are also flammable[79]. Phosphates having aromatic side-chains are characterised by low flammability but low frost resistance. Linear plasticisers—sebacates and adipates—confer fairly high frost resistance on p.v.c., but are flammable. To obtain frost-resistant polymeric materials, even in this case it is advisable to use mixtures of plasticisers, including chloroalkanes and other halogenated compounds. The frost resistance of p.v.c. containing nitrophthalic esters is higher than with equivalent molar quantities of phthalates.

Fillers and pigments usually lower the frost resistance of plastics[11,42,81,82] and require additional quantities of plasticisers. From an examination of the viscoelastic properties of poly(vinyl chloride) plasticised with tritolyl phosphate and dioctyl adipate, however, Eirich has shown[83] that small amounts of a very finely disperse limestone filler act as an additional plasticiser, somewhat lowering the moduli and increasing the relative elongation under tension.

The frost resistance of polymers is improved by orientation and by preliminary drawing. Aleksandrov[6] notes that highly oriented polymers retain their flexibility at temperatures several tens of degrees below the glass point. Drawn poly(vinyl chloride) acquires flexibility which varies little with fall in temperature[11]. The effect of drawing is greater the lower the plasticiser content. The greatest effect was achieved by combining a frost-resistant mixture with a softener and mechanical drawing. Several other workers[84,19] have observed an improvement in frost resistance on drawing.

Orientation is especially valuable in the manufacture of films. Compared with unoriented p.v.c. films, oriented films possess superior mechanical properties and good frost resistance[85,86].

Several workers have established[87] that atmospheric aging influences the temperature of impact brittleness more than other mechanical properties. Atmospheric conditions have a greater effect on the frost resistance of films plasticised with a single plasticiser the greater the plasticiser content. All methods aimed at stabilising polymers usually maintain also the frost resistance of materials based on them. On the whole, however, insufficient study has been made of the variation in the frost resistance of polymers during aging.

The increase in the frost resistance of linear polymers due to the introduction of a sufficient quantity of gel-forming plasticisers is usually accompanied by a decrease in strength. In some cases, however, the frost resistance of materials can be enhanced with a simultaneous increase in strength by partial "cross-linking" of the polymers[88,89].

Kargin et al.[90] have established that several properties of polymers depend on the character of the supermolecular secondary structures. Conferring the optimum structure on polymers[91] will probably enable their physical properties to be influenced, including the frost resistance of materials obtained from them. Such investigations would be of great scientific interest.

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Department of Plastics, Kazan
Institute of Civil Engineering

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Advances in the Chemistry of Adamantane

V.V.Sevost'yanova, M.M.Krayushkin, and A.G.Yurchenko

The review deals with the latest data on the chemistry of adamantane and its nearest homologues—noradamantane and homoadamantane. A systematic account is given of the methods for the preparation of adamantane derivatives. The reactivities of the bridgehead and bridge sites in the adamantane structure have been considered in detail.
The bibliography includes 192 references.

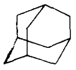
CONTENTS

I. INTRODUCTION

In the last two decades there has been an increase of interest in the chemistry of skeletal compounds. Adamantane occupies a special place among them—it was the first hydrocarbon which proved to have a diamond-like structure and it has in fact served as a touchstone for the investigation of the chemical and physicochemical properties of substances of this type. In the 1960's several reviews on the chemistry of polyhedral compounds were published[1-6].

The number of reports on the chemistry of adamantane increases sharply each year. In the last 2–3 years interesting and fundamentally new methods for synthesising adamantane and its derivatives have been developed. There has been an increase of interest in adamantane derivatives as biologically active substances.

The aim of the present review is to give a general account of the latest data on the chemistry of adamantane(I) and its nearest homologues—noradamantane (II) and homoadamantane (III).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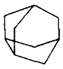
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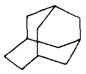
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On the basis of quantitative physicochemical data for adamantane and their comparison with data for other carbocyclic compounds, an attempt is made to estimate quantitatively the characteristics of the chemical behaviour of adamantane and to determine its position in the series of other cyclic systems.

Heteroadamantanes are not considered in the review; as far as possible, the literature up to July 1969 is included.

II. SYNTHESIS OF THE ADAMANTANE STRUCTURE

1. Synthesis of Adamantane by the Isomerisation of Organic Compounds of Various Classes

The range of compounds capable of isomerisation to the adamantane structure has been extended so much that the term "adamantisation"[7] now appears quite natural and valid. While initially polycyclic perhydroaromatic hydrocarbons containing ten and more carbon atoms were subjected to adamantisation[8-11], nowadays a much wider range of compounds, including derivatives with different functional groups, has been investigated in this reaction. The isomerisation of cholesterol, cholestane, abietic acid, cedrene, caryophyllin, cyclohexane, squalene, squalane, and dodecane leads to the formation of a mixture of alkyladamantanes in 2–45% yield[12]. The reaction is carried out under pressure in the presence of aluminium halides at 110–130°C for 2–5 days. The solvents employed are cyclohexane and carbon disulphide or the reaction is carried out without a solvent. It is interesting to note that adamantane itself has not been detected in the isomerisation products—the main products were 1,3,5,7-tetramethyl-, 1,3,5-trimethyl-, and 1,3-dimethyl-adamantanes; 1-methyl- and 3-ethyl-1-methyl-adamantanes were isolated only in small amounts.

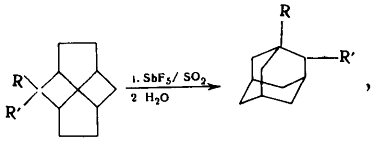
Possibly the above study will serve as the starting point of the search for industrial methods for the synthesis of polyalkyladamantanes. The isomerisation of cedrane[12,13] is already the best method for the synthesis of 7-ethyl-1,3,5-trimethyladamantane.

1,3-Dimethyladamantane is formed in the isomerisation of 1-ethyladamantane[14] and *endo*- and *exo*-2,2-dimethyltetrahydrodicyclopentadiene[15] in the presence of aluminium chloride.

An effective isomerisation catalyst proposed by Robinson[11] consists of a mixture of t-butyl bromide and aluminium bromide; the catalyst is employed in the form of a suspension in the hydrocarbon to be isomerised.

Schneider et al.[16] made a detailed study of the conversion of a mixture of isomeric C_{14} perhydroanthracenes and perhydrophenanthrenes into the adamantane system. The experimental data convincingly show that alkyladamantanes, particularly those substituted at the nodal sites (methyladamantanes), are stable final isomerisation products. Careful calculations by the authors of the enthalpies and entropies of the initial hydrocarbons and various products of their skeletal isomerisation showed that adamantane homologues are thermodynamically the most stable isomers. For example, in the isomerisation of perhydrophenanthrene four carbon atoms are "squeezed" out of the ring structure and the spherical 1,3,5,7-tetramethyladamantane, with the lowest energy among all the isomers investigated, is formed.

Twistane and several of its derivatives are very easily adamantised[7]. Apart from Lewis acids, SbF_5 or an SbF_5/SO_2 mixture were investigated as catalysts; the reaction was carried out at -80°C for 30 min:

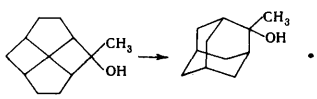


(IVa, b)

where R = R' = H in (IVa) and R = H and R' = OH in (IVb).

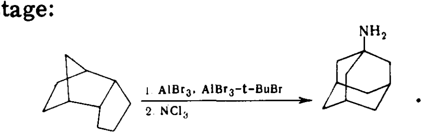
The transition from the twistane structure to the adamantane structure, which includes the "untwisting" of one methylene bridge, takes place via the initial formation of a cation. Experiments with deuterated compounds showed that the removal of hydrogen takes place during the rearrangement and the adamantyl cation formed is stable in relation to hydrogen exchange.

2-Methyl-2-adamantanol was obtained under the same conditions in the isomerisation of 2-methyl-2-twistanol (V):



(V)

The recently developed method for the synthesis of 1-aminoadamantane from tricyclo[5,2,1,$0^{2,6}$]decane (VI)[17,18] undoubtedly merits attention. The isomerisation and amination with nitrogen trichloride may be carried out in a single stage:



(VI)

The above reaction is interesting because it made it possible for the first time to introduce a functional group in the isomerisation process and to obtain a high yield of 1-aminoadamantane (amantidine), which is now in the stage of comprehensive clinical tests.

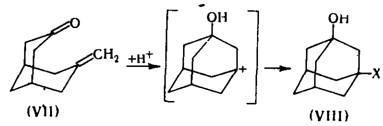
Thus the isomerisation conditions developed at the present time permit the synthesis with fairly high yields of adamantane, its homologues, and certain functional derivatives from a wide range of organic compounds.

All these studies are of undoubted theoretical interest also in another connection; they throw light on the origin of skeletal and in particular adamantane compounds in petroleum[4,19]. A number of studies have been made on the development of methods for the isolation of adamantane and its homologues from petroleum[20-22].

2. Synthesis of the Adamantane Nucleus from Bicyclic Systems.

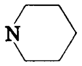
The greatest number of studies have been made on the synthesis of adamantane derivatives from compounds containing the bicyclo[3,3,1]nonane system. Although the methods for the synthesis of bicyclo[3,3,1]nonane derivatives as a rule involve many stages, they make it possible to obtain adamantane derivatives with substituents which are difficult to introduce by direct procedures.

Alkaline hydrolysis of (3-bromo-1-adamantyl)urethane, carried out by Stetter and coworkers[23], is accompanied by fragmentation which results in the formation of 3-methylenebicyclo[3,3,1]-7-nonanone (VII). Cyclisation of this compound[24], which is a modification of the Prins reaction, takes place in an acid medium with the initial formation of the 3-hydroxy-1-adamantylcarbonium ion, capable of further addition with formation of compound (VIII):



(VII) (VIII)

where X = OH, OC_2H_5, SC_2H_5, Cl, $NHCOCH_3$, NH_2, or



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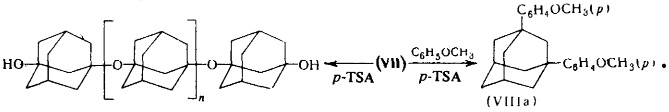
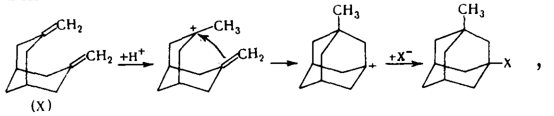
Compound (VII) undergoes ring closure to adamantane not only in an acid medium but also in the reaction with ammonia and amines (piperidine). The authors suggest that in this case the reaction initially involves the carbonyl group and that on heating a carbonium ion is formed, which subsequently undergoes further ring closure to adamantane[24].

When (VII) is heated with anisole, (VIIIa) is readily formed and heating of (VII) in a solvent (benzene, chlorobenzene, or carbon tetrachloride) leads to the formation of the polyester (IX); both reactions are catalysed by *p*-toluenesulphonic acid (*p*-TSA)[24]:

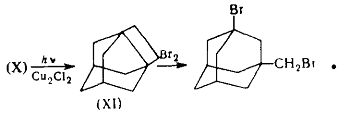


3,7-Dimethylenebicyclo[3,3,1]nonane (X), which undergoes ring closure to adamantane derivatives under the action of electrophilic reagents[25,26], is formed from (VII) by the Wittig reaction. The conversion of (X) into adamantane derivatives undoubtedly involves an ionic mechanism:

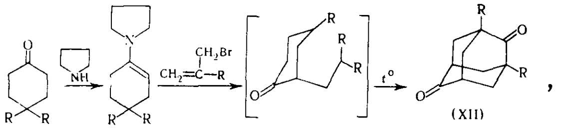


where X = Cl, Br, I, OH, OCH_3, $NHCOCH_3$, or *p*-$C_6H_4OCH_3$.

Photoinitiation of the cyclisation of (X)[27] leads to the formation of tetracyclo[$4,3,1,1^{4,8},0^{1,4}$] undecane (XI), a highly strained compound, which on refluxing in bromine combines with one mole of the latter:

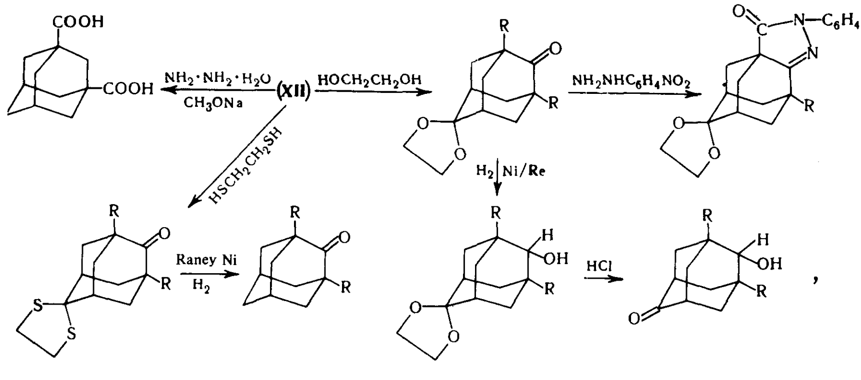


The recently developed method for the synthesis of the diethyl ester of 2,6-dioxa-adamantane-1,3-dicarboxylic acid (XII) is attractive because of the ready availability of the starting material, high yields at all stages, and the possibility of obtaining polysubstituted adamantanes[28,29]:



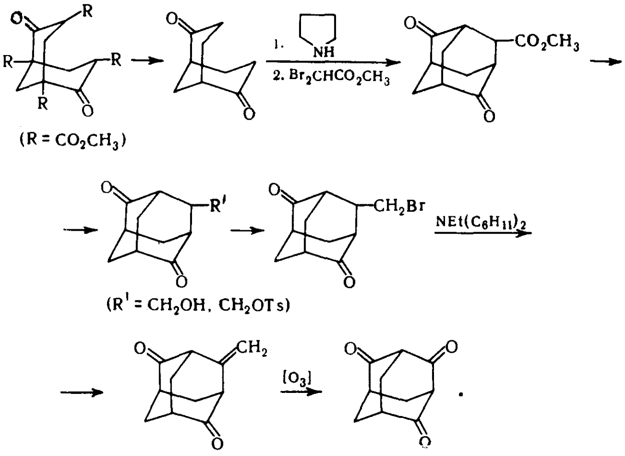
where R = $CO_2C_2H_5$.

Starting from compound (XII), the authors carried out the following series of reactions[29]:

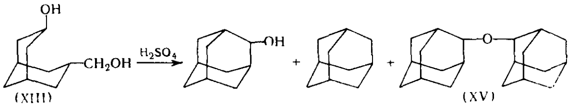


where R = $CO_2C_2H_5$.

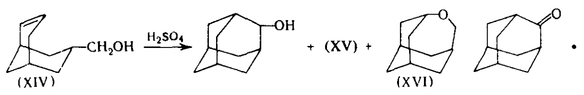
The methyl ester of 2,6-dioxoadamantane-4-carboxylic acid was obtained from Meerwein's ester and some of its reactions have been investigated[30]:



In contrast to the cyclisation of 3,7-disubstituted bicyclo[3,3,1]nonanes, which leads to the formation of 1,3-disubstituted adamantanes, the cyclisation of 3-hydroxymethylbicyclo[3,3,1]-7-nonanol (XIII) and 3-hydroxymethylbicyclo[3,3,1]non-2-ene (XIV) in the presence of sulphuric acid gives 2-monosubstituted adamantanes[31]. On treatment with 48% sulphuric acid in dioxan, a mixture of 2-hydroxyadamantane (39%), adamantane (17%), and 2-adamantyl ether (XV) (26%) is formed from (XIII):

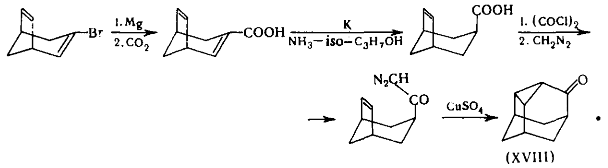


The cyclisation of (XIV) under the same conditions leads to the formation of 2-hydroxyadamantane (80%), small amounts of (XV), 2-oxatricyclo[$4,3,1,1^{4,8}$]undecane (XVI) and adamantanone:



The idea of the possible synthesis of adamantane derivatives by the ring closure in the 3- and 7-positions of bicyclo[3,3,1]nonane was already put forward in the first studies on the synthesis of the adamantane nucleus. The novel feature of the studies quoted above consists in the fact that the adamantane system is formed as a result of intramolecular condensation; a methylene bridge is formed from the carbon atom already present in the bicyclo[3,3,1]nonane ring.

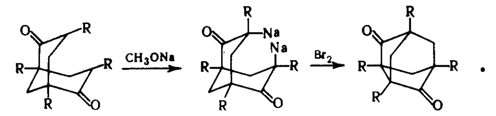
An interesting scheme for the synthesis of the adamantane structure was recently proposed by Baldwin and Foglesong[32]. They started with 3-bromobicyclo[3,2,1]-octa-2,6-diene (XVII), which was converted into 8,9-dehydro-2-adamantanone (XVIII) by the mechanism below:



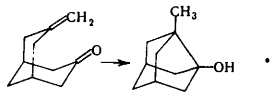
III. SYNTHESIS OF NEAREST HOMOLOGUES OF ADAMANTANE.

In this review we are considering only two nearest homologues of adamantane: tricyclo[3,3,1,0^{3,7}]nonane (noradamantane) and tricyclo[4^{3},1,1^{3,8}]undecane (homoadamantane).

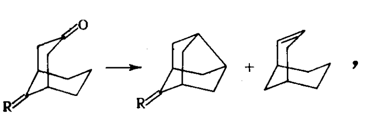
Meerwein was the first to obtain the noradamantane system by the cyclisation of the Meerwein ester[33]:



Many years later disubstituted noradamantane was obtained by the reduction of 3-methylenebicyclo[3,3,1]-7-nonanone with sodium in wet ether[34]:

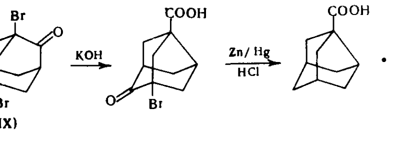


The noradamantane structure is formed on dry distillation of salts of the tosylhydrazone of bicyclo[3,3,1]-3-nonanone[35]:



where R = H_2 or $-OCH_2CH_2O-$. In both cases the transannular cyclisation of the bicyclo[3,3,1]nonane system to the noradamantane system takes place extremely readily.

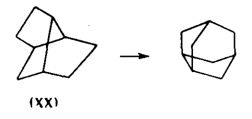
A completely different approach to the synthesis of the noradamantane system was achieved by Vogt and Hoover, who started with 1,5-dibromoadamantane-2,6-dione (XIX), which was converted by the Favorskii reaction into substituted noradamantane[36]:



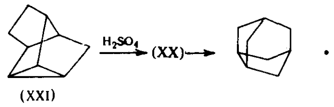
This method merits attention for two reasons: firstly, there is no doubt about the noradamantane structure obtained in this way and, secondly, the presence of three functional substituents permits the preparation of a wide variety of derivatives.

Noradamantane as well as adamantane may be obtained by the isomerisation of tri- and tetra-cyclic hydrocarbons in the presence of Lewis acids. Hitherto this isomerisation has been investigated only for a few isolated examples.

Brexane—tricyclo[4,3,0,0^{3,7}]nonane (XX)—isomerises very readily to noradamantane in the presence of aluminium bromide; the reaction is carried out for 30 min in carbon disulphide at 25°C, the yield of noradamantane being 75%[37]:



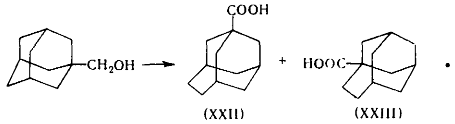
Deltacyclane (XXI), which is a convenient starting material for the formation of the brexane skeleton, can isomerise to noradamantane under the action of 96% sulphuric acid[38]:



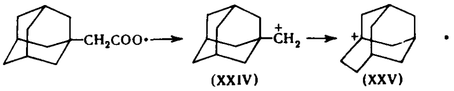
Depending on the method of treatment of the product, after isomerisation it is possible to obtain noradamantane with various substitutents in the 2-position.

Noradamantane is a white crystalline substance melting at 203–204°C and readily subliming. Its chemical and physical properties have so far been little investigated.

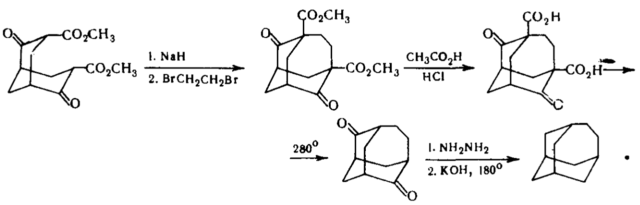
The principal method for the preparation of homoadamantane derivatives involves the expansion of one of the rings in the adamantane nucleus. In 1959 Stetter and coworkers[39] obtained homoadamantane-3-carboxylic acid from 1-hydroxymethyladamantane by the Koch–Haaf reaction. A more detailed study of the properties of this compound[40,41] showed that the substance obtained by Stetter consisted of a mixture of 80% of homoadamantane-1-carboxylic acid (XXII) and 20% of homoadamantane-3-carboxylic acid (XXIII):



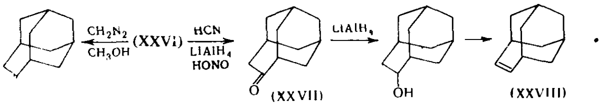
When the sodium salt of adamantane-1-acetic acid is electrolysed, the radical AdCH$_2$COO$^{\cdot}$, which is formed at the anode, loses carbon dioxide and is oxidised further to the cation (XXIV), which then rearranges to the 3-homoadamantyl cation (XXV)[42,43]:



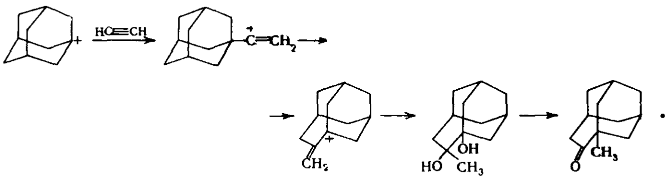
A specific synthesis of homoadamantane was achieved by Vogt[44] from bicyclo[3,3,1]nonane:



Promising methods for the synthesis of the homoadamantane system have been demonstrated[45,46]. In both cases the authors started with the readily available adamantanone (XXVI):

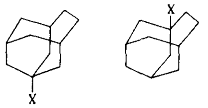


Subsequent reduction of 4-homoadamantanone (XXVII) leads to the formation of the corresponding alcohol, the dehydration of which gives 4,5-dehydrohomoadamantane (XXVIII). The formation of small amounts of homoadamantyl derivatives has been noted in the reaction of adamantane with acetylene[47]. The author suggested the following mechanism:



Other cases of the formation of the homoadamantane structure have also been observed but the reactions described are not unsuitable for preparative purposes[4].

The electrolysis of homoadamantanecarboxylic acids was investigated in the studies already mentioned[42,43]. Electrolysis of homoadamantane-1-carboxylic acid in methanol gives 1-methoxyhomoadamantane and homoadamantane-3-carboxylic acid is converted under the same conditions into 3-methoxyhomoadamantane. Two series of homoadamantane derivatives with substituents in the 1- or 3-position have been synthesised from the methoxy-derivatives[42]:



where X = OCH_3, Br, Cl, OH, $NHCOCH_3$, NH_2, COOH, $COOCH_3$, or CN.

The position of the substituents in the 1- and 3-bromo-derivatives of homoadamantane is confirmed also by a comparison of the relative rates of solvolysis. 1-Bromohomoadamantane is solvolysed only three times faster than 1-bromoadamantane, while 3-bromohomoadamantane is solvolysed 500 times faster[42].

IV. PHYSICOCHEMICAL PROPERTIES OF ADAMANTANE.

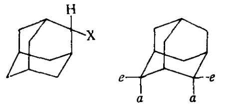
The principal physicochemical properties of adamantane have been very thoroughly described in the review mentioned above[3]. Subsequent studies dealt mainly with the revision and checking of results already published. Thus Nordman and Schmitkons[48] assert that at room temperature adamantane has a disordered face-centred cubic structure, probably belonging to the F_m3_m group rather than $F\overline{43}m$ suggested previously. The same workers confirmed the occurrence of a phase transition at −65°C and determined the parameters of the low-temperature unit cell.

A phase transition to the tetragonal structure at 208.62°K was established by Resing[49] using the "spin echo" method. The phase behaviour of adamantane was also investigated at elevated temperatures and pressures[50].

It has been noted[3] that an experimental test of the lack of strain in adamantane is impossible without knowing the enthalpy of sublimation. Bratton and Szilard measured the vapour pressure of adamantane in the range 40−80°C and calculated the enthalpy of sublimation from the integral form of the Clausius−Clapeyron equation. It proved to be 14.0 kcal $mole^{-1}$. Subsequent calculations by the authors confirmed the conclusion that adamantane has a low strain energy[51]. The results of Bower et al.[54], who reported the formation of an adamantane radical-anion, were checked by Jones[52] and Gerson et al.[53], who showed that these data are erroneous. The signals in the ESR spectra assigned to the adamantane radical-anion are in fact due to contamination by benzene.

The NMR spectra of adamantane substituted at the bridgehead positions were already partly discussed in the review of Fort et al.[3] A detailed publication[55] showed that the NMR spectra yield much information about the structure of adamantane derivatives by virtue of the additivity of the chemical shifts of all the protons in the adamantane nucleus. The spectra of polysubstituted adamantanes may be calculated by the algebraic summation of the chemical shifts of the β-, γ-, and δ-protons of the corresponding monosubstituted adamantane derivatives in relation to unsubstituted adamantane. The relatively large difference between the chemical shifts, the absence of geminal spin−spin coupling, and the low vicinal coupling constant made the interpretation of the spectra easy. When the lines overlap, the use of benzene as a solvent makes it possible to elucidate all the structural detail. The effect of aromatic solvents on the NMR spectra of adamantane derivatives was studied in detail by Fort and Lindstrom[56], who postulated the presence of a 1 : 1 complex with the solvent in solutions of 1-halogenoadamantanes in benzene, which, however, is so unstable that it could not be detected by any method other than NMR spectroscopy.

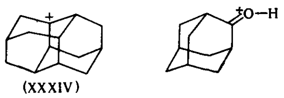
The symmetry of adamantane derivatives with the substituent in the 2-position is much lower than that of 1-derivatives and therefore analysis of the spectra of such compounds is much more complicated. The NMR spectra of 2-derivatives of adamantane consist of a series of poorly resolved lines which do not show appreciable vicinal splitting. Analysis of the spectra recorded at a 100 MHz using double resonance established that J_{vic} = 2.6 Hz and J_{gem} = 12 Hz for compounds (XXIX)−(XXXIII). The chemical shifts for the majority of protons have also been determined[57]:



where X = Cl for (XXIX), X = Br for (XXX), X = I for (XXXI), X = OH for (XXXII), and X = NH_2 for (XXXIII).

2,4-Dihalogeno-derivatives of adamantane can exist in three stereoisomeric forms—2a, 2e; 2a, 4e; 2e, 4a. Analysis of the NMR spectra[58] of 2,4-dichloro-, 2,4-dibromo-, and 2,4-di-iodo-adamantanes established the configuration of these compounds and it was found that the chemical shifts of the protons of adamantane derivatives with substituents at the secondary carbon atoms are additive.

In individual NMR studies adamantane derivatives were also investigated among other compounds. Thus Olah and Lucas[59], who studied the behaviour of cycloalkanes in "magic" acid (a mixture of fluorosulphonic acid and antimony pentafluoride), found that, on dissolution in this mixture, adamantane loses a hydride ion and forms the adamantyl cation. Trimethylenenorbornane is also converted under these conditions into the adamantyl cation with loss of a hydride ion. Diadamantane (“congressane”) behaves analogously, losing a hydride ion from the tertiary position in the “belt” [(XXXIV)]. Adamantanone forms an oxonium species in “magic” acid[60]:

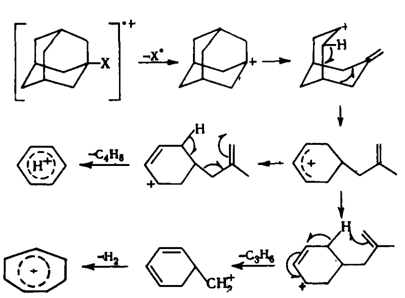


(XXXIV)
diamantane (“congressane”)

Oleneva et al.[61] examined the infrared and Raman spectra of mono- and 1,3-di-substituted derivatives of adamantane. They noted that the absorption bands of the C–H and CH_2 groups are located in the regions characteristic of cyclohexane structures. The skeletal vibrations of the adamantane structure differ appreciably from those of the corresponding cyclohexane vibrations but they are not characteristic and probably cannot be used to identify the adamantane nucleus.

A combined approach to the study of alkyladamantanes has been demonstrated[62,63]. The authors characterise alkyladamantane on the basis of its infrared and Raman spectra and gas–liquid chromatography.

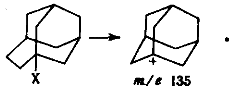
A detailed study of the behaviour of adamantane derivatives on electron impact has been made only for 1-substituted adamantanes[64]. Depending on their behaviour under electron impact, 1-derivatives of adamantane can be divided into two groups: compounds whose molecular ions split off the substituent in the form of a neutral fragment, while the remaining fragment $C_{10}H_{15}^{+}$ is further cleaved according to the mechanism



where X = Cl, Br, NO_2, CH_2OH, $COCH_3$, COOH, $COOCH_3$, C_6H_{11}, or $C_{10}H_{15}$, and compounds (X = OH, NH_2, $NHCOCH_3$, C_6H_5, or OCH_3) which split off olefin molecules, forming charged fragments where the substituent is retained. Adamantane itself gives a very intense peak due to the molecular ion which decomposes with elimination of olefins.

In contrast to adamantane, the molecular ion of homoadamantane[41] fragments into neutral radicals, forming thereby significant ionic species with odd masses. Like the 1-derivatives of adamantane, homoadamantane derivatives containing a substituent both in the 1-position and the 3-position can be divided into two groups differing in the nature of the mass spectra. The 1- and 3-derivatives of homoadamantane with Cl, Br, COOH, and $COOCH_3$ substituents give rise on electron impact to a molecular ion which splits off the substituent in the form of a neutral fragment and breaks down further with elimination of olefins.

Thermal rearrangement of the Wagner–Meerwein type to adamantane derivatives, leading to the formation of a fragment with $m/e = 135$ ($C_{10}H_{15}^{+}$) is characteristic of 3-substituted homoadamantanes of this group.



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The presence or absence of the ion with $m/e = 135$ makes it possible to distinguish the 1- and 3-substituted homoadamantane derivatives.

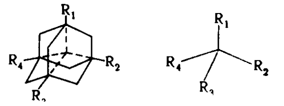
The molecular ions of 1- and 3-derivatives of homoadamantanes containing OH, OCH_3, NH_2, and $NHCOCH_3$ substituents split off neutral radicals and all the principal ions retain the substituent. The most intense peak in the mass spectra of compounds of this group is that corresponding to the $M - C_5H_{11}$ ion. The ratio of the intensity of this ion to that of the $M - C_4H_9$ ion in the case of the 1-substituted derivatives is 10 : 1 or above, while in the case of 3-substituted derivatives it is not more than 3 : 1, which makes it possible to distinguish these series of isomers.

In a study of the mass spectra of adamantane-1-acetic and homoadamantane-3-carboxylic acids deuterated in the carboxy-group, it was found that vigorous deuterium exchange with the nucleus takes place. Probably the 2-position of the adamantane or homoadamantane nucleus is capable of exchange.

Other spectroscopic methods were used to study adamantane derivatives to a much lesser extent. Chadwick et al.[65] calculated from the parameters of microwave spectra the carbon–halogen bond length in 1-halogenoadamantanes.

Certain properties of the ultraviolet and circular dichroism spectra have been investigated for β-substituted adamantanones[66].

Adamantane with four different substituents at the bridgehead carbon atoms may be regarded as a formal analogue of a compound with an asymmetric carbon atom:



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The attempts to separate into optical isomers 3,5 and 3,5,7-substituted adamantane-1-carboxylic acids were unsuccessful[67]. By fractional crystallisation, Hamill and McKervey isolated an optically active dehydroabietylammonium salt of 5-bromo-3-methyladamantane-1-carboxylic acid[68]. The bromo-acid isolated from the salt proved to be optically inactive, but after conversion into 5-bromo-3-methyl-1-adamantylurethane and subsequent fragmentation, the optically active 1-methyl-3-methylenebicyclo[3,3,1]-7-nonanone ($[\alpha]_D^{23} = 10.4°$) was obtained.

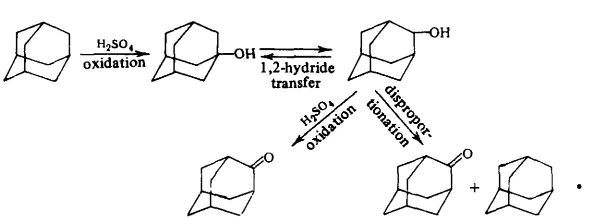
V. CHEMICAL PROPERTIES OF ADAMANTANE

During the last five years the chemistry of adamantane has developed very rapidly. The hydride transfer reactions, which permit the interchange of functional groups between bridgehead and bridge positions in the adamantane ring, must be regarded as the most important achievements in this field. Notable advances have been made in the synthesis of adamantane derivatives with substituents in the bridge positions. Finally, the increasing interest in the radical reactions of adamantane may be noted.

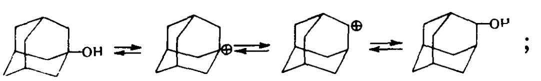
1. Hydride Transfer Reactions in the Adamantane Ring

These include in the first place oxidation of adamantane by sulphuric acid and the disproportionation of its hydroxy- and halogeno-derivatives.

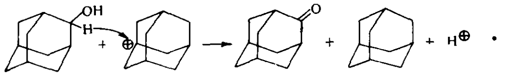
In 1967 Geluk and Schlatmann reported the direct oxidation of adamantane to adamantanone by sulphuric acid[69,70]. The mechanism of this multistage process is as follows:



They established that the individual stages in the conversion of adamantane into adamantanone are: (a) oxidation of adamantane to 1-adamantanol; (b) 1,2-hydride transfer leading to the equilibrium

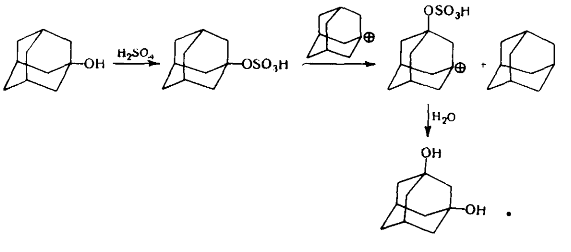


(c) intermolecular hydride transfer in which the adamantyl cation functions as a hydride ion acceptor:

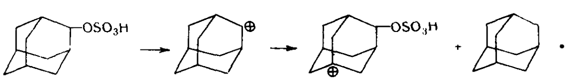


Adamantanone is formed also in the oxidation of 2-adamantanol by nitric acid.

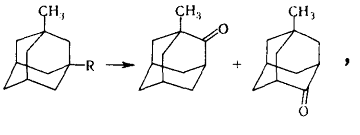
The composition of the products formed in the reaction of 1-hydroxy- or 2-hydroxy-adamantane with sulphuric acid depends to a considerable degree on the concentration of sulphuric acid, temperature, and duration of reaction. The 1,2-hydride transfer mentioned above [process (b)] takes place readily in 96% acid, while in 70% acid 1,3-hydride transfer takes place[71]:



Here too the acceptor is the adamantyl cation and the donor the sulphate ester of 1-adamantanol formed in sulphuric acid. In 70% sulphuric acid 2-adamantanol is similarly converted into an equimolar mixture of adamantane and 1,4-dihydroxyadamantane:

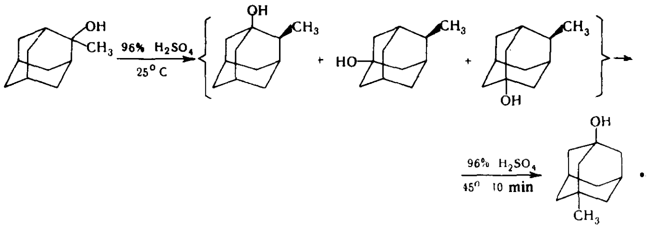


The structure of 1,4-dihydroxyadamantane obtained in the form of a mixture of two stereoisomers was rigorously demonstrated by the authors and on its basis a series of 1,4-disubstituted adamantanes were obtained. 1-Methyladamantane, 3-bromo-1-methyladamantane, and 3-hydroxy-1-methyladamantane as well as unsubstituted adamantane are oxidised by sulphuric acid to a mixture of isomeric 1-methyladamantanones[72]:

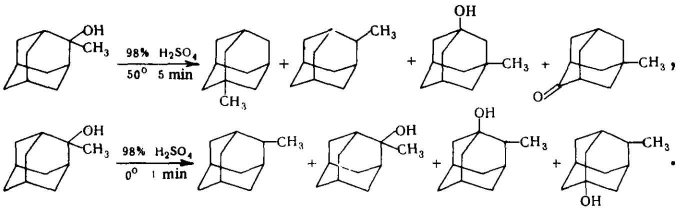


where R = Br, H, or OH.

The behaviour of 2-hydroxy-2-methyladamantane in sulphuric acid is fairly complex, which is probably the reason for a somewhat contradictory nature of the available literature data on its reaction products. At room temperature 2-hydroxy-2-methyladamantane[73] is immediately isomerised in 96% sulphuric acid to a mixture of 3 isomeric hydroxymethyladamantanes, the hydroxy-group being located at a bridgehead carbon atom. At 45°C the methyl group is also located at a tertiary carbon atom, as shown in the mechanism below:



The isomerisation of 2-hydroxy-2-methyladamantane in concentrated sulphuric acid at 0° and 50°C is likewise accompanied by intermolecular hydride transfers[73]:



The authors believe that the 2-methyl-2-adamantyl cation formed initially rapidly isomerises to a mixture of all other tertiary cations.

Patent data have also been published on the ready isomerisation of 2-hydroxyadamantane derivatives to the corresponding 1-hydroxyadamantanes[74]. 2-Hydroxyadamantane disproportionates under the influence of phosphoric and perchloric acids or Lewis acids[70].

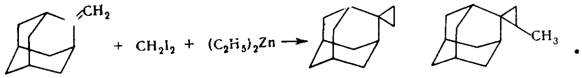
The rate of isomerisation of 2-hydroxy-2-methyladamantane is apparently sharply reduced when the temperature is decreased, since the only product of the isomerisation of 2-hydroxy-2-methyltwistane in an SbF_5/SO_2 mixture at −78°C is 2-hydroxy-2-methyladamantane[7].

2. Reactions Involving the Bridge Positions in the Nucleus.

Starting with adamantanone, which is now readily available, the following derivatives have been obtained by standard methods: 2-hydroxy-, 2-chloro-, 2-bromo, 2-carboxy-, 2-amino-, 2-cyclopentyl-, and 2-methylene-adamantanes[75,76].

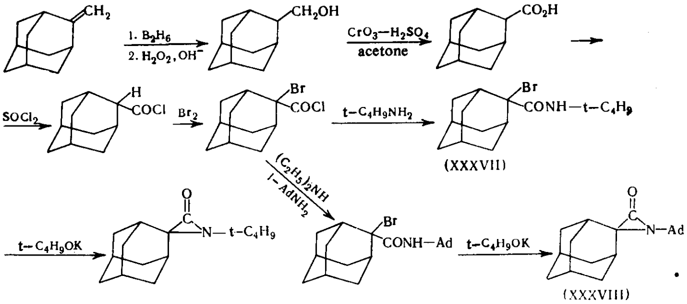
Methyleneadamantane also serves as a starting material for the synthesis of adamantanes substituted in the 2-position.

Like other olefins, methyleneadamantane reacts with methylene iodide and diethylzinc, forming spiro[adamantane-2,1′-cyclopropane] (XXXV) [77]; under the same conditions, 2-methylspiro[adamantane-2,1′-cyclopropane] (XXXVI) is formed from ethylideneadamantane:



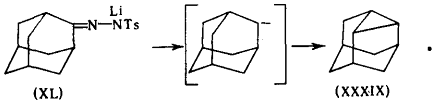
(XXXV) (XXXVI)

The α-lactams (XXXVII) and (XXXVIII) can also be obtained from methyleneadamantane by the following mechanism[78]†:



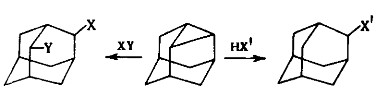
The lactams (XXXVII) and (XXXVIII) thus obtained are quite stable despite containing β-hydrogen atoms, since the latter are located at the bridgehead positions and the isomerisation of lactams with ring opening is blocked.

A fundamentally new method for the synthesis of adamantanes with substituents in bridge positions was developed starting from 2,4-dehydroadamantane (XXXIX) obtained by the pyrolysis of the dry lithium salt of the *p*-tosylhydrazone of adamantone (XL) at 130−140°C [79]:



(XL) (XXXIX)

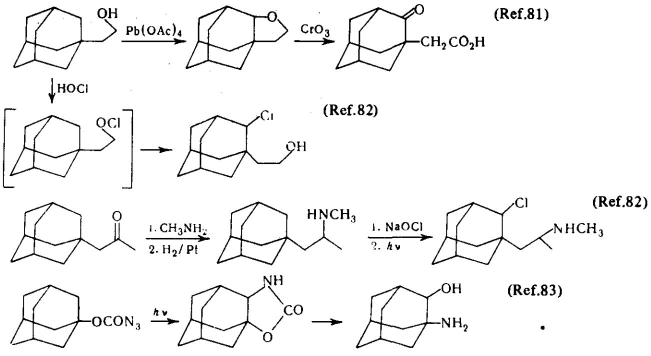
Compound (XXXIX), which is a readily available hydrocarbon with m.p. 202.5−203.5°C, is a very convenient starting material for the synthesis of 2-monosubstituted and 2,4-disubstituted adamantane derivatives[80]:



where X = Cl, H, Br, I, OH, =O, or $NHCOCH_3$, Y = Cl, Br, I, C_6H_5, OH, or H, and X′ = $OCOCH_3$, OCH_3, C_6H_5, (*o* + *p*)-$C_6H_4CH_3$, or (*o* + *p*)-$C_6H_4OCH_3$.

Reactions with the opening of the three-membered ring proceed under mild conditions and lead to the synthesis of the final products in high yields. A series of new 2-monosubstituted and 2,4-disubstituted adamantanes have been obtained by this reaction.

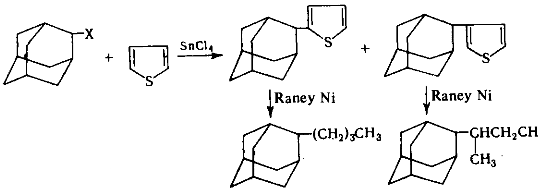
A general method for the preparation of 1,2-disubstituted adamantane derivatives is intramolecular cyclisation with participation of the vicinal carbon atoms of the adamantane nucleus with subsequent ring opening and the formation of 1,2-derivatives[81-83]:



The intramolecular ring closure to give 1-substituted adamantanes has so far been very little investigated; the use of photolysis in the ring closure stage appears to be promising.

The Koch synthesis of carboxylic acids from 2-hydroxyadamantane yields a mixture of adamantane-1-carboxylic and adamantane-2-carboxylic acids, the greatest yield of the latter being obtained when the ratio 2-hydroxyadamantane:H_2SO_4 = 1 : 1500. A series of adamantane derivatives substituted in the 2-position has been obtained from adamantane-2-carboxylic acid[84].

Hock and coworkers developed an interesting method for the introduction of butyl and isobutyl groups into the adamantane nucleus[85]. This method consists in the alkylation of halogenoadamantanes with thiophen and subsequent hydrogenolysis of the resulting compounds. 2-Halogenoadamantanes are less readily alkylated than 1-halogeno-derivatives, but the final products can nevertheless be obtained in a yield of about 40%:



where X = Cl or Br.

2-Butyladamantane was also obtained in a high yield by the reaction of adamantanone with butyl-lithium[86].

In an overall assessment of this section on the chemistry of adamantane, the striking progress in this new field is noteworthy. It is sufficient to recall that only a few years ago even the synthesis of adamantanone was an extremely laborious process. It is to be expected that in the near future the study of the reactivity of polyhedranes at the bridgehead and bridge positions will lead to many applications of this unusual type of compounds in the solution of important synthetic and applied problems.

3. Free-radical Reactions

The first chemists who began a comparative study of the stability of skeletal radicals were Applequist and Kaplan[86]. A convenient reaction for such study is decarbonylation of aldehydes. The authors investigated the ease of the loss of carbon monoxide by the acyl radicals

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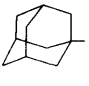
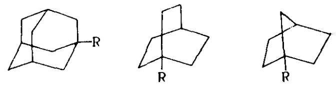
† Here and henceforth Ad = 

$\dot{R}CO$, where R is subject to different degrees of limitation of skeletal coplanarity:

$$\begin{tikzcd}R\dot{C}O \arrow[r, "k_1"] \arrow[d, "CCl_4"', "k_2"] & R\cdot + CO \arrow[d] \\ RCOCl & RH, RCl\end{tikzcd} .$$

The stability of the radicals is estimated in terms of the ratio k_1/k_2, since the rate of capture of the $R\dot{C}O$ radicals by the solvent (carbon tetrachloride) is less sensitive to the nature of R (i.e. k_2 is almost constant). Data for the relative stabilities of the radicals investigated‡ and the relative rates of solvolysis of the corresponding bromides§ are presented below:



		$(CH_3)_3CR$			
Relative stability of radicals k_1/k_2	R=CHO	1.00	2.5	1.2	0.007
Relative rate of solvolysis	R=Br	1.00	10^{-3}	10^{-6}	10^{-14}

Although these data do demonstrate a real difference between the stabilities of the t-butyl and 1-adamantyl radicals, when account was taken of the energies of the dissociation of the corresponding hydrocarbons into radicals, the authors concluded that the 1-adamantyl radical is more stable approximately to the extent of [only] 1 kcal than the t-butyl and 1-bicyclo[2,2,2]octyl radicals. The significant difference between the relative stabilities of the free radicals and carbonium ions is noteworthy. Probably steric factors play a greater role in ionic reactions than in radical reactions.

On the other hand, Chick and Ong[87] believe that the 1-adamantyl radical is less stable than the t-butyl radical, but unfortunately they do not quote quantitative data.

Free-radical substitution in adamantane was investigated in detail by Oda and coworkers[88-90]. They studied the fundamental problem of the relative reactivities of the 1- and 2-positions in radical reactions. While the 1-position is subject to steric limitations (the 1-adamantyl radical cannot be planar), the 2-position can give rise to a normal secondary free radical (sp^2-hybridisation is possible). Experiments on the radical halogenisation of adamantane[88,89] led the authors to the following conclusions:

1. In radical reactions the 1-adamantyl radical is formed more readily than the 2-adamantyl radical.
2. The bridgehead adamantyl radical is less stable than the bridge radical; the selectivity in this reaction (the ratio of the reactivities in the 1- and 2-positions) is 4.

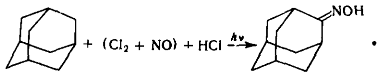
The different selectivities of the adamantyl radicals are also shown in the Hünsdiecker reaction[88]: in chlorine-containing solvents (carbon tetrachloride) the 1-adamantyl radical abstracts chlorine preferentially from the solvent molecule relative to the 2-adamantyl radical.

In the radical chlorocarbonylation of adamantane[90] the 1- and 2-isomers are formed in proportions of 55:45. Among other advantages, this reaction provides a convenient method for the preparation of adamantane-2-carboxylic acid or its ester:

$$Ad + (COCl)_2 \xrightarrow{(C_6H_5COO)_2} \underset{55\%}{AdCOCl\ (1)} + \underset{45\%}{AdCOCl\ (2)} .$$

In a recent paper Gleicher et al.[91] described the effect of atomic bromine (generated photochemically from *N*-bromosuccinimide) on adamantane and some of its 1-substituted derivatives; the reactions were carried out in carbon tetrachloride at 40°C. In each case a complex mixture of products is formed since both bridgehead and bridge positions are substituted by chlorine (from carbon tetrachloride) and bromine.

An interesting observation was made when deuterated adamantane was subjected to direct photochemical hydroximation with a mixture of chlorine and nitric oxide[92]. This reaction, which in all probability has a radical mechanism[93], does not involve the bridgehead positions in adamantane:



Peroxides of the adamantane series constitute a new little investigated class of compounds and therefore it is appropriate to mention here a study of the kinetics of the decomposition of the t-butylperoxy-ester of adamantane-1-carboxylic acid, which takes place via the intermediate formation of the adamantyl radical according to the mechanism[94]

$$Ad\text{-}\!\!\!\!\!\!\!\quad\overset{O}{\overset{\|}{C}}O\text{-}OC(CH_3)_3 \longrightarrow Ad\cdot + CO_2 + (CH_3)_3CO\cdot .$$

4. Reactions Involving the Bridgehead Positions

A large number of studies on the reactivity of adamantanes in the bridgehead positions have been made. The present review quotes all the investigations in this field, but only the most interesting and original of these are considered in detail.

Again much attention is devoted to the problem of the halogenation of adamantane. In the presence of aluminium chloride adamantane is readily chlorinated by agents such as acetyl chloride, propyl and isopropyl chlorides[95], and thionyl chloride[96]. The replacement of substituents in certain adamantane derivatives by bromine takes place readily on refluxing with anhydrous bromine[97]:

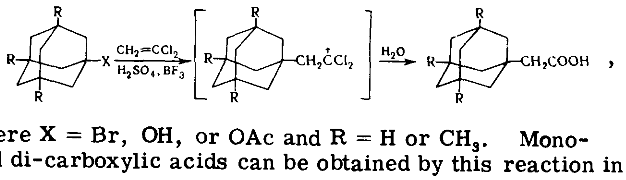
$$Ad - X \xrightarrow{Br_2} AdBr ,$$

where X = H, F, Cl, or OH. The reaction does not occur when X = CN, CO_2H, CH_3, or p-$NO_2C_6H_4$. The interchange of halogens of the bridgehead positions of adamantane is also possible using hydrogen halides[98]:

$$\begin{tikzcd}& AdBr \arrow[dl, shift right, "HF"'] \arrow[dr, shift left, "HCl"] & \\ AdF \arrow[ur, shift right, "HBr"'] \arrow[rr, shift left, "HCl"] & & AdCl \arrow[ul, shift left, "HBr"] \arrow[ll, shift left, "HF"]\end{tikzcd}$$

A number of studies have been made on the bromination catalysts[99,100]. The bromination of the side chain in adamantanes does not present difficulties; bromine in this position exhibits its normal mobility[100].

Bott extended his previously developed method for the synthesis of carboxylic acids using 1,1-dichloroethylene[101] to compounds of the adamantane series[102]:



where X = Br, OH, or OAc and R = H or CH_3. Mono- and di-carboxylic acids can be obtained by this reaction in

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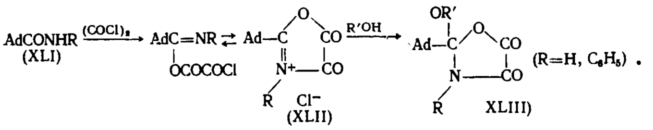
‡ The decarbonylation reactions were carried out at 135°C in carbon tetrachloride using di-t-butyl peroxide as an initiator.

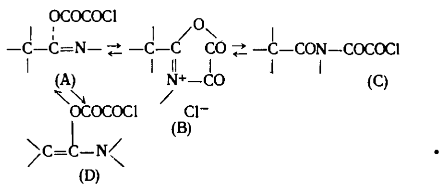
§ The solvolysis was carried out in 80% ethanol at 25°C.

high yields. When 1,1,2-trichloroethylene is introduced into this reaction, the same series of acids is formed with the chlorine atom in the α-position[103].

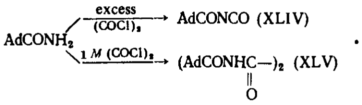
While the reactions of adamantylacetic acid involving the carbonyl group take place in the usual way and lead to a series of derivatives[104], the reactions of adamantane-1-carboxamides with oxalyl chloride have a mechanism different from that which usually obtains[105]. The reaction of adamantane-1-carboxamide (XLI) with oxalyl chloride at 0°C results in the intermediate formation of the unstable oxazoline-4,5-dione (XLII), which on treatment with protic solvents gives rise to substances with the general formula (XLIII):



The previously described reactions of carboxamides with oxalyl chloride lead to the formation of open-chain compounds (of types C or D):



The reaction of adamantane-1-carboxamide with oxalyl chloride in various molar proportions at a temperature above 20°C leads to the formation of adamantane-1-carbonyl isocyanate (XLIV) and *NN*-bis(adamantane-1-carbonyl) oxamide (XLV):



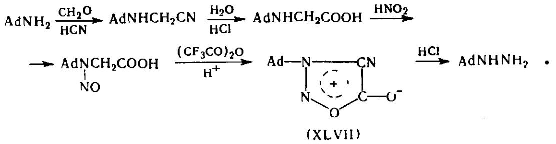
1-Aminoadamantane and its derivatives formed using the amino-group continue to attract the attention of chemists and biochemists as physiologically active substances. This concentration on the chemistry of 1-aminoadamantane proved very fruitful not only from the standpoint of medical chemistry but is also extremely interesting in its synthetic aspect. There are very many relevant examples and some of them will be considered.

For instance, the application of the Ritter reaction to 1-bromoadamantane and its subsequent development gave high yields of various *N*-(1-adamantyl)amides (XLVI)[106]:

$$AdBr \xrightarrow{H_2SO_4} Ad^+HSO_4^- \xrightarrow{RCN} AdN{=}\overset{+}{C}RHSO_4^- \xrightarrow{H_2O} \underset{(XLVI)}{AdNHCOR}\ .$$

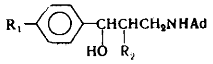
The alkylation of aliphatic and aromatic amines with 1-bromoadamantane has been investigated[107,108]; the reaction takes place under severe conditions.

1-Hydrazinoadamantane cannot be obtained directly but only via the intermediate formation of the sydnone (XLVII)[109]:

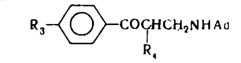


(XLVII)

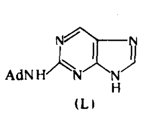
The synthesis of 1-(3-aryl-3-hydroxypropylamino)adamantanes (XLIX)[110], 1-(3-aryl-3-hydroxypropylamino)adamantanes (XLVIII)[110], and adamantyl derivatives of aminopurines (L), aminopyrimidines (LI)[111], *p*-aminobenzamide, and *p*-aminobenzenesulphonamide[112] also required far-reaching development:



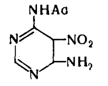
(XLVIII)



(XLIX)



(L)



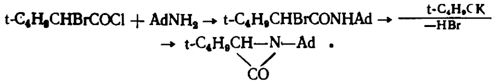
(LI)

This applies equally to the synthesis of adamantane compounds containing in the side chains, diethylamine, piperidine, morpholine, and pyrrolidine residues[113].

For biochemists, the reactions of aminoadamantanes in the organism are of primary interest; the microbiological oxidation of some of these compounds has been studied[114].

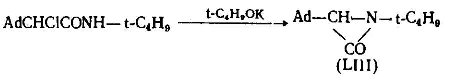
The synthesis, and chemical and physical properties of α-lactams of the adamantane series are of considerable interest. This is due to the fact that the α-lactams are the only class of three-membered heterocycles with a carbonyl group; a disadvantage of these reactive compounds is their low thermal stability, which of course hinders the study of their properties.

1-(1-Adamantyl)-3-t-butylaziridinone (LII), synthesised by the mechanism presented below, proved to be very stable[115,116], which made possible a detailed study of the chemical properties and spectroscopic characteristics of compounds of this class:



(LII)

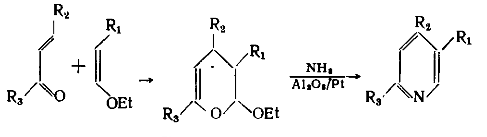
The α-lactam (LIII) was obtained by the same mechanism[117]:



(LIII)

The behaviour of 1-aminoadamantane in the Dem'yanov reaction has been investigated[118]. Numerous derivatives have been synthesised from aldehydes and ketones of the adamantane series. Aldehydes derived from adamantane have been obtained by the oxidation of the corresponding alcohols with lead tetra-acetate[119], by the reaction of organomagnesium derivatives of bromoalkyladamantanes with orthoformic ester[120], and also by other methods[117,121].

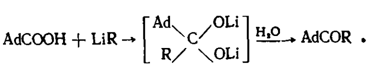
Unsaturated aldehydes are formed as a result of crotonic condensation[120] or by the condensation of acetals with ethyl vinyl ether via 1,1,3-triethoxyalkanes[122]. The acetals of adamantane aldehydes are converted into 1-adamantyl vinyl ethers when pyrolysed on magnesium phosphate[122]. Glutaric aldehydes of the adamantane series[123] and adamantylpyridines[124] have been obtained from unsaturated aldehydes or vinyl ethers via the corresponding pyrans:



where R_1 = H, Ad, or CH_2Ad, R_2 = H or CH_2Ad, and R_3 = H or Ad.

Aldehydes of the adamantane series form cyanohydrins which are hydrolysed to α-hydroxyacids, undergo the crotonic condensation, and are very readily oxidised (unusually so for aliphatic aldehydes) to the corresponding carboxylic acids on standing in air[120].

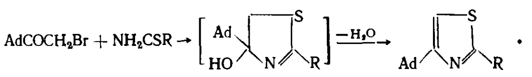
A convenient method for the synthesis of adamantyl ketones consists in the reaction of adamantane-1-carboxylic acid with alkyl-lithium[125]:



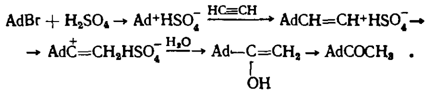
$$\mathrm{AdCOOH + LiR} \rightarrow \left[\begin{matrix}\mathrm{Ad}\diagdown & & \diagup\mathrm{OLi}\\ & \mathrm{C} & \\ \mathrm{R}\diagup & & \diagdown\mathrm{OLi}\end{matrix}\right] \xrightarrow{\mathrm{H_2O}} \mathrm{AdCOR}\ .$$

where R = CH_3, C_2H_5, or iso-C_3H_7.

Adamantyl methyl ketone enters into the Reformatskii reaction with bromosuccinic ester and the Mannich reaction with formaldehyde and dimethylamine[126]. The introduction of bromine into the α-position relative to the carbonyl group is possible by direct bromination or by the decomposition of the diazoketone obtained from the chloride of adamantanecarboxylic acid and diazomethane. The bromoketone can condense with acid thioamides to form thiazoles[127]:



The interest in derivatives of adamantane with multiple bonds, which is the most recent and little investigated group of substances of this type, can be readily understood. Sasaki et al.[128] reported the formation of a vinyl cation and its rearrangement on addition of the adamantyl cation to acetylene. The reaction proceeds as follows:

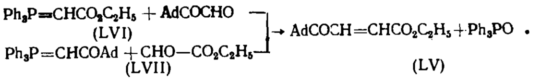


$$\mathrm{AdBr + H_2SO_4 \rightarrow Ad^+HSO_4^- \xrightarrow{HC\equiv CH} AdCH{=}CH^+HSO_4^- \rightarrow}$$
$$\mathrm{\rightarrow Ad\overset{+}{C}{=}CH_2HSO_4^- \xrightarrow{H_2O} Ad{-}\underset{\displaystyle OH}{\underset{|}{C}}{=}CH_2 \rightarrow AdCOCH_3}\ .$$

1-Vinyladamantane was obtained by the thermal cleavage of β-(1-adamantyl)ethyl-S-methylxanthate (LIV) in the Chugaev reaction[129]:

$$\underset{\mathrm{(LIV)}}{\mathrm{AdCH_2CH_2O{-}CS{-}SCH_3}} \rightarrow \mathrm{AdCH{=}CH_2 + CH_3SH + COS}\ .$$

The ethyl ester of β-(1-adamantoyl)acrylic acid (LV) may be synthesised either from 1-adamantylglyoxal and ethoxycarbonylmethylenetriphenylphosphorane (LVI) or from ethyl glyoxalate and (1-adamantoylmethylene)triphenylphosphorane (LVII) [130]:



$$\left.\begin{matrix}\mathrm{Ph_3P{=}CHCO_2C_2H_5 + AdCOCHO}\\ \mathrm{(LVI)}\\ \mathrm{Ph_3P{=}CHCOAd + CHO{-}CO_2C_2H_5}\\ \mathrm{(LVII)}\end{matrix}\right] \rightarrow \mathrm{AdCOCH{=}CHCO_2C_2H_5 + Ph_3PO}\ .\qquad \mathrm{(LV)}$$

Unfortunately the literature information about polyadamantanes is very scanty. It is noteworthy that the polyadamantane obtained by the Wurtz condensation of 3,3-dibromo-1,1-diadamantane is crystalline to the extent of more than 80% [131].

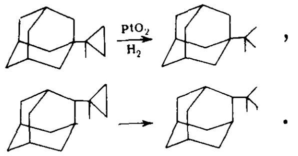
Alkylation of benzene with bromoadamantanes takes place readily[132,133] and, depending on the conditions, yields either adamantane containing several phenyl groups[134] or benzene containing up to three adamantyl residues[135]. These compounds are interesting because they comprise the adamantane nucleus with a tendency towards nucleophilic substitution reactions and the benzene ring which undergoes the characteristic electrophilic substitution reactions. Experiments have shown[132,133] that both nuclei exhibit their characteristic reactivities.

Alkylation of adamantane with olefins takes place readily in the presence of aluminium halides[136]. Under the same conditions 1-adamantylacetaldehyde is formed from 1-hydroxyadamantane[47].

It is very remarkable that the reaction of oestrone with adamantol did not yield an alkylation product; in this case adamantol reacted as a dehydrated agent and $\Delta^{9(11)}$-oestrone was isolated[137].

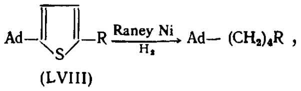
Organometallic derivatives of adamantane in which the metal is directly linked to the nucleus for a long time remained a "blank spot" in the chemistry of substances of this class. In 1965 Landsbury and Sidler[138] described for the first time the preparation of lithioadamantane by the action of t-butyl-lithium on iodoadamantane[138]. Bromoadamantane and alkyl-substituted adamantanes containing bromine in the side chain form Grignard reagents[139]. The synthesis of 1-(3-aryl-3-hydroxypropylamino)ada-bromo-derivatives of adamantane and zinc leading to the formation of 3,7-dimethylenebicyclo[3,3,1]nonane and 1,3,5,7-tetramethylenecyclo-octane.

Among new trends, one may include the study of the catalytic reactions and the pyrolysis of adamantane compounds. Hydrogenolysis of adamantanes containing the cyclopropane ring in the side chain takes place under mild conditions and yields compounds with a t-butyl substituent[140]:



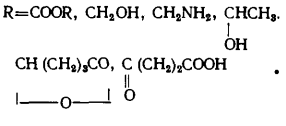
Pyrolysis of adamantane and its catalytic reactions in the presence of aluminosilicate or aluminium–chromium catalysts were investigated by Kazanskii and coworkers[141,142]; it was shown that the composition of the products in the catalytic reaction and pyrolysis is similar (mainly monocyclic aromatic hydrocarbons).

The catalytic desulphuration of adamantane derivatives of type (LVIII) is a convenient method for the synthesis of adamantanes containing a functional group in the side chain[143]:



(LVIII)

where



$$\mathrm{R{=}COOR,\ CH_2OH,\ CH_2NH_2,\ \underset{\displaystyle OH}{\underset{|}{C}H}CH_3,}$$
$$\mathrm{\underbrace{CH(CH_2)_3CO}_{O},\ \underset{\displaystyle O}{\underset{\|}{C}}(CH_2)_2COOH}\ .$$

The oxidation of adamantane and its homologues takes place smoothly when chromium oxide in an acid medium is employed as an oxidising agent. Then, depending on the amount of oxidant employed, mono- or di-hydroxyderivatives of adamantane are formed[144].

A number of studies[145–151] illustrate the usual course of the reaction in the adamantane side chain.

VI. QUANTITATIVE STUDY OF THE REACTIVITY OF ADAMANTANE.

Much work has been done on the reactivity of adamantane. One of the promising studies in the field is the comparative investigation of the stability of the adamantyl cation in a series of other polycyclic structures. Using the concept of the preferential planar configuration of the cations, Schleyer, Fort, and Gleicher proposed an elegant theory to account for the differences in the rates of solvolysis of the tertiary bromo-derivatives of adamantane, homoadamantane, bicyclo[2,2,2]octane, bicyclo[3,2,1]-nonane, bicyclo[2,2,1]heptane, bicyclo[2,1,1]hexane, and bicyclo[3,3,1]nonane and t-butyl bromide[3,6,152]. An undoubted achievement of their investigations is a satisfactory agreement between the experimental rate constants for the solvolysis of 1-chlorobicyclo[3,3,1]nonane and 1-bromobicyclo[3,3,1]nonane and the constants predicted by the theory[153,154].

Nucleophilic substitution reactions of bromine in 1-bromoadamantane take place exclusively by a unimolecular S_N1 mechanism. From this point of view, 1-bromoadamantane is exceptionally convenient for a detailed study of the structure of the transition state in unimolecular reactions. In this connection the problem of the involvement of the solvent in the activated complex is of interest. The studies in which the kinetics of the solvolysis of 1-bromoadamantane in aqueous ethanol and dimethyl sulphoxide were investigated[155,156] are probably the first stage of such investigations.

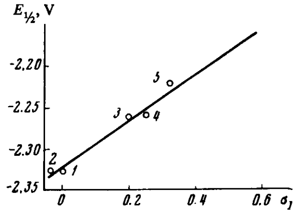


Figure 1. Variation of the half-wave potential $E_{1/2}$ with the σ_I constants of the substituents for 3-substituted 1-bromoadamantanes with the following substituents: 1) H; 2) CH_3; 3) CH_2COOCH_3; 4) OH; 5) $COOCH_3$.

The effect of substituents on the stability of the adamantyl and adamantylmethyl cations has been studied[157-159]. As was to be expected, the introduction of electronegative groups lowers the stability of the cation. It is remarkable that the presence of methyl groups at the bridgehead positions retards the solvolysis of bromoadamantane. Similar "anomalies" in the effect of the methyl group were also noted earlier[160]. Schleyer and coworkers suggest that in this case the anomaly is associated with some deformation of the cation in the transition state due to the presence of the methyl group. However, the problem remains open, because in other processes involving the formation of a cation the methyl groups exhibit electron-donating properties or have no effect[139].

The results obtained in the solvolysis of 3-substituted 1-bromoadamantanes were compared[157] with the σ^* constants and a fairly high correlation coefficient ($r = 0.996$) was obtained. In an analogous study[158] carried out using a large number of polar constituents, a correlation between the rate constants and the pK_a for the corresponding adamantanecarboxylic acid ($r = 0.986$) was obtained. The existence of such correlation is evidence that the substituents do not influence the geometrical structure of the adamantyl cation during its formation or their effect is negligibly small.

The mutual effects of the substituents in the adamantane nucleus are clearly shown in the hydrolysis of substituted acylamino-derivatives of adamantane. Depending on the nature of the substituent, the nitrogen–adamantane or the nitrogen–acyl group bond is cleaved[161,162]. In a number of studies a quantitative estimation of the influence of the substituents was undertaken. As usual, the first step was to investigate the ionisation constants of adamantanecarboxylic acids[163,165].

The correlation coefficient between the pK_a of 3-substituted adamantane-1-carboxylic acids and σ^* constants is 0.950–0.987 depending on whether account is taken of all the substituents or whether part of the points deviating to the greatest extent are rejected. The coefficient of sensitivity for this series $\rho^* = 0.263$. For bicyclo[2,2,2]-octane and *trans*-1,4-cyclohexane systems, these quantities are respectively 0.295 (in 50 wt.% ethanol) and 0.247. Such close values of ρ^* for systems where the substituents and the reaction centres are separated by different numbers of carbon atoms are evidence in favour of the hypothesis that the effect of substituents is transmitted mainly through space[160,166].

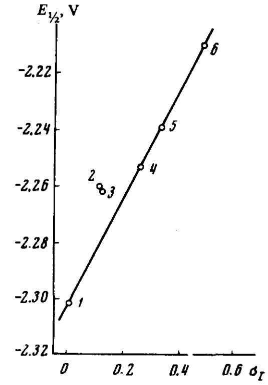


Figure 2. Variation of the half-wave potential $E_{1/2}$ with the σ_I constants of the substituents for 3-substituted 1-bromomethyladamantanes with the following substituents: 1) H; 2) C_6H_5; 3) CH_2COOCH_3; 4) OH; 5) $COOCH_3$; 6) Cl.

The effect of substituents on the reactivity has also been demonstrated by Leibzon et al.[167], who investigated the polarographic behaviour of derivatives of 1-bromoadamantane and 1-bromomethyladamantane. Bromine was reduced in 90% aqueous dimethylformamide at room temperature. Figs. 1 and 2 show the variation of the half-wave potentials $\epsilon_{1/2}$ with the σ_I constants of the substituents.

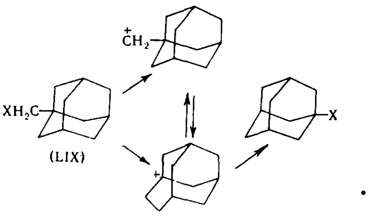
The sensitivities ρ_I of the reaction series for 1-bromomethyladamantanes and 1-bromoadamantanes were respectively 0.168–0.196 and 0.284–0.294. The correlation coefficient varied from 0.947 to 0.999. The low sensitivities of this reaction series are due to the considerable distance of the substituents from the reaction centre.

Using Palm's method[166], Leibson et al. estimated the contribution of the effect of substituents transmitted through space as 25% of the total effect. For the ionisation of adamantanecarboxylic acids, in which unit charge is produced, this quantity amounts to as much as 50% {57% for the bicyclo[2,2,2]octane system and 70% for the *trans*-1,4-cyclohexane system}.

In an overall assessment of studies concerned with the quantitative estimation of the effect of substituents, a similarity between the behaviour of cyclohexane, bicyclooctane, and adamantane systems may be noted.

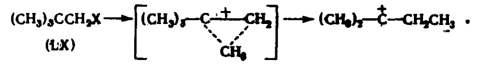
The exceptional properties of the adamantane structure—freedom from Baeyer and Pitzer strain—led to extensive application of adamantane derivatives as models for the solution of theoretical problems in organic chemistry.

Reactions with formation of 1-adamantylmethyl cations are known to involve a rearrangement of the adamantane structure to the homoadamantane structure, which is sterically more strained:



This finding has been used to elucidate the mechanism of the neopentyl rearrangement[168]. The problem of whether the neopentyl rearrangement takes place by the stepwise mechanism (1) or whether the ionisation process and the rearrangement occur simultaneously [mechanism (2)] is still controversial.

$$(CH_3)_3CCH_2X \longrightarrow (CH_3)_3C\overset{+}{C}H_2 \longrightarrow (CH_3)_2\text{—}\overset{+}{C}\text{—}CH_2CH_3\ , \qquad (1)$$



$$\underset{(LX)}{(CH_3)_3CCH_2X} \longrightarrow \left[(CH_3)_2\text{—}C\overset{+}{\text{—}}CH_2 \cdots CH_3\right] \longrightarrow (CH_3)_2\text{—}\overset{+}{C}\text{—}CH_2CH_3\ . \qquad (2)$$

To solve this problem, some investigators suggest the use of a model compound of the neopentyl type, which, reacting by the ionic mechanism, would undergo rearrangement with greater difficulty than the neopentyl derivative. 1-Adamantylmethyltoluene sulphonate $AdCH_2OTS$ (LIX) has been suggested as a compound of this kind. It was postulated that the rates of solvolysis of neopentyltoluene sulphonate (LX) and of compound (LIX) should be similar if the rate-limiting step involves simple ionisation with formation of $Ad\overset{+}{C}H_2$ and $(CH_3)_3C\overset{+}{C}H_2$ respectively.

If, on the other hand, the rate-limiting step involves simultaneous ionisation and rearrangement, then neopentyltoluene sulphonate should be solvolysed faster (the migration of the methyl group takes place more readily than the rearrangement of the adamantane to the homoadamantane system, which is sterically more strained). It was found that the rate constants for the solvolysis of adamantylmethyltoluene sulphonate are actually somewhat higher than the corresponding rate constants for the neopentyl derivative (evidently owing to the inductive effect of the adamantane nucleus). According to the authors, these results are evidence in favour of the stepwise mechanism of the neopentyl rearrangement [mechanism (2)], in which ions (ion pairs) are formed in the first stage.

Grob and coworkers[169,170] investigated the mechanism of the fragmentation of γ-amino- and γ-alkyl-halogeno-derivatives using as an example the solvolysis of the amino- and alkyl derivatives of 1-bromoadamantane in 80% aqueous ethanol. They showed that the rate constants for the solvolysis of 3-amino-1-bromoadamantane and its *N*-methyl derivatives greatly exceed those for the corresponding 3-alkyl-1-bromoadamantanes. The activation entropy is lower in the first case than in the second. Moreover, whereas the sole products of the solvolysis of 3-alkyl-1-bromoadamantanes are their hydroxy-derivatives, in the case of the amino-compounds products indicating the fragmentation of the initial compounds were detected.

This led the authors to the conclusion that the solvolysis of alkyl-substituted 1-bromoadamantanes takes place by the usual unimolecular nucleophilic substitution mechanism.

The data on the solvolysis of the amino-derivatives are evidence in favour of the synchronous fragmentation of γ-amino-substituted halides of the following type:

$$R_2N\text{—}\underset{|}{\overset{|}{C}}\text{—}\underset{|}{\overset{|}{C}}\text{—}\underset{|}{\overset{|}{C}}\text{—}X \rightarrow R_2\overset{+}{N}\text{=}C\langle + \rangle C\text{=}C\langle + X^- \ .$$

The authors attribute the reason for the synchronous occurrence of this type of five-centre reaction to the exceptionally favourable geometrical disposition of all the components of the structure.

Owens et al.[171] investigated the abstraction of hydrogen from 1-substituted adamantanes by the trichloromethyl radical. They noted that the reaction involves mainly bridgehead positions. The yield of side products does not exceed 10%. Treatment of the results using the Taft equation leads to $\rho^* = -0.40 \pm 0.04$ with a high correlation coefficient ($r = 0.980$).

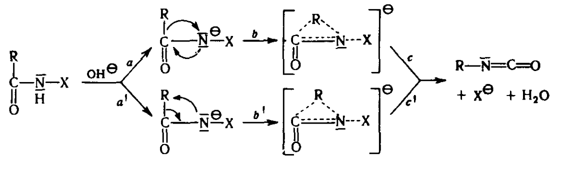
Using the Kirkwood–Westheimer equation describing the interaction between a dipole and a point charge, the authors described the transition state by a set of canonical structures:

$$RH \cdot CCl_3 \leftrightarrow R \cdot H\text{—}CCl_3 \leftrightarrow R^+H\text{—}CCl_3$$

and determined the amount of ionic character of the transition state as 10–12%.

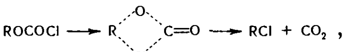
An analogous approach to the determination of the transition state was employed by Gleicher et al.[91] They investigated the reaction of 1-substituted adamantanes with atomic bromine generated from *N*-bromosuccinimide. The sensitivity of this reaction $\rho^* = -0.59$, i.e. is somewhat greater than in the reaction with the trichloromethyl radical. The authors determined the "degree of ionic character" of this process as 17%.

The pronounced electron-donating properties of the adamantane nucleus threw light on the hitherto not entirely clear mechanism of rearrangements at the nitrogen atom (the Hofmann, Curtius, and Lossen rearrangements)[172]. On the basis of the available experimental data, the mechanism of these rearrangements may be represented thus:



Strictly speaking, the experimental data do not allow a choice between pathways *a–c* or *a′–c′*, although the majority of workers adopt the first without any stipulation. The above rearrangements take place readily and with high yield also in the adamantane series[161,172,173], although it is known that adamantane readily forms the 1-adamantyl cation and the formation of the 1-adamantyl anion is not typical for this compound, i.e. the adamantyl group cannot migrate to the nitrogen atom with its electron pair. Therefore the mechanism of the rearrangement via the pathway $a'-b'-c'$ must be regarded as more likely.

Kevill and Weitl[174] attempted to revise the mechanism of the decomposition of alkyl formates using 1-adamantyl formate as an example. They assert that, of the two alternative mechanisms of the decomposition of alkyl formates



(I)

$$ROCOCl \longrightarrow R^{+}Cl^{-} + CO_2 \longrightarrow RCl \qquad \text{(II)}$$

mechanism (II) is more likely.

Baldwin and Foglesong[175,176] adduced the results obtained in the solvolysis of 8,9-dehydro-2-adamantyl 3,5-dinitrobenzoate as a model compound to account for the unexpectedly high reactivity of cyclopropylmethyl derivatives. They concluded that in the transition state both structures give rise to a non-classical carbonium ion and in the case of adamantane the 2-, 8-, and 9-positions are approximately equivalent.

In conclusion we may note certain purely theoretical studies dealing with adamantane.

The high symmetry of adamantane, which greatly simplifies calculations, was used by Kitaigorodskii et al.[177], who attempted to calculate the Debye temperature θ for the face-centred cubic crystal of adamantane, having adopted intermolecular interaction as a basis. The values of θ obtained are quite reasonable, but it is so far difficult to test the results experimentally.

Quantum-chemical calculations on adamantane by the LCAO-MO method permit the calculation of the energies of the highest occupied molecular orbital (usually set equal to the ionisation potential with the sign reversed) and the charges at the carbon atom[178]. The latter proved to be −0.09 for the carbon atoms of the methylene (CH_2) groups and +0.18 for the methylidyne (C−H) groups. It is so far difficult to decide whether such calculations have any practical value, particularly since the differences between the reactivities at the bridgehead and bridge positions in adamantanes are quite definitely caused by the geometry of the transition state.

Maksic and Klasinc[179] employed the maximum overlap method proposed by Murrell[180] to calculate the degree of hybridisation of the carbon atoms in adamantane. They found that the hybridisation is somewhat different from sp^3 hybridisation, which they believe to be consistent with the slight deviations of the valence angles from the tetrahedral values.

VII. APPLICATIONS¶

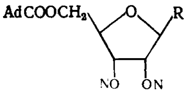
Adamantane derivatives have found the widest application as physiologically active substances.

1-Aminoadamantane (amantidine) is an effective prophylactic agent against diseases due to viruses of groups A, A′, and A-2. Amantidine does not act directly on the virus but prevents its penetration into the cell[181-183]. For the same reason amantidine prevents the development of sarcoma centres on a nucleated culture[184]. Amantidine is relatively non-toxic (λD_{50} = 700 mg kg^{-1}), but can have a side effect on the functioning of kidneys[185].

A number of adamantane derivatives of the type 1-R-Ad, where R = NH_2, NHEt, $NHCONH_2$, NCO, NCS, NHCONO, NHCOHN, or NHCONHPh sensitise the contraction of the smooth muscle initiated by 5-hydroxytryptamine[186].

Esters of adamantane-1-carboxylic acid readily dissolve in lipids and are resistant to hydrolysis owing to steric hindrance. This makes possible specific changes in the properties of testosterone[187].

The esters of adamantanecarboxylic acid and certain nucleosides with the general structure where R = 6-azauracil, 6-mercaptopurine,



adenine, or hypoxanthine, exhibit antineoplastic activity[188].

$(CH_3)_3AdCON(^{14}CH_3)_2$ has been used to investigate the rate of oxidative *N*-demethylation[189].

Substituted amides of adamantane carboxylic acid,

$AdCONR_1R_2$	R_1	H	H	CH_3	H	H	H	H	H
	R_2	H	CH_3	CH_3CH_2	CH_2OH	$COCH_3$	CHO	COPh	CO_2Et

may serve as sedatives[190].

The introduction of the adamantyl residue into 2-hydroxynaphthoquinone yields antimalarial preparations[191]. Polychloro- and polyfluoro-derivatives of adamantanecarboxylic acid exhibit insecticidal activity[192].

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Zelinskii Institute of Organic
Chemistry, USSR Academy of
Sciences, Moscow

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The Structure of Aliphatic Diazo-compounds and Their Isomers

O.P.Studzinskii and I.K.Korobitsyna

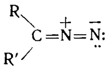
The review describes the modern concepts concerning the electronic fine structure of aliphatic diazo-compounds based on experimental data (from infrared, ultraviolet, and PMR spectroscopy) and also quantum-mechanical calculations by the LCAO-MO method. These concepts explain many chemical properties of diazoalkanes and sometimes make it possible to predict them. Apart from "classical" aliphatic diazo-compounds, the structures and properties of the isomers—linear (*N*-isocyanamine) and cyclic (diazirines)—are considered.
The bibliography comprises 99 references.

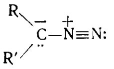
CONTENTS

I. INTRODUCTION

About ten years have elapsed since the publication of extensive reviews [1] and monographs [2,3] on the structure and properties of diazoalkanes. During this period many papers have appeared on the fine structure of aliphatic diazo-compounds and their isomers. In the present review an attempt is made to give a general account of these new data, which are important for theoretical organic chemistry. The literature up to 1969 inclusive has been compiled.

The problem of the structure of aliphatic diazo-compounds arose soon after their discovery by Curtius [4-10] in 1883. It was not until 50 years later that Boersch [11,12] demonstrated by physical methods and subsequently Clusius [13] by chemical methods the linear structure of diazo-compounds. In 1920–1930 it was suggested that the structure of diazoalkanes by represented by formulae (I), (II), and (III):[14-18]


(I)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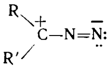
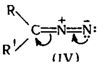

(III)

Usually in the discussion of the structure of the CN_2 group of diazoalkanes in the ground state formulae (I) and (II) only are employed with the coordinate bonds $N\rightleftharpoons N$ and $C\leftarrow N$ respectively. This is because formula (III) corresponds to a less stable molecular state compared with (I) and (II), since it contains fewer covalent bonds and the charges are removed to a greater distance [2].

The interatomic distances in diazomethane measured by Boersch by electron diffraction are inconsistent with the values calculated for these formulae on the basis of the additivity of the covalent radii even after correction for the atomic charges [19,20]. The experimental interatomic distances are intermediate between the values calculated for structures (I) and (II). This deviation is explained by the equalisation of electron density in the CN and NN bonds. The CN and NN bonds are non-integral: the CN bond is intermediate between a double and a single bond and the NN bond is intermediate between a double and triple bond. The negative charge of the CN_2 group is in fact distributed between the α-carbon and β-nitrogen atoms, which can be expressed by formulae (IV), (V), and (VI):[2]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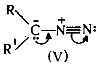
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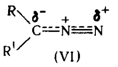

(VI)

The most correct representation of diazoalkanes is by a combination of the limiting formulae (I) and (II) each making a definite contribution to the resonance hybrid. However, partly because these contributions are not known and partly for the sake of simplicity, only one of them is employed. Formulae (IV)–(VI) are somewhat more rigorous.

Some data on the distribution of electron density in diazoalkane molecules can be derived by studying their chemical properties. In many reactions diazoalkanes exhibit nucleophilic properties, since the carbon and the β-nitrogen atoms of the CN_2 group are negatively charged and the positively charged α-nitrogen atom has already formed the maximum number of covalent bonds and cannot serve as a source of electrophilic activity [2].

It follows from the above considerations that the nucleophilic properties of diazoalkanes become weaker on introduction of electron-accepting substituents (for example, carbonyl or alkoxycarbonyl groups) and the thermal stability and the resistance to acids of diazo-compounds increase, while the introduction of electron-donating substituents (for example alkyl groups) make diazoalkanes more nucleophilic, reducing their stability at the same time. These problems are described in detail in Huisgen's review [1] and the monographs of D'yakonov [2] and Zollinger [3].

A more thorough study of the fine structure of diazoalkanes and the elucidation of the problem of the distribution of electron density in aliphatic diazo-compounds became possible only as a result of the application of spectroscopic and quantum-mechanical research methods.

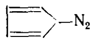
II. ELECTRONIC FINE STRUCTURE OF ALIPHATIC DIAZO-COMPOUNDS

1. Diazohydrocarbons and Diazocarbonyl Compounds (Structural Studies by Spectroscopic Methods)

In structures (I) and (II) different electron densities arise at the α-carbon atom and in substituents R and R′, to that the chemical shifts of the protons at the α-carbon atom or in its substituents are then different depending on which particular form predominates. It is to be expected that the greater is the contribution of structure (II), i.e. the greater the negative charge at the α-carbon atom, the greater will be the chemical shift of the protons (on the τ scale) and conversely.

In 1964 Ledwith and Friedrich[21] measured the PMR spectra of a series of diazo-compounds and interpreted the results. Table 1 lists the chemical shifts of the protons at the α-, β-, and γ-carbon atoms and the protons in the aromatic rings of the substituents. The results show that the chemical shift of the protons in diazomethane is much greater than in allenes, olefins, and aldehydes[21], which suggests a higher degree of screenings of the methylene protons and consequently a greater contribution of the carbanion structure (II) compared with structure (I).

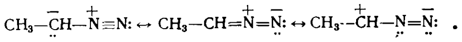
Table 1. Chemical shifts of the protons in diazoalkanes.

Diazo-compound	Chemical shift of protons on τ scale, p.p.m*	Multiplicity of signal
CH_2N_2	α 6.92	
CH_3CHN_2	α 6.78 β 8.30	 doublet
$CH_2{=}CH{-}CHN_2$	α 5.42 β 6.71 γ 8.93	multiplet quartet triplet
$C_2H_5OOCCHN_2$ $CH_3OOCCHN_2$	α 5.04 α 5.04	
	α 3.38 β 4.14	quartet quartet
$PhCHN_2$	α 5.42 Ar 3.10	multiplet
Ph_2CN_2	Ar 2.74	singlet

*The operating frequency was 40 MHz and the following solvents were employed: carbon tetrachloride, methylene chloride, and trichlorotrifluoroethane. The effect of the solvent on the chemical shift is slight.

Koster[22], who made a thorough study of the PMR spectra of diazomethane in various solvents, holds similar views. However, one cannot exclude the possibility that such increase in the screening of α-protons in diazomethane and its alkyl-substituted derivatives can be partly accounted for also by the diamagnetic anisotropy of the diazo-group, as happens in acetylenes and nitriles[23,24].

The chemical shift of the α-protons of diazoethane is similar to that of the protons in diazomethane and therefore diazoethane is best described by formula (VIIa):

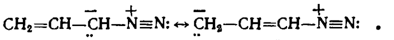


$$CH_3{-}\overset{-}{C}H{-}\overset{+}{N}{\equiv}N: \leftrightarrow CH_3{-}CH{=}\overset{+}{N}{=}\overset{-}{N}: \leftrightarrow CH_3{-}\overset{+}{C}H{-}N{=}\overset{-}{N}: .$$

(VIIa) (VIIb) (VIIc)

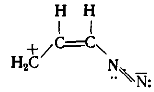
One of the limiting structures (VIIc) is probably not achieved at all, since any appreciable contribution by this formula to the resonance hybrid would result in descreening of the β-protons, while their experimental chemical shift has the normal value for a methyl group joined to an unsaturated system.

Among all the protons of vinyldiazomethane, the greatest chemical shift (τ = 8.93 p.p.m.) corresponds to the protons at the γ-carbon atom. This finding is analogous to the increase of the screening of the carbanion methylene protons in allylmagnesium halides[25-27]:



$$CH_2{=}CH{-}\overset{-}{C}H{-}\overset{+}{N}{\equiv}N: \leftrightarrow \overset{-}{C}H_2{-}CH{=}CH{-}\overset{+}{N}{\equiv}N: .$$

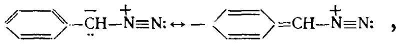
(VIIIa) (VIIIb)



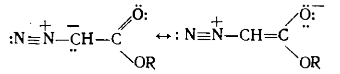
(IX)

The relative chemical shifts of the α-, β-, and γ-protons might lead to the conclusion that structure (VIIIb), in which there is the greatest negative charge at the γ-carbon atom, makes the most appreciable contribution to the real state of the molecule. However, this kind of interpretation of the PMR spectra of vinyldiazomethane must be treated with caution, since such appreciable screening of the γ-methylene protons is possible also when vinyldiazomethane exists in the *cis*-form (IX); it is then postulated that the screening effect of the NN bond is similar to that of the C=C and C=O bonds[28].

The chemical shifts of the α-protons of phenyldiazomethane and diazoacetic ester also indicate a greater contribution by the carbanion structure (II) compared with structure (I); the carbanion forms (Xa) and (XIa) of these diazo-compounds can be additionally stabilised by the transfer of the negative charge from the α-carbon atom to the phenyl or alkoxycarbonyl group [structures (Xb) and (XIb)].

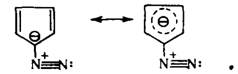


(Xa) (Xb)



(XIa) (XIb)

In diazocyclopentadiene the chemical shift of the β-ring proton is similar to the shift of the proton in cyclopentadienyl-lithium, which suggests that diazocyclopentadiene (XII) has almost entirely the carbanionic structure in the ring which thus has the properties of a non-benzenoid aromatic system[29,30]†.



(XIIa) (XIIb)

Thus the carbanionic and nucleophilic nature of diazoalkanes, which is assessed on the basis of their chemical properties, are consistent with qualitative PMR spectroscopic data.

It must be emphasised that the terms "carbanionic" nature and "carbanionic" structure should not be understood solely as implying the transfer of the negative charge of the CN_2 group to the α-carbon atom (which can in fact occur only in diazomethane). They should be understood in a wider sense as the transfer of a major fraction of the negative charge to the α-carbon atom and to the substituents linked to it, which in fact occurs in all diazomethane derivatives

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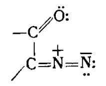
†Another aliphatic diazo-compound, which is also representative of a non-benzenoid aromatic system—diazocyclononatetraene—has been recently reported[31]. Its properties are being investigated.

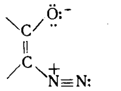
It follows from the above that the PMR spectroscopic method is used mainly to investigate the electronic structure of diazo-compounds with hydrogen atoms or hydrocarbon groups linked directly to the α-carbon atom. On the other hand, the interpretation of PMR spectroscopic data for α-diazocarbonyl and particularly α-diazo-$\beta\beta'$-dicarbonyl compounds is difficult and therefore infrared spectroscopy is widely employed to investigate the structures of these diazo-compounds.

α-Diazocarbonyl and α-diazo-$\beta\beta'$-dicarbonyl compounds occupy a somewhat special place among aliphatic diazo-compounds. They have a number of unusual properties for diazoalkanes: high resistance to the action of acids and heat, the absence of characteristic carbonyl reactions in many cases, and the capacity of individual compounds to form derivatives similar in type to aromatic diazonium salts[32].

Two limiting structures have been proposed for aliphatic diazocarbonyl compounds, for which the terms "diazo-oxide" (XIIIa) and "diazoanhydride" (XIIIb) have become established in the literature[32]:



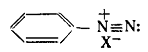
(XIIIa)



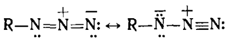
(XIIIb)

The contributions by these structures to the resonance hybrid are estimated on the hypothesis that the transition from structure (XIIIa) to (XIIIb) will entail corresponding changes in the infrared spectrum. In consequence of the decrease of the double bond character in the carbonyl group, a shift of the absorption band to the long-wavelength region compared with the usual frequency for the keto- (or alkoxycarbonyl) group is to be expected. In the diazo-group there will be a change from a system of cumulative bonds in (XIIIa) to the NN triple bond of the diazonium structure in (XIIIb), which should give rise in the infrared spectrum to a shift of the absorption band associated with the NN stretching vibrations towards shorter wavelengths compared with diazohydrocarbons. These shifts of the absorption bands due to CO and NN stretching vibrations in fact characterise the contributions by structures (XIIIa) and (XIIIb) to the real state of the molecule[32-37].

In order to discover the region in which the absorption bands of the diazo-group in diazocarbonyl compounds may be located, we shall consider the aromatic diazonium salts (XIV) and the azides (XV):



(XIV)



$$R{-}\overset{+}{N}{=}\overset{-}{N}{=}\ddot{N}{:} \leftrightarrow R{-}\overset{=}{\ddot{N}}{-}\overset{+}{N}{\equiv}N{:}$$

(XV)

The real state of diazonium salts can be quite justifiably expressed by structure (XIV), the diazo-group absorbing in the region 2200–2300 cm^{-1}; on the other hand, the absorption by azides (XV), where the contributions by both structures are approximately equal, is observed in the region 2100–2160 cm^{-1}.[38,39]

Thus the diazo-group in diazocarbonyl compounds should absorb in the region 2000–2300 cm^{-1}. The greater is the shift within these limits towards higher frequencies, the greater is the contribution by structure (XIIIb) to the resonance hybrid, and the greater is the shift towards lower frequencies, the greater is the contribution by structure (XIIIa) (Table 2).

Naturally, the contribution by the diazoanhydride structure is particularly large in those compounds where the transition to the diazo-oxide form is impossible for some reason; an example of this is 5-diazouracil (ν_{N_2} = 2190 cm^{-1}).[32]

Absorption by the CO groups in diazocarbonyl compounds is to be expected in the region between 1720 cm^{-1} (absorption by the carbonyl group in ordinary ketones) and 1600 cm^{-1} (absorption by the carbonyl group in enolised β-dicarbonyl compounds with an intramolecular hydrogen bond)[32]. The greater is the shift towards lower frequencies, the greater is the contribution of the CO group to the formation of structure (XIIIb) and conversely (Table 3).

Table 2. The colour of aliphatic diazo-compounds and the frequencies of the absorption bands due to the diazo-group[32-37,40-42].

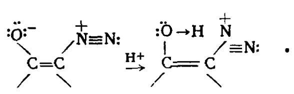
Diazo-compound	ν_{N_2}, cm^{-1}	Colour
Cyclic diazodicarbonyl compounds	2150-2190	colourless
R'-CO-CN$_2$-CO-R	2140-2160	colourless, yellow
R-CO-CN$_2$-R' (linear and cyclic)	2080-2130	greenish-yellow
Diazohydrocarbons	2020-2120	greenish-yellow, red

It was found[33,34] that not only the magnitude of the shift of the absorption band of the NN stretching vibrations but also the molar integral absorption corresponding to this band may serve as a criterion of the involvement of the limiting forms (XIIIa) and (XIIIb) in the resonance hybrid. The greater is the contribution by the diazoanhydride form (XIIIb) and therefore the greater is the high-frequency shift of the NN stretching vibration band, the lower is the molar integral absorption corresponding to this band. For example, for diazodicarbonyl compounds with an enhanced contribution of the diazoanhydride form, it is smaller by a factor of 1.5–2 than for diazomonocarbonyl compounds, amounting to (3.2–4.1) × 10^{-4} litre mole^{-1} cm^{-1} for the former and (4.6–5.2) × 10^{-4} litre mole^{-1} cm^{-1} for the latter[33-35].

Table 3. Absorption by the CO group in carbonyl and diazocarbonyl compounds[32].

Diazocarbonyl compound	$\nu_{C=O}$ in diazocarbonyl compounds, cm^{-1}	$\nu_{C=O}$ in carbonyl compounds, cm^{-1}
R—CN$_2$—CO—R'	1640—1670	1705—1725
R—CN$_2$—COOR'	1670—1720	1735—1750
R—CN$_2$—CH$_2$—COOR'	1735—1750	1735—1750
H—CN$_2$—CO—R'	1620—1630	1705—1725
H—CN$_2$—COOR'	1690	1735—1750

The structure of diazocarbonyl compounds approaches more closely the diazonium structure the greater is the number of carbonyl groups adjacent to the diazo-group. Then in the series of aliphatic diazo-compounds there is an increase in stability; thus diazoketones, which usually have a yellow or a greenish-yellow colour, are decomposed slowly by acetic and benzoic acids and fairly rapidly by inorganic acids. Diazodicarbonyl compounds are much more resistant to the action of acids. They can be frequently dissolved in concentrated sulphuric acid and be isolated unchanged on dilution with water. They are decomposed by concentrated acids only on heating. The explanation is that in diazodicarbonyl compounds, where the structure (XIIIb) makes a particularly large contribution, the proton is attached to the strongly electronegative oxygen atom and not to the α-carbon atom [form (XIIIa)] with formation of an unstable diazonium ion:



For this reason, the greater is the contribution by structure (XIIIb), the more resistant is the diazocarbonyl compound to the action of acids[32].

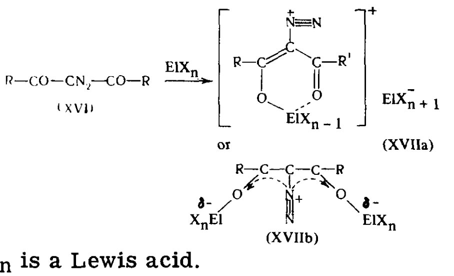
All the findings described above hold also for α-diazocarbonyl compounds; the carbonyl group in the β-position relative to the diazo-group makes no contribution to the formation of the diazoanhydride structure (Table 3). The contribution by structure (XIIIb) to the real state of the molecule increases when electron-accepting substituents (halogens and carbonyl or alkoxycarbonyl groups) are present next to the carbonyl or diazo-groups and decreases on introduction of electron-donating groups (for example, alkyl groups), which is confirmed by the spectroscopic and chemical properties in the series of diazocarbonyl compounds[33-35].

The decrease of the quantum yield of the photolysis of diazocompounds on passing from diazohydrocarbons to diazocarbonyl compounds is also explained by the increased contribution of the more stable diazonium structure (XIIIb)[43] (Table 4).

Table 4. Quantum yields of the photolysis of diazo-compounds[43].

Diazo-compound	Quantum yield
Ph_2CN_2	0.78
$C_2H_5OOCCHN_2$	0.66
$PhCOCHN_2$	0.46
$(PhCO)_2CN_2$	0.31
p-$(N_2CHCO)_2C_6H_4$	0.15

There exist also derivatives of aliphatic diazo-compounds whose structure is very close to that of diazonium salts; these are adducts of diazodicarbonyl compounds with Lewis acids—(XVIIa) or (XVIIb):[44-48]



where ElX_n is a Lewis acid.

Colourless crystalline compounds are formed as a result of the addition of the Lewis acid to the oxygen atom, which entails additional withdrawal of the negative charge from the carbon atom of the CH_2 group and the structure acquires the properties of an aromatic diazonium salt. This is indicated by the shift of the absorption band of the diazo-group of the adduct to the region 2180–2140 cm^{-1} relative to the absorption by the initial diazodicarbonyl compounds (XVI) (2130–2150 cm^{-1}).

Thus α-diazocarbonyl and particularly α-diazo-$\beta\beta'$-dicarbonyl compounds are intermediate as regards their chemical properties and spectroscopic characteristics between diazohydrocarbons and aromatic diazonium salts. A group of very interesting compounds—*o*- and *p*-quinone diazides and *p*-iminoquinone diazides[49], the discussion of which is outside the scope of the present review—also belong to this class.

The spectroscopic characteristics of aliphatic diazo-compounds examined in this section suggest with a fair degree of certainty that either the carbanion form or the diazoanhydride form similar to it (in the case of diazocarbonyl compounds) make the greatest contribution to the real state of these compounds. However, it must be emphasised that these conclusions are purely qualitative, whereas for some time now it has been necessary to examine the structures of diazo-compounds also on a quantitative basis‡.

2. LCAO-MO Calculations for Aliphatic Diazo-compounds

Calculations on the π-electron structure of diazoalkanes by the LCAO-MO method have been carried out by Schuster and Polansky[50] and by Simon and Badilescu[51]. They found the values of π-electron energy, delocalisation energy, the bond orders, and atomic charges. On this basis, attempts were made to establish to what extent the calculated data agree with experiment and what additional information about the structure and properties of aliphatic diazo-compounds may be obtained with their aid.

The delocalisation (E_D) and combination (E_C) energies of diazoalkanes may be used as criteria of their relative resistance to the action of acids and heat[50]. The combination energy is regarded as the energy contribution when diazo-compounds are formed from the π-electron system of the CN_2 group and the π-electron systems of the substituents. Table 5 lists the values of E_D and E_C for a number of diazoalkanes. It shows that, with decrease if the resistance to the action of acids and heat in the series diazomethane, diazoethane, and dimethyldiazomethane[2], there is a parallel decrease of the E_D values for these compounds. However, on passing from diazomethane and its alkyl-substituted derivatives to diazoalkanes, where the substituents exhibit a conjugation as well as an inductive effect, E_D ceases to be a good criterion of the stability of diazo-compounds, becoming inconsistent with experimental data.

In order to account for the difference in the resistance of these diazoalkanes to the action of acids, it is best to

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‡For a quantitative estimation of the contributions by the diazonium and diazohydrocarbon structures to the resonance hybrid of diazo-compounds, Fahr attempted to employ the difference between the frequencies of the NN stretching vibrations of the diazo-group and molecular nitrogen (ν_{NN} = 2331 cm^{-1}): the smaller the difference the closer is the structure to the diazonium form and conversely the greater the difference the closer is the structure to the diazohydrocarbon form. There are corresponding changes also in the chemical properties of the compounds (private communication).

employ the values of E_C: the increase of the resistance of diazo-compounds to acids in most cases agrees with the increase of their E_C values. Table 5 shows that only diphenyldiazomethane, which is in fact more stable than phenyldiazomethane, deviates from this series. The authors explain this by the fact that the angle of rotation of both phenyl groups relative to the plane of the diazo-group was chosen arbitrarily to facilitate the calculation.

Table 5. Delocalisation energies (E_D), combination energies (E_C), and the losses of the delocalisation energy ($E_D^* - E_D$) of diazoalkanes[50,51].

Diazo-compound	E_D, β	E_C, β	$\lvert E_D^* - E_D \rvert$, β
CH_2N_2	0.7674	—	1.8946
CH_3CHN_2	0.6981	—	—
$(CH_3)_2CN_2$	0.6588	—	—
$C_2H_5OOCCHN_2$	1.5702	0.5106	1.207
CH_3COCHN_2	1.4284	0.5406	—
$PhCOCHN_2$			1.1458
$PhCHN_2$	3.3298	0.6240	—
Ph_2CN_2	5.3193	0.5519	1.1160
$(C_2H_5O_2C)_2CN_2$	2.3154	1.5480	—
$N_2CHCO—(CH_2)_2—COCHN_2$			1.1190
Diazofluorene	6.3709	1.2201	—
Diazocyclopentadiene	2.8653	1.6258	—

If one remembers that diazoalkanes are nucleophilic agents whose reactivity should be determined to a first approximation by the localisation of the negative charge in the CH_2 group (without taking into account steric and certain other factors), then we should have the following general tendency: a decrease of the reactivity of diazoalkanes with increasing E_D and E_C. In fact in the series of diazomethane and its alkyl-substituted derivatives the increase of nucleophilic activity is accompanied by a decrease of E_D; there is a similar decrease of E_C in the series of diazo-compounds whose substituents are conjugated with the diazo-group.

Another criterion of the reactivity of diazo-compounds, proposed by Simon[51], is the loss of delocalisation energy ($E_D^* - E_D$). Its value characterises the decrease of E_D on transition from the ground state of the molecule to the activated complex in which the conjugation is weakened at the CN bond to be dissociated. It is believed[51] that $E_D^* - E_D$ can be usefully employed only to characterise adiabatic reactions, i.e. reactions in which the radical formed is in a singlet state. On the other hand, when the reaction is non-adiabatic, i.e. there is a change in electron spin in the activated complex with subsequent formation of a triplet ground state, this criterion is no longer valid.

Table 5 lists the values of $E_D^* - E_D$; in general (with the exception of diazomethane) there is an increase of the thermal and photolytic stability of diazoalkanes with increase of $E_D^* - E_D$.

Schuster and Polansky[50] determined the π-electron contribution to the enthalpy of decomposition of diazonium cations (ΔH_π) characterising the change in π-electron energy on passing from the diazonium cation to a carbanion cation and nitrogen: $RN_2^+ \rightarrow R^+ + N_2$. The results are presented in Table 6.

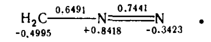
It is seen that the phenyldiazonium cation is more stable than the methyldiazonium cation to the extent of 0.63 β. Such quantum-mechanical examination of diazo-compounds permits the solution of many problems, in particular the problem of the structure of the simplest representative of this class—diazomethane.

The dipole moment of diazomethane (μ = 1.5 D) does not provide unambiguous information about the relative contributions of the two forms [(I) and (II)] to the real state of the molecule[52]. The dissociation energy of the CN bond in diazomethane found from mass-spectrometric data is low (1.9 eV)[53] and closer to the energy of a single than a double bond, i.e. this suggests that structure (II) predominates. The above results (p. 835) of the study of the PMR spectra of diazomethane also confirm its carbanionic structure.

Table 6.

R	CH_3	C_6H_5	p-$(CH_3)_2N—C_6H_4$
$\Delta H_\pi \beta$	−0.2463	+0.3831	+0.4056

The molecular diagram (XVIII) of diazomethane calculated by Schuster and Polansky[50] also confirms the greater contribution by the carbanionic structure, as can be inferred from the negative charges at the α-carbon and β-nitrogen atoms and the bond orders:



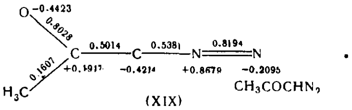
$$\underset{-0.4995}{H_2C}\overset{0.6491}{—}\underset{+0.8418}{N}\overset{0.7441}{\equiv}\underset{-0.3423}{N} \,.$$

(XVIII)

The molecular diagrams of other diazo-compounds[50] also confirm their carbanionic structure, deduced experimentally in earlier studies, and agree well with qualitative data derived from their PMR spectra.

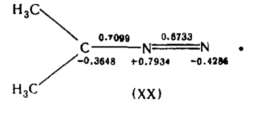
The PMR spectroscopic data suggested a transfer of part of the negative charge from the α-carbon atom of the CN_2 group to the substituents linked to it. This assumption is consistent with the molecular diagrams of phenyl- and diphenyl-diazomethane, diazoacetic ester, and others, and also with their chemical behaviour (for example, in reactions with ketones and α-diketones[54-58]).

The molecular diagrams of diazocarbonyl compounds likewise confirm that the diazoanhydride structure predominates to a considerable extent over the diazo-oxide structure, which is reflected in a transfer of the negative charge from the diazo-group to the carbonyl oxygen and an increase of the C–C bond order between the carbonyl and the diazo-group approximately to 1.5 units [see, for example, diagram (XIX)]:



(XIX)

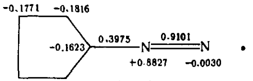
The calculated data show that only in dimethyldiazomethane, where the two methyl groups have a considerable +*I* effect, the contribution of the carbanionic structure is somewhat less than that of the non-carbanionic structure (XX):



(XX)

In all the remaining cases the carbanionic form with delocalisation of the negative charge over the α-carbon atom and the substituents linked to it makes the major contribution.

Diazocyclopentadiene is known to be very stable; it does not enter into typical reactions of diazoalkanes, but is capable of electrophilic substitution. These properties are consistent with the high value of E_C; it follows from the molecular diagram (XXI),



(XXI)

that electrophilic substitution should take place preferentially in the 2- and 5-positions; however, the difference between the charges in these positions compared with the 3- and 4- positions is not very great. When diazocyclopentadiene is nitrated, α- and β-nitrodiazocyclopentadienes are formed in proportions of 3 : 2.

Until recently it was believed that the α-nitrogen atom in diazo-compounds transmits electron density but its own charge remains unchanged. The calculated data[50] show that this is probably not entirely true and the positive charge of the α-nitrogen atom changes, albeit not very greatly [see, for example, the molecular diagrams (XVIII)–(XXI)].

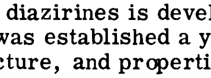
The data quoted show that the qualitative description of the structure of aliphatic diazo-compounds based on the study of the PMR and infrared spectra is confirmed quantitatively when quantum-mechanical computational methods are applied to diazo-compounds. Altogether the experimental and calculated data make it possible to describe accurately not only the fine structure of aliphatic diazo-compounds, which explains their behaviour in chemical reactions, but sometimes it is also possible to predict such behaviour.

III. ISOMERS OF ALIPHATIC DIAZO-COMPOUNDS

1. Cyclic Isomers (Diazirines)

Cyclic isomers of diazoalkanes (diazirines) were discovered in 1960–1961 independently by Paulsen[59] and Schmitz and Ohme[60]. The discovery of this new class of compounds was highly unexpected, since in earlier investigations[7,61] cyclic structures were discussed as possible alternatives for aliphatic diazo-compounds, but it was never suggested that the cyclic isomers can exist as a separate class of compounds.

However, it was found that frequently it is easier to obtain the more stable cyclic isomers than the less stable linear diazo-compounds. The usual method of preparation of diazirines (XXIII) is by oxidising diaziridines (XXII):



(XXII) (XXIII)

The chemistry of diazirines is developing very rapidly and their structure was established a year after discovery. The synthesis, structure, and properties of diazirines have been described in detail in a monograph by Schmitz[62] and therefore here we shall consider them very briefly.

The bond lengths in diazirine were determined from its microwave spectra: 1.48 Å (C–N) and 1.23 Å (N–N). Its dipole moment is 1.59 D, i.e. very close to the dipole moment of diazomethane (see p. 838).[63-65]

The PMR spectrum of diazirine in carbon tetrachloride has a singlet at τ = 9.60 p.p.m. The signal of the protons at the ring carbon atom is located in a relatively high field, which indicates the presence of a strained three-membered ring[66].

The equivalence of both nitrogen atoms was demonstrated in pentamethylenediazirine as an example using a tracer atom method[67].

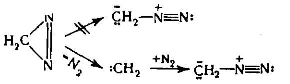
The ultraviolet spectra of diazirines have an absorption maximum at 340 nm, which is close to the absorption of azomethane (λ_{max} = 343 nm) but differs sharply from the absorption by the isomeric compounds diazomethane (λ_{max} = 412 nm) and *N*-isocyanamine (λ_{max} = 247 nm).[68,69]

In the infrared spectra the absorption band of the azo-group at 1580–1600 cm^{-1} is observed instead of the absorption band of the linear diazo-group in the region of 2000–2200 cm^{-1}.

The difference between the structures leads also to a sharp difference between the chemical properties; diazoalkanes are some of the most reactive substances known in organic chemistry, while diazirines are much more stable. Thus diazirine is more stable that diazomethane to the extent of 30 kcal mole^{-1} (according to mass-spectrometric data, the heats of their formation are respectively 79 and 49 kcal mole^{-1}).[53,70-72] Aliphatic diazo-compounds are extremely sensitive to acids, while alkyl-substituted diazirines decompose only when treated with concentrated inorganic acids (80–90% sulphuric acid).

In almost all reactions of diazoalkanes new C–C bonds are formed, while in the case of diazirines Thiele's view that the N=N bond is more reactive is confirmed. For example, hydrogen and Grignard reagents readily add to the nitrogen–nitrogen double bond. However, there are also similarities between the reactions of these two classes of compounds: both diazoalkanes and diazirines decompose on photolysis and thermolysis with evolution of nitrogen and the formation of carbenes.

Diazirines can be converted into linear diazo-compounds: it has been shown by infrared spectroscopy that, when diazirine is irradiated in a solid nitrogen matrix at 20°K, diazomethane is formed[72]. Experiments using labelled nitrogen suggest that the mechanism involving the splitting off of molecular nitrogen and its subsequent addition to the carbene with formation of the linear diazomethane is more likely than the cleavage of the three-membered ring and direct formation of diazomethane:



It has also been shown[73] that diazomethane is formed in the photolysis of diazirine in the gas phase too. In the liquid phase the formation of the linear diazo-compound is observed in the photolysis of pentamethylenediazirine[74]. Studies dealing with the conversion of diazirines into linear diazo-compounds and designed to determine the mechanism of this process are being continued.

2. Linear Isomers (*N*-Isocyanamines)

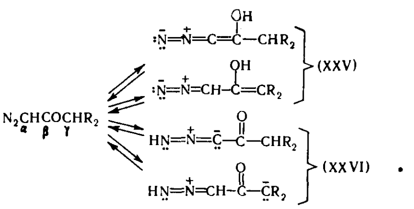
For a long time there existed the hypothesis of a possible tautomeric equilibrium between two linear structures, namely between diazomethane and isodiazomethane[75,76]:

$$\ddot{\bar{C}}H_2-\overset{+}{N}\equiv N: \rightleftarrows CH\equiv\overset{+}{N}-\ddot{\bar{N}}H$$

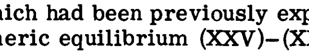
(XXIV)

Only in recent years, as a result of Koster's work[22] on the PMR spectra of diazomethane at different temperatures and a careful study of the infrared spectra of 12 diazomethane specimens prepared in different ways[77], was the absence of diazo–isodiazo tautomerism in diazomethane demonstrated.

The absence of tautomerism in diazohydrocarbons did not allow an *a priori* rejection of such isomerism in diazocarbonyl compounds, where the mobility of the α- and γ-hydrogen atoms should be enhanced owing to the influence of the carbonyl group. In this case two types of tautomerism could be postulated: keto–enol (XXV) and diazo–isodiazo (XXVI):[78]



However, Fahr[79] made a detailed study in 1959 of the ultraviolet spectra of diazocarbonyl compounds and showed that the change in the spectroscopic characteristics of these substances on passing from hydrocarbon to hydroxylated solvents, which had been previously explained by a shift of the tautomeric equilibrium (XXV)–(XXVI), is in fact due to the formation of a hydrogen bond:



Thus it has now been rigorously demonstrated that there is no tautomerism in aliphatic diazo-compounds. However, there exists a linear isomer of diazomethane, discovered more than 30 years ago[80–82]. It was obtained by Müller[80–83] by the action of an aqueous solution of ammonium chloride on the compound formed by the reaction of diazomethane with methyl-lithium. Three limiting structures [(XXVIIa)–(XXVIIc)] were suggested for the very unstable compound (called "isodiazomethane") isolated after vacuum distillation of the solvent:

$$\underset{a}{\underset{..}{\overset{-}{C}}H=\overset{+}{N}=\underset{..}{N}H} \leftrightarrow \underset{b}{\overset{+}{C}H=\underset{..}{N}-\underset{..}{\overset{-}{\ddot{N}}}H} \leftrightarrow \underset{c}{CH\equiv\overset{+}{N}-\underset{..}{\overset{-}{\ddot{N}}}H}\ .$$

(XXVII)

Thus, on the basis of the electronic configuration, the isomeric diazomethane, whose properties differ appreciably from those of the usual diazomethane, was regarded[82] as an analogue of hydrazoic acid (XXVIII). This analogy was apparently confirmed by the instability of both compounds and the similarity of their ultraviolet spectra.

$$:N\equiv\overset{+}{N}-\underset{..}{\overset{-}{\ddot{N}}}H \leftrightarrow \underset{..}{\overset{-}{\ddot{N}}}=\overset{+}{N}=\underset{..}{N}H\ .$$

(XXVIII)

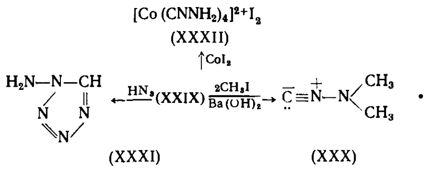
However, the latest studies have shown quite rigorously that "isodiazomethane" is in fact *N*-isocyanamine (the amide of fulminic acid) (XXIX):

$$\underset{..}{\overset{-}{C}}\equiv\overset{+}{N}-\underset{..}{N}H_2 \leftrightarrow :C=\underset{..}{N}-\underset{..}{N}H_2\ .$$

(XXIX)

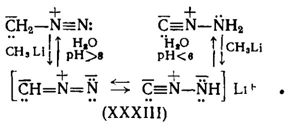
This structure of the isomeric diazomethane is also confirmed by infrared and PMR spectroscopic data[83]. The infrared spectrum of compound (XXIX), like that of cyanamide[84], contains absorption bands associated with the NH stretching vibrations (3170 and 3290 cm^{-1}) and deformation vibrations (1630 cm^{-1}) and also a weak absorption at 2130 cm^{-1} attributed to the isonitrile group. The PMR spectrum of the isomeric diazomethane contains only one broad band (τ = 3.6 p.p.m.) which is not split when the temperature is sharply reduced and resembles in shape and position the corresponding signal from carboxylic acid amides (τ = 3.5–3.8 p.p.m.). The compound readily exchanges both hydrogen atoms for deuterium and under the action of alkali is rapidly converted into diazomethane. In the first case the signal in the PMR spectrum completely disappears and in the second it is replaced by the signal due to the protons in the diazomethane molecule (τ = 6.8 p.p.m.).[21]

The chemical reactions of the isomeric diazomethane are satisfactorily consistent with the spectroscopic data, confirming that its structure is (XXIX). Thus it proved possible to carry out a reaction involving the aminogroup: *N*-isocyanodimethylamine (XXX), previously described in the literature, was obtained[85]:



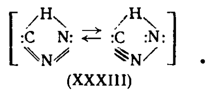
Like other isonitriles, *N*-isocyanamine readily forms the corresponding tetrazole (XXXI) by reaction with hydrazoic acid and complexes (XXXII) with cobalt and iron salt. Other reactions of compound (XXIX) characteristic of isonitriles have also been investigated[83,85–87]. Consequently both physical and chemical research methods fairly clearly demonstrate that the isomeric diazomethane is the first member of the series of *N*-isocyanoalkylamines and *N*-isocyanodialkylamines, which were described for the first time quite recently[88].

Compared with diazirine, *N*-isocyanamine shows somewhat greater similarity to diazomethane. This is shown by the instability of both isomers and by their capacity for ready interconversion, whereas diazomethane is not converted into diazirine. The diazomethane–fulminic acid amide interconversions do not take place directly but only via their deprotonated form—the diazomethyl anion (XXXIII)—which is readily obtained by the action of methyl-lithium on diazomethane or its isomer (XXIX). On hydrolysis in an acid medium, diazomethyl-lithium forms the amide (XXIX) and on hydrolysis in an alkaline medium diazomethane is formed:



(XXXIII)

The tautomeric conversion of the anion is apparently facilitated by the hydrogen bond in the transition state (XXXIII):[83]

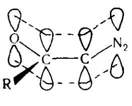


(XXXIII)

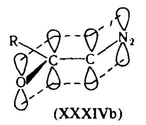
Nor can one exclude the possibility that the protonation of the diazomethyl anion involves the formation of isodiazomethane proper (XXIV), which is an extremely unstable intermediate in the transformation of diazomethane into *N*-isocyanamine (and conversely). However, this hypothesis requires rigorous tests.

3. *cis*-*trans*-Isomerism of Diazocarbonyl Compounds

It follows from the above (pp. 836–837) that whatever the contribution of structure (XIIIb) to the real state of the molecule of the diazocarbonyl compound, the C—C bond between the carbonyl and the CN_2 group will always exhibit a certain amount of double bond character. This should prevent free rotation about the C–C bond and consequently the existence of two forms of diazocarbonyl compounds may be expected: *cis* - [(XXXIVa)] and *trans*- [(XXXIVb)]. In this case the terms "*cis*" and "*trans*" refer to the relative positions of the π-electron clouds of the carbonyl group and diazo-group, while the group linked to the carbonyl is located in the *trans*-position relative to the diazo-group in the *cis*-form (and conversely):



(XXXIVa)
cis-



(XXXIVb)
trans-

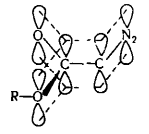
The hypothesis of conformational isomerism of α-diazoketones was put forward by Pecile et al.[89] and later by Leveson and Thomas[90] to account for certain characteristics of their infrared and ultraviolet spectra. However, the evidence which they adduced in favour of this assumption was not sufficiently rigorous.

A decisive proof of the real existence of the conformational isomerism of α-diazoketones was obtained by Kaplan and Melloy who investigated the PMR spectra of diazocarbonyl compounds (XXXV) at different temperatures[91–93]:

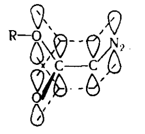
$RCOCHN_2$ a. R=H; d. R= t-C_4H_9; g. R=C_2H_5O;
(XXXV) b. R=CH_3; e. R=Ph—CH_2; h. R=Ph;
c. R=C_2H_5; f. R=CH_3O; i. R=*p*=NO_2—C_6H_4.

They made the following observations: in the majority of the diazocarbonyl compounds investigated (XXXVa, b, c, e, f, g) the signal of the methylidyne proton is gradually broadened as the temperature is reduced and finally splits into two components. This type of change in the PMR spectra is characteristic of an equilibrium mixture of two substances: the average signal is observed at high rates of interconversion and two signals are observed at low rates. The constancy of the spin–spin coupling constant for the methylidyne proton ($J_{^{13}C-H}$) corresponding to the average signal and the signals of each of the substances undergoing conversion is evidence that any type of tautomerism involving the methylidyne proton is impossible. Consequently in this case only a *cis*–*trans* isomeric equilibrium can exist and the two peaks in the low-temperature spectra correspond to the *cis*- and *trans*-forms of the diazocarbonyl compound. On the basis of analogies in the literature[94,95], the signal in the stronger field was attributed to the *trans*-form, whence the ratio of the *cis* - and *trans* -conformers may be obtained from the ratio of the signal intensities.

Table 7 shows this ratio for the diazocarbonyl compounds (XXXV) investigated varies markedly as a function of the group R. The high content of the *cis*-conformer in compounds (XXXVb, c, e) compared with diazoacetaldehyde can probably be explained by the steric hindrance to the formation of the *trans*-forms of these diazocarbonyl compounds. In general, one may expect that the *cis*/*trans* ratio will increase as the steric requirements of the substituents become more stringent. However, this factor is not always decisive. Thus, on the basis of steric considerations, an appreciable predominance of the *cis*-form might have been expected in diazoacetic esters (XXXVf, g), but the *cis*/*trans* ratio is in fact only a little in excess of unity. This can probably be accounted for by the fact that the π-electron systems of both forms have the same geometry (XXXVIa, b), which leads to identical interactions: as a result, the difference between the free energies ΔF of the two conformers is insignificant.



(XXXVIa)



(XXXVIb)

Table 7. Compositions in, and activation energies E_a for, the *cis*–*trans* interconversion of diazocarbonyl compounds[92].

Compound	Fraction		E_a, kcal mole^{-1}(°C)
	cis	*trans*	
(XXXVa)	0.690	0.310	
(XXXVb)	0.924	0.076	15.5±0.9 (11.8)
(XXXVc)	0.941	0.059	16.1±0.6 (6.5)
(XXXVd)	0.990	0.010	
(XXXVe)	0.962	0.038	18.1±0.6 (1)
(XXXVf)	0.538	0.462	12.5±0.9 (—25)
(XXXVg)	0.540	0.460	9±0.8 (—32)

For a number of compounds (XXXVd, h, i), only one signal is observed over the entire temperature range investigated. Among the explanations proposed for this experimental finding, the most acceptable is the hypothesis that all these diazoketones exist mainly in the *cis*-form owing to the strong steric interaction between the diazo-group and the bulky R radical in the *trans*-form.

The activation energy E_a which determines the barrier to free rotation, varies from 9 to 18 kcal mole^{-1} (Table 7)§. Comparison of the values of E_a and the orders of the central C–C bond[50] shows that a decrease of the double bond character of this linkage lowers the barrier to free rotation.

The existence of diazoketones in the *cis*- and *trans*-forms can be used to explain some of their reactions (in particular, their decomposition processes); it is then of course necessary to take into account the relative rates of the reaction and of the *cis*–*trans* transition. Naturally, the possibility of the formation of the reaction products from the preferred conformation must be considered only when the rate of interconversion of the two forms is lower than the rate of the decomposition reaction.

Assuming that the formation of ketens in the Wolff rearrangement takes place as a concerted synchronous process[97] and only via the *cis*-form of the diazoketone, which is the most favourable for this purpose, Kaplan and Melloy made a fairly successful attempt to account for the results of certain reactions of α-diazoketones[92,98,99].

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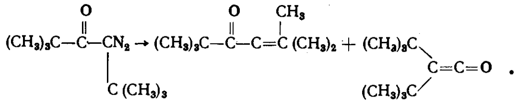
§E_a for the interconversion of the *cis*- and *trans*-conformers of diazoacetone was recently calculated[96] by Hückel's molecular orbital method. The calculated value (about 14 kcal mole^{-1}) agrees well with the experimental activation energy found by Kaplan and Melloy (Table 7).

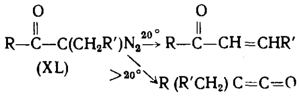
Thus, owing to the powerful repulsion of the two t-butyl groups, the diazoketone (XXXVII) cannot exist in the *cis*-form and therefore its photolytic, thermal, and catalytic decomposition results in the formation of compound (XXXVIII) and only traces of the keten (XXXIX):



$$(CH_3)_3C-\overset{\overset{O}{\parallel}}{C}-\underset{\underset{C(CH_3)_3}{|}}{C}N_2 \rightarrow (CH_3)_3C-\overset{\overset{O}{\parallel}}{C}-C=\overset{\overset{CH_3}{|}}{C}(CH_3)_2 + ((CH_3)_3C)_2C=C=O\ .$$

(XXXVII) (XXXVIII) (XXXIX)

At low temperatures the diazoketones (XL) also exist mainly as the *trans*-conformers. However, the formation of the *cis*-form is less sterically hindered and on raising the temperature the energy received by the molecules is apparently sufficient for the formation of appreciable amounts of the *cis*-conformer. For this reason, the photolytic and catalytic decomposition of diazoketones (XL) at 20°C leads mainly to compounds (XLI). At higher temperatures the ketens (XLII) are mainly obtained:



$$R-\overset{\overset{O}{\parallel}}{C}-C(CH_2R')N_2 \xrightarrow{20^\circ} R-\overset{\overset{O}{\parallel}}{C}-CH=CHR' \quad (XLI)\ .$$
$$\xrightarrow{>20^\circ} R(R'CH_2)C=C=O \quad (XLII)$$

(XL)

Thus the study of the conformational isomerism of diazoketones, which is itself of considerable theoretical interest, will undoubtedly prove useful also for a better understanding of the mechanism of the reactions of this class of compounds.

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Zhdanov Leningrad State University

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Dual Reactivity of Ambident Anions

S.A.Shevelev

The present state of the problem of the dual reactivity of ambident anions, i.e. anions with two reactive centres, is reviewed. The factors influencing the reactions of such anions are discussed and certain relations are interpreted from the standpoint of the principle of hard and soft acids and bases.
The bibliography includes 120 references.

CONTENTS

I. INTRODUCTION

Ambident anions are those which have two reactive centres linked into a single conjugated (mesomeric) system[†]. Ambident anions are capable of forming two series of derivatives in reactions with electrophilic agents, i.e. according to Nesmeyanov and Kabachnik[3] they exhibit dual reactivity. Examples of anions of this kind are the enolates of β-dicarbonyl compounds, phenoxides, cyanide, thiocyanate, and nitrite ions, the anions of nitro-compounds, oximes, carboxylic acid amides, dialkyl phosphorothioites, and dialkyl phosphorothioates, the anions of heterocyclic aromatic compounds or their derivatives (pyrrole, indole, 2-hydroxypyridine, hydroxypyrimidine, etc.), and others.

The capacity of such anions to react in two ways has been known for a long time but the factors influencing the mode of reaction have been virtually unknown and only in the last fifteen–twenty years have studies illuminating this problem been carried out.

Although there exist two modern reviews on the dual reactivity of ambident anions, published in 1964[2] and 1965[4] respectively, this field is developing so rapidly that a new review of the literature is required, particularly since during the period which has elapsed new hypotheses, which can be applied to this problem, have appeared and become established in chemistry. On the other hand, a fairly large number of contradictory data have accumulated in the literature and require a detailed discussion.

Therefore the author's aim is not to review the entire enormous literature on the dual reactivity of ambident anions, particularly since extensive literature data, apart from the reviews already mentioned[2,4], have been compiled also in a number of earlier publications[1,3,5,6], but merely to give a general account of the present state of the problem in the light of the work carried out in recent years.

II. RELATIONS BETWEEN THE STRUCTURE AND DUAL REACTIVITY OF AMBIDENT ANIONS

As already stated, both reactive centres of the ambident anion form a single mesomeric system and therefore the negative ionic charge is distributed between the two atoms which can be involved in the formation of a covalent bond on reaction with electrophilic agents. However, as a rule the main bulk of the charge is concentrated at one of the nucleophilic atoms and usually the atom which is more electronegative (according to Pauling's electronegativity scale of atoms); at the same time the less electronegative donor atom is more polarised[1,3,7][‡]. Thus the bulk of the negative charge in enolate anions and the anions of nitro-compounds is concentrated at the oxygen atom, while the carbon atom is more polarised; a similar relation obtains between the oxygen and nitrogen atoms in the nitrite ion and the anion of 2-hydroxypyridine, and between the nitrogen and carbon atoms in the pyrrole and cyanide anions.

Despite the fact that one donor atom has a higher electron density than the other, the reactions with electrophilic agents by no means always take place at the point with the highest electron density; very often the covalent bond is formed with the less electronegative atom. Nesmeyanov and Kabachnik[3] call this phenomenon reactive centre transfer[§]. They note[3] that the capacity of ambident anions to react with reactive centre transfer is related not so much to the distribution of the negative charge in the anions as to the capacity of the conjugated system for the electromeric shift of electron density necessary for the reaction, for example:

[†] The term “ambident anion” was proposed by Kornblum[1]. Gompper[2] suggests that such compounds be called “ambifunctional”, but this name is less widely used. The term “polydent anions” is employed to designate anions with three and more reactive centres.

[‡] The high polarisability of the less electronegative atom is probably due either to the considerable double bond character of its linkage, as in the case of the α-carbon atom in enolates, or a significant polarisability of the atom as such (phosphorus, sulphur, etc. atoms).

[§] The old concept that the reason for the dual reactivity of ambident anions is the existence of two anionic tautomers, each of which gives rise to its own series of derivatives, was disproved in the same investigation[3].

Thus the problem of the relation between the structure of the ambident anion and its capacity to react in different ways reduces largely to finding the relation between the structural parameters of the anion and the ease of the electromeric shift of electron density.

It is well known that certain ambident anions show a greater tendency to react in a particular way than others even though their structures are similar. Thus the anions of acetoacetic ester and acetylacetone exhibit a much greater tendency to react via the oxygen atom, than the anion of malonic ester; the anion of phenol also tends to react much more readily via the oxygen atom than the anion of β-naphthol (see, for example, Kornblum and Lurie[8]). In contrast to the anions of monobasic carboxylic acids, the phthalimide ion is alkylated virtually only at the nitrogen atom[3]. More such examples may be quoted. At the same time it must be emphasised that these data are purely qualitative, since so far very few studies have been made in which the dual reactivities of various ambident anions, including those with similar structures, were compared in sufficient detail under standard conditions using electrophiles of different types.

Unfortunately there are no reliable criteria which would relate the electron structure or some other parameters of ambident anions (or their conjugate acids) to their capacity to react with transfer of the reaction centre.

An attempt has been made[9] to relate the dual reactivity of the anions of β-dicarbonyl compounds to the distribution of π-electron density and certain other electronic parameters, obtained by the LCAO-MO method (in the Hückel approximation). However, as stated above, the capacity of the ambident anion to react in a particular way is not directly related to the distribution of electron density. At the same time one cannot exclude the possibility that this approach will prove fruitful in the case of electrophiles with significant positive charges, which usually react at the site with the greatest electron density (see Section V). Moreover, the tendency to react via the oxygen atom can probably be estimated using data for the variation of the electron density at this atom in a series of related anions[9]. However, we believe that in the general case the electron density at a carbon atom cannot be correlated with its reactivity (as was done by Gren and Vanag[9]) (see also Klopman[10]).

This does not of course imply that in principle the quantum-chemical approach is inapplicable to the estimation of the dual reactivity. The recent study by Klopman[10], where the possibility in principle of a quantum-mechanical calculation of the reactivity of ambident systems (by the method of polyelectron perturbation) was demonstrated, has attracted attention from this standpoint.

Thus the relation between the structure and dual reactivity of ambident anions constitutes one of the least investigated problems.

III. THERMODYNAMICALLY AND KINETICALLY CONTROLLED REACTIONS

In the discussion of the factors influencing the mode of the reactions of ambident anions, it is necessary to distinguish clearly thermodynamically and kinetically controlled reactions. In kinetically controlled reactions the composition of the products is determined by the relative nucleophilicity of each of the donor atoms in the ambident anion in relation to the given electrophilic agent. On the other hand, in thermodynamically controlled reactions the most stable compound is the final product regardless of the reaction mechanism. The energy (heat) of formation of the compound, which can be estimated from the bond and conjugation energies[2], is a measure of its stability.

The reaction is thermodynamically controlled when the interaction of the electrophilic agent with the ambident anion is reversible. When the relative amounts of the reaction products are not determined by the nucleophilicity of the donor atoms but by their basicity in relation to the atom at which the substitution takes place—for example in alkylation by the basicity in relation to a saturated carbon atom[11].

It has been noted[2] that in many cases conclusions concerning the products of thermodynamically controlled reactions can be drawn from the basicity of particular donor atoms in relation to the proton: an electrophilic agent will form a bond preferentially with the atom of the ambident anion which is most basic in relation to the proton (the basicity in relation to the proton usually decreases in the series C > N > O > S).

The available data confirmed this hypothesis. For example, the product of the alkylation of the enolates of β-dicarbonyl compounds at the more basic atom (the carbon atom) is thermodynamically more stable than the O-alkylation product[12]. Similarly the product of the N-alkylation of the nitrite ion (nitroalkane) is more stable than the O-alkylation product (the corresponding alkyl nitrite)[13].

The question arises: in which cases should one expect the reaction with electrophilic agents to be thermodynamically controlled? In other words, in which cases are the reaction products capable of decomposing into the starting materials? Gompper[2] noted that this occurs frequently when the experiments are carried out with stable cations or when relatively stable cations (for example triarylcarbonium ions, the carbonium ions formed in the Mannich reaction, and aryldiazonium ions) are formed as intermediates. Thermodynamic control is also observed in reactions with electrophilic agents containing multiple bonds (for example, aldehydes and ketones—the addition of ambident anions to the carbonyl group). Moreover the tendency to undergo thermodynamically controlled reactions should increase with the stability of the anion. Thermodynamically controlled reactions are dealt with in greater detail by Gompper[2].

Henceforth in the discussion of factors influencing the dual reactivity of ambident ions, we shall consider only kinetically controlled reactions, although one must bear in mind that the possibility of thermodynamic control was not fully excluded in all the investigations considered.

IV. NUCLEOPHILIC PROPERTIES OF THE REACTIVE CENTRES OF AMBIDENT ANIONS

The problem of the dual reactivity of ambident anions in kinetically controlled reactions is the problem of the relative nucleophilicity of each of the donor atoms of the anion linked into a single mesomeric system.

The reactivity of the electron donor (nucleophilic agent) in substitution reactions (nucleophilicity) is determined by a number of factors[7,14-16]. The principal of these are the basicity and polarisability of the given nucleophilic atom and also the α-effect (the presence of an unshared electron pair at an adjacent atom)[7,17]. It follows that the contribution of each of these parameters to the overall reactivity of the nucleophilic agent depends to a considerable degree on the nature of electrophilic atoms at which the substitution takes place[7,14].

However, in the case of ambident anions it is impossible to determine the polarisability and basicity of each reaction centre independently of one another and consequently it is impossible to estimate in this way their nucleophilicity, since the two nucleophilic atoms are not independent but are linked into a single mesomeric system. Indeed in order to determine a parameter such as polarisability, it is necessary to know the molecular refraction of each of the donor atoms of the anion[7,17], whereas in fact it is only possible to determine the refraction of the anion as a whole. As regards the basicity (in relation to the proton), it is found that the protonation of the anion necessary to determine the basicity takes place with very significant redistribution of electron density in the conjugated system and consequently the equilibrium position does not reflect the "independent" basicity of each donor atom in the anions, particularly the atom with the lower electron density.

At the same time, although it is impossible to estimate quantitatively (or semiquantitatively) the reactivity of the donor centres of the ambident anion, it is possible to make a purely qualitative estimate of the relative nucleophilicities of both atoms of the anion in relation to a specific type of electrophilic agent. The principle of hard and soft acids and bases recently put forward by Pearson[13,18–21] is particularly suitable in this context. According to this principle, all Lewis bases (electron donors or nucleophilic agents) can be divided into two classes: hard and soft bases (some of these bases occupy an intermediate position). Similarly Lewis acids (electron acceptors or electrophilic agents) are also divided into two classes—hard and soft acids—some occupying an intermediate position.

Hard bases are Lewis bases with a high electronegativity, low polarisability, and resistant to oxidation, i.e. hard bases firmly retain their valence electrons.

Soft bases are Lewis bases with a low electronegativity, high polarisability, and readily oxidised, i.e. they retain their valence electrons less firmly.

Hard acids are Lewis acids with a high electronegativity, and a low polarisability; these properties correspond to a high positive charge and a small size of the acceptor atom and the absence from it of an unshared electron pair.

Soft acids are Lewis acids with a low electronegativity and a high polarisability; this property corresponds to a low positive charge (or absence of charge), a large size of the acceptor atom, and the presence of an unshared electron pair (*p* or *d* electrons) at this atom. It has been noted that not all the properties enumerated must necessarily be present together to assign an acid to a particular class[20].

The fundamental postulate of the concept of hard and soft acids and bases is as follows: hard bases are preferentially coordinated to hard acids and soft bases to soft acids.

According to Pearson, organic and inorganic molecules are regarded as acid–base complexes. For example, CH_3I is a complex of the acid CH_3^+ and the Lewis base I^-, CH_3COCl is a complex of the acid CH_3CO^+ and the base Cl^-, etc.[13,20] Consequently, it is possible to estimate the hardness (softness) of a given molecule in particular reactions, i.e. to estimate the hardness or softness of a particular reaction centre (atom) and of course it is necessary to take into account the mutual effects of all components of the complex.

Pearson enumerates the most widespread hard and soft acids and bases[19,20]. Examples of hard bases are: OH^-, H_2O, RO^-, ROH, R_2O, F^-, Cl^-, $CH_3CO_2^-$, SO_4^{2-}, NO_3^-, and RNH_2; soft bases: RS^-, RSH, R_2S, I^-, R_3P, C_2H_4, H^-, R_3C^-, and others.

Examples of hard acids are: the proton, cations of alkali and alkaline earth metals, aluminium, the carbonyl carbon atom (RCO^+), the phosphorus atom in the phosphoryl group (R_2PO^+), the sulphur atom in the sulphonyl group (RSO_2^+), and the hydrogen atom involved in the formation of a hydrogen bond; soft acids: cations of univalent copper, silver, univalent and divalent mercury, the sulphenyl sulphur atom (RS^+) and selenium and tellurium atoms in analogous groupings (RSe^+, $ReTe^+$), iodine, bromine, and oxygen atoms in those molecules where they behave as electrophilic centres (I^+, Br^+, HO^+, RO^+), BH_3, carbenes, and others. Among acids with intermediate properties mention should be made of the saturated carbon atom (R_3C^+) and the aromatic carbon atom ($C_6H_5^+$). For a more detailed list of soft and hard acids and bases, see Pearson[19,20] (and also Pearson and Songstad[13]).

It should be noted that the principle of hard and soft acids and bases is empirical and in fact constitutes a generalisation of experimental data. However, recently Klopman[10] gave a theoretical explanation of the principle of hard and soft acids and bases using the quantum-mechanical perturbation theory. He showed that[10] the softness (hardness) of a particular acid (acceptor atom) is determined by the energy of the lowest vacant orbital and the softness of a base (donor atom) by the energy of the highest occupied orbital, and, apart from the energies of orbitals themselves, account must be taken also of the solvation energy, i.e. the softness (hardness) is influenced by the solvent.

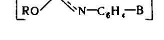
We shall now consider the applications of the concept of hard and soft acids and bases to ambident anions. As shown in Section II, one of the atoms of the ambident anion is usually more electronegative and the major part of the negative ionic charge is concentrated there, while the second atom is more polarisable.

Comparison of these data with the characteristic features of hard and soft bases (see above) leads to the conclusion that usually the less electronegative and more polarisable donor atom of the anion is a soft base while the more electronegative atom is a hard Lewis base[7,10,13,22]¶.

Thus in enolate anions the oxygen atom is hard and the carbon atom is soft[10,22]; in the thiocyanate anion the nitrogen atom is hard and the sulphur atom is soft[10]; in the nitrite ion the oxygen atom is hard and the nitrogen atom is soft[10]; etc.

The application of the principle of hard and soft acids and bases to ambident anions makes it possible to predict the preferential mode of reaction of these anions with various electrophilic agents: the soft donor atom of the ambident anions will be preferentially bound to a soft electrophilic agent, while the harder atom will be bound to a hard electrophilic agent. As will be shown below, this useful principle is confirmed by numerous experimental data.

¶ There are of course sometimes also ambident anions where both donor atoms have similar electronegativities and are included, according to Pearson's classification in a common series of bases (soft or hard). However, in this case too one of the atoms will be softer than the other. Such a situation will arise when, for example, both donor atoms are the same and differ only in substituents, as in the anions of *OO*-dialkyl-*NN'*-diarylphosphamidines (see Kabachnik and Gilyarov[23] and the references quoted by them):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An important conclusion, which may be derived from this principle, is as follows: the order of the relative nucleophilicities of the donor atoms of ambident anions can be decisively influenced by the nature of the electrophilic atoms at which substitution takes place. Therefore subsequently the principal features of the behaviour of ambident anions will be examined for each type of electrophilic centre separately. In the first place we shall examine substitution at a saturated carbon atom for which there are most data and then at other electrophilic centres (a carbonyl carbon atom, certain heteroatoms, etc.). This does not, of course, imply that the relative nucleophilicities of the donor atoms are the sole factors which influence the mode of reaction of ambident anions. As will be shown in subsequent sections, factors such as steric effects, solvent effects, the state of the salt in solution, and certain others frequently play a very considerable and sometimes a decisive role.

V. BEHAVIOUR OF AMBIDENT ANIONS IN SUBSTITUTION REACTIONS AT A SATURATED CARBON ATOM (ALKYLATION)

The factors which influence the mode of reactions of ambident anions have been investigated in greatest detail for the alkylation of these anions (substitution reactions at a saturated carbon atom). These data will be examined in the present section.

1. Electronic Effects in the Alkylating Agent

In 1955 two papers appeared almost simultaneously and proved to have a very significant influence on the understanding of the dual reactivity in ambident systems at the present time. In the first of these by Nesmeyanov and Kabachnik[3], apart from the general postulates concerning the causes of dual reactivity and the relation between the phenomenon with tautomerism, mentioned above, the fundamental relations determining the mode of reaction of ambident anions were generalised insofar as it was possible on the basis of the experimental data available at the time.

In particular it was pointed out that the mode of reaction is very significantly influenced by the electrophilic properties of the alkylating agent. Thus in salts of keto-enols or carboxylic acid amides where the bond between the oxygen atom of the anion and the metal cation is highly ionised and the alkylating agent is a cation or a strongly electrophilic molecule, a reaction involving the oxygen atom frequently takes place; on the other hand, when the electrophilic properties of the reactant are weak, the reaction takes place at the carbon atom of the enolate anion or correspondingly at the nitrogen atom of the amide anion.

Thus the electronic structure of the alkylating agent has a very significant influence on the mode of reaction of ambident anions.

In another paper, by Kornblum et al.,[1] it was shown that, when silver nitrite reacts with alkyl halides, the tendency towards alkylation at the atom with the maximum electron density, i.e. at the oxygen atom of the ambident nitrite ion, increases sharply on passing from primary to secondary and then to tertiary halides. This behaviour is related to the finding that the reaction of silver nitrite with alkyl halides takes place via an intermediate S_N2–S_N1 mechanism and, with increasing S_N1 character (the carbonium character) of the transition state, there is an increase in the tendency towards *O*-alkylation of the nitrite ions; on the other hand, the carbonium character of the transition state increases in the above series of alkyl halides.

Indeed, the silver ion coordinated to the halogen atom of the alkyl halide polarises the carbon–halogen bond, induces at the carbon atom a partial positive charge, and thereby increases the S_N1 character of the transition state, the ease of polarisation of the carbon–halogen bond increasing on passing from primary to secondary and further to tertiary alkyl halides and consequently the carbonium character of the transition state also increases in this series†.

Kornblum et al.[1] quoted a number of other data confirming his idea of the decisive effect of the nature of the transition state on the mode of alkylation of the nitrite ion; in particular, it was shown for the reaction of substituted benzyl bromides with $AgNO_2$ that the proportions of *O*- and *N*-alkylation of the nitrite ion are not associated with steric effects.

Generalising their own and the literature data, Kornblum et al.[1] put forward an extremely important rule, the essential feature of which may be formulated as follows: when an ambident anion reacts with electrophilic agents, an increase in the S_N1 character of the transition state increases the tendency towards the reaction at the most electronegative atom, i.e. the atom with the highest electron density. Conversely, an increase in the S_N2 character of the transition state leads to an increase of the tendency towards the formation of a bond with the less electronegative atom (that is, the more polarisable atom with a lower electron density).

In the light of this rule, the difference in the behaviour of silver and alkali metal salts of ambident anions becomes understandable. Silver ions are a very effective means of increasing the carbonium character of the transition state, polarising the carbon–halogen bond by electrophilic interaction with the halogen atom, while alkali metal atoms do not have this property.

Hence, when silver salts are employed, there should be an increase in the tendency towards reactions at the atom with the maximum electron density (compared with alkali metal salts). Conversely, when silver salts are replaced by alkali metal salts, there is an increase in the tendency towards the formation of a covalent bond with the atom of the ambident anion where the electron density is lower.

Kornblum et al. quote a number of examples confirming this conclusion. Thus in the reaction of nitrite ions with alkyl halides, the replacement of silver nitrite by sodium nitrite (or other alkali metal nitrites) leads to a sharp increase in the fraction of *N*-alkylation products and a corresponding decrease of the fraction of *O*-alkylation products[1,24]. Similarly in the alkylation of the anion of 2-hydroxypyridine by ethyl iodide the silver salt gives mainly the *O*-derivative, while the potassium salt gives only *N*-ethylpyridone[25,26]. Alkylation of the silver salts of carboxylic acid amides by alkyl halides favours *O*-alkylation in a similar manner, while the alkali metal salts give the *N*-derivatives (for the literature, see Kornblum et al.[1]). Alkali metal cyanides react with alkyl halides to form mainly nitriles, while silver cyanide forms isonitriles[27,28], etc.

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† This is associated with the fact that the more stable the carbonium ion which the alkyl halide can form the greater is the degree of polarisation of the carbon–halogen bond under the influence of the silver ion.

It should not of course be thought that the use of silver salts will always lead solely to alkylation products at the site of maximum electron density. The capacity to react in a particular way is in the first place the function of the structure of the alkyl halide. In the case of alkyl halides which are incapable of undergoing a significant polarisation of the carbon–halogen bond under the influence of silver ions, the reaction at the less electronegative centre may prevail. For example, in the interaction of the esters of α-iodocarboxylic acids with silver nitrite the yield of N-alkylation products reaches 80–85%.[29] In the methylation of the silver salt of 2-hydroxypyridine by methyl iodide (in dimethylformamide) the yield of the N-alkylation product is 74% and that of the O-alkylation products only 12%.[30]

Moreover, the ratio of the products will also depend on the nature of the anion: in the case of anions which are particularly apt to undergo reactions at the more polarisable centre, even in the presence of silver ions, the reaction involves virtually exclusively this centre, as happens, for example, in the alkylation of the silver salts of 2-hydroxypyrimidine and 2-hydroxy-5-nitropyrimidine by primary alkyl halides (the N-alkylation products are mainly formed)[31].

Apart from silver ions, the carbonium ion character in the transition state can of course be effectively increased also by other metal ions, for example those of mercury and copper, which are capable of polarising the carbon–halogen bond and inducing a positive charge at the carbon atom. Similarly other well known factors promoting the occurrence of the S_N1 process will increase the tendency towards reactions at the centre with the maximum electron density.

Kornblum et al.[1] quote certain examples of this kind. Thus the sodium salt of acetoacetic ester is alkylated by primary alkyl halides only at the carbon atom (in solvents of relatively low polarity) while chloromethyl ether, which usually reacts with nucleophilic agents by an S_N1 mechanism, forms only the O-derivative[32]. Certain other examples of the greater tendency of α-chloroethers towards reactions at the oxygen atom, compared with alkyl halides, are quoted by Nesmeyanov and Kabachnik[3].

It should be borne in mind that the nature of the transition state is by no means always as clear as in the case of silver salts. Even when electrophiles with a high tendency towards reaction by an S_N1 mechanism are employed, the nature of the process is quite obscure, since the reaction mechanism is influenced, apart from the structure of the alkylated agent, also by other factors, the nature of the solvent being decisive in most cases‡.

One should also be on one's guard against a misunderstanding of Kornblum's rule. From the standpoint of present-day knowledge, this rule should not be interpreted as implying that, when a reaction takes place via an S_N2 mechanism, the product resulting from the attack on the least electronegative atom is always formed. Kornblum's rule implies only that, for a given specific ambident anion, the transition from the S_N2 mechanism to an intermediate mechanism S_N2–S_N1 (and further to S_N1) will be accompanied by an increase of the fraction of the products of the alkylation of the centre with the maximum electron density and that, other conditions being equal, this increase will be greater the more pronounced is the carbonium ion character of the transition state. Conversely, for a given anion the transition from an S_N1 mechanism to an S_N2 mechanism will lead to a decrease of the fraction of this product. On the other hand, the relative amounts of the products in an S_N2 process will depend on other factors (see below) including the structure of the anion itself and its capacity for a transfer of reaction centre. Kornblum's rule can be readily interpreted in terms of Pearson's principle of hard and soft acids and bases (see Section IV). Indeed the increase of carbonium ion character of the transition state under the influence of the solvent or an electrophilic catalyst (for example, silver ions) implies that the C–X bond is polarised in the alkylating agent R_3C–X, in consequence of which a partial positive charge appears (or increases) at the carbon atom and hence its polarisability diminishes. This implies that the carbon atom at which the substitution takes place becomes harder. On the other hand, an increase in the hardness of an electrophilic centre will increase, in accordance with the principle of hard and soft acids and bases, the tendency towards reactions at the harder atom of the ambident anion, i.e. the atom with the maximum electron density (usually the more electronegative atom).

The interpretation with the aid of the principle of hard and soft acids and bases extends the scope of Kornblum's rule. In the first place it should be noted that the appearance of a significant positive charge at the carbon atom of the electrophile and the decrease of the polarisability of this atom (increase of its hardness) may be related not only to the effect of particular reagents (electrophilic catalysts or the solvent) but also to the effect of highly electronegative polar groups or atoms in the electrophile itself. Examples of this kind will be quoted below in connection with the problem of the effect of the substituting group on the mode of reaction.

Moreover, factors which increase the hardness of the saturated carbon atom will of course operate also in relation to other electrophilic centres.

Consequently Kornblum's rule can be formulated as follows in a general form: an increase in the positive charge at an electrophilic centre (for example a carbon atom) and also a decrease in its polarisability will increase the tendency towards the reaction at the atom in the ambident anion with the greatest electron density§. The converse postulate holds for the donor atom with the lowest electron density.

It must be emphasised that the effect of the electrophilic properties of the substrate on the mode of reaction of ambident anions (see above), noted by Nesmeyanov and Kabachnik[3], agrees well with the above postulate, since an increase in the electrophilic properties of the substrate is identical with an increase in the hardness of the acceptor atom.

Indeed, although the order of the electrophilic reactivities depends on the nature of the nucleophilic agent, one usually has in mind the electrophilicity in relation to highly basic nucleophiles with little tendency towards polarisation, i.e. hard Lewis bases. Consequently in this sense an increase in electrophilicity implies a higher reactivity in relation to the harder donor atom of the ambident anion.

Since its publication (1955), Kornblum's rule became generally recognised. However, recently a number of papers have been published in which the rule is criticised.

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‡ Usually the reaction mechanism is strongly affected also by electrophilic catalysts: for example Ag^+ and Hg^{2+} ions or compounds such as $AlCl_3$, SbF_5, AsF_6, and certain others.

§ That is, the contribution of electrostatic forces to the overall reactivity increases.

Thus Cardillo et al.[33] found that, in the alkylation of the sodium derivative of indole in tetrahydrofuran (THF), the yield of *C*-alkylation products increases and that of *N*-alkylation products falls on transition from primary to secondary and further to tertiary alkyl bromides. Hence the authors conclude that, contrary to Kornblum's rule, an increase in the S_N1 character of the process favours attack at the least electronegative atom (carbon atom).

However, we believe that the observed relations, are not associated with a change in mechanism (the reaction is carried out in a relatively non-polar aprotic solvent which does not favour S_N1 processes) but merely with steric effects, since models show that in indoles alkylation at the nitrogen atom is sterically more difficult than at a carbon atom (in the 3-position of the pyrrole ring).

Cardillo et al.[33] and Le Noble and Puerta[34] consider that another contradiction with Kornblum's rule is the fact that allyl and benzyl halides, which the authors believe should impart to the transition state an appreciable S_N1 character, show a considerable tendency to alkylate the centre with the minimum electron density, greatly exceeding in this property the corresponding saturated alkyl halide.

This type of behaviour is general, since it is observed in the alkylation of various ambident systems: the enolates of acetoacetic ester[34] and acetophenone derivatives[35], the β-naphthoxide anion[36,37], salts of 2-hydroxypyridine[30], 2-hydroxypyrimidine[31], pyrrole[38], indole[33], etc. In all these examples the fraction of *O*- or correspondingly *N*-alkylation in the presence of benzyl and allyl derivatives is much less than when the corresponding n-propyl and ethyl halides are employed and is approximately at the level for methyl halides.

However, the widely held view that allyl and benzyl halide derivatives react preferentially by a unimolecular nucleophilic substitution mechanism (S_N1) is erroneous. Indeed, despite the fact that these halides are capable of forming relatively stable carbonium ions even in media favouring S_N1 processes (water, alcohols), the reaction with nucleophilic agents takes place only via an S_N2 mechanism[39]. Alkylation of the ambident phenoxide anions by halides of this kind in water is also an S_N2 process[40,41]. Moreover, allyl and benzyl halides are greatly superior in their reactivity in typical S_N2 reactions to the corresponding saturated halides[42].

Thus the contradiction with Kornblum's rule is only apparent, particularly since in the studies quoted above the alkylation was investigated in the majority of cases in aprotic dipolar solvents for which S_N1 processes are relatively a typical[43].

It is noteworthy that the reactivities of nucleophiles towards a particular electrophile in S_N2 reactions may be expressed by the equation[44,45]

$$\lg (k_N/k_0) = \alpha E_n + \beta H,$$

where k_N is the rate constant for the given nucleophilic agent, k_0 the rate constant for a standard nucleophilic agent (usually the solvent), E_n and H are constants characterising the nucleophiles, and α and β are constants characterising the electrophiles; α is the polarisability of the atom at which the substitution takes place[46] and β is a measure of the positive charge at this atom[47].

In substitution at a saturated carbon atom the β constant is so low that the term βH may be neglected[48] (see also Palm[49]) and the reactivity of the electrophilic agent in S_N2 reactions can be measured simply by the polarisability of its acceptor atom (in the absence of significant steric effects).

Consequently the higher reactivity of allyl and benzyl halides in S_N2 reactions compared with the corresponding saturated halogeno-derivatives is related to the higher polarisability of the allyl (benzyl) carbon atom. This implies in turn that the allyl (benzyl) carbon atom is a softer Lewis acid than the acceptor carbon atom of the corresponding saturated halide, which we believe to account for the very high tendency of allyl and benzyl derivatives to react at the more polarised, i.e. the softer centre in the ambident anion.

If this view is correct, then in general an increase in the reactivity of the alkylating agent in bimolecular nucleophilic substitution reactions will increase the tendency towards reactions involving the more polarised atom in the ambident anion¶.

Indeed, the available data confirm that the tendency to react at the more polarised (less electronegative) atom decreases in the series (see, for example, Refs. 30, 34, 35, 50) $CH_3X > C_2H_5X > n\text{-}C_3H_7X > iso\text{-}C_3H_7X$ (for the same groups X and identical conditions), which corresponds to the variation of reactivity in S_N2 processes.

In many cases this relation can of course be explained by steric effects, particularly for branched-chain halides. In addition, particularly strong steric effects, which prevent the attack on one of the centres of the ambident anion, may reverse this series. Such examples will be quoted in the next subsection.

It has now become clear that the nature of the substituted group X in the alkylating agent RX has a significant influence on the mode of reaction of ambident anions. Thus in the alkylation of the anion of the acetoacetic ester in solvents of a wide variety of polarities the fraction of *O*-alkylation products increases when X† is varied in the series $RI < RBr < RCl < (RO)_2SO_2$, i.e. the tendency towards reaction at the atom with the maximum electron density increases with increase of the electronegativity of X[34,51–54].

A similar relation was observed also in the alkylation of certain other anions. For example, in the ethylation of the anions of the series of monocarbonyl compounds the fraction of *O*-alkylation products increases sharply on transition from C_2H_5Br to $p\text{-}CH_3C_6H_4SO_2OC_2H_5$.[35] In the alkylation of the pyrrole anion the fraction of the *N*-alkylation product increases on passing from allyl bromide to allyl toluenesulphonate[38]. In the reaction of salts of p-toluenesulphinic acid with CH_3I the *S*-methylation product (sulphone) is mainly formed, and, when dimethyl sulphate, methyl toluenesulphonate or alkoxyphosphonium salts are employed as alkylating agents, the *O*-methylation product is formed (ester of sulphinic acid)[55].

The question arises how the effect of the substituted group on the mode of reaction of ambident anions may be explained‡. One of the explanations was given by Beletskaya, Reutov, and coworkers[53]: when the electronegativity of the X group increases, there is a simultaneous increase of the partial positive charge at the carbon atom at which the substitution takes place and a decrease in its polarisability[47], which indicates an increase in the electrophilicity of the alkylating agents. In other words, there is an increase in the hardness of the acceptor carbon atom

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¶ The same idea was put forward by le Noble and Puerta[34] albeit without any explanation.

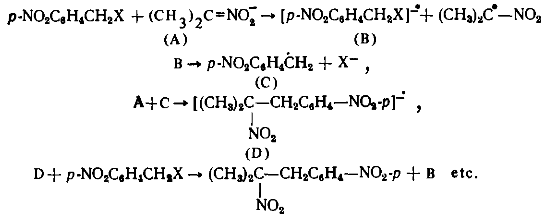
† When R and the reaction conditions remain constant.

‡ This effect is not related to a change in mechanism, since in the studies quoted the reactions were carried out under the conditions of an S_N2 process.

and consequently an increase in the tendency towards reaction at the harder centre of the ambident anion.

Another explanation of this phenomenon in terms of the principle of hard and soft acids and bases was given by Pearson and Songstad[13,22]. By considering the transition state of S_N2 processes, these workers concluded that the grouping of several soft or several hard bases around the carbon atom at which substitution takes place stabilises the transition state and hence increases the rate of reaction (the so called symbiotic effect). Hence it follows that, when the substituting group X is eliminated as an anion which is a hard Lewis base (X = Cl or OSO_2OR), the electrophilic agent reacts at a higher rate at the harder centre of the ambident anion. Conversely, when X^- is a soft base (X = Br or I), then the reaction at the softer centre predominates. It must be emphasised that not all ambident anions are equally sensitive to changes in the substituted group. Thus in the anions of 2-hydroxypyridine[30] and particularly 2-hydroxypyrimidine and its derivatives[31] the change in the group eliminated has little effect on the mode of reaction.

An apparent contradiction with the above relations in the alkylation of certain ambident anions by *p*-nitrobenzyl derivatives ($p\text{-}NO_2C_6H_4CH_2X$) should be pointed out. Thus in the reaction of these derivatives with the lithium salt of 2-nitropropane the fraction of the *O*-alkylation product decreases in the following sequence as X is varied: $I > Br > p\text{-}CH_3C_6H_4SO_2O > Cl$, with a corresponding increase in the fraction of *C*-alkylation[56,57]. However, subsequently it was found that in this case *C*-alkylation is a radical-anion chain process and not a nucleophilic substitution reaction[58-61]:



$$p\text{-}NO_2C_6H_4CH_2X + \underset{(A)}{(CH_3)_2C{=}NO_2^-} \rightarrow \underset{(B)}{[p\text{-}NO_2C_6H_4CH_2X]^{-\bullet}} + (CH_3)_2\overset{\bullet}{C}{-}NO_2$$

$$B \rightarrow \underset{(C)}{p\text{-}NO_2C_6H_4\dot{C}H_2} + X^-\,,$$

$$A + C \rightarrow \underset{(D)}{[(CH_3)_2\underset{\substack{|\\NO_2}}{C}{-}CH_2C_6H_4{-}NO_2\text{-}p]^{-\bullet}}\,,$$

$$D + p\text{-}NO_2C_6H_4CH_2X \rightarrow (CH_3)_2\underset{\substack{|\\NO_2}}{C}{-}CH_2C_6H_4{-}NO_2\text{-}p + B \quad \text{etc.}$$

On the other hand, nucleophilic substitution leads solely to *O*-alkylation.

The ratio of the *C*- and *O*-alkylation products reflects merely the competition between two different reactions. When nucleophilic substitution is faster than the radical-anion process, then *O*-alkylation predominates (X = I); on the other hand, when nucleophilic substitution is slow (for example, when X = Cl), the radical reaction predominates and consequently *C*-alkylation takes place preferentially. The anion of 2-ethoxycarbonyl-3-coumaranone reacts by a similar mechanism with *p*-nitrobenzyl derivatives[62,63].

In connection with the problem of the effect of the substituted group, the alkylation of ambident anions by trialkyloxonium salts should be examined. The trialkyloxonium cation R_3O^+ is strongly electrophilic, i.e. it should be fairly hard and should exhibit an appreciable tendency towards reactions involving the centre with the highest electron density. The available literature data largely confirm this conclusion.

For example, the anions of acetoacetic ester and of acetylacetone are usually alkylated by primary alkyl halides at a carbon atom in media of low polarity[6,50], while in the reaction where the triethyloxonium salt (in ether) is employed *C*-alkylation is accompanied by appreciable *O*-alkylation[64]. The triethyloxonium salt reacts similarly with the diethyl phosphorothioate anion (a mixture of *S*- and *O*-derivatives is formed; with alkyl halides, only *S*-alkylation takes place[65]), the anion of 2-hydroxypyridine (both *O*- and *N*-alkylation take place)[66], and certain other ambident systems. The anions of nitroalkanes give only *O*-alkylation products[67-69].

However, in the alkylation of the anion of acetoacetic ester in hexamethylphosphoramide (HMP) the triethyloxonium salt gives an unexpectedly lower amount of the *O*-alkylated product than the less electrophilic diethyl sulphate[52,53]. The authors suggest that in this case the alkylating agent is not the triethyloxonium cation itself but its complex with HMP, which reduces significantly its electrophilicity.

It is noteworthy that in the general case the interaction of an ambident anion with an alkylating agent of opposite sign need not by any means necessarily lead to products of attack on the centre with the maximum electron density. According to Kornblum[1], for reaction at the most electronegative atom to occur, it is more important that the bond between the alkyl residue and the group to be eliminated should break readily, which is not always so with 'onium salts. Moreover, examples are known where 'onium salts show a lower tendency towards reactions involving the centre with the maximum electron density than other alkylating agents.

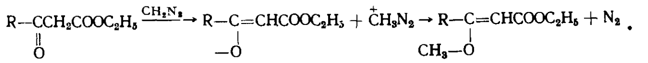
Thus, in the alkylation of the anion of acetoacetic ester with a benzyldimethylphenylammonium salt, the *C*-alkylation product is formed in high yields[70]. The anions of mononitroalkanes usually give only *O*-alkylation products, but in the reaction with diphenyliodonium salts they are phenylated at a carbon atom[71,72]. Other examples are also known.

Carbonium ions are harder Lewis acids than oxonium salts and consequently in kinetically controlled reactions they should alkylate preferentially the centre of maximum electron density. However, the available data, although extremely limited, show that this is not always the case.

Thus for the most reactive carbonium ion selectivity may be lost owing to the extremely high reactivity; a decrease in the energy of the carbonium ion may lead to an increase of selectivity. Relations of this kind are observed in reactions of phenoxide ions with carbonium ions[8]: on passing from $(CH_3)_3C^+$ via $(C_6H_5)_2\overset{+}{C}H$ to $(C_6H_5)_3\overset{+}{C}$, the fraction of *O*-alkylation increases. While the trimethylcarbonium ion gives about 25% of the *O*-alkylated isomer and about 75% of the *C*-alkylated isomer, the percentages of the two isomers produced by the triphenylcarbonium ion are about 95% and about 5% respectively.

Diazomethane, which is rather an unusual alkylating agent, in many cases methylates preferentially the centre with the maximum electron density in reactions with the conjugate acids of ambident anions (see, for example Refs. 55, 73, and 74).

Kornblum[1] explained this phenomenon by the following sequence of reactions:



$$R{-}\underset{\substack{\|\\O}}{C}CH_2COOC_2H_5 \xrightarrow{CH_2N_2} R{-}\underset{\substack{|\\-O}}{C}{=}CHCOOC_2H_5 + \overset{+}{C}H_3N_2 \rightarrow R{-}\underset{\substack{|\\CH_3-O}}{C}{=}CHCOOC_2H_5 + N_2\,.$$

i.e. in the first stage of the process diazomethane behaves as a base, which results in the formation of an ambident anion and a methyldiazonium ion. The latter, which exhibits an appreciable tendency towards *O*-alkylation reactions, methylates the centre with the maximum electron density.

The amount of data on the application of other diazoalkanes is much less. It is known that in the alkylation of α-pyridones diazoethane gives a much higher yield of the *O*-alkylation product than diazomethane[75].

In conclusion of this section, we may note that according to Pearson a saturated carbon atom is an intermediate (boundary) Lewis acid (see Section IV) and therefore, as can be seen from the data quoted above, even relatively slight changes in the structure of the alkylating agent and also in the reaction conditions (see below) lead to appreciable alteration in the mode of alkylation of ambident anions.

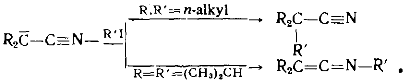
2. Steric Effects

In those cases where one of the reaction centres of the ambident anion is sterically more accessible than the other, steric factors have a very appreciable influence on the mode of reaction, frequently surpassing in this respect the electronic effect, particularly when the steric requirements of the alkylating agent are also stringent.

Thus, in the alkylation of potassium phenoxide by alkyl iodides (in a mixture of t-butyl alcohol and the dimethyl ether of tetraethylene glycol), only the *O*-alkylation product is formed, while in the case of 2,6-di-(t-butyl)phenoxide both *O*- and *C*-alkylated derivatives are formed under these conditions, the fraction of the *C*-alkylation products (mainly in the *p*-position) increasing sharply on passing from methyl iodide to ethyl and further to isopropyl iodide (in the latter case *C*-alkylation takes place exclusively)[76].

Thus a decrease in the steric accessibility of the oxygen atom compared with a carbon atom (particularly in the *para*-position) has a very significant effect on the mode of reaction. This effect increases with steric hindrance in the alkyl halide and leads to results opposite to those which would have been expected from purely electronic effects in the alkyl halide (see p. 6).

Alkylation of α-cyanocarbanions usually leads only to *C*-alkylated isomers:



However, when R and R′ are isopropyl groups, appreciable amounts of the *N*-alkylation product are formed[77].

In the enolates of carbonyl compounds the oxygen atom is sterically more accessible than the carbon atom[78]. For this reason, the fraction of *O*-alkylation increases significantly both with the size of the substituent at the carbon reaction centre of the anion and with increasing steric hindrance in the alkyl halide.

Thus alkylation of the anions of acetoacetic ester and acetylacetone by primary alkyl halides in alcohols or non-polar solvents usually takes place exclusively at the carbon atom, while in the presence of secondary alkyl halides under the same conditions, appreciable amounts of enolic ethers are produced[50].

In the alkylation of the anion of acetoacetic ester in polar aprotic solvents the fraction of *O*-alkylation also increases significantly with the branching of the hydrocarbon group in the alkyl halide[34,78]; for example, with neopentyl chloride only the *O*-alkylated isomer is formed[78].

In the alkylation of the enolates of α-substituted acetophenones the amount of the *O*-alkylated product increases sharply with the size of the α-substituents[35], which indicates a significant effect of steric hindrance in the enolate on the mode of reaction. The alkylation of the anions of 2-hydroxypyrimidine and its derivatives is hardly affected by the nature of the solvent, the cation, and the group substituted. The structure of the alkyl halide has the main influence: on passing from methyl to isopropyl halide, the fraction of *O*-alkylation increases, which the authors attributed solely to steric effects, since models show that alkylation at the nitrogen atom imposes more stringent steric requirements than attack on the oxygen atom[31]. A similar conclusion was reached also for the anion of 2-hydroxypyridine[30].

Steric effects have also been used to account for the increase of the fraction of *O*-alkylation of the anion of benzophenone oxime and its derivatives on passing from methyl bromide to benzyl bromide[79].

3. Effects of the Solvent

The solvent usually has a very significant influence on the mode of reaction of ambident anions. Earlier (see p. 5) the effect of the solvent on the behaviour of alkylating agents was already noted. Here we shall consider the interaction of the solvent with the ambident anion–counterion system and the influence of such interaction on the mode of alkylation.

In a study of the behaviour of ambident anions in aprotic solvents the following general feature was observed: an increase in the polarity of the aprotic solvent favours alkylation at the centre with the maximum electron density. For example, in the alkylation of the anions of 2,6-dimethylphenol the fraction of *O*-alkylated products decreases in the following sequence as the solvent is varied: ethyl ether > isopropyl ether > toluene > benzene[80]. The fraction of the *N*-alkylation products of the anion of pyrrole decreases in the sequence tetrahydrofuran > dioxan > isopropyl ether > ethyl ether > benzene, toluene, n-heptane, methylcyclohexane[81].

The tendency towards reactions at the centre with the maximum electron density increases even more when dipolar aprotic solvents are employed—dimethylformamide (DMF), dimethylacetamide (DMAA), dimethyl sulphoxide (DMSO), hexamethylphosphoramide (HMP), and others.

Such behaviour is observed in the alkylation of a wide variety of ambident anions: the enolates of β-dicarbonyl compounds (see, for example Kurts et al.[54]), β-naphthoxides[36], salts of pyrrole[38], indole[33], 2-hydroxypyridine[30], and others. The effect of aprotic solvents was investigated in greatest detail during recent years[36,54,78,81]. It is noteworthy that dipolar aprotic solvents also differ significantly among one another in terms of their influence on the mode of alkylation of ambident anions. Thus in the alkylation of the anions of acetoacetic ester and acetylacetone the greatest yield of the *O*-alkylated isomers is observed in hexamethylphosphoramide and the tetramethyldiamide of methylphosphonic acid. These are followed by aprotic solvents of the amide type: DMF, DMAA, tetramethylurea, etc., and also dimethyl sulphoxide in which the fraction of the *O*-alkylated isomer is lower; the amount of *O*-alkylated derivatives is reduced still further in acetone, acetonitrile, and tetramethylene sulphone. These are followed by solvents of the ether type which are of relatively low polarity and also certain halogeno-derivatives in which the amount of *O*-alkylated products is as a rule close to zero[54] (see also Refs. 34, 51–53, 78, 82).

This does not of course imply that the use of dipolar aprotic solvents always leads to preferential alkylation of the centre with the maximum electron density. The final result depends both on the properties of the anion itself, and on the relative importance for the given anion of particular factors which influence the mode of reaction.

For example, silver nitrite in a relatively non-polar solvent (ethyl ether) is appreciably alkylated at the oxygen atom[1], while the use of alkali metal nitrites in a dipolar aprotic solvent (DMF) significantly increases the fraction of *N*-alkylation[1,24], i.e. in the case of nitrite ions, the alkylating agent (or more correctly its form produced by modification under the influence of silver ions) has a greater effect than the solvent. On the other hand, the solvent has virtually no influence on the mode of reaction of the anions of 2-hydroxypyrimidine on some of its derivatives[31].

The question arises of the reasons for the influence of aprotic solvents on the mode of reaction of ambident anions. Aprotic solvents, including dipolar solvents, as a rule solvate anions only very slightly[43] and therefore the change in the mode of reaction is probably not associated to any appreciable extent with the interaction between the aprotic solvent and the anion.

Kornblum[36] attributed the effect of aprotic solvents to their dielectric properties. However, subsequently, it was found that the effect of such solvents is not determined by their dielectric constants[54,78] but by their capacity to solvate cations[35,38,54,78,81].

This type of relation can be explained as follows. Like other electrolytes[83,84], the salts formed by ambident anions and their counterions are associated to some extent in the majority of organic solvents to ion pairs (or more highly aggregated species). In view of the electrostatic orientation of ions, it is likely that the cation will be preferentially coordinated to the atom in the ambident anion with the maximum electron density§ (hard nucleophilic atom)[2], i.e. in the association of the ambident anion and the counterion the centre with the highest electron density is screened, which hinders the reaction at this site; in consequence, the relative reactivity of the second nucleophilic centre increases (an approach to this problem, in many ways similar to that described, was employed by Nesmeyanov and Kabachnik[3]). The increase in the degree of solvation of the cation by the solvent, for example on passing from solvents of low polarity to dipolar aprotic solvents, leads to a weakening of the coordination of the cation to the ambident anion and hence facilitates the reaction at the atom with the maximum electron density.

The increase in the degree of solvation of cations by the solvent can probably lead both to a weakening of the bond between the cation and anion within the ion pair and to an increase of the degree of dissociation of the ion pair. Both these effects will facilitate attack on the harder atom of the ambident anion. However, at present the available experimental data are insufficient to estimate in a specific case which of these effects is responsible for the change in the mode of reaction.

It is noteworthy that the determination of the capacity of the solvent to solvate cations is not a simple problem although such estimates have been made for a series of the most widely used solvents[43]. In this connection the correlation[78] between the relative amounts of both *O*- and *C*-alkylated isomers in the alkylation of the anion of acetoacetic ester and the basicity of the solvent (the increase of the fraction of the *O*-alkylated isomer with the basicity of the solvent) merits attention. However, at present there are too few data to arrive at a conclusion concerning the applicability of such correlations to a wide range of systems.

Protic solvents—alcohols, unsubstituted amides, and others—behave as hydrogen bond donors and, in contrast to aprotic solvents, usually readily solvate anions[43].

Kornblum found for phenoxides[40,41] and β-naphthoxides[36] that, despite the fact that protic solvents effectively solvate cations[43], alkylation in them greatly promotes reactions involving the most polarised (soft) centre of the ambident anion and prevents attack on the centre with the maximum electron density.

The effectiveness of protic solvents as media promoting reactions at the softer nucleophilic atom of the ambident anion very greatly increases when solvents capable of forming stable hydrogen bonds are employed. For example, phenol salts in aprotic solvents (dimethylformamide, tetrahydrofuran, ethyl ether, and even toluene) are alkylated exclusively at the oxygen atoms; the use of protic solvents such as methyl, ethyl, and t-butyl alcohols also does not alter the mode of reaction. However, in solvents such as water, fluorinated alcohols, and phenol, which form significantly stronger hydrogen bonds than simple aliphatic alcohols[85,86], *C*-alkylation of phenoxide anions takes place to a considerable degree (the yield of *C*-alkylated isomers approaches 80% in some cases)[40,41]. It has been noted that in this case both *C*- and *O*-alkylation takes place via an S_N2 mechanism.

According to Kornblum[40,41], the effect of protic solvents can be accounted for as follows: owing to hydrogen bonding, these solvents selectively and effectively solvate the centre with the maximum electron density (for example, the oxygen atom)¶, as a result of which the accessibility of this centre is greatly reduced and substitution at the other centre (a carbon atom) may successfully compete with that at the oxygen atom. Hence it becomes clear why the solvent capable of forming the strongest hydrogen bonds (water, phenol, fluorinated alcohols) are especially effective: an increase in the strength of the hydrogen bond will increase the energy required to desolvate the atom with the maximum electron density and hence will increase the activation energy for reaction at this atom.

Kornblum[41] suggested the name "selective solvation" for the capacity of protic solvents to solvate selectively the centre with the maximum electron density and thereby prevent the reaction at this centre. This type of effect of protic solvent on the mode of reaction is observed also for other ambident anions. For example, in the alkylation of the anion of acetoacetic ester the yield of the *O*-alkylated isomer falls sharply on passing from dipolar aprotic solvents to alcohols (ethyl and t-butyl alcohols) and to a substituted amide (*N*-methylacetamide) and in alcohols the yield of the *O*-alkylated isomer falls almost to zero[54].

In the alkylation of the enolates of monocarbonyl compounds[35] and 2-hydroxypyridine salts[30] transition from polar aprotic solvents to alcohols also leads to a significant decrease of the amount of the *O*-alkylated isomer. It is noteworthy that even relatively small amounts of added protic solvents influence the mode of reaction[34,52,53,87]. Thus in the ethylation of the enolate of acetoacetic ester in hexamethylphosphoramide the addition of equimolar amounts of protic solvents (water, t-butyl alcohol) significantly increases the fraction of *C*-alkylation[52,53,87].

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§ At least in the case of alkali and alkaline earth metal cations and also ammonium ions, i.e. hard Lewis acids (see Section IV). For metal cations which are soft Lewis acids (for example Hg^{2+}), there is a possibility of coordination at the most polarised atom in the ambident system.

¶ We may recall that the hydrogen atom behaves as a hard Lewis acid in the formation of a hydrogen bond (see Section IV).

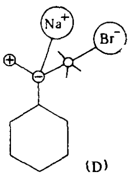
At the present time the explanation of the effect of protic solvents on the mode of reaction given by Kornblum is generally accepted, (see, for example, Refs. 30, 35, 52, 54, 87)†.

Factors such as the heterogeneity or homogeneity of the medium in which the reaction is carried out are closely related to the influence of solvents.

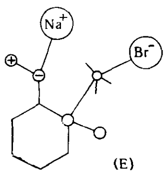
In 1959, Kornblum and Lurie[8] found that the alkylation of phenol and *p*-t-octylphenol salts under truly heterogeneous conditions, i.e. on the surface of the crystals of the salts, leads exclusively to *C*-alkylation products, while the same reaction in solution yields only *O*-alkylation products. Their explanation of these results is as follows[8]. The alkylation of the oxygen atom should involve a linear transition state (D) in which the negative charge of oxygen is transmitted to the halogen atom of the alkylating agent. There are two factors which make such a transition state energetically unfavourable. In the non-polar solvents employed for the heterogeneous reaction the halide ion eliminated is solvated to only a very slight extent. However, a still more important factor is that the transfer of electron density from the oxygen atom will lead to electrostatic repulsion between the positively charged metal ions and to a sharp increase of the energy of the system, since in the crystal lattice the metal ions cannot move apart.

In a homogeneous medium the formation of the ether (the *O*-alkylation product) does not give rise to difficulties of this kind even if the entire salt is present in the form of ion pairs or larger aggregates, since in solution metal ions can readily move apart.

In contrast to the formation of ethers, *C*-alkylation takes place via a non-linear transition state (E) where the halide ions is "solvated" owing to the formation of an ion pair with the metal ion; moreover, the formation of this ion pair will prevent electrostatic repulsion between the metal ions when the oxygen atom loses its negative charge. Consequently, under heterogeneous conditions *C*-alkylation takes place preferentially:



(D)



(E)

It is at present impossible to state whether this factor ("heterogeneity") does indeed have such an appreciable influence also in the case of other ambident anions or whether it applies only to phenol and similar systems, since there have been no studies of dual reactivity showing clearly that the "heterogeneous" reaction investigated takes place only on the surface of the crystal and not in solution.

4. Effect of the Cation and the State of the Salts in Solution

The nature of the counterion (cation) frequently has an appreciable effect on the mode of reaction of ambident anions. Above (see pp.4 – 5) the specific effect of the silver cation and similar ions (electrophilic catalysts) has already been reported. Here we shall examine the effect of other cations.

In a study of the alkylation of ambident anions in aprotic solvents a single general relation was observed: the tendency of the ambident anions to react at the centre with the maximum electron density increases in the following sequence of cations: $Li^+ < Na^+ < K^+ < Rb^+ < Cs^+ < NR_4^+$. Moreover, it has been shown in a number of cases that the Li^+ ion promotes the reaction at the centre with the maximum electron density more than the Mg^{2+} ion (β-naphthoxides[37], pyrrole salts[38]).

This type of relation has been observed in a wide variety of ambident systems: enolates of β-dicarbonyl[34,51-53,87] and monocarbonyl compounds[89], salts of naphthols[36,37], phenols[80], pyrrole[38,81], 2-hydroxypyridine[30], and others. The effect of the cations obtains both in relatively non-polar aprotic solvents and in dipolar aprotic solvents. Thus the tendency towards reactions involving the centre with the maximum electron density diminishes with decreasing radius of the cation and, for equal radii (Li^+ and Mg^{2+}), with increase of the charge, i.e. with increase of the hardness of the cation (see Section IV).

As already stated (see p. 9), salts formed by ambident anions and their counterions in solution are to some extent associated into ion pairs and the alkali metal or alkaline earth metal cation is preferentially coordinated to the hard nucleophilic atom of the ambident anion, which hinders the reaction at this atom. With increase of the hardness of the cation (decrease of the radius and increase of the charge), the degree of association of the cation with the centre having the maximum electron density will become more pronounced (a more "closely linked" ion pair will be formed) and thereby the reaction at this centre will be hindered. In consequence, the relative reactivity of the second, softer nucleophilic centre will increase.

The strengthening of the bond between the cation and anion leads to both an increase of the energy required to descreen the hard reaction centre and to a decrease of the degree of dissociation of the ion pairs. Both these factors will hinder the reaction at the atom with the maximum electron density. At the present time it is impossible to say in a specific case which of these factors is responsible for the change in the mode of reaction as the cation is varied.

It is important to note that, in contrast to Kornblum's hypothesis[36], the effect of the change of the cation can be followed also in dipolar aprotic solvents (dimethylformamide, dimethyl sulphoxide, and others), for example in the case of the anions of acetoacetic ester[34,51-53,87] and pyrrole[81], i.e. even in these solvents there is some association of the ambident anions with their counterions to form ion pairs‡. Only in solvents such as hexamethylphosphoramide, which very strongly solvates cations, have cases been found where a change of the cation does not affect the mode of reaction (the acetylacetonate anion[54] and also the anion of acetoacetic ester at elevated temperatures[78]). Probably in such cases the reactive species is the anion not combined in an ion pair[54,78] and the mode of reaction is determined solely by the mesomerism of the anion itself[54].

The postulate of the strengthening of the bond between the cation and the centre in the ambident anion having the

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† Recently the hypothesis of the selective solvation by protic solvents of the hard centre in ambident anions was proved by spectroscopic methods for salts of phenols and certain nitro-compounds as examples[88].

‡ It has been shown by ultraviolet spectroscopy that the salts of phenol and acyclic β-dicarbonyl compounds are in most cases associated in dimethylformamide even at concentrations in the range 10^{-4}–10^{-5} M.[90]

maximum electron density as the radius of the cation is reduced was confirmed by spectroscopic methods for alkali metal salts of phenols and β-dicarbonyl compounds in 1,2-dimethoxyethane and dimethylformamide solutions [90]. It was also shown [90] that in these aprotic solvents association of the alkali metal cations with the anions of phenols and enols does not involve the formation of covalent bonds even for the most "closely linked" ion pairs and the interaction is purely ionic.

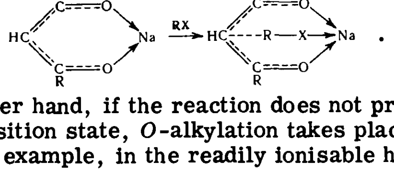
The effect of the cation in protic solvents has been investigated to a very limited degree. However, the available data show that, despite the high solvation capacity of polar protic solvents in relation to cations and anions [43], in many cases a cationic effect is observed [37,80,91], although examples may be quoted when the effect of the cation is insignificant [79]. Nevertheless there is no doubt that more detailed studies will lead to the discovery of ambident systems where the effect of the cation will be significant even in such media, particularly since in many cases association into ion pairs of ambident anions and their counterions has been observed even in a solvent such as water (see, for example, Zaugg and Schaefer [90]).

Thus the data presented show that association with cations reduces the tendency of the ambident anion towards reaction at the centre with the maximum electron density, at least in aprotic solvents. An example of direct experimental proof of this hypothesis is provided by the study by Smith and Milligan [92] of the effect of ion pair association on the mode and rate of alkylation of the fluorinone oxime anion.

However, in protic solvents in those cases where the centre with the maximum electron density in the ambident anion is more firmly solvated via hydrogen bonding than via association with the cation there is also a possibility of the opposite relation: a greater tendency towards reactions at this centre in ion pairs than in the unassociated anion [36,93].

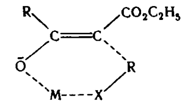
It must be emphasised that the state in solution of salts formed by ambident anions with their counterions (degree of association into ion pairs as a function of the solvent and the cation, the nature of the ion pairs formed—with the two ions in direct contact or separated by solvent species, the size of the ionic aggregates, etc.) has so far been clearly inadequately investigated, which hinders a quantitative estimation of the dual reactivities of both the associated species and the "free" anions.

According to Brändström [5,94], the formation of chelate compounds, for example by metal derivatives of β-dicarbonyl compounds, has a very significant influence on the mode of reaction. The chelates have a ring structure and have pseudoaromatic properties; according to Brändström's hypothesis [5,94], *C*-alkylation of these systems is a multicentre process and proceeds via the energetically favourable six-membered transition state:



On the other hand, if the reaction does not proceed by a cyclic transition state, *O*-alkylation takes place. This happens, for example, in the readily ionisable halogenoderivatives (RX), where the coordination with a metal ion or the effect of the solvent lead to the formation of a carbonium cation, which reacts at the site with the maximum electron density—at the oxygen atom.

It has recently been suggested that [95] the formation of a six-membered transition state (owing to coordination between the metal ion and the "nucleophilic" part of the alkylated agent), promoting *C*-alkylation, is possible also in the case of non-chelate structures, as can be seen from the scheme below:



This type of transition state should be promoted by solvents which cause least dissociation of the enolate and ionisation of the alkylated agent (protic and aprotic media of low polarity).

5. Effect of Certain Other Factors

Comparatively few data are available on the effect of factors other than those described above on the mode of reaction of ambident anions. In a number of examples it has been shown that, as the concentration of the "ambident" salts in aprotic solvents is reduced, the yield of the product of the alkylation of the centre with the maximum electron density increases [35,38,80,81,87]. Whereas in dipolar aprotic solvents [87] this phenomenon can be accounted for by an increase of the degree of dissociation of the ion pair, in aprotic media of low polarity (ethyl ether, tetrahydrofuran, and others [38,80,81]) the existence of unassociated anions is extremely doubtful; possibly in these media dilution leads to the dissociation of highly aggregated species into smaller aggregates, which increases the accessibility of the hard centre.

It has been found for the anions of monocarbonyl compounds that, in contrast to aprotic media, in protic solvents the fraction of *O*-alkylation diminishes with dilution [35], which the authors attribute to enhanced effectiveness of the hydrogen bond§.

Even fewer data are available on the effect of temperature. In the alkylation of pyrrole salts in dioxan and toluene the fraction of the *N*-isomer increases with temperature [38]. In the case of the enolates of acetoacetic ester an increase of temperature entails an increase of the fraction of *O*-alkylation when the reaction is carried out in dimethyl sulphoxide [51].

The observed behaviour can be accounted for by an increase of the degree of dissociation of ion pairs (or larger aggregates) with increasing temperature, particularly since for the acetoacetic ester anions in hexamethylphosphoramide, where the reacting species is believed to be the "free" anion, a temperature effect is not observed [78]. However, this view does not explain the decrease of the fraction of *O*-alkylation of the enolate of acetoacetic ester with increasing temperature in N^1-methylpyrrolidinone [51].

A change in hydrostatic pressure does not usually affect the mode of alkylation, particularly when the reaction is performed in aprotic solvents [96,97]. However, in the alkylation of phenoxide and β-naphthoxide ions in protic media, an increase of pressure (to several thousand atmospheres) causes some increase in the fraction of *C*-alkylation [96-99], which is explained by an enhancement of the "selective" solvation of the oxygen atom (via hydrogen bonding) as the pressure rises [97-99].

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§ Apparently in this case "selective" solvation has a greater influence on the mode of reaction than association with the cation.

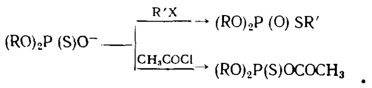
VI. BEHAVIOUR OF AMBIDENT ANIONS IN SUBSTITUTION REACTIONS AT AN UNSATURATED CARBON ATOM AND AT HETEROATOMS

In contrast to substitution at a saturated carbon atom, the behaviour of ambident anions in substitution reactions at an unsaturated carbon atom has been much less investigated; there are even fewer data on substitution at heteroatoms. It is reasonable to suppose that many of the factors which influence the mode of alkylation will operate also in the case of other electrophilic agents. However, here one should take into account in the first place the nature of the electrophilic agent itself and its tendency to react at a particular centre of the ambident anion. The examples quoted below show that the principle of hard and soft acids and bases (see Section IV) is very useful for the estimation of such properties of electrophilic agents.

Substitution at an unsaturated carbon atom has been investigated mainly in acylation reactions (substitution at a carbonyl carbon atom). Since the carbonyl carbon atom is a hard Lewis acid,[13] (see also Section IV), it is to be expected that in acylation the reaction will take place to a considerable degree at the harder atom of the ambident anion (at the centre with the maximum electron density), and the tendency to react at this centre should be much greater than in alkylation (a saturated carbon atom is an intermediate Lewis acid).

The available data fully confirm this hypothesis, at least when carboxylic acid anhydrides and halides are employed as the acylating agents. Thus in the acylation of the enolates of monocarbonyl compounds, *O*-acylated isomers are formed preferentially, whereas under the same conditions alkylation gives either *C*-alkylated products or a mixture of the *C*-alkylated and *O*-alkylated isomers[89,100–102]. The enolates of β-dicarbonyl compounds are capable of giving both *C*- and *O*-acyl derivatives but in acylation they tend to undergo reaction at the oxygen atom more than in alkylation (see, for example, Refs. 3, 5, 94, and 103). Acylation of the phenoxide anion by acid halides probably takes place only at the oxygen atom under these conditions[2].

The salts of phosphorothioic acids are alkylated at the sulphur atom[104–106]; on the other hand, the acylation of these salts by acyl halides takes place preferentially at the oxygen atom[105,107]:



$$(RO)_2P(S)O^- \begin{cases} \xrightarrow{R'X} (RO)_2P(O)SR' \\ \xrightarrow{CH_3COCl} (RO)_2P(S)OCOCH_3 \end{cases} .$$

Thiocyanate ions are acylated by acetyl chloride at the nitrogen atom, while alkylation takes place at the softer sulphur atom[13].

The mode of acylation of ambident anions is probably influenced by the same factors as in alkylation. Thus in the acylation of the anions of β-diketones an increase of the carbonium character of the transition state leads to an increase of the fraction of the *O*-acylated isomer[108]. The use of silver salts instead of alkali metal salts (with acyl chlorides as acylating agents) increases the tendency towards the acylation of the more electronegative atom[37,109].

An increase in electrophilicity (and consequently in the hardness) of the acylating agent increases the tendency towards reactions at the harder centre of the ambident anion. For example, in the acylation of the anions of 2-ethoxycarbonylcyclanones the fraction of *O*-acylation increases in the series[110]

$$ClCOOEt < ClCH_2COCl < CH_3COCl < CH_3COClO_4$$

Steric effects can also have a significant influence. Thus despite the fact that the salts of phenol are acylated only at the oxygen atom, the 2,6-di-t-butylphenoxide anion, the oxygen atom of which is strongly screened by bulky groups, is acylated by benzoyl chloride to give a *C*-acyl derivative[111].

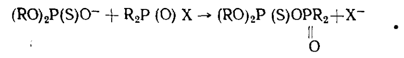
As in alkylation, an increase of the polarity of the aprotic solvent favours the reaction at the centre with the maximum electron density (see, for example, Ferris et al.[110]). A change of the cation probably has the same effect as in alkylation[37,110].

The formation of chelates has a significant influence on the mode of acylation, as in alkylation reactions. It has been shown for the chelates of β-diketones that *C*-acylation is promoted when the reaction proceeds via a six-membered transition state (owing to the coordination of the "nucleophilic" part of the acylating agent to the metal ion and of the "electrophilic" part to the carbon reaction centre)[108,112].

The behaviour of ambident anions in substitution reactions at an olefinic carbon atom is illustrated using an example the substitution of the β-carbon atom in compounds of the type $RCOCH = CHX$, where X is the group eliminated (the β-ketovinylation reaction). The ketovinylation of the anions of β-dicarbonyl compounds and nitrocompounds and cyanide, thiocyanate, and nitrite ions takes place at the most polarised (softest) centre of the ambident anion[113]. At the same time the phenoxide anion is ketovinylated only at the oxygen atom even in water[113,114]. Thus the behaviour of ambident anions in the β-ketovinylation reaction is apparently in many respects similar to the behaviour of these anions in alkylation.

The information about the behaviour of ambident anions in substitution reactions at heteroatoms is extremely limited. However, the general tendency of electrophilic agents of this type to react at a particular centre of the ambident anion may be predicted by estimating the properties of the electrophilic agent as a Lewis acid (hard or soft).

Thus the phosphorus atom in the phosphoryl group is a hard Lewis acid (see Section IV), which is reflected in the behaviour of this electrophilic agent in relation to ambident anions. For example, the phosphorylation of phosphorothioate salts takes place, as in acylation, at the harder atom (the oxygen atom)[115]:



$$(RO)_2P(S)O^- + R_2P(O)X \rightarrow (RO)_2P(S)O\underset{\underset{O}{\|}}{P}R_2 + X^- .$$

Similarly the phosphorylation of the thiocyanate ion takes place at the harder centre (the nitrogen atom)[16].

The silylation of enolates by chlorotrimethylsilane takes place only at the oxygen atom[116] (while alkylation takes place only at the carbon atom[101]), which is consistent with the classification of the silicon atom as a hard Lewis acid[20].

The sulphur atom in the sulphenyl group is a soft Lewis acid (see Section IV), which is confirmed by the marked tendency of this electrophilic agent to react at the softer (more polarised) atom of the ambident system. Thus in the reaction of the anions of mononitroalkanes with sulphenyl chlorides, only the corresponding *C*- substituted derivatives (α-nitrosulphides) are formed[117,118]; on the other hand, the alkylation of these anions as a rule leads only to *O*-substituted products[119].

The capacity of perchloryl fluoride ($FClO_3$) to fluorinate the anions of ketoenols, phenols, and nitroalkanes, at the carbon atom[120] suggests that the fluorine atom in this compound may be classified as a soft Lewis acid[7].

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The data, in their entirety, show that certain general relations controlling the dual reactivity of ambident anions can now be traced and knowledge of them can help the investigator in many cases to control the process in a particular way.

At the same time many problems still await solution. The author attempted to indicate these unsolved problems throughout the review. One of the most important problems of this kind is the relation between structure and dual reactivity of the anion. It is difficult to solve because the "true" reactivity of the ambident system is frequently subject to very marked changes under the influence of various factors (association with the cation, selective solvation, and others). Hence another problem arises—that of estimating the relative sensitivities of various anions to particular effects.

However, purely experimental data for the reactions of the various anions with a wide variety of electrophilic agents under comparable conditions are at present quite inadequate for the solution of these problems. Moreover, in connection with the introduction of precise methods of analysis and improved research techniques, many old data require revision.

In conclusion, we may note that one cannot exclude the possibility that in future, following a more detailed study of the reactivity of ambident anions and their structure, new concepts may appear, providing a deeper and more complete explanation of certain characteristics of the behaviour of ambident systems.

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Zelinskii Institute of Organic
Chemistry, USSR Academy of
Sciences, Moscow

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Prototropic Isomerisation of Olefins with Functional Groups and Its Use in Organic Synthesis

L.A.Yanovskaya and Kh.Shakhidayatov

The characteristics and mechanism of the prototropic isomerisation of olefins with functional groups in the presence of bases, acids, metal carbonyls, and other catalysts and also by thermal and photochemical activation have been examined together with its application in organic synthesis.
The bibliography includes 180 references.

CONTENTS

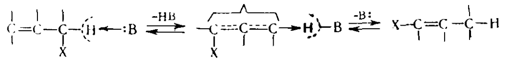
I. INTRODUCTION

In recent years there has been a considerable growth of interest in the problem of the migration of double bonds in olefins with functional groups. A number of new effective isomerisation catalysts have been proposed and novel methods of synthesis based on prototropic isomerisation have been developed. This review gives a general account of the advances in the study of the mechanism and use in syntheses of the prototropic shift in olefins with functional groups achieved in the last 10–15 years.

A brief review of the literature on this problem up to 1960–1961 is given in "The Chemistry of Alkenes",[1] but it does not deal at all with isomerisation in the presence of metal carbonyls and with thermal and photochemical isomerisation. Information about base-catalysed isomerisation of olefins including some with functional groups is given in the review by Hubert and Reimlinger[2].

II. ISOMERISATION IN THE PRESENCE OF BASES

The prototropic shift under the influence of bases in olefins with functional groups takes place by a carbanionic mechanism[3,4]:



The reaction is reversible. The position of equilibrium depends on the structure of the olefin and the nature of the functional group X, as shown already in the classical work of Kon and Linstead[2,3] on the prototropic isomerisation of unsaturated acids, their esters, and nitriles, and confirmed in subsequent investigations.

For the system $CH_2{=}CHCH_2X \rightleftharpoons CH_3CH{=}CHX$, where X may be conjugated with an $\alpha\beta$-double bond via an unshared electron pair (X = OR, SR, NR$_2$, etc.) or p electrons (X = COOH, COOR, CN, CHO, COR, etc.), the equilibrium is usually displaced towards the conjugated system. For example, alkyl allyl[5], allyl aryl[6], and allyl vinyl[7] ethers are almost completely converted into propenyl ethers on heating with potassium t-butoxide. Similarly, under the influence of alkoxides and other bases, alkyl allyl sulphides[8] and allyl aryl sulphides[9] form equilibrium mixtures where the ratio of the propenyl and allyl forms is 99 : 1. Allyl phenyl selenide isomerises quantitatively to phenyl propenyl selenide in the presence of potassium t-butoxide[10]. The isomerisation of *NN*-disubstituted allylamines[11-13] to enamines goes to completion in the presence of bases and in most cases the equilibrium constants cannot be determined. Under the action of alkalis, vinylacetic acid is converted into an equilibrium mixture containing 98% of crotonic acid[14]. The equilibrium in mixtures of vinylacetonitrile with crotononitrile or of ethyl vinylacetate with ethyl crotonate is also almost completely displaced towards the $\alpha\beta$-isomer[15].

If the group X is incapable of conjugation with the $\alpha\beta$-double bond (X = SO, SO$_2$, etc.), then the equilibrium mixture contains an appreciable amount of the $\beta\gamma$-isomer. Thus the equilibrium mixture of allyl methyl sulphoxide and methyl propenyl sulphoxide contains 17–20% of the $\beta\gamma$-isomer[16] and a mixture of allyl methyl sulphone and methyl propenyl sulphone contains 44% of the $\beta\gamma$-isomer[17]. The equilibrium position in alkyl cycloalkyl sulphones[18] and in cyclic sulphones[18,19] is likewise shifted towards the $\beta\gamma$-isomer.

Substitution (in the first place in the γ-position) in a three-carbon system has an enormous influence on the equilibrium position (Table 1). Table 1 shows that substituents in the γ-position displace the equilibrium towards the $\beta\gamma$-isomer, which may actually predominate. For alkyl groups, this can be explained by the competition between the effect of the conjugation of the functional groups with the double bond, which stabilises the $\alpha\beta$-form, and the effect of the hyperconjugation of the alkyl group with the double bond, which stabilises the $\beta\gamma$-form. If the latter effect prevails, then the $\beta\gamma$-isomer predominates in the equilibrium mixture. The decrease of the hyperconjugation effect in the sequence $H < (CH_3 > C_2H_5 > \text{iso-}C_3H_7 > \text{t-}C_4H_9)$ results in a somewhat smaller effect of higher alkyl groups on the equilibrium position. An alkyl group in the α-position additionally stabilises the $\alpha\beta$-isomer owing to hyperconjugation and therefore the $\alpha\beta$-isomer predominates in the equilibrium mixture even in the presence of a substituent in the γ-position. In βγ-disubstituted derivatives the content of the αβ-form is also somewhat increased. The presence of a substituent in the α- or β-position only has hardly any influence on the equilibrium. Thus mesityl oxide contains only 1.3% of the βγ-form[22,23].

Table 1. Equilibrium positions in certain three-carbon systems.

αβ-Isomer	%	βγ-Isomer	%	References
$C_6H_5CH_2CH{=}C(CH_3)OCH_3$	90	$C_6H_5CH{=}CHCH(CH_3)OCH_3$	10	20
$RCH_2CH{=}CHSCH_3$		$RCH{=}CHCH_2SCH_3$		17
$R{=}H$	67	$R{=}H$	33	
$R{=}n\text{-}C_3H_7$	66	$R{=}n\text{-}C_3H_7$	34	
$RR'CHCR''{=}CR'''COOH$		$RR'C{=}CR''CH\,R'''COOH$		21
$R{=}R'{=}R''{=}R'''{=}H$	98	$R{=}R'{=}R''{=}R'''{=}H$	2	
$R{=}CH_3,\ R'{=}R''{=}R'''{=}H$	68	$R{=}CH_3,\ R'{=}R''{=}R'''{=}H$	32	
$R'{=}C_2H_5,\ R'{=}R''{=}R'''{=}H$	74	$R{=}C_2H_5,\ R'{=}R''{=}R'''{=}H$	28	
$R{=}R'{=}CH_3,\ R''{=}R'''{=}H$	6	$R{=}R'{=}CH_3,\ R''{=}R'''{=}H$	94	
$R{=}R'''{=}CH_3,\ R'{=}R''{=}H$	81	$R{-}R'''{=}CH_3,\ R'{=}R''{=}H$	19	
$R{=}CH_3,\ R'{=}R'''{=}H,\ R''{=}C_2H_5$	21	$R{=}CH_3,\ R'{=}R'''{=}H,\ R''{=}C_2H_5$	79	
$R{=}C_2H_5,\ R'{=}R'''{=}H,\ R''{=}H{=}n\text{-}C_3H_7$	34	$R{=}C_2H_5,\ R'{=}R'''{=}H,\ R''{=}n\text{-}C_3H_7$	66	
$RCH_2CH{=}CHS(O)CH_3$		$RCH{=}CHCH_2S(O)CH_3$		16, 17
$R{=}H$	80	$R{=}H$	20	
$R{=}CH,$	3	$R{=}CH_3$	97	
$R{=}n\text{-}C_9H_{19}$	4	$R{=}n\text{-}C_9H_{19}$	96	

The stabilisation of the βγ-isomer by hyperconjugation has been confirmed by a number of investigations. Thus in the system $n\text{-}C_4H_9C(R){=}CHCH(CH_3)COOC_2H_5 \rightleftharpoons n\text{-}C_4H_9CH(R)CH{=}C(CH_3)COOC_2H_5$ the fraction of the αβ-isomer in the equilibrium mixture increases from 45 to 86% on passing from $R = CH_3$ to $R = t\text{-}C_4H_9$, in agreement with the decrease of the hyperconjugation effect[21]. Analogous results were obtained for ethyl *trans*-2-methyl-4-*p*-R-phenylbutenoates, where the effect of steric factors is excluded and there is no *cis–trans* isomerisation during the attainment of equilibrium[24] (Table 2).

Table 2. $p\text{-}RC_6H_4CH{=}CHCH(CH_3)COOC_2H_5 \rightleftharpoons p\text{-}RC_6H_4CH_2CH{=}C(CH_3)COOC_2H_5$.

R	αβ-Isomer, %	βγ-Isomer, %	R	αβ-Isomer, %	βγ-Isomer, %
H	59.2	40.8	iso-C_3H_7	50	50
CH_3	39.8	60.2	t-C_4H_9	52.4	47.6
C_2H_5	45.9	54.1			

In the equilibrium mixture $C_6H_5CH_2SO_2CH{=}CHSO_2R \rightleftharpoons C_6H_5CH_2SO_2CH{=}CH{-}CH_2SO_2R$ the content of the first isomer also depends on the inductive effect of R, increasing in the series C_2H_5 (39%) < $n\text{-}C_3H_7$ (40%) < $n\text{-}C_4H_9$ (53%) < < $t\text{-}C_4H_9$ (60%).[25] The hyperconjugation effect accounts for the shift of equilibrium towards the second sulphone in the system $(C_2H_5)_2NO_2SCH{=}CHCH(CH_3)SO_2N(C_2H_5)_2 \rightleftharpoons (C_2H_5)_2N{-}O_2SCH_2CH{=}C(CH_3)SO_2N(C_2H_5)_2$.[26]

Apart from the conjugation and hyperconjugation effects, the inductive effect of the functional group plays a major role in the stabilisation of the αβ- and βγ-forms. This is evident from a comparison of the equilibrium constants *K* for mixtures of certain unsaturated sulphides, sulphoxides, and sulphones[8] (Table 3).

Table 3 shows that the stability of the αβ-form decreases in a series $SO_2R > SOR > SR$, i.e. in order of increasing inductive effects. It should be borne in mind that in the system $RCH_2{-}CH{=}CHX \rightleftharpoons RCH{=}CHCH_2X$ the effect of the substituent X is greater than that of CH_2X.

Table 3. Equilibrium constants for mixtures of certain unsaturated sulphides, sulphoxides, and sulphones $RCH_2CH{=}CHX \rightleftharpoons RCH{=}CHCH_2X$.

R	X	*K*	R	X	*K*
H	SCH_3	0.01	$n\text{-}C_3H_7$	SO_2CH_3	99.0
H	$SOCH_3$	0.2—0.25	$n\text{-}C_9H_{19}$	SCH_3	0.5
H	SO_2CH_3	0.78	$n\text{-}C_9H_{19}$	$SOCH_3$	24.0
$n\text{-}C_3H_7$	SCH_3	0.51	$n\text{-}C_9H_{19}$	SO_2CH_3	24.0
$n\text{-}C_3H_7$	$SOCH_3$	24.0			

Electron-accepting substituents increased the mobility of the α-hydrogen atom in $RCH{=}CHCH_2X$ and favour the prototropic shift in accordance with the magnitude of the $-I$ effect. However, such substituents at the double bond destabilise the αβ-form, provided that they cannot show a $+M$ or a $-M$ effect. Accordingly, the SR group stabilises the αβ-form and the SOR and SO_2R groups destabilise it in accordance with the magnitude of their $-I$ effects.

The equilibrium relations among nitro-olefins and phosphorus-containing olefins have been little investigated. According to the available data[27-30], regardless of substitution, an equilibrium mixture of nitro-olefins contains appreciable amounts of βγ-isomers (13–19% for the systems $CH_2{=}CHCH(CH_3)NO_2 \rightleftharpoons CH_3CH{=}C(CH_3)NO_2$[27] or $CH_2{=}C(CH_3)CH_2NO_2 \rightleftharpoons (CH_3)_2C{=}CHSO_2$).[29,30] This indicates a lower stabilisation of the αβ-form by the nitro-group compared with OR, SR, NR_2, COOR, CN, etc., possibly owing to the greater $-I$ effect.

Diallylphosphine is converted on refluxing with C_2H_5ONa into dipropenylphosphine in 90% yield[31]; similarly, when potassium hydroxide in methanol is employed, diallylphosphine oxide and allyl phenylphosphinic acid isomerise to dipropenylphosphine oxide and phenylpropenylphosphinic acid respectively (yield 90–95%). However, allylphosphonic acid is stable under these conditions.

Diethyl allylphosphonate isomerises completely to the propenyl isomer in the presence of sodium ethoxide even at room temperature, whereas under these conditions diethyl 3-phenylprop-2-enylphosphonate does not change and diethyl but-2-enylphosphonate gives an equilibrium mixture containing only 25% of the αβ-isomer[32]. Thus the phenyl and even the methyl group interacts with the double bond more strongly than the $P(O)(OC_2H_5)_2$ group. It is quite possible that in phosphine oxides and phosphinic acids the prototropic shift is due solely to the inductive effect of the PO and P(O)OH groups. Nor can one exclude in phosphines of the type R_3P the possible stabilisation of the propenyl form by the overlapping of the *p* orbitals of carbon with the *d* orbitals of phosphorus.

The capacity of various functional groups for stabilising the αβ-form may be estimated by comparing the equilibrium positions in systems with two different functional groups. Thus in the presence of $(C_2H_5)_3N$ an equilibrium mixture of 34% of 1-cyano-1-ethoxy-3,3-dichloroprop-2-ene and 58% of *trans*- and 8% of *cis*-1-cyano-1-ethoxy-3,3-dichloroprop-1-ene is formed[33-35]. The equilibrium mixture of ethyl 4,4-dichlorobutenoate contains different amounts of the αβ- and βγ-isomers[35].

Under the influence of potassium ethoxide in t-butyl alcohol at 35°C, methyl *trans*-3-methoxycrotonate is almost completely converted into methyl *cis*-4-methoxybut-3-enoate[36]:

$$CH_3OCH_2CH{=}CHCOOCH_3 \rightarrow CH_3OCH{=}CHCH_2COOC_2H_5\,.$$

The isomer where the double bond is conjugated to the SR group predominates slightly in an equilibrium system incorporating the SCH_3 and $COOC_2H_5$ groups[36]:

$$\underset{42\%\ (trans)}{CH_3SCH_2CH{=}CHCOOC_2H_5} \rightleftarrows \underset{24\%\ (cis)\ +\ 34\%\ (trans)}{CH_3SCH{=}CHCH_2COOC_2H_5}\,.$$

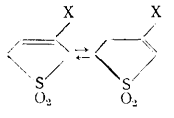
Thus the alkoxy and sulphide groups stabilise the conjugated isomer to a greater extent than the alkoxycarbonyl group. It is interesting to note that, when diethylamine acts upon the *trans*-isomer of ethyl 3,4-di(ethylthio)but-2-enoate, the latter is converted quantitatively into ethyl 3,4-di(ethylthio)but-3-enoate (a mixture of 80% of the *trans*-isomer and 20% of the *cis*-isomer), i.e. the double bond is fully displaced from conjugation with the $COOC_2H_5$ group[37].

On heating with potassium t-butoxide in dimethyl sulphoxide, an equilibrium mixture of 1% of *cis*- and 2% of *trans*-4-methoxy-1-methylthioprop-1-ene and of 32% of *cis*- and 65% of *trans*-4-methoxy-1-methylthioprop-2-ene is formed[36]:

$$CH_3OCH_2CH{=}CHSCH_3 \rightleftarrows CH_3OCH{=}CHCH_2SCH_3\,.$$

Thus in this case too the isomer with the double bond conjugated with the OR group is more stable, which is consistent with the relative +*M* effects of the OR and SR groups.

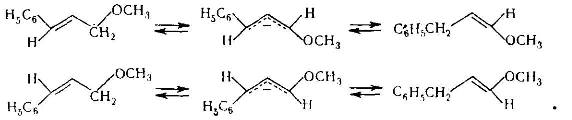
In the system



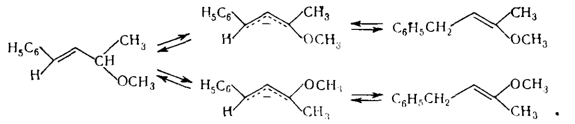
the content of the αβ-isomer increases in the sequence of substituents X = H ~ Cl < CH_3 ≪ OCH_3, n-C_4H_9S and in the last two cases the αβ-isomer predominates entirely. This can be accounted for by a donor–acceptor interaction between the substituent X, which has a free electron pair, and the sulphur atom in the SO_2 group[38].

Prototropic isomerisation is very greatly complicated by *cis–trans* isomerisation and this is why there is contradictory information in the literature about the stereochemistry of the prototropic shift. At the present time, however, it is known that prototropic isomerisation can be either stereospecific or lead to mixtures of *cis*- and *trans*-isomers depending on the structure of the olefin. It has been established that allyl ethers, for example, undergo a rigorously stereospecific isomerisation on heating with potassium t-butoxide to *cis*-propenyl ethers[5,39]. Under the reaction conditions, n-propyl *trans*-propenyl ether is not converted into the *cis*-isomer, i.e. the *cis*-isomer is indeed the primary isomerisation product.

It has recently been established[40] that the presence of substituents in the β-position has an appreciable influence on the stereochemistry of the isomerisation of allyl ethers to vinyl ethers. Thus, when potassium t-butoxide in dimethoxyethane acts at 25°C on the methyl ether of *trans*-cinnamyl alcohol, the latter gives predominantly the *cis*-isomer of 1-methoxy-3-phenylprop-1-ene (the content of the *trans*-isomer does not exceed 10%), while the methyl ether of *cis*-cinnamyl alcohol gives largely the *trans*-isomer (the content of the *cis*-isomer is about 25%):

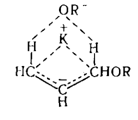


In the case of the methyl ether of 1-methylcinnamyl alcohol the isomerisation in the presence of potassium t-butoxide in dimethyl sulphoxide takes place non-stereospecifically, a mixture of different amounts of stereoisomeric vinyl ethers being formed[40]:

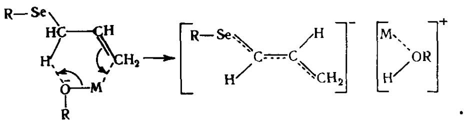


Allyl aryl selenides also isomerise stereospecifically, but in this case the *trans*-isomers are formed[10].

On the other hand, the isomerisation of allyl sulphides always leads to mixtures of 60–80% of the *cis*-isomer and 20–40% of the *trans*-isomer[8]. The differences in the stereochemistry of the isomerisation of allyl ethers, allyl sulphides, and allyl selenides are probably due to the differences in the geometry of the transition state. The formation of a stable *cis*-allyl carbanion incorporating the cation (K)[39]



has been postulated for allyl ethers. It is believed that, by virtue of the lower electronegativity and greater radius of the selenium atom, in allyl selenides the formation of a *cis*-transition complex is sterically hindered and the carbanion assumes a transoid configuration, where delocalisation of the carbanionic charge is facilitated by conjugation with the electrons in the *d* orbitals of selenium[10]:



The non-stereospecificity of the isomerisation of allyl sulphides can be explained by the fact that in this case there is a possibility of both a *cis*- and a *trans*-transition state, since sulphur is intermediate in its characteristics between oxygen and selenium.

It has been shown that, under the action of a solution of sodium in liquid ammonia, *N*-allyl-*N*-methylaniline, *N*-allyl-*N*-ethyl-*p*-toluidine, *NN*-diallylamine, etc. isomerise stereospecifically to *cis*-propenylamines. However, the compounds obtained rapidly isomerise to the thermodynamically stable *trans*-isomers even on storage in nitrogen; admixtures of alcohols or acids accelerate this process[12] and therefore in the majority of cases the isomerisation of allylamines leads to mixtures of *cis*- and *trans*-isomers (see also Riviere and Lattes[41]).

The isomerisation of $CH_2{=}CHCH(R)X$ in acetonitrile in the presence of $(C_2H_5)_2NH$ leads entirely to the formation of $CH_3CH{=}C(R)X$; there is no *cis–trans* isomerisation.

The data on the stereochemistry of this isomerisation are presented in Table 4.[15]

The stereochemistry of the reaction is independent of both the solvent (hexamethylphosphoramide, dimethyl sulphoxide, dimethylformamide, acetone, tetrahydrofuran, ether, dioxan, and others) and of the catalyst (piperidine, diethylamine, n-butylamine, isopropylamine, triethylamine, etc.) and is determined solely by the stereochemistry of the intermediate carbanion:

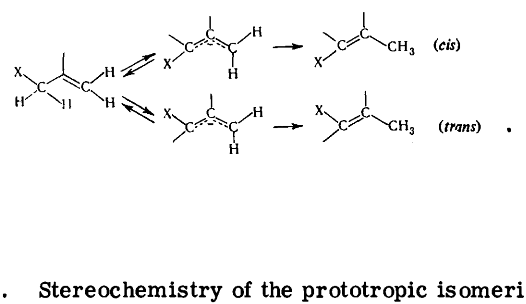
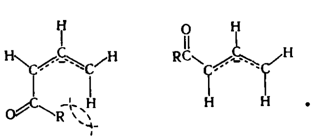


Table 4. Stereochemistry of the prototropic isomerisation $CH_2=CYCH(R)X \rightleftharpoons CH_3CY=C(R)X$.

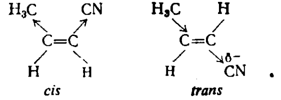
R	X	Y	*trans*-Form, %	R	X	Y	*trans*-Form, %
H	CN	H	35	Cl	COOH	H	100
H	$COOC_2H_5$	H	85	SC_2H_5	$COOC_2H_5$	H	90
H	COOH	H	94	H	CN	Cl	6
H	COC_2H_5	H	100	H	$COOC_2H_5$	Cl	0
Cl	CN	H	90	H	COOH	Cl	0
Cl	$COOC_2H_5$	H	100				

The relative amounts of the *cis*- and *trans*-isomers in the final product are determined by the ratio of the *cis*- and *trans*-carbanions, i.e. the free energies of the carbanions, the thermodynamically more stable carbanion being formed more rapidly. Evidently the thermodynamic stability of the carbanion is not necessarily the same as that of the final product. The stability of the carbanion depends on the electronic interaction between the substituents in the $\alpha\beta$- and $\alpha\gamma$-positions and on steric factors. In systems of the type $CH_2=CHCH_2X \rightleftharpoons CH_3CH=CHCHX$ the stability of the carbanion is controlled by the interaction of the $\alpha\gamma$-substituents (i.e. the H and X groups); when $X = COOC_2H_5$, COR, or COO^-, a greater stability of the *trans*-carbanion is to be expected:



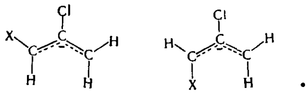
cis *trans*

By virtue of the smaller bulk of the CN group, in nitriles the interaction of the α-CN group and the γ-H atom plays a less important role; moreover, in this case the *cis*-form is stabilised by dipole–dipole interaction to a greater extent than the *trans*-form and therefore there is a possibility of the formation of a mixture of *cis*- and *trans*-isomers in proportions corresponding to the stabilities of the intermediate carbanions:



cis *trans*

For a system of the type $CH_2=OClCH_2X \rightleftharpoons CH_3CCl=CHX$, the interaction of the substituents in the $\alpha\beta$-positions promotes the formation of the *cis*-carbanion:



cis *trans*

These considerations proved to be valid also in the study of other systems, for example $CH_2=C(SR)CHClCOOC_2H_5 \rightleftharpoons CH_3(SR)=CClCOOC_2H_5$ or $CH_3=C(SR)CH(SR')COOC_2H_5 \rightleftharpoons CH_3C(SR)=C(SR')COOC_2H_5$.[42]

The carbanionic mechanism of prototropic isomerisation has been confirmed by a number of experimental findings. Thus the isomerisation of allyl or propenyl derivatives in deuteroalcohols always leads to the formation of α- or γ-deutero-derivatives respectively[17,43–45]. For example, the following reaction takes place on refluxing in deuterobutanol in the presence of potassium t-butoxide[43]:

$$\underset{}{CH_2=CHCH_2OR} \rightarrow \underset{27.8\%}{CH_3CH=CHCH_2OR} + \underset{69.7\%}{CH_2DCH=CHCH_2OR} + \underset{2.5\%}{CHD_2CH=CHCH_2OR}\ .$$
$$(R=C_9H_{19})$$

Similarly at room temperature we have the reaction[44]

$$C_9H_{19}CH_2CH=CHS(O)CH_3 \rightarrow C_9H_{19}CH=CHCD_2S(O)CH_3\ .$$

At 175 °C deuterium exchange takes place and an equilibrium is established[43]:

$$CH_2=CHCH_2OR \rightleftarrows \underset{47\%}{CH_3CH=CHOR} + \underset{40\%}{CH_2DCH=CHCHOR} + \underset{11\%}{CHD_2CH=CHOR} + \underset{1.3\%}{CD_3CH=CHOR}\ .$$

All these data are consistent with a carbanionic mechanism:

$$CH_2=CHCH_2X \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} CH_2\text{---}\bar{C}H\text{---}CHX \underset{k_{-2}}{\overset{k_2}{\rightleftarrows}} CH_3CH=CHX$$
$$k_1 > k_2,\ k_{-1} > k_{-2}\ .$$

Kinetic studies on prototropic isomerisation[15,46,47] also confirm the carbanionic mechanism. The rate of isomerisation depends on the affinity of the catalyst for the proton[47]. For the system

$$CH_2=C(R)CH(R')X \rightleftarrows CH_3C(R)=C(R')X \quad {}^{15}$$

the reaction obeys second-order kinetics. Certain data on the effect of the nature of the base on the rate of isomerisation in this system are presented in Table 5, which shows that the catalytic activity of amines depends on the degree of substitution at the nitrogen atom (the rate of isomerisation increases with decreasing steric hindrance at the nitrogen atom) and on solvation [the more solvated primary amines are less active than the less solvated $(C_2H_5)_2NH$].

The basicity of the catalyst is also of great importance. Thus 1,3-diphenylprop-2-en-1-ol isomerises only under the action of alcoholic alkali but not pyridine or triethylamine[48], while the isomerisation of 1,3,3-triphenylprop-2-en-1-ol requires the use of potassium t-butoxide in dimethyl sulphoxide but not aqueous alkali[49].

The rate of reaction depends very markedly on the nature of the solvent, reaching a maximum in aprotic polar solvents (hexamethylphosphoramide, dimethylformamide, dimethyl sulphoxide, acetonitrile, etc.)[15], which is typical of reactions with a carbanionic mechanism. Table 6 presents certain data on the effect of solvents on the rate of isomerisation.

The rate of reaction is determined by the formation of the carbanion. All factors facilitating the formation of the carbanion increase the rate of reaction. Thus in the $CH_2=CHCH_2X$ system the rate of isomerisation increases in the following sequence of X: $COOH < COOC_2H_5 < CN < COR$, which is the same as the familiar series of substituents with increasing $-M$ effects[15] and can be accounted for by the facilitation of the heterolysis of the α-C–H bond. The introduction of a chlorine atom into the α-position of the system increases the rate of isomerisation owing to the –*I* effect and the acceleration of the reaction in the presence of chlorine in the β-position is due to the additional stabilisation of the carbanion by the involvement of lone-pair electrons of the chlorine atom in delocalisation[15]. The systems examined above are characterised by low activation energies (about 10 kcal) and highly negative activation entropies (about –35 e.u.), which indicates a high degree of order in the transition state. It has been suggested[15] that in the transition state the formation of the B–H bond preceeds the heterolysis of the highly polarised α-C–H bond and the transition state itself is a highly solvated still incompletely dissociated ion pair.

Table 5. Rate of isomerisation and the nature of the base $CH_2{=}CRCHR'COOC_2H_5 \rightarrow CH_3CR{=}CR'COOC_2H_5$*.

Base	R=H, R′=Cl** *k*, litre $mole^{-1}\ s^{-1}$	R=Cl, R′=H*** *k*, litre $mole^{-1}\ s^{-1}$
$(C_2H_5)_2NH$	0.90	0.092
n-$C_4H_9NH_2$	0.51	0.039
iso-$C_3H_7NH_2$	0.35	0.032
iso-$C_3H_7)_2NH$	0.12	0.0116
$(C_2H_5)_3N$	0.09	0.0123

*The reaction carried out in ether at 24.7°C, goes to completion.

**Only the *trans*-isomer is formed.

***Only the *cis*-isomer is formed.

Prototropic isomerisation in the presence of bases has found wide application in organic synthesis. Several novel methods are based on the isomerisation of unsaturated alcohols where the alcoholic group is converted into a carbonyl group as a result of prototropic shift:

$$RCH{=}CHCH(OH)R' \rightarrow RCH_2CH{=}C(OH)R' \rightarrow RCH_2CH_2COR' \ .$$

The conversion of allyl alcohols themselves into carbonyl compound has found only limited application in the synthesis of aliphatic-aromatic ketones stable to alkalis (for example, see Refs. 46–48). However, a prototropic shift in substituted allyl alcohols constitutes the foundation of several preparative syntheses.

Thus when hot dilute alkalis act upon the cyanohydrin of ββ-diphenylacrolein or the amide of 2-hydroxy-4,4-diphenylbut-3-enoic acid, prototropic isomerisation is accompanied by the hydrolysis of the nitrile and amide groups and the formation of α-oxo-γγ-diphenylbutyric acid in high yields[50]:

$$(C_6H_5)_2C{=}CHCH(R)OH \rightarrow (C_6H_5)_2CHCH{=}C(R)OH \rightarrow (C_6H_5)_2CHCH_2COCOOH \ ,$$

where R = CN or $CONH_2$. This method is of general importance for the synthesis of α-ketoacids.

A prototropic shift is the rate-determining stage in the synthesis of succinic acid by refluxing β-formylacrylic acid with a solution of potassium cyanide, which takes place according to the following mechanism[51]:

$$HOOCCH{=}CHCHO \xrightarrow{CN^-} HOOCCH{=}CHCH(CN)OH \rightarrow HOOCCH_2CH{=}C(CN)OH \rightarrow$$
$$\rightarrow HOOCCH_2CH_2COCN \xrightarrow{OH^-} HOOCCH_2CH_2COOH \ .$$

A similar mechanism constitutes the basis of a simple method for the synthesis of esters of β-substituted propionic acids by the action of an excess of acetone cyanohydrin and triethylamine on αβ-unsaturated aldehydes with electron-accepting substituents in the β-position[52]. The intermediate cyanohydrin isomerises to a β-ketonitrile, which in the presence of an excess of acetone cyanohydrin or alcohol (as a solvent) gives an ester of propionic acid:

$$RCH{=}CHCHO \xrightarrow{CN^-} RCH{=}CHCH(CN)OH \rightarrow RCH_2CH{=}C(CN)OH \rightarrow$$
$$\rightarrow RCH_2CH_2COCN \xrightarrow{R'O^-} RCH_2CH_2COOR' \ .$$

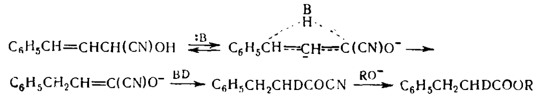
Table 6. Effect of solvents on the rate of isomerisation. $CH_2{=}CHCHClCOOC_2H_5 \rightarrow CH_3CH{=}CClCOOC_2H_5$*.

Solvent	*k*, litre $mole^{-1}\ s^{-1}$	Solvent	*k*, litre $mole^{-1}$ s^{-1}
Hexamethylphosphoramide	instantaneous reaction	Tetrahydrofuran	0.35
Dimethylformamide	reaction ends after 5 min	Monoglyme	0.084
Acetonitrile	2.47	Ether	0.0136
Acetone	1.99		

*The base is $(C_2H_5)_2NH$; temperature 0.2° ± 0.2°C.

The intermediate formation of the cyanohydrin is confirmed by the fact that, when acetone cyanohydrin and triethylamine act on the cyanohydrin of cinnamaldehyde, an ester of β-phenylpropionic acid is also formed[53].

In the reaction of cinnamaldehyde and α-methylcinnamaldehyde with deuteroacetone cyanohydrin in the presence of triethylamine, 75–80% of the deuterium enters into the α-position of the ester. Thus the transfer of hydrogen in this case takes place largely intramolecularly:



$$C_6H_5CH{=}CHCH(CN)OH \overset{:B}{\rightleftharpoons} C_6H_5CH{\cdots}\underline{C}H{\cdots}C(CN)O^- \rightarrow$$
$$C_6H_5CH_2CH{=}C(CN)O^- \xrightarrow{BD} C_6H_5CH_2CHDCOCN \xrightarrow{RO^-} C_6H_5CH_2CHDCOOR \ .$$

When polyene aldehydes take part in the reaction, the process involves only the αβ-double bond[54]; in this way, it is possible to synthesise αβ-dihydro-derivatives:

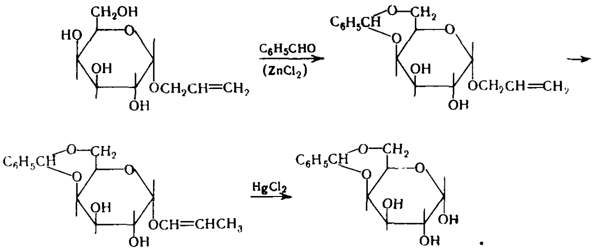
$$R(CH{=}CH)_nCHO \rightarrow R(CH{=}CH)_{n-1}CH_2CH_2COOR' \ ,$$

where R = CH_3, C_6H_5, or $COOC_2H_5$, and *n* = 2 or 3.

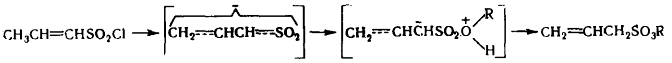
The isomerisation of allyl ethers has found fairly wide application in the synthesis of propenyl ethers (for examples, see Refs. 5–7 and 55–59). Among the catalysts proposed, potassium t-butoxide is particularly effective when dimethyl sulphoxide is used as a solvent[5,6,58]. The isomerisation of allyl ethers by heating with potassium t-butoxide is a convenient preparative method for the synthesis of propenyl ethers especially those which are difficult to obtain by other methods—ethers derived from polyhydric alcohols. For example, tetrapropenylpentaerythritol was obtained from tetra-allylpentaerythritol in about 83% yield[5]:

$$C(CH_2OCH_2CH{=}CH_2)_4 \rightarrow C(CH_2OCH{=}CHCH_3)_4 \ .$$

The easy isomerisation of allyl ethers to propenyl ethers suggested the use of the allyl group as a protecting group in carbohydrate chemistry[60–65]. After the necessary operations, the allyl ether isomerises to the propenyl ether and its protecting group is removed in a suitable way (by acid hydrolysis, ozonolysis, oxidation by alkaline potassium permanganate, and by treatment with $HgCl_2$). The allyl protecting group is particularly convenient in the synthesis of benzyl and benzylidene derivatives of sugars. Thus 4,6-*O*-benzylidene-D-galactose can be obtained from 1-allyl-D-galactopyranoside[65]:



An interesting method for the synthesis of esters of $\beta\gamma$-unsaturated sulphonic acids otherwise difficult to obtain is based on the alcoholysis of $\alpha\beta$-unsaturated sulphonyl chlorides in the presence of triethylamine[66]. The reaction involves a mechanism with prototropic isomerisation via sulphenes.



$$CH_3CH{=}CHSO_2Cl \rightarrow \left[\overset{-}{\overbrace{CH_2{\cdots}CHCH{\cdots}SO_2}}\right] \rightarrow \left[CH_2{\cdots}CH\bar{C}HSO_2\overset{+}{O}\begin{smallmatrix}R\\H\end{smallmatrix}\right] \rightarrow CH_2{=}CHCH_2SO_3R$$

In the presence of triethylamine, allyl aryl sulphones isomerise smoothly to propenyl sulphones[67,68]. Thus on heating allyl β-naphthyl sulphone in dioxan or alcohol with triethylamine for 15–17 h, β-naphthyl propenyl sulphone was obtained:

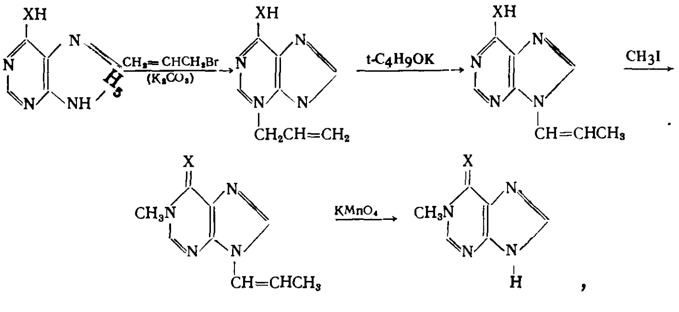
$$\beta\text{-}C_{10}H_7SO_2CH_2CH{=}CH_2 \rightarrow \beta\text{-}C_{10}H_7SO_2CH{=}CHCH_3\ .$$

The isomerisation of allylamines in the presence of potassium t-butoxide in dimethyl sulphoxide[11,12], a dispersion of sodamide on alumina in pentane or hexane[69], or a solution of sodium in liquid ammonia[70] at room temperature is a very convenient method for the synthesis of *NN*-disubstituted enamines in high yields (60–100%):

$$CH_2{=}CHCH_2NRR' \rightarrow CH_3CH{=}CHNRR'\ .$$

A method has been developed for the synthesis of *N*-propenylpyrrolidinone and *N*-propenylcaprolactam in 50–80% yield by the isomerisation of the corresponding allyl derivatives at 165–180°C in the presence of potassium t-butoxide[71]. *N*-Allylthiolactams isomerise in the presence of potassium t-butoxide in dimethyl sulphoxide even at room temperature[72].

The use of the allyl group to protect the amino-group in purine bases has been suggested[73]. 1-Methyladenine and 1-methylhypoxanthine have been obtained using such protection via the 9-allyl derivatives by the mechanism



where X = O or NH.

A prototropic shift constitutes the basis of a new method for the synthesis of iminoethers by the action of potassium cyanide and primary amines on $\alpha\beta$-unsaturated aldehydes in the presence of potassium hydroxide or sodium methoxide in methanol at room temperature[74]. The reaction takes place by the mechanism

$$RCH{=}CHCHO \rightarrow RCH{=}CHCH(CN)NHR' \rightarrow RCH_2CH{=}C(CN)NHR' \rightarrow$$
$$\rightarrow RCH_2CH_2C(OCH_3){=}NR'\ .$$

$\alpha\beta$-Unsaturated aldehydes react by a similar mechanism with acetone cyanohydrin and primary or secondary amines with formation of α-cyanoimines or α-cyanoenamines respectively[75]:

$$RCH{=}CHCHO \rightarrow RCH{=}CHCH(CN)NR' \rightarrow RCH_2CH{=}C(CN)\,NHR' \rightarrow RCH_2CH_2C(CN){=}NR'$$
$$RCH{=}CHCHO \rightarrow RCH{=}CHCH\,(CN)\,NR'R'' \rightarrow RCH_2CH{=}C(CN)NR'R''\ .$$

The intermediate formation of aminonitriles has been demonstrated by their synthesis in the reaction of cinnamaldehyde with acetone cyanohydrin and piperidine, morpholine, or aniline[75,76]:

$$C_6H_5CH{=}CHCHO \rightarrow C_6H_5CH{=}CHCH\,(CN)\,R\ ,$$

where R = NCH_6H_5 diagrams.

When potassium cyanide in methanol was allowed to react with cinnamaldehyde cyanohydrin, methyl β-phenylpropionate was obtained[77].

1-Cyano-1-piperidino-3-phenylprop-1-ene isomerises smoothly to an enaminonitrile on being passed through an alumina column[76]; a product with the hydrogen atom and the amino-group in *cis*-positions is formed.

The product of a prototropic shift was obtained on refluxing 3-chloro-3-*p*-nitrophenylprop-1-ene in benzene with triethylamine[78]:

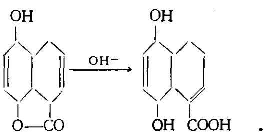
$$p\text{-}O_2NC_6H_4CHClCH{=}CH_2 \rightarrow p\text{-}O_2NC_6H_4CCl{=}CHCH_3\ .$$

The formation of small amounts of an ester of but-1-enylmethylphosphinic acid on methylation of but-2-enylphosphonic ester can also be accounted for by a prototropic shift[79]:

$$CH_3CH{=}CHCH_2P(O)\,(OC_3H_7\text{-iso})_2 \xrightarrow{CH_3I} CH_3CH{=}CHCH_2P(CH_3)\,(O)\,(OC_3H_7\text{-iso})$$
$$CH_3CH_2CH{=}CHP(CH_3)(O)(OC_3H_7\text{-iso})$$

The formation of methyldiphenyl-(1-phenylprop-1-enyl)-phosphonium iodide on methylation of diphenyl-(1-phenylallyl)phosphine can be interpreted similarly[80].

Isomerisation in the presence of bases is used for the synthesis of $\alpha\beta$-unsaturated acids, esters, nitriles, lactones, ketones, etc. from the corresponding $\beta\gamma$-derivatives (for examples, see Refs. 81–86). For instance, *cis*-5,8-dihydroxy-1,4,5,8,9,10-hexahydronaphthoic acid is obtained by refluxing with aqueous alcoholic alkali the 1,8-lactone of *cis*-5,8-dihydroxy-3,4,5,8,9,10-hexahydronaphthoic acid[86]:



When nucleophilic agents act upon $CHCl{=}CHCH_2X$,[87] $CH_2{=}CClCH_2X$,[80,81] or $CH_2{=}CHCHClX$,[87] other reactions, apart from prototropic isomerisation, can occur depending on the reactant, the position of the chlorine atom, and the reaction conditions. Thus, regardless of the configuration of the initial compound, hydrolysis of $CHCl{=}CHCH_2COOC_2H_5$ by aqueous alkali leads to the formation of *trans*-3-chlorocrotonic acid, i.e. the isomerisation and hydrolysis take place with retention of the chlorine atom:

$$CHCl{=}CHCH_2COC_2H_5 \rightarrow CH_2ClCH{=}CHCOOH \quad .$$

When the reaction is carried out in alcoholic solution, isomerisation with simultaneous addition of the alcohol and retention of the chlorine atom takes place:

$$CHCl{=}CHCH_2COOC_2H_5 \rightarrow CH_2ClCH(OC_2H_5)CH_2COOC_2H_5 \quad .$$

However, on refluxing with an aqueous solution of sodium carbonate, the shift of the double bond is accompanied by the exchange of the chlorine atom for a hydroxy-group:

$$CHCl{=}CHCH_2X \rightarrow CH_2(OH)CH{=}CHX \quad ,$$

where X = CN or $COOC_2H_5$.

In the case of $CH_2 = CClCH_2X$ the isomerisation takes place with retention of the chlorine atom or its replacement, depending on the nature of X; moreover, in a number of instances an elimination reaction is observed[87,88]:

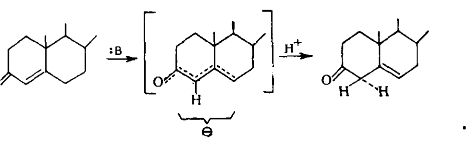
$$CH_2{=}CClCH_2COOC_2H_5 + C_2H_5O^- \rightarrow CH_3C(OC_2H_5){=}CHCOOC_2H_5 \quad ,$$
$$CH_2{=}CClCH_2N + C_2H_5O^- \rightarrow CH_3CCl{=}CHCN + CH_3C(OC_2H_5){=}CHCN \quad .$$

Isomerisation with or without replacement of the chlorine atom and sometimes the formation of addition products occur with $CH_2{=}CHCHClX$:[87]

$$CH_2{=}CHCHClCOOC_2H_5 + (C_2H_5)_2NH, \rightarrow CH_3CH{=}CClCOOC_2H_5 \quad ,$$
$$CH_2{=}CHCHClCOOC_2H_5 + C_2H_5ONa \rightarrow CH_3CH{=}CClCOOH + CH_3CH{=}CClCOOC_2H_5 +$$
$$+ CH_3CH(OC_2H_5)CHClCOOC_2H_5 \quad .$$

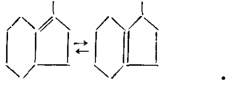
Base-catalysed isomerisation is used to convert Δ^5-3-oxosteroids into Δ^4-3-oxosteroids. Thus Δ^5-pregnenedione has been converted in high yield into progesterone[89].

A method has also been developed for the conversion of Δ^4-3-oxosteroids into Δ^5-3-oxosteroids. For this purpose, Δ^4-3-oxosteroids are heated with potassium t-butoxide in t-butyl alcohol and the resulting carbanions are then protonated by acetic acid, forming Δ^5-3-oxosteroids[90]:

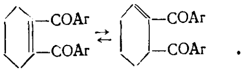


The reaction is based on the fact that in this case protonation at the C_4 atom is faster than at the C_6 atom. This possibility is confirmed by the fact that, on refluxing, for example, 6,6-dimethylcyclohex-2-enone with deuterium oxide, the vinyl hydrogen atom is exchanged 170 times faster than the allyl hydrogen atom[91]. This method has been used to prepare 17α-methyl-Δ^5-androst-17β-en-2-one from 17-methyltestosterone. Ketones with several conjugated bonds remain unchanged when treated in this way[90].

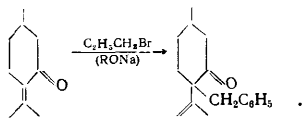
It is interesting that on heating (for 24 h) 1-acetyl-$\Delta^{1,8}$-perhydroindane with potassium methoxide in methanol, an equilibrium mixture is formed containing 80% of the $\Delta^{8,9}$-isomer[92]:



Similarly, on heating (72 h) with a potassium hydroxide solution, 1,2-diaroylcyclohexene is converted to the extent of 90% into 1,6-diaroylcyclohexene[93]:

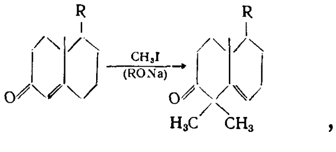


The different reactivities of the α- and β-positions of carbanions with functional groups are used in the synthesis of α-alkyl and αα-dialkyl-substituted βγ-unsaturated acids, esters, ketones, etc. by alkylating the αβ-unsaturated isomers in an alkaline medium (for examples, see Refs. 94–109). Thus the alkylation of sorbic acid in liquid ammonia with CH_3I in the presence of potassamide leads to 2,2-dimethylhexa-3,5-dienoic acid[94]. The alkylation of ketones with a tetrasubstituted ethylene bond by alkyl halides in the presence of sodium alkoxides gives α-monoalkyl derivatives[96,97]. For example:



α-Monoalkyl derivatives can also be obtained by maintaining specially selected reaction conditions[98,99]. Thus, a 44% yield of 4-methyltestosterone is obtained by the gradual addition of 1.2 equivalents of methyl iodide to testosterone in boiling t-butyl alcohol in the presence of 1.5 equivalents of potassium t-butoxide.

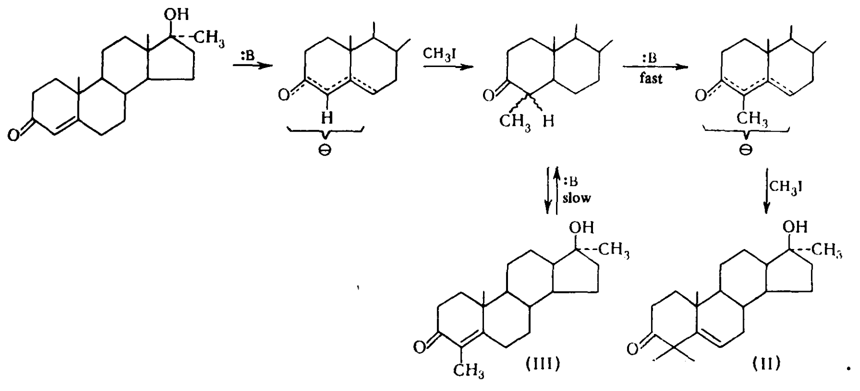
Dialkylation of αβ-unsaturated cyclic ketones has found extensive application in the chemistry of terpenes and steroids. Thus bicyclic ketones, which are necessary for the synthesis of terpenes of the labdanolic acid type[100] or triterpenes of the β-amyrin type[101], were obtained via the mechanism



where R = H or OH.

Alkylation of cholestenone with CH_3I in t-butyl alcohol in the presence of potassium t-butoxide leads to 4,4-dimethylcholest-5-en-3-one[102,105]; 4,4-dimethylandrost-3-ene[106] and 4,4-dimethylergosta-5,7,22-trien-3-one[107] were obtained in this way from testosterone and ergosterone respectively; 3-oxo-Δ^4-derivatives of androstene and pregnane are methylated similarly[108].

The formation of dialkyl derivatives is explained by the fact that secondary alkylation and (or) the formation of a tertiary carbanion are faster than the primary alkylation and (or) the formation of a secondary carbanion. In fact, the reaction of CH_3I with the carbanion formed from the ketone (I) by brief treatment with potassium t-butoxide leads to the ketone (II) in 74% yield, while methylation of the α-methyl ketone (III) under the same conditions gives the ketone (II) in a yield of only 6%:[110]



When alcohols are allowed to react with the chlorides of $\alpha\beta$-unsaturated acids in the presence of tertiary amines, the main reaction products are esters of vinylacetic acid[111,112]:

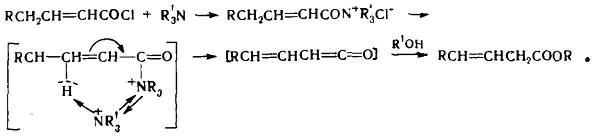
$$RCH_2CH{=}CHCOCl + R'OH\,(R_3'N) \rightarrow RCH{=}CHCH_2COOR' + RCH_2CH{=}CHCOOR'\,.$$

The nature of the amine and the structure of the acid chloride (Table 7) affect the ratio of the $\alpha\beta$- and $\beta\gamma$-isomers.

Table 7. Effect of the nature of the amine and the structure of the acid chloride on the ratio of the $\alpha\beta$- and $\beta\gamma$-isomers $CH_2{=}C(R)CH_3COOCH_2(IV) \rightleftharpoons CH_3C(R){=}CHCOOCH_3(V)$.

Amine	pK	Mixture composition, %			
		IV, R=H	V, R=H	IV, R=CH₃	V, R=CH₃
Triethylamine	10.7	87.8	12.2	83.1	16.9
N-Ethylpiperidine	10.4	83.5	16.4	89.6	10.4
Triallylamine	8.3	47.5	52.5	44.1	55.9
N-Ethylmorpholine	7.7	65.3	34.7	69.1	30.9
Pyridine	5.2	1.6	98.4	0.6	99.4

The results show that the ratio of the reaction products is controlled by the initial abstraction of a proton. It has been suggested that, when highly basic amines (p$K > 10$) are employed, the reaction takes place via the following mechanism[112]:



$$RCH_2CH{=}CHCOCl + R_3'N \rightarrow RCH_2CH{=}CHCON^+R_3'Cl^- \rightarrow$$

$$\left[\begin{array}{c} RCH{-}CH{=}CH{-}C{=}O \\ \quad H \qquad\quad {}^+NR_3 \\ \overset{+}{N}R_3' \end{array}\right] \rightarrow [RCH{=}CHCH{=}C{=}O] \xrightarrow{R'OH} RCH{=}CHCH_2COOR\,.$$

Thus the reaction consists in the prototropic isomerisation of the intermediate acylammonium salt with elimination of an NR_3 group and the formation of a keten, which then combines with the alcohol.

It has been shown in recent years[113-116] that prototropic isomerisation is also the basis of the Varrentrapp reaction, which is carried out by heating *cis*- or *trans*-unsaturated acids with central double bonds at 300–360°C with potassium hydroxide in an inert atmosphere; this results in the formation of acetic and a saturated acid containing two carbon atoms less than the initial unsaturated acid:

$$CH_3(CH_2)_nCH{=}CH(CH_2)_mCOOH \rightarrow CH_3(CH_2)_{n+m}COOH + CH_3COOH + H_2\,.$$

Thus palmitic acid was obtained from oleic or petroselinic acid in yields of 80–85% and 78% respectively, nonanoic acid was obtained from undec-10-enoic acid in 80% yield, and heptanoic acid was obtained from non-2-enoic acid in 80% yield also.

A detailed study of the Varrentrapp reaction using oleic acid as an example showed that the prototropic shift plays the main role and that in the initial stages the migration of double bonds takes place to an equal extent on either side. However, when, as a result of a series of reversible shifts, the double bond reaches the $\alpha\beta$-position, a reversible cleavage takes place and the entire system of equilibria is displaced towards the carboxy-group. The overall reaction mechanism may be represented thus:

$$R(CH_2)_{n-1}CH{=}CH(CH_2)_{n+1}COO^- \rightleftharpoons R(CH_2)_{n-1}CH\cdots\bar{C}H\cdots CH(CH_2)_mCOO^- \rightleftharpoons$$

$$R(CH_2)_nCH{=}CH(CH_2)_mCOO^- \rightleftharpoons R(CH_2)_nCH\cdots\bar{C}H\cdots CH(CH_2)_{m-1}COO^- \rightleftharpoons$$

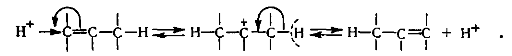
$$R(CH_2)_{n+1}CH{=}CH(CH_2)_{m-1}COO^- \rightleftharpoons \ldots\ldots\ldots\ldots \rightleftharpoons$$

$$R(CH_2)_{n+m-1}CH\cdots\bar{C}H\cdots CHCOO^- \rightleftharpoons R(CH_2)_{n+m}CH{=}CHCOO^- \rightarrow$$

$$R(CH_2)_{n+m}COOH + CH_3COOH + H_2\,.$$

III. ISOMERISATION IN THE PRESENCE OF ACIDS

It has been known for a long time that the prototropic shift of the double bond in olefins can be induced by acids. The reaction involves the intermediate formation of a carbonium cation and is frequently accompanied by allyl isomerisation and structural changes. For this reason, acid-catalysed isomerisation has found much less application than base-catalysed isomerisation. The overall process mechanism can be represented as follows:



$$H^+ \rightarrow \overset{|}{\underset{|}{C}}{=}\overset{}{\underset{|}{C}}{-}\overset{|}{\underset{|}{C}}{-}H \rightleftharpoons H{-}\overset{|}{\underset{|}{C}}{-}\overset{+}{\underset{|}{C}}{-}\overset{|}{\underset{|}{C}}{-}H \rightleftharpoons H{-}\overset{|}{\underset{|}{C}}{-}\underset{|}{C}{=}\overset{|}{\underset{|}{C}} + H^+\,.$$

The acid-catalysed isomerisation of allyl alcohols to carbonyl compounds[117], which has found industrial application for the synthesis of isobutyraldehyde from 2-methylprop-2-en-1-ol[118], has been most thoroughly investigated. It has been shown that, as in base-catalysed isomerisation, the reaction depends appreciably on the structure of the allyl alcohol. The allyl alcohol itself and its linear homologues of the type $RCH{=}CHCH_2OH$ are hardly isomerised on refluxing with 0.44 *N* sulphuric acid solution[110,111]. On the other hand, β-alkylallyl alcohols are smoothly converted in high yields (88–92%) into aldehydes:

$$CH_2{=}CH(R)CH_2OH \rightarrow CH_3CH(R)CHO\,,$$

where $R = CH_3$, C_2H_5, iso-C_3H_7, or t-C_4H_9.

$\beta\gamma$-Substituted allyl alcohols undergo simultaneously a prototropic shift (the formation of aldehydes) and oxotropic isomerisation (formation of ketones), the latter predominating judging from the yields:

$$RCH{=}C(R')CH_2OH \rightarrow RCH_2CH(R')CHO + RCOCH(CH_3)R'$$

R	R′	Yield of aldehyde, %	Yield of ketone, %	R	R′	Yield of aldehyde, %	Yield of ketone, %
CH_3	CH_3	25	63	CH_3	C_2H_5	36	52
C_2H_5	CH_3	15	71	n-C_3H_7	C_2H_5	19	69 .

Alcohols of the type $RR'C{=}CR''CH_2OH$ are readily dehydrated. Secondary alcohols of the type $CH_2{=}C(R)CH(R')OH$ are smoothly converted into ketones:

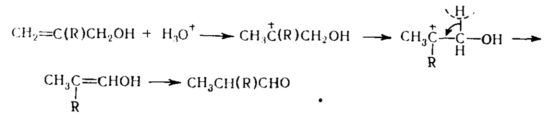
$$CH_2{=}C(R)CH(R')OH \rightarrow CH_3CH(R)COR' \text{ (yield 86–92\%)} .$$

Only traces of aldehydes—products of oxotropic rearrangement with a subsequent prototropic shift—are observed.

The prototropic isomerisation of secondary alcohols of the type $RCH{=}C(R')CH(R'')OH$ also takes place without complications:

$$RCH{=}C(R')CH(R'')OH \rightarrow RCH_2CH(R')COR'' .$$

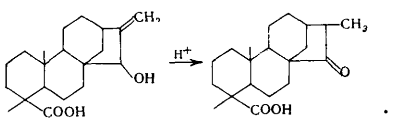
The study of the kinetics and the effect of the acidity of the medium on the rate of conversion of β-alkylallyl alcohols into aldehydes and of the kinetics of the conversion of the glycols $CH_3C(R)(OH)CH_2OH$ into the same aldehydes confirms the carbonium ion mechanism of the acid isomerisation of allyl alcohols[119-121]:



$$CH_2{=}C(R)CH_2OH + H_3O^+ \longrightarrow CH_3\overset{+}{C}(R)CH_2OH \longrightarrow CH_3\underset{R}{\overset{+}{C}}{-}\underset{H}{\overset{H}{C}}{-}OH \longrightarrow CH_3\underset{R}{C}{=}CHOH \longrightarrow CH_3CH(R)CHO .$$

Thus the proton adds to the double bond with subsequent elimination of a proton from the α-position. This mechanism is consistent with the results of the isomerisation of 1-[^{14}C]methylallyl alcohol, which leads to the formation of isobutyraldehyde labelled with carbon-14 at the carbonyl group[122].

The acid-catalysed isomerisation of alcohols has found limited application in the synthesis of certain cycloalkanones[123] and certain complex cyclic ketones[124,125]. For example:

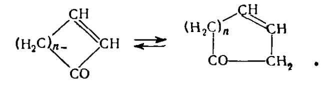


Little is known about the effect of the structure of the olefin on the equilibrium position in acid-catalysed isomerisation in $RCH_2CH{=}CHX \rightleftharpoons RCH{=}CHCH_2X$ systems. It has been noted that the $\alpha\beta$-isomer predominates in the equilibrium mixture of aliphatic ketones[126]:

$$\underset{\sim 93\%}{(CH_3)_2C{=}CHCOCH{=}C(CH_3)_2} \rightleftarrows \underset{\sim 7\%}{(CH_3)_2C{=}CHCOCH_2C(CH_3){=}CH_2} \rightleftarrows \underset{\text{traces}}{CH_2{=}C(CH_3)CH_2COCH_2C(CH_3){=}CH_2} .$$

However, in the hydrolysis of *cis*-β-chlorocrotononitrile with sulphuric acid at room temperature, the amide of *cis*-β-chlorovinylacetic acid was obtained in high yield[83].

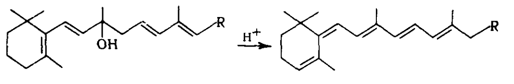
The equilibrium between cycloalk-2-enones and cycloalk-3-enones on refluxing in benzene in the presence of p-$CH_3C_6H_4SO_3H$ depends on ring size[127]:



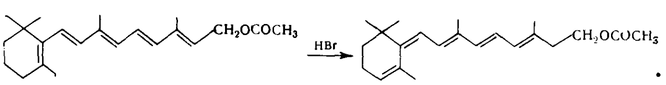
n	Time of attainment of equilibrium, h	Composition of equilibrium mixture, %	
		$\alpha\beta$-isomer	$\beta\gamma$-isomer
3	fast.	99.0	1.0
4	1	73.0	27.0
5	2	20.0	80.0
6	22	0.3	99.7

The shift of equilibrium towards the $\beta\gamma$-isomer with increasing number of units is probably associated with the fact that the double bond and the carbonyl group become non-coplanar. This leads to the destabilisation of the $\alpha\beta$-isomer, which in the absence of conjugation is thermodynamically less stable than the $\beta\gamma$-isomer. An approximate estimation of the angle of rotation Θ between the planes of the CO group and the double bond on the hypothesis that the difference between the chemical shifts in the H NMR spectrum of cyclononones $\gamma_B - \gamma_A$ (A = H at C_2 and B = H at C_3) is proportional to cos Θ, showed that Θ increases progressively with the number of units in the ring[127]. Possibly this is due to the fact that, on increasing the number of units, the conformations where the CO group and the double bond are located in the same plane become hindered, as shown, for example, by the conformational analysis of cyclo-oct-2-enone, in which full coplanarity of the CO group and the double bond is achieved only in the model where there should be strong *trans*-annular interaction between the H atom at C_4 and the *cis*-H atom at C_8.

In connection with the problem of the synthesis of biologically active preparations of the type of vitamin A, a detailed study was made of the acid-catalysed prototropic isomerisation in the vitamin A series, which has been called retroionylidene rearrangement. This rearrangement takes place in the acid-catalysed dehydration of hydroxy-derivatives and when acidic reagents act upon compounds where the side chain is fully conjugated with the ring double bond and consists in the shift of the entire conjugated bond system from the functional group towards the ring[128-131]:

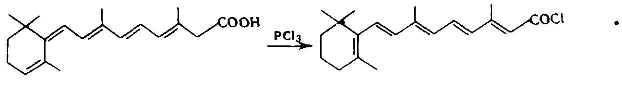


where R = CH_2OCH_3, CHO, COOR, etc.;



This results in the formation of biologically inactive species—the so called retroionylidene structures. The rearrangement is due to the fact that in a molecule of the vitamin A type there is appreciable steric interaction between the methyl groups of the ring and the side chain; when acted upon by acids, such compounds should be converted into the thermodynamically more stable retroionylidene compounds. The transition from such structures to ionylidene compounds is possible on treatment with alkaline agents (potassium hydroxide, sodium hydroxide, alkoxides, etc.) or by chromatography on aluminosilicate columns[130,132,133].

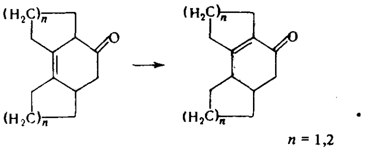
Acids with the retroionylidene structure are converted into straight-chain acid chlorides on treatment with specially purified phosphorus trichloride[132]. For example:



Acid-catalysed prototropic isomerisation may complicate many processes. Thus the hydration of divinylacetylenes in aqueous solutions in the presence of sulphuric acid and mercuric sulphate results in the formation of divinyl ketones instead of the expected allyl vinyl ketones[134]:

$$RCH{=}CHC{\equiv}CCH{=}CHR' \rightarrow RCH{=}CHCOCH{=}CHCH_2R' \ .$$

A method has been proposed for the synthesis of $\alpha\beta$-unsaturated tricyclic ketones by refluxing the $\beta\gamma$-isomers with a 3% methanol solution of hydrogen chloride or a 0.1% benzene solution of p-$CH_3C_6H_4SO_3H$.[135] 4-Oxo-$\Delta^{8a(8)}$-decahydro-*as*-indacene and 9-oxo-$\Delta^{4(8a)}$-dodecahydrophenanthrene were obtained in this way:



A method has also been proposed for the synthesis of aryl propenyl sulphones by heating allyl aryl sulphones with a solution of boron trifluoride in sulphuric acid[136]:

$$ArSO_2CH_2CH{=}CH_2 \rightarrow ArSO_2CH{=}CHCH_3 \ (43\text{–}50\%) \ .$$

IV. ISOMERISATION IN THE PRESENCE OF METAL CARBONYLS

It has been established by investigations in recent years that metal carbonyls [$Fe(CO)_5$,[137-141] $CoH(CO)_4$,[142] or $Co(CO)_8$[143]] are effective catalysts of the prototropic isomerisation of substituted olefins with functional groups; they may contain functional groups with free electron pairs (allyl alcohols[137-140,142] and allyl ethers[140,141]) or they are esters of unsaturated acids capable of π–π conjugation[141]. The principal advantage of metal carbonyls is the fact that in their presence the reaction may be carried out in a neutral medium (although examples are also known where the reaction was carried out in the presence of alkalis).[137] Thus this method may be used to achieve the shift of double bonds when the initial or final products are sensitive to acids and alkalis.

The isomerisation of unsaturated alcohols has been most thoroughly investigated. Secondary allyl alcohols isomerise particularly smoothly on heating with 10–20 mole % $Fe(CO)_5$ without a solvent at 110–125°C or on refluxing in octane. The yields of ketones reach 60–80%:[140]

$$CH_2{=}C(R)\,CH(OH)\,R' \rightarrow CH_3CH(R)COR' \ .$$

Alcohols of the type $CH_2{=}CH(CH_2)_nCH(OH)R$ enter into the reaction with equal success[140].

However, primary alcohols and cyclohex-2-enol gives low yields of products under these conditions. The yield increases to 29–54% when the reaction is carried out in pentane at room temperature in the presence of 3–5 mole % $Fe(CO)_5$ with simultaneous ultraviolet irradiation[140]. For example:

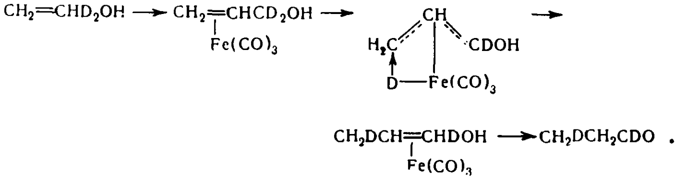
$$RCH{=}CH\,(CH_2)_n\,CH_2OH \rightarrow R\,(CH_2)_{n+2}\,CHO \ ,$$

where $n = 1$ and $R = C_2H_5$ (*cis*-isomer) (29%) or $n = 7$ and $R = H$ (54%).

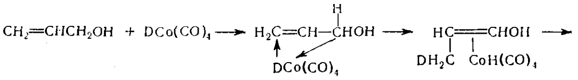
The isomerisation of allyl, crotyl, and other unsaturated alcohols in the presence of $CoH(CO)_4$ is complicated by hydroformylation and leads to low yields (3–21%) of carbonyl compounds[142].

On heating (to 130–160°C) with $Fe(CO)_5$, cyclo-oct-3-enol and cinnamyl alcohol give cyclo-octanone and 3-phenylpropionaldehyde in yields of 90 and 100% respectively.

As regards the reaction mechanism, it is suggested that initially the allyl system and the metal carbonyl form a π-complex[138,142,144,145], within which a 1,3-hydrogen transfer takes place. This is confirmed by the fact that, in the isomerisation of 1,1-dideuteroallyl alcohol in the presence of $Fe(CO)_5$, only 1,3-dideuteropropionaldehyde is formed[144]:



This mechanism is also confirmed by the formation of 3-deuteropropionaldehyde in the isomerisation of allyl alcohol in the presence of $CoD(CO)_4$:[142]

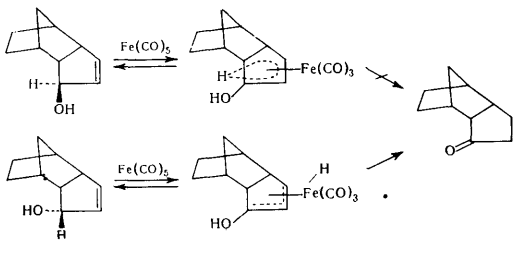


$$CH_2{=}CHCH_2OH + DCo(CO)_4 \longrightarrow \underset{\uparrow\ DCo(CO)_4}{H_2C{=}CH{-}\overset{H}{C}HOH} \longrightarrow \underset{DH_2C\quad CoH(CO)_4}{HC{=}CHOH} \longrightarrow$$

$$HCo(CO)_4 + CH_2DCH{=}CHOH \longrightarrow CH_2DCH_2CHO \ .$$

Possibly the π-complex exists in equilibrium with a δ-complex.

Additional confirmation of the mechanism of the rearrangement via the formation of a π-complex between the allyl system and the metal carbonyl was obtained in a study of the isomerisation of *endo*-α-1-hydroxy-5,6-dihydrocyclopentadiene to *endo*-β-1-hydroxy-5,6-dihydrocyclopentadiene. It was found that the first compound does not isomerise on heating with iron pentacarbonyl even at 160°C, while the second gives the ketone in about 40% yield on heating to 130°C for 16 h with 10% of iron pentacarbonyl in an atmosphere of nitrogen[145]:



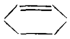
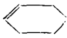
This shows that the rearrangement takes place via a π-complex, since in both cases the attack by the iron carbonyl can take place from the least screened *exo*-side, but only in the second case is there a possibility of the formation of a transition state in which a hydrogen atom can be readily transferred.

The isomerisation of allyl ethers takes place quantitatively in the presence of 5 mole % $Fe(CO)_5$ in pentane under ultraviolet illumination[140,146]. This leads to the formation of a mixture of approximately equal amounts of the *cis*-isomer (44–52%) and the *trans*-isomer (48–56%). Under these conditions, diallyl ether gives a mixture of 26%, 42%, and 31% of *cis*, *cis*-; *cis*, *trans*-; and *trans*, *trans*-dipropenyl ethers respectively[146] and 1-methoxybut-3-ene forms a mixture of products of complete and partial isomerisation:

$$CH_2{=}CHCH_2CH_2OCH_3 \rightarrow \underset{25\%}{CH_3CH{=}CHCH_2OCH_3} + \underset{34\%\ cis + 41\%\ trans}{CH_3CH_2CH{=}CHOCH_3} \ .$$

The stability of the tautomers was estimated by studying their relative amounts in isomerisation mixtures of different types derived from unsaturated ethers (Table 8).[140] The Table shows that the $\alpha\beta$-isomers of ethers in which the double bond is conjugated to the ether group are the most stable. The ratio of the Δ^3-isomer and the Δ^2-isomer is 1.5 : 1 both for open-chain and cyclic ethers, which indicates an important role of the inductive destabilisation of the $>CHOCH_3$ group.

Table 8. Relative amounts of tautomers in isomerisation mixtures of ethers.

Initial ether	Total yield, %	Relative amounts of isomers, %			
		Δ^1	Δ^2	Δ^3	Δ^4
$CH_3OCH{=}CH(CH_2)_2CH_3$	91	84.0	6.0	9.0	1
$CH_3O(CH_2)_3CH{=}CH_2$	90	85.0	5.0	9.0	1
—OCH$_3$	93	93.5	3.9	3.6	
—OCH$_3$	96	95.0	2.0	3.0	

In the isomerisation of ethers of the type $CH_2{=}CH(CH_2)_nOCH_3$ (n = 1, 2, 3, 4, 8, 9) there is an increase of the overall amount of isomers with more remote double bonds and a decrease of the content of the $\alpha\beta$-isomer in the equilibrium mixture. The ratio of the vinyl ether to each non-conjugated isomer (with the exception of the $\beta\gamma$-isomer) is approximately 10 : 1. Calculation shows that the replacement of the alkyl group by a methoxy-group at the vinyl carbon atom increases the stability of the isomer by 1.5 kcal.

Table 9. Relative amounts of tautomers in isomerisation mixtures of esters.

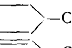
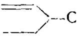
Ester	Relative amounts of esters in mixture, %						
	Δ^1	Δ^2	Δ^3	Δ^4	Δ^5	Δ^6	Δ^7
$C_5H_{11}CH{=}CHCOOCH_3$	...	18.1	8.1	20.4	23.6	28.5	1.5
$C_2H{=}CH(CH_2)_5COOCH_3$	...	17.8	7.3	20.8	24.2	28.7	1.2
—COOCH$_3$	88.8	3.6	7.6	—	—	—	—
—COOCH$_3$	86.8	4.4	8.8	—	—	—	—

Table 9 presents certain data on the relative amounts of tautomers obtained in the isomerisation of esters by refluxing in octane in the presence of 10–20 mole % $Fe(CO)_5$.[141] The equilibrium ratio of the $\alpha\beta$- and $\beta\gamma$-isomers of the octenoates is 2.5 : 1 according to the data obtained. However, the overall sum of the Δ^4-, Δ^5-, and Δ^6-isomers exceeds the content of the $\alpha\beta$-isomer, because the $-M$ and $-I$ effects of the $COOCH_3$ group do not affect the stability of the internal isomers stabilised mainly by hyperconjugation.

Among cyclic isomers, the $\alpha\beta$-isomer stabilised by the $-M$ affect of the $COOCH_3$ group and hyperconjugation is the most stable. It has recently been established that $Fe(CO)_5$ is an effective catalyst of the isomerisation of N-allylimides to N-propenylimides[147].

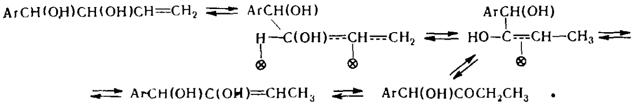
V. ISOMERISATION IN THE PRESENCE OF VARIOUS CATALYSTS

The catalytic isomerisation of olefins with functional groups can be of preparative or industrial value, but, although it was described long ago[117], it has not been adequately investigated. The literature quotes almost exclusively examples of isomerisation under conditions of heterogeneous catalysis. Thus it has been noted that allyl and crotyl alcohols are converted into propionaldehyde and butyraldehyde respectively when the alcohol vapours are passed over copper or cobalt at 150–400°C.[148–150] Vinyl glycols of the type $ArCH(OH)CH(OH)CR{=}CHR'$ (Ar = C_6H_5 or α-furyl) passed in the vapour phase at 200°/15 mmHg over Cu/Cr_2O_3 [151,152] or 5–10% $Pd/CaCO_3$ [153] give the ketols $ArCH(OH)COCHRCH_2R'$ in yields of 30 to 65% in addition to other products. Similarly, when the vapour of the glycol $CH_3CH{=}CHCHOHCHOHCH{=}CHCH_3$ is passed over Cu/Cr_2O_3 at 130°/15 mmHg, dibutyryl is formed in 45% yield[154].

A promising method has been proposed for the catalytic isomerisation of N-alkylallylamines to N-alkylpropenylamines in 26–50% yield when the vapour is passed at 260 to 270°C over alumina promoted by potassium hydroxide; at the same time 5–15% of N-alkylidenealkylamines is formed[155]:

$$CH_2{=}CHCH_2NHR \rightarrow CH_3CH{=}CHNHR + CH_3CH_2CH{=}NR\ .$$

Vinyl glycols of the type $ArCH(OH)CH(OH)CH{=}CH_2$ are also isomerised on simple distillation over $Pd/CaCO_3$ [156] or reduced copper[152], forming the ketols $ArCH(OH)COC_2H_5$ (yield 62–75%). The following possible mechanism of the formation of ketols under the conditions of heterogeneous catalysis, the first stage of which is adsorption of the unsaturated molecule on the catalyst metal, has been proposed:



The isomerisation of allyl alcohols and glycols takes place also on distillation over Raney nickel. Thus n-valeraldehyde was obtained in 80% yield from pent-3-enol[157] and methyl 12-oxostearate was obtained from methyl ricinoleate[158]. It is suggested that in this case the alcohol may be dehydrogenated with subsequent hydrogenation of the double bond.

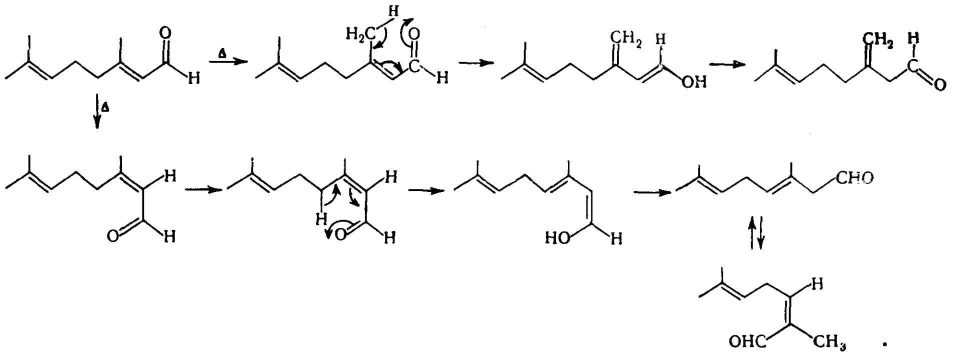
The conversion of allyl alcohols into aldehydes was observed in the reduction by zinc treated with alkali[159] or by the Zn/Cu couple[160]. In some cases there is a possibility of isomerisation under conditions of homogeneous catalysis. Thus phenylvinylglycol is converted into 1-hydroxy-1-phenylbutan-2-one on heating in solution with *cis*-$PdCl_2[P(C_6H_5)_3]_2$:[151]

$$C_6H_5CH\,(OH)\,CH\,(OH)\,CH{=}CH_2 \rightarrow C_6H_5CH\,(OH)\,COC_2H_5\ .$$

The yield greatly depends on the nature of the solvent, reaching 85–100% in dimethylformamide. In benzene, diglyme, and nitromethane the reaction scarcely occurs, in chloroform the yield of the ketol is 10–12%, and in ethylene glycol and hexamethylphosphoramide the yield is 20–30%. Saturated glycols do not change under the experimental conditions. Probably the isomerisation takes place via the formation of a π-complex.

VI. THERMAL ISOMERISATION

The thermal prototropic isomerisation has been little investigated. For example, citral (a mixture of *cis*- and *trans*-isomers in proportions of 2 : 1) isomerises on heating (130–175°C) in a vacuum (15–130 mmHg) to isocitral (also a mixture of the *cis*- and *trans*-isomers) in yields up to 70% and 3-methylene-7-methyloct-6-enal in yields up to 30%. An intramolecular cyclic electron transfer mechanism has been proposed for the thermal isomerisation of citral, isocitral being formed from the *cis*-form of citral and 3-methylene-7-methyloct-6-enal from the *trans*-form of citral[162]:



The thermal isomerisation of nitro-olefins at 110–140°C, which leads to the formation of equilibrium mixtures[163] (Table 10), was investigated in greater detail. The data in Table 10 show that in the case of unsubstituted nitro-olefins or derivatives substituted only in the α-position the equilibrium is wholly displaced towards the αβ-isomer. The effect of substituents in the β- or γ-positions results in the appearance in the equilibrium mixture of appreciable amounts of the βγ-isomer. The equilibrium position is also influenced by the nature of the solvent: polar aprotic solvents promote a shift of equilibrium towards the βγ-isomer (Table 11).

Table 10. Thermal isomerisation of nitro-olefins $RCH_2C(R')=C(R'')NO_2 \rightleftharpoons RCH=C(R')CH(R'')NO_2$.

R	R′	R″	Content in equilibrium mixture, %	
			αβ-isomer	βγ-isomer
H	H	H	100	0
CH_3	H	H	86	14
H	CH_3	H	75	25
H	H	CH_3	100	0
H	CH_3	CH_3	90	10

The study of the thermal isomerisation of vinylnitriles[164] showed that unsubstituted nitriles or derivatives with substituents in the α- or β-positions only do not isomerise. In the presence of two methyl groups or electron-accepting substituents (C_6H_5, C_6H_5O) in the γ-positions the equilibrium is displaced towards the βγ-isomer:

$$RR'CHC(R'')=C(R''')CN \rightleftarrows RR'C=C(R'')CH(R''')CN\ .$$

R	R′	R″	R‴	αβ-isomer %	βγ-isomer %
H	H	H	H	100	0
H	H	$CH_3(C_6H_5)$	H	100	0
H	H	H	$CH_3(C_6H_5)$	100	0
CH_3	CH_3	H	CH_3	100	0
CH_3	CH_3	H	H	28	72
C_6H_5	H	H	H	36	64
C_6H_5O	H	H	H	5	95

However, the γ-substituted nitrile does not isomerise when there is a methyl group in the α-position.

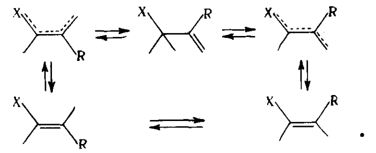
The stereochemistry of the thermal isomerisation of nitriles is independent of temperature and solvent. In the initial stages of the process the *cis*-isomer predominates and the *trans*/*cis* ratio increases only in the course of the reaction, which can be readily accounted for by the *cis*–*trans* isomerisation occurring simultaneously. As a result, the ratio of the *cis*- and *trans*-isomers established is approximately 1.4.

Table 11. Effect of solvents on the position of equilibrium in the system $(CH_3)_2C=CHNO_2 \rightleftharpoons CH_2=C(CH_3)CH_2NO_2$.

Solvent	Temp., °C	Content in equilibrium mixture, %	
		αβ-isomer	βγ-isomer
Cyclohexane	140	83	17
Benzene	140	80	20
Toluene	140	75	25
Acetonitrile	140	75	25
Dioxan	140	67	33
Dimethyl sulphoxide	25	68	32
Hexamethyl-phosphoramide	25	52	48

The rate of reaction increases in the following series of solvents: toluene < dioxan < acetonitrile < dimethyl sulphoxide ≪ hexamethylphosphoramide[164].

The stereochemistry of the reaction and the effect of solvents on the rate of reaction and also the effect of substituents and solvents on the position of equilibrium are consistent with a carbanion mechanism of the thermal isomerisation[163,164]:

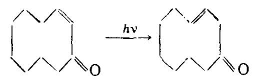


VII. PHOTOCHEMICAL ISOMERISATION

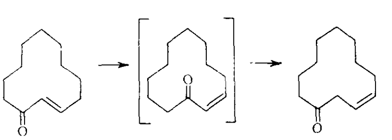
A fairly large number of examples of the migration of the double bond in carbonyl compounds under the influence of ultraviolet light have now been described. The principal feature of the photochemical isomerisation is that in this case the shift of the double bond takes place always from a conjugated to a non-conjugated position, i.e. the $\beta\gamma$-isomer is formed from the $\alpha\beta$-isomer. Thus, on irradiation of 4,5,5-trimethylhex-3-en-2-one, the product is pure 4-methylene-5,5-dimethylhexan-2-one, which on standing is spontaneously partially converted into vinyl ketone, giving an equilibrium mixture in proportions of 1 : 1.[165]

The study of the photochemical isomerisation of aliphatic $\alpha\beta$-unsaturated ketones of the type $RR'C=C(R'')COCH_3$ in ether showed[166] that ketones without substituents or containing substituents in the α- or β-positions only or simultaneously in the γ- and α- or β-positions do not isomerise. On the other hand, γ-substituted ketones readily enter into the reaction. Thus 5-methylhex-4-en-2-one was obtained in 75% yield from 5-methylhex-3-en-2-one, while hex-3-en-2-one gave a mixture of the *cis*- and *trans*-isomers of hex-4-enone[166]. When phorone is irradiated in methanol or hexane, 2,6-dimethylhepta-1,5-diene-4-one is formed in high yield[167,168] together with traces of 2,6-dimethylhepta-1,6-diene-4-one.

The results of the photolysis of $\alpha\beta$-unsaturated cyclic ketones are related to ring size[169]. In the case of cyclodec-2-enone[170] and cyclododec-2-enone[171] the double bond migrates from the $\alpha\beta$- to the $\beta\gamma$-position:



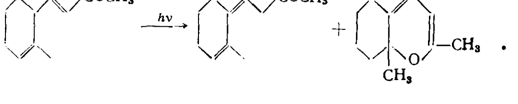
cis-isomer 59% (mixture of *cis*- and *trans*-isomers) ,



trans-isomer *cis*-isomer 92% .

Before isomerisation *trans*-isomers are converted into the *cis*-form. After prolonged irradiation of *cis*-cyclodec-2-enone, 2-vinylcyclo-octanone was formed in a yield up to 35% in addition to the cyclodec-3-enone.

Several examples of the photochemical shift of the double bond in the α-ionone series have been described[172,173]. However, the reaction is frequently complicated by the formation of bicyclic structures. For example:



Photochemical isomerisation has been used to convert 7-oxocholesteryl acetate into 3β-acetoxycholest-4-en-7-one[174] and 10α-testosterone into 17α-hydroxy-3-oxo Δ^5-10α-androstene[175].

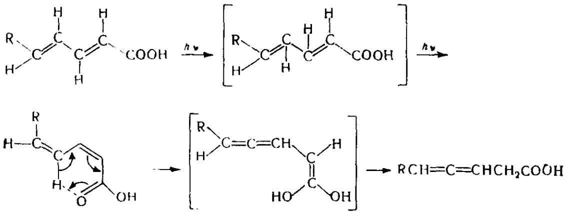
It has been noted that, when crotonaldehyde vapour is irradiated at 30°C with light at 245–400 nm, vinylacetaldehyde is formed[176].

Esters of crotonic, pent-2-enoic, 4-methylpent-2-enoic, and 2-methylcrotonic acids are smoothly isomerised on illumination with ultraviolet light, giving quantitative yields of vinylacetic ester and its substituted derivatives[177]. Under the same conditions, ethyl 1,3-dimethylcrotonate gives ethyl 2,3-dimethylbut-3-enoate with a yield of only 7%. The reaction is promoted by polar solvents, low concentrations of the reactants, and high temperatures.

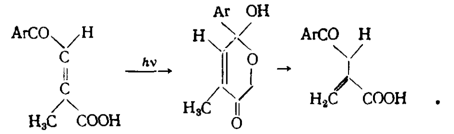
An interesting method for synthesising allenic acids of the type $RCH=C=CHCH_2COOH$ is based on the photochemical reaction of dienoic acids (sorbic and penta-2,4-dienoic) in ether in the presence of traces of formic acid[178]. The yield of the final product is 20–32%:

$$RCH=CHCH=CHCOOH \rightarrow RCH=C=CCH_2COOH \quad .$$

Salts of the acids do not isomerise under these conditions, which indicates an important role of the unionised carboxy-group in the reaction. The following mechanism has been proposed for the isomerisation:

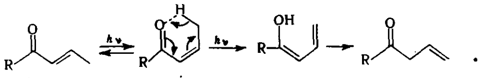


The isomerisation of α-methyl-β-aroylacrylic acids under the influence of sunlight takes place with deconjugation of the aroyl group[179]:



The process proceeds via the lactone, which can be isolated when the reaction is interrupted at the initial stage.

In accordance with all available data for the mechanism of photochemical reactions[169,180], it is believed that the photochemical isomerisation of $\alpha\beta$-unsaturated carbonyl compounds to $\beta\gamma$-isomers takes place by the mechanism (for the *trans*-isomers)



trans *cis*

This mechanism has been confirmed by the fact that the isomerisation of $(CH_3)_2CHCH=CHCOCH_3$ in deuteromethanol (CH_3OD) resulted in 90% conversion into deuterated $\beta\gamma$-unsaturated ketone, where 90% of the hydrogen in the 3-position was replaced by deuterium, which is possible only when the process proceeds via the enol [$(CH_3)_2C=CHCH_2COCH_3$ does not exchange hydrogen in the 3-position for deuterium under identical conditions].[166]

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Zelinskii Institute of Organic Chemistry,
Moscow

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Investigation of Rapid Proton Exchange by Proton Magnetic Resonance

V.K.Pogorelyi and I.P.Gragerov

The review presents a critical compilation and a general account of the published data on rapid proton exchange processes obtained by proton magnetic resonance (PMR). An attempt has been made to establish wherever possible the dependence of the rate and mechanism of the exchange on the chemical structure of the reactants, particularly on the properties of the hydrogen bonds formed by them.
The bibliography includes 163 references.

CONTENTS

I. INTRODUCTION

Many of the most important types of chemical reactions reduce to proton transfer between molecules or ions. This group includes, for example, the dissociation of acids and bases, neutralisation, acid–base catalysis, a number of cases of solvolysis, various tautomeric transformations, rapid isotope exchange of hydrogen, and other processes. One of the central problems of theoretical chemistry involves understanding the driving forces, kinetics, and mechanisms of such processes as a function of the structure of the reactants and the experimental conditions.

Advances in this field are due to the application of relaxation methods[1,2], which allow, in particular, the study of the kinetics of rapid protolytic reactions in ions of different charge types, and the PMR method. The latter proved particularly convenient in the investigation of the detailed mechanism of protolytic reactions and the role of solvation processes in them.

This review deals with studies on rapid proton exchange reactions by the PMR method. In order to supplement several review articles already available[3–8], the relevant literature is considered up to the end of 1968. Particular attention has been concentrated on the dependence of the rate and mechanism of exchange on the chemical structure of the reactants and especially on the properties of the hydrogen bonds formed by them. The role of these bonds in proton exchange was discussed in some studies (see, for example, Refs. 9–16), but has usually been underestimated in the treatment of the experimental data obtained by the PMR method.

We shall not consider in detail the theory of the nuclear magnetic resonance (NMR) method and its application in the study of rapid reactions; the treatment will be restricted to the formulation of certain concepts needed here, the description of the fundamental principles involved in calculating the rates of exchange, and the references to appropriate sources.

The application of the NMR method to problems of chemical kinetics is based on the study of the form of spectral lines. The multiplet structure of the spectrum and the width and intensity of the lines are partly determined by dynamic processes, which can be divided into two types: intermolecular exchange of atoms, groups of atoms, or electrons, and intramolecular processes, for example hindered rotation of atomic groups, inversion of configuration, and rearrangements. We shall examine here the exchange of protons between two molecules:

$$AH^{*}+BH \leftrightarrows AH+BH^{*}\,. \qquad (1)$$

When the exchange is very slow [the lifetimes of the proton in the molecules AH and BH (τ_A and τ_B) are greater than 1 second], the PMR spectrum of such a system shows two narrow resonance signals associated with the magnetic non-equivalence of the two hydrogen nuclei. With increase of the rate of exchange (decrease of τ_A and τ_B), the magnetic environment of the protons in the A–H and B–H bonds becomes averaged, the absorption lines therefore broaden and at a certain exchange frequency merge into a single signal, which becomes narrower on further acceleration of the exchange.

The first approximate relations between the change in line shape and the rate of exchange were proposed by Gutowsky and coworkers[17–19], who used a solution of the Bloch equations[20] in which the time variation of the nuclear magnetisation vector was taken into account by introducing an exponential multiplier, which depends on the lifetime of the proton in a given state. In these studies it was also shown that exchange processes whose frequency is comparable to the difference between the chemical shifts ($\Delta\nu = \nu_A - \nu_B$) of the protons undergoing exchange may be observed by the PMR method.

A more rigorous treatment was proposed by McConnell[21], who introduced into the Bloch equation a number of additional terms, characterising the exchange. The following assumptions were made: (a) proton exchange is a reversible process in which hydrogen nuclei are transferred from one electronic environment to another; (b) the lifetime of the protons in positions AH and BH is much greater than the time necessary for the transfer of protons from A to B and conversely; (c) the probability of finding the protons in the equilibrium positions P_A and P_B and the equilibrium exchange time τ are related to τ_A and τ_B as follows in accordance with the principle of detailed balance:

$$P_A=\frac{\tau_A}{\tau_A+\tau_B};\ P_B=\frac{\tau_B}{\tau_A+\tau_B};\ \tau=\frac{\tau_A\cdot\tau_B}{\tau_A+\tau_B}\ .$$

He also regards the quantities P_A and P_B as the statistical weight fractions of the protons in the corresponding positions. We shall consider in greater detail certain special cases of proton exchange.

1. Under conditions of "slow" exchange when τ_A and $\tau_B \gg \Delta\nu^{-1}$, PMR spectra show two separate signals. Their width Δ increases with decrease of τ (acceleration of exchange). These quantities are related by the equation[22]

$$\pi\Delta_A = T_{2A}^{-1} + \tau_A^{-1} ,$$

which allows the lifetime of the proton (duration of the exchange) τ_A to be determined from the width of the signal when exchange is absent ($T_{2A}^{-1} = \pi\Delta_0$).

2. In the case of "rapid" exchange, where τ_A and $\tau_B \ll \Delta\nu^{-1}$ the spectrum shows a single common signal, whose position depends on the ratio of P_A and P_B and whose width is related to τ_A and τ_B by the equation[23]

$$\pi\Delta = T_2^{-1} + P_A^2 P_B^2 (\tau_A + \tau_B) ,$$

from which τ is found. At very high rates of exchange the contribution of the second term to line width may be negligible and the above formula becomes unsuitable for the determination of τ. In these cases τ may be found from the change in the intensity of the combined signal[24].

3. In the region of intermediate rates of exchange where τ_A and τ_B are comparable to $\Delta\nu^{-1}$, τ may be determined in several ways. One of these consists in comparing the absorption curves calculated for different τ with the experimental spectra. The most general solution of this problem was obtained by Rogers and Woodbrey[25]. Gutowsky and Holm[19] obtained the following expression for the signal intensities q_ν on the assumption that $P_A = P_B$, $\tau_A = \tau_B = 2\tau$, and $T_{2A} = T_{2B} = \infty$ (in the absence of exchange the absorption lines are infinitely narrow):

$$q_\nu = \frac{K\tau\,(\nu_A - \nu_B)^2}{\left[\left(\frac{\nu_A + \nu_B}{2}\right) - \nu\right]^2 + 4\pi^2\tau^2\,(\nu_A - \nu)^2(\nu_B - \nu)^2} .$$

They also derived an equation for the more general case where $T_{2A} = T_{2B}$ is finite and $P_A \neq P_B$. The determination of the rate of exchange can be significantly simplified by obtaining a universal curve (suitable for any values of $\Delta\nu$ and T_2) which relates τ to line width at half the height or to the ratio of the maximum and minimum signal intensities. This problem has been solved for a doublet of lines of equal intensity[26,27] and for the case where $P_A \neq P_B$[28]. A method has also been developed for the determination of τ from the distance between the maxima ($\Delta\nu_{max}$) of the signals due to the states involved in the exchange[19]. The resulting equation is simplest for an infinitely narrow line ($T_{2A} = T_{2B} = \infty$):

$$\tau^{-1} = \sqrt{2}\,\pi\,(\Delta\nu^2 - \Delta\nu_{max}^2)^{\frac{1}{2}} .$$

It shows that the signals merge when $\tau^{-1} = \sqrt{2}\pi(\nu_A - \nu_B)$. Such merging is characteristic of these systems and may serve for the estimation of τ.

In contrast to the two-centre exchange described above, the derivation of analytical expressions for many-centre exchange is fairly complex and has been achieved only in the simplest cases[29-33]. The general expression for an n-centre exchange in the absence of spin–spin coupling between non-equivalent protons was obtained by Piette and Anderson[22].

When the absorption lines corresponding to the mobile protons in the molecules A–H and B–H have a multiplet structure due to spin–spin coupling, the exchange of protons (both equivalent and non-equivalent) leads to a broadening and merging of the components of the multiplet. The rate of exchange may be assessed from these changes. Thus Solomon and Bloembergen[34] solved the problem of the broadening of the lines of the multiplet in "rapid" exchange. Kaplan[35,36] developed a general theory which includes "rapid" and "slow" exchange as limiting cases. Kaplan's method was used by Alexander[37,38] for exchange between different molecules. General methods for the calculation with a spin doublet have been put forward[39-43]. Equations relating the rate of proton exchange to changes in the form of a triplet[29,30,44] and quartet[42] are also available.

More detailed information about the calculation of the rate of proton exchange from NMR spectra may be found in monographs by Pople et al.[45] and Emsley et al.[46]

The lifetime τ_A of the proton in the HA molecule is related to the rate constant k for proton exchange. Evidently the relation between τ_A, the concentration of the substance HA, and the rate of exchange is of the form

$$\tau_A = [\mathrm{HA}]/-\frac{d[\mathrm{HA}]}{dt} \quad \text{or} \quad \tau_A^{-1} = -[\mathrm{HA}]^{-1}\cdot\frac{d[\mathrm{HA}]}{dt} .$$

On the other hand,

$$-\frac{d[\mathrm{HA}]}{dt} = k\,[\mathrm{HA}]^m\,[\mathrm{HB}]^n .$$

Consequently

$$R = \tau_A^{-1} = k\,[\mathrm{HA}]^{m-1}\,[\mathrm{HB}]^n ,$$

where R is the relative rate of proton exchange.

With the aid of NMR it is possible to measure τ in the range 1–10^{-4} s. When the values outside this range are encountered, the rate of exchange is altered by varying the concentration, temperature, or the solvent, in order to make it measurable.

The NMR method has advantages over other procedures for the investigation of rapid reactions—it permits a more detailed study of their mechanism and yields more accurate values of the rate constants. It is significant that, in contrast to relaxation methods, equilibrium in the test system is not displaced or hindered during the measurement. The disadvantages of the NMR method include low sensitivity, which makes it difficult to investigate dilute solutions or gases at a low pressure.

2. PROTON EXCHANGE IN OH GROUPS

The exchange in water has been investigated in several studies by Meiboom, Loewenstein, and their coworkers[23,47,48]. Oxygen contains a certain amount of the ^{17}O isotope, which has a nuclear spin. Spin–spin coupling with protons should lead to a multiplet structure of the PMR spectrum of water in the absence of exchange. However, the spectrum consists of a single line, which is explained by a rapid exchange reaction. Its rate increases in the presence of acid or alkali, which is evident from the narrowing of the line. These small changes in line form cannot be observed under the usual steady-state conditions. They have been measured by the spin–echo method[49] in water specimens enriched in oxygen-17 as a function of the pH and the rate constants for the processes leading to exchange have been found:

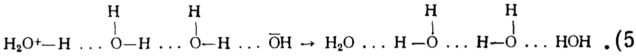
$$H_2O + OH^- \overset{k_1}{\rightleftarrows} HO^- + OH_2 , \qquad (2)$$

$$H_2O + H_3O^+ \overset{k_3}{\rightleftarrows} H_3O^+ + H_2O , \qquad (3)$$

$$H_2O + H_2\overset{*}{O} \overset{k_5}{\leftleftarrows} H_2\overset{*}{O} + H_2O . \qquad (4)$$

At 25°C they have the following values: $k_1 = 3.8 \times 10^9$ litre mole^{-1} s^{-1}, $k_3 = 10^{10}$ litre mole^{-1} s^{-1}, and $k_5 = 2.2 \times 10^5$ s^{-1}. The activation energies E and the preexponential factors A for the reactions were determined from the temperature variation of the rate of exchange in the range 20–80°C: $E_1 = 4.8$ kcal mole^{-1} and $E_3 = 2.6$ kcal mole^{-1}, $A_1 = 2 \times 10^{12}$ and $A_3 = 10^{12}$. The values of E were later revised[50] to $E_1 = 2.1$ kcal mole^{-1} and $E_3 = 2.4$ kcal mole^{-1}, which agree well with the values calculated from the anomalous mobility of these ions in water. It is of interest to compare these data with $k = 1.4 \times 10^{11}$ litre mole^{-1} s^{-1}, $E = 2$–3 kcal mole^{-1}, and $A = 9 \times 10^{12}$ found by Eigen and de Maeyer[51–53] by a relaxation method for proton transfer between H_3O^+ and OH^- ions.

The above results are important for the understanding of the mechanism of proton transfer and the anomalous mobility of the ions in water. The rate constants quoted agree with the values found from the anomalous mobilities of hydrogen and hydroxide ions based on electrical conductivity data. The rate constant for the reaction between H_3O^+ and OH^- corresponds to the value calculated for a process which is diffusion-controlled with a distance of approach of the ions of about 7 Å, which corresponds to their separation by 2–3 layers of water molecules. Hence it is concluded that, when the ions approach one another as a result of diffusion to this distance, the reaction occurs rapidly by the migration of protons along hydrogen bond chains:



$$H_2O^+{-}H \ldots \overset{\displaystyle H}{\overset{|}{O}}{-}H \ldots \overset{\displaystyle H}{\overset{|}{O}}{-}H \ldots \bar{O}H \rightarrow H_2O \ldots H{-}\overset{\displaystyle H}{\overset{|}{O}} \ldots H{-}\overset{\displaystyle H}{\overset{|}{O}} \ldots HOH\ . \quad (5)$$

An analogous mechanism accounts for the anomalous mobility of hydrogen ions in water. The reaction proceeds in two stages. The first consists in the formation of a chain of hydrogen bonds with a suitable orientation of the molecules achieved by their rotation. In the second protons are transferred along this chain. The rate is limited by that of the first step. Probably a mechanism of this type obtains in all rapid reactions with participation of H_3O^+ and OH^- ions†.

It is noteworthy that in alcohols (see below) the rate constants for proton exchange are smaller by several powers of ten than in water and the mobility of hydrogen ions is also much lower. Since the strength of hydrogen bonds in alcohols and in water is almost the same[55], which implies that the activation energy for proton exchange is also almost the same (see Section VII), it may be supposed that the rate of exchange in alcohols, as in water, is limited by the rate of formation of hydrogen bond chains of type (5), which is hindered by bulky hydrocarbon groups.

Data have been published on the rate of proton exchange between water molecules in various organic solvents[56]. The exchange proved to be slower the greater the electron-donating capacity of the solvent. These observations were explained by the fact that the solvent dissociates the hydrogen bond between water molecules and forms hydrogen bonds with the water protons, which reduces their mobility.

Rapid proton exchange in alcohols was discovered by Zimmerman and coworkers[57,58], but the first quantitative study was made by Arnold[29], who estimated the values of τ from the change in the form of the triplet due to the hydroxyl protons in ethanol as the pH was changed.

A detailed study of the exchange in ethanol and methanol has been made[59–61]. In neutral ethanol the reaction is slow and the PMR spectrum consists of a triplet due to CH_3, two overlapping quartets due to CH_2, and a triplet due to OH. When the ethanol contains water, the single signal due to the latter appears between the multiplets of the CH_2 and OH groups. In acidified alcohol or in the presence of alkali the signal due to methylene protons is converted into a simple quartet, the hydroxyl triplet is converted into a singlet, and the separate water peak is not observed. These changes in the spectrum are caused by a decrease in the lifetime of the proton in the hydroxy-group due to two consecutive processes.

In anhydrous alcohol only the protons of the OH group undergo exchange and the values of τ found from the analysis of the form of the CH_2 and OH signals are the same. On the other hand, when the alcohol contains water, two exchange reactions take place—between alcohol molecules and between alcohol and water. The rate of the overall process R was found from the change in the form of the methylene signals and the rate of exchange with water R_W from the width of the water line. The rate of the alcohol–alcohol exchange R_A was determined from the equation $R_A = R - R_W$. It was found that R_A and R_W depend linearly on the concentration of acid or alkali. The rate constants for the reactions leading to exchange were found from the slope of the straight line obtained and the equilibrium constants which determine the values of the ratios $[H_3O^+]/[ROH_2^+]$ and $[OH^-]/[RO^-]$:

$$ROH + OH^- \overset{k_1}{\rightleftarrows} RO^- + H_2O\ , \qquad (6)$$

$$ROH^* + HOH + RO^- \rightleftarrows RO^- + H^*OH + ROH\ ,$$

or

$$ROH + RO^- \overset{k_2}{\rightleftarrows} RO^- + ROH\ , \qquad (7)$$

$$ROH + H_3O^+ \overset{k_3}{\rightleftarrows} ROH_2^+ + H_2O\ ,$$

or

$$ROH_2^+ + HOH^* + ROH \rightleftarrows ROH + HOH + RO^+HH^*\ , \qquad (8)$$

$$ROH + RO^+H_2 \overset{k_4}{\rightleftarrows} RO^+H_2 + ROH\ , \qquad (9)$$

$$ROH^* + HOH \overset{k_5}{\rightrightarrows} ROH + HOH^*\ . \qquad (10)$$

We may note that in the system isopropyl alcohol–water[62] the mechanism of the exchange in an acid medium was found to depend on the relative amounts of the alcohol and water. The reaction takes place via mechanism (8) when the solvent is the alcohol and via the mechanism

$$H_3O^+ + ROH^* + OH_2 \rightrightarrows H_2O + ROH + H^*O^+H_2$$

when the solvent is water.

In contrast to ethanol, even in highly purified methanol the doublet due to the methyl protons and the quartet due to the hydroxyl are broadened. In aqueous solution the water line appears in the vicinity of the broadened quartet. The overall rate of exchange was found from the change in the form of the doublet and R_W from the broadening of the water line. The results proved to be analogous to those obtained for ethanol with the sole difference that in neutral anhydrous methanol the reaction

$$ROH^* + ROH \rightleftarrows ROH + ROH^*\ ,$$

which in ethanol is too slow to be investigated by the NMR method, makes an appreciable contribution to the overall rate of exchange. The activation energy for methanol proton exchange in an acid or alkaline medium is 2–3 kcal mole^{-1}, which corresponds to the activation energy for a diffusion process. There are data[63] showing an increased activation energy for the exchange in degassed methanol, compared with the alcohol saturated by oxygen.

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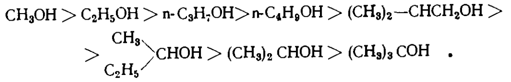
† An analogous mechanism was recently proposed for the exchange between $H_2PO_4^-$ and HPO_4^{2-} ions in water[54].

The rate constants for the exchange reactions in ethanol and methanol and also in isopropyl and isobutyl alcohols[64] and in water are compared in Table 1.

The kinetics of proton exchange between various alcohols and water in a neutral solution have been investigated[64-66] as a function of the concentration of water; the rate of exchange decreases in the following sequence:



$$CH_3OH > C_2H_5OH > n\text{-}C_3H_7OH > n\text{-}C_4H_9OH > (CH_3)_2{-}CHCH_2OH > \left.\begin{matrix}CH_3\\ C_2H_5\end{matrix}\right\rangle CHOH > (CH_3)_2\,CHOH > (CH_3)_3\,COH\ .$$

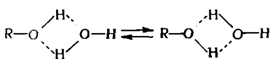
Table 1. Rate constants for proton exchange in alcohols and water.

R—OH	k_1	k_2	k_3	k_4	k_5
H—OH	$3.8\cdot10^{9}$*	—	$1\cdot10^{10}$*		$2.2\cdot10^{5}$*
CH_3—OH	$2.6\cdot10^{6}$	$7.4\cdot10^{8}$*	10^{8}	$3.5\cdot10^{9}$*	3
C_2H_5—OH	$2.8\cdot10^{6}$	$1.4\cdot10^{6}$	$2.8\cdot10^{6}$	$1\cdot10^{8}$	0.8
n-C_3H_7—OH	—	$0.6\cdot10^{6}$	—	$8\cdot10^{6}$	—
$(CH_3)_2CHCH_2$—OH	—	$2.7\cdot10^{6}$	—	$2\cdot10^{7}$	—

Note. The designations of the constants k (litre mole^{-1} s^{-1}) are the same as in Eqns. (2)–(4) and (6)–(10). The temperatures are 20° ± 2°C but 25°C for the values distinguished by an asterisk.

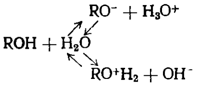
As already mentioned, the decrease of the rate of catalysed exchange in alcohols compared with water is due to the steric effect of the hydrocarbon residues, which hinder the orientation of the molecules and screen the hydroxy-group, and this inhibits the formation of complexes of type (5), the rate-limiting step in the exchange process. The data in Table 1 confirm this idea, since the rate decreases in the series of alcohols as the bulk of the hydrocarbon group increases. Possibly the decreased acidity of alcohols, which weakens the hydrogen bond formed by them, plays a certain role. This factor is probably not of decisive importance, since the changes in acidity (and in the strength of the hydrogen bond) are small compared with the changes in the rate of exchange. The above relation fails for isobutyl alcohol.

In a neutral medium the rate constants for the exchange are lower by many powers of ten than when catalysed by an acid or alkali. Bearing in mind that the rates of formation of the reaction complex in the neutral alcohol and in catalysis by an acid or alkali should be similar, one may suppose that the rate of neutral exchange is limited by the migration of protons along the hydrogen bonds in the complex. A synchronous mechanism of exchange in the cyclic association complex



(11)

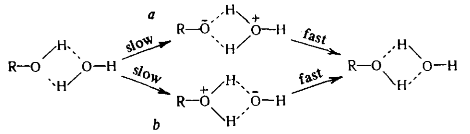
or a mechanism including slow dissociation into ion pairs and their rapid recombination,



(12)

have been proposed for this case[65].

The second mechanism is unlikely because of the high energy expenditure on the separation of the ions. The formation of "close" ion pairs linked by hydrogen bridges is more acceptable:



(13)

Among the pathways described, only pathway *a* accounts for the observed acceleration of exchange with increasing acidity of the alcohol. It is difficult to reconcile this acceleration with mechanism (11), according to which the rate should be independent of the acidity of the alcohol. We may also note that the formation of four-centre complexes assumed in mechanisms (11) and (13) is unlikely. It is unfavourable on energetic grounds[13-15] and has not been confirmed by determinations of the reaction order.

We have already noted that in the PMR spectrum of pure neutral methanol both multiplets are broadened. It has been found[67] that the addition of acetone to alcohols leads to a narrowing of the lines of the multiplet due to localisation of the hydroxyl proton in the hydrogen-bonded alcohol–acetone complex. This localisation hinders the exchange between the alcohol molecules, distorting the form of the spectrum. Such an effect of complex formation on the rate of proton exchange has already been noted in the discussion of studies on water. As will be shown below, it is of general importance.

We may refer to two studies on proton exchange in hydrated acetaldehyde[68] and its hemiacetal[69], in which a rapid exchange between the hydrogen atoms of the OH groups of the hydrate, hemiacetal, alcohol, and water is observed.

Proton exchange between hydrogen peroxide and water has been investigated[70]. The spectrum of a mixture of these substances consisted at room temperature of a single line whose width depended on the hydrogen peroxide concentration and the pH. In the pH range 2.5–4 the rate of exchange was proportional to the concentration of H_3O^+ ions and at 27°C $k = 1.6 \times 10^7$ litre mole^{-1} s^{-1}. The rate-limiting stage is probably

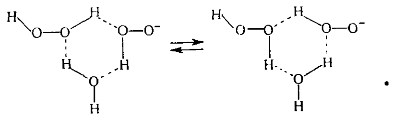
$$H_2O_2 + H_3O^+ \rightleftarrows H_3O_2^+ + H_2O\ . \qquad (14)$$

At pH 5.0–6.5 the rate proved to be proportional to the concentration of OH^- and the peroxide and was determined by the rate of the reaction

$$HO_2H + H^*OH + HO_2^- \rightleftarrows HO_2^- + HOH + H^*O_2H \qquad (15)$$

with $k = 7.3 \times 10^7$ litre mole^{-1} s^{-1} at 27°C.

Since the collision of three molecules is improbable and cannot lead to rapid reactions, it was assumed[70] that the process proceeds via a stage of complex formation between the peroxide or the HO_2^- ion and water and occurs in a cyclic activated complex:



(16)

We note that the rate of exchange between hydrogen peroxide and water is lower by several powers of ten than in water itself but is close to the rate of exchange in alcohols.

The exchange between t-butyl hydroperoxide and water has been investigated[71]. In an acid medium a mechanism analogous to mechanism (14) was established and it was found that the rate of reaction is virtually the same as for hydrogen peroxide: $k = 1.1 \times 10^7$ litre mole^{-1} s^{-1} at 23°C. On the other hand, in an alkaline medium the mechanism proved to be different. The relative rate no longer depended on the concentration of the peroxide and was proportional to the concentration of alkali alone ($k = 6.5 \times 10^6$ litre mole^{-1} s^{-1} at 23°C). The observed change in the mechanism may be due to the fact that the hydroperoxide cannot form a cyclic complex of type (16).

A series of studies have been made on the proton exchange in phenols. The exchange between phenol and water catalysed by sodium phenoxide[72] is characterised by a rate constant $k_B = 7.1 \times 10^8$ litre mole^{-1} s^{-1} at 25°C and an activation energy $E_B = 4.2$ kcal mole^{-1}. The rate of reaction is proportional to the concentration of phenol and alkali; the equation for the exchange reaction includes one or several water molecules:

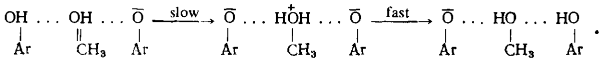
$$\mathrm{PhOH} + (\mathrm{H_2O})_n + \bar{\mathrm{O}}\mathrm{Ph} \rightleftarrows \mathrm{Ph}\bar{\mathrm{O}} + (\mathrm{H_2O})_n + \mathrm{PhOH} \quad . \qquad (17)$$

Grunwald and Puar[73] studied the exchange between phenols and water catalysed by acids and alkalis. Somewhat different characteristics are obtained for reaction (17): $k_B = 5.7 \times 10^8$ litre mole^{-1} s^{-1} at 25°C. $E_B = 3.2$ kcal mole^{-1} and it was shown that one water molecule is involved. The following mechanism was proposed for an acid medium:

$$\mathrm{H_3O^+} + \mathrm{PhOH} + \mathrm{H_2O} \rightleftarrows \mathrm{H_2O} + \mathrm{PhOH} + \mathrm{H_3O^+} \quad , \qquad (18)$$

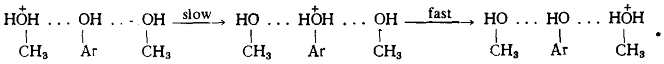
where $k_A = 1.5 \times 10^7$ litre mole^{-1} s^{-1} at 25°C and $E_A = 5.5$ kcal mole^{-1}.

Studies on the exchange between substituted phenols and methanol[74,75] led to a more profound understanding of the mechanism of processes of type (17) and (18). It was found that in an alkaline medium the rate of reaction for a series of phenols varies in parallel with their acidity. These data were explained by an exchange process involving a dissociative mechanism in a trimolecular complex. The proton is transferred from the phenol to the alcohol in the slow stage:



$$\underset{\mathrm{Ar}}{\mathrm{OH}} \ldots \underset{\mathrm{CH_3}}{\mathrm{OH}} \ldots \underset{\mathrm{Ar}}{\bar{\mathrm{O}}} \xrightarrow{\text{slow}} \underset{\mathrm{Ar}}{\bar{\mathrm{O}}} \ldots \underset{\mathrm{CH_3}}{\mathrm{H\overset{+}{O}H}} \ldots \underset{\mathrm{Ar}}{\bar{\mathrm{O}}} \xrightarrow{\text{fast}} \underset{\mathrm{Ar}}{\bar{\mathrm{O}}} \ldots \underset{\mathrm{CH_3}}{\mathrm{HO}} \ldots \underset{\mathrm{Ar}}{\mathrm{HO}} \ . \qquad (19)$$

In the acid-catalysed process the rate varies inversely with the acidity of the phenols. Consequently the slow stage in the exchange is protonation of the phenol:



$$\underset{\mathrm{CH_3}}{\mathrm{H\overset{+}{O}H}} \ldots \underset{\mathrm{Ar}}{\mathrm{OH}} \ldots \underset{\mathrm{CH_3}}{\mathrm{OH}} \xrightarrow{\text{slow}} \underset{\mathrm{CH_3}}{\mathrm{HO}} \ldots \underset{\mathrm{Ar}}{\mathrm{H\overset{+}{O}H}} \ldots \underset{\mathrm{CH_3}}{\mathrm{OH}} \xrightarrow{\text{fast}} \underset{\mathrm{CH_3}}{\mathrm{HO}} \ldots \underset{\mathrm{Ar}}{\mathrm{HO}} \ldots \underset{\mathrm{CH_3}}{\mathrm{H\overset{+}{O}H}} \ . \qquad (20)$$

Analogous results were obtained[76] for the reactions of a series of other phenols with water in dioxan or dimethyl sulphoxide solutions. It was noted[75] that the rate of exchange between phenols and methanol in an acid medium is lower the greater is the bulk of the substituents in the *ortho*-position in the phenol molecule. This observation may be explained by steric hindrance to the transfer of protons to the phenol in the slow stage of process (20) due to the substituent. Such interpretation is consistent with the results of studies on the hydrogen bond in sterically hindered phenols[77-82]. We may note that a less marked steric effect of substituents may be expected for exchange in an alkaline medium, since steric hindrance has a smaller effect on the acid dissociation of phenols, the rate-limiting stage in process (19), than on the protonation of phenols in reaction (20). The effect of steric hindrance on the exchange between 2,6-disubstituted phenols and methanol in a neutral medium has been investigated[82].

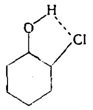
The rate of exchange decreases in the following series of substituents: $\mathrm{H} > \mathrm{CH_3} > (\mathrm{CH_3})_2\mathrm{CH} > (\mathrm{CH_3})_3\mathrm{C}$; since the activation energy is constant, this was explained by an increase in the entropy of activation in the above series.

The study of association in and the proton exchange between a series of *para*-substituted phenols and ethanol showed[83] that the activation energy for the exchange is lower the stronger is the hydrogen bond in the association complex of the phenol and alcohol. This provided one of the first experimental proofs of the predicted relation[14] between the height of the potential barrier to the exchange and the energy of the hydrogen bond in the reaction complex.

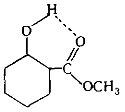
An intramolecular hydrogen bond has a significant influence on the rate of proton exchange in phenols. Thus the uncatalysed exchange between *o*-chlorophenol (I) and methanol is much slower than the exchange between phenol and the same alcohol. Probably the rate is determined by the stage involving the formation of an ion pair:

$$\mathrm{PhOH} + \mathrm{CH_3OH} \rightarrow \mathrm{PhO^-} + \mathrm{CH_3O^+H_2} \quad .$$

The rate constant is 9×10^2 s^{-1} and the activation energy is 4.6 kcal mole^{-1}. The relatively low rate of exchange is explained by the fact that, despite its low energy ($\Delta H = -2.4$ kcal mole^{-1}), the intramolecular hydrogen bond OH...Cl lowers significantly the capacity of compound (I) to form intermolecular-hydrogen bonds. This interpretation was confirmed by the fact that methyl salicylate (II), salicylaldehyde (III), and *o*-hydroxyacetophenone (IV),



(i)



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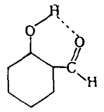

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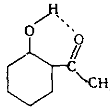
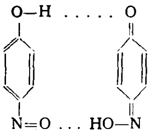


(IV)

which form stronger intermolecular hydrogen bonds, undergo exchange at a much lower rate than compound (I)[84]. Compounds (III) and (IV) were investigated in greater detail[85]. It was found that (III) undergoes exchange faster than (IV), because the latter has a stronger intramolecular hydrogen bond by virtue of the electron-donating effect of the methyl group.

The interesting case of proton exchange between tautomeric forms of *p*-nitrosophenol has been studied[86]. The relative rate of reaction in a neutral medium is proportional to the concentration and therefore two molecules, probably the molecules of both tautomeric forms, are involved in the elementary step. It is natural to suppose that the exchange takes place in hydrogen-bonded complexes, for example:



In the presence of acids or bases the rate of exchange increases. Catalysis by bases has been explained by the ionisation of the substrate:

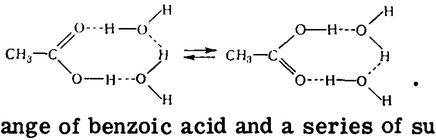
$$\mathrm{HOC_6H_4NO} + [\mathrm{OC_6H_4NO}]^- \rightleftarrows [\mathrm{OC_6H_4NO}]^- + \mathrm{OC_6H_4NOH} \quad ,$$
$$\mathrm{OC_6H_4NOH} + [\mathrm{OC_6H_4NO}]^- \rightleftarrows [\mathrm{OC_6H_4NO}]^- + \mathrm{HOC_6H_4NO} \quad .$$

The catalysed reaction takes place with a lower activation energy than the uncatalysed reaction.

Proton exchange in organic acids was investigated in a number of cases. Thus Luz and Meiboom[87] studied the system acetic acid–water enriched in oxygen-17. The rate proved to be too high to be accounted for by the dissociation of acid:

$$CH_3COOH + H_2O \rightleftarrows CH_3COO^- + H_3O^+ \ .$$

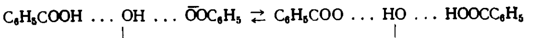
The limiting rate of dissociation may be calculated from the dissociation constant and the rate of reaction between the ions CH_3COO^- and H_3O^+, which cannot exceed the limit set by diffusion. The upper limit to the rate of dissociation found in this way proved to be below the observed rate of exchange by several powers of ten. For this reason, a synchronous cyclic reaction mechanism was proposed:


(21)

The exchange of benzoic acid and a series of substituted benzoic acids (HA) with methanol was investigated by Grunwald and coworkers[88–90], who found that the expression for the rate of reaction in an alkaline medium includes two terms corresponding to an uncatalysed and a catalysed process:

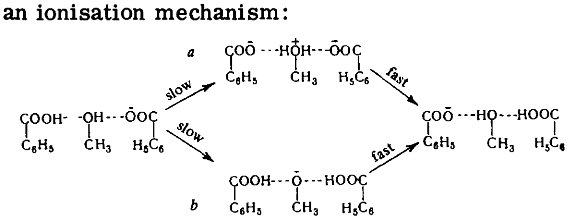
$$R = k_1 + k_B [A^-] \ . \qquad (22)$$

The values of k_1 and k_B for benzoic acid proved to be 1.3×10^5 s^{-1} and 1.2×10^8 litre mole^{-1} s^{-1} at 24.8°C. It was established that in the uncatalysed process two alcohol molecules participate together with an acid molecule and in the catalysed process the reactants are an acid and an alcohol molecule and an acid anion. The rate of the first reaction is much higher than the limiting value which could be accounted for by the dissociation of the acid and has a negative entropy of activation. Therefore the authors proposed a mechanism analogous to that given in equation (21). The displacement of protons in this complex can take place both synchronously and asynchronously with formation of "close" ion pairs in the slow stage. In the catalysis by alkali the exchange in the open-chain trimolecular complex can also take place via mechanisms of two types—a synchronous mechanism:


(23)

$$C_6H_5COOH \ldots \underset{\displaystyle CH_3}{OH} \ldots \bar{O}OCC_6H_5 \rightleftarrows C_6H_5COO \ldots \underset{\displaystyle CH_3}{HO} \ldots HOOCC_6H_5 \qquad (23)$$

or an ionisation mechanism:

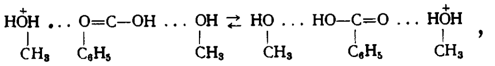


(24)

The rate of reaction by these mechanisms should depend in different ways on the acidity of HA. The ratio $d\ \lg k/d.\lg K_A$, which Grunwald and coworkers used to infer the mechanism, is a measure of the sensitivity of the rate to changes in acid strength. The ratio should be +1 if the rate is limited by acid dissociation [mechanism (24 a)] and −1 when it is determined by the protonation of the base [mechanism (24 b)]. In the synchronous mechanism the ratio should be independent of acid strength, since an increase in the acidity of HA is fully compensated by a decrease in the basicity of A^-. It was found that $d\ \lg k_1/d.\lg K_A = 0.53$ and $d\ \lg k_B/d\ \lg K_A = 0.26$. Therefore it was concluded that the uncatalysed and base-catalysed exchange involves both synchronous and ionisation mechanisms [formula (24 a)]. We believe that these conclusions have little justification, since they do not take into account a number of factors which influence the exchange. We may point, for example, to the fact that a change in acidity alters the strength of hydrogen bonds in complexes of types (21) and (23), on which depends not only the ease of migration of protons in the complexes but also their concentration. Other criteria whereby synchronous and ionisation mechanism may be distinguished are formulated below (see Section V).

Results analogous to those presented above were obtained in a study of the base-catalysed exchange between neopentyl alcohol and acetic, cyanoacetic, and trichloroacetic acids[91]. In this case the ratio $d\ \lg k_1/d\ \lg K_A$ proved to be 0.55. However, the authors concluded that a synchronous exchange mechanism of type (23) operates, since they did not observe a variation of the ratio $d\ \lg k/d.\lg K_A$ with the dielectric constant of the solvent, which would have been expected for a mechanism of type (24 a).

Grunwald and Jumper[90] obtained a rate constant $k_A = 2.52 \times 10^8$ litre mole^{-1} s^{-1} for the exchange between benzoic acid and methanol in an acid medium and proposed a termolecular reaction complex:


(25)

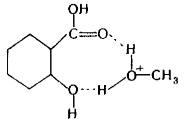
$$\underset{\displaystyle CH_3}{H\overset{+}{O}H} \ldots \underset{\displaystyle C_6H_5}{O{=}C}{-}OH \ldots \underset{\displaystyle CH_3}{OH} \rightleftarrows \underset{\displaystyle CH_3}{HO} \ldots HO{-}\underset{\displaystyle C_6H_5}{C{=}O} \ldots \underset{\displaystyle CH_3}{H\overset{+}{O}H} \ , \qquad (25)$$

but the reaction order with respect to the alcohol was not determined.

The effect of the intramolecular hydrogen bond in salicylic acid on the rate of proton exchange between carboxy- and hydroxy-groups on the one hand and methanol on the other in an acid medium at −80°C was studied by Puar and Grunwald[92]. The following kinetic equations were derived:

$$R_{COOH} = k_1 + k_A [HCl] \text{ and } R_{OH} = k'_A [HCl]$$

with $k_1 = 440$ s^{-1}, $k_A = 1.35 \times 10^5$ litre mole^{-1} s^{-1}, and $k'_A = 5.8 \times 10^3$ litre mole^{-1} s^{-1}. These equations are analogous to the expressions describing the exchange between benzoic acids and phenols on the one hand and acidified methanol on the other. Therefore mechanisms of types (21) and (25) were proposed for the reaction involving the carboxyl and mechanism (20) for the exchange involving the hydroxyl. The constant k_1 for salicylic acid is much higher than for benzoic acid, because the former is a stronger acid and the intramolecular hydrogen bonds in salicylic acid dissolved in methanol are probably disrupted and do not interfere with the formation of complexes of type (21). On the other hand, the constants k_A and k'_A are lower than for benzoic acid and phenols, which was explained by the stability of the complex



whose formation lowers the concentration of termolecular complexes and thereby retards the reactions via mechanism (20) and (25).

The exchange of protons between the OH and COOH groups of *p*-hydroxybenzoic acid was studied in various solvents[27]. The reaction was found to be retarded on passing from acetone to dimethylformamide and dimethyl sulphoxide. This is due to the increased electron-donating capacity of the solvent and the stability of its association complexes with the acid. Association with the solvent hinders the formation of acid dimers in which the exchange takes place.

In a series of isomeric hydroxybenzoic acids the rate of the uncatalysed reaction in dimethyl sulphoxide solution increased in the *ortho* > *para* > *meta* series. The exchange of *m*-hydroxybenzoic acid was studied in greater detail in a later investigation[93].

III. PROTON EXCHANGE IN NH GROUPS

The study of proton exchange in NH groups was begun by Ogg[94,95] using ammonia. The PMR spectrum of thoroughly dried liquid or gaseous ammonia consists of a triplet with a splitting of about 46 Hz. It arises as a result of spin–spin coupling between the proton and the ^{14}N nucleus, the spin of which is unity. In the presence of traces of water in liquid ammonia the triplet merges into a singlet owing to the rapid reaction

$$NH_3 + H_2O \rightleftarrows NH_4^+ + OH^- .$$

This conclusion contradicts the results of other investigations[96–98], in which separate NH and OH peaks were observed ("slow" exchange) for solutions containing less than 50% of water. The explanation offered for the discrepancy[98] is that Ogg observed a reaction catalysed by traces of ammonium ions generated in the reaction between ammonia and the protons adsorbed on glass. The exchange in liquid ammonia is also catalysed by potassamide. The following reaction probably occurs:

$$NH_3 + NH_2^- \rightleftarrows NH_2^- + NH_3 \ .$$

Its rate constant is close to 10^9 litre mole^{-1} s^{-1}. In the gas phase the form of the spectrum is independent of the presence of water vapour and therefore the rapid reaction with water does not take place.

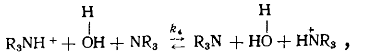
The exchange between ammonium salts and water was investigated in a large series of studies. We shall consider these studies using methylammonium chloride as an example[41,99–101]. In an acid medium (pH ~ 1) the rate of exchange is low and the spectrum shows a quartet due to the methyl protons, arising by virtue of the spin–spin coupling with the protons of the NH_3^+ group, a triplet due to the NH_3^+ protons generated by coupling with ^{14}N, and a singlet corresponding to water. With increase of the pH, the rate of exchange rises. The peaks of the methyl quartet are broadened and merge into a single broad line, which then becomes narrower, while the NH_3^+ triplet continues to become broader and finally disappears.

Both these effects may serve as a measure of the average lifetime of the protons in NH_3^+. The water singlet broadens, merges with the signal due to the NH protons, and the combined peak becomes narrower. A study of the above spectral changes provided evidence for the following exchange reactions:

$$R_3NH^+ + H_2O \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} R_3N + H_3O^+ \ , \tag{26}$$

$$R_3NH^+ + OH^- \overset{k_2}{\rightleftarrows} R_3N + H_2O \ , \tag{27}$$

$$R_3NH^+ + R_3N \overset{k_3}{\rightleftarrows} R_3N + R_3NH^+ \ , \tag{28}$$



$$R_3NH^+ + \overset{\overset{\displaystyle H}{|}}{O}H + NR_3 \overset{k_4}{\rightleftarrows} R_3N + H\overset{\overset{\displaystyle H}{|}}{O} + H\overset{+}{N}R_3 \ , \tag{29}$$

and made possible the determination of the corresponding rate constants. The overall rate of exchange is determined by the relation

$$R = k_1 + \frac{1}{[H^+]}\{k_2\ K_w + (k_3 + k_4) \cdot K_A [R_3\overset{+}{N}H]\} \ ,$$

where K_W is the ionic product of water and K_A is the acid dissociation constant of R_3NH^+. The constants k_1, k_2, and $k_3 + k_4$ were determined from the relation between R (calculated from the change in the form of the CH_3 quartet) and the pH and the R_3NH^+ concentration. The individual values of k_3 and k_4 were obtained by analysing the broadening of the water line. It was found that at a low pH the contribution by reactions (26) and (27) to the overall rate is low and that k_4 for any ratios of the reactant concentrations is approximately 1.5 times greater than k_3. In a later study[99] the rate constants were revised to allow for changes in the viscosity. The results are listed in Table 2.

Table 2. Rate constants for the proton exchange of ammonium salts in water at 22°C*.

R_3NH^+	k_1	$k_{-1} \cdot 10^{-10}$	$k_2 \cdot 10^{-11}$	$k_3 \cdot 10^{-8}$	$k_4 \cdot 10^{-8}$	$K_A \cdot 10^{10}$
NH_4^+	25	4.4	10	11.7	0.9	5.68
$CH_3NH_3^+$	—	—	1	4.0	5.3	0.242
$(CH_3)_2NH_2^+$	—	—	1	0.5	9.0	0.168
$(CH_3)_3NH^+$	4.7	3.0	1	0.3	3.4	1.57
$(C_2H_5)_3NH^+$ **	0.31	2.0	0.17	—	1.8	0.155
$CH_3\overset{+}{N}H_2CH_2COOH$	1.10	3.2	—	—	—	30

* The units of k_1 are s^{-1} and of k_{-1} and k_2–k_4 are litre mole^{-1} s^{-1} respectively.

** Temperature 25–30°C.

Ammonium[102–104], dimethyl- and trimethyl-ammonium[42,105–107], triethylammonium[108], and $CH_3\overset{+}{N}H_2CH_2COOH$[109] ions were investigated similarly and their exchange was explained by the same mechanisms (26)–(29). The rate constants obtained are compiled in Table 2, which shows that, as was to be expected, the constants k_1 vary in parallel with the acidity of the ammonium ions. The rate constants for the reverse reaction k_{-1} have values characteristic of processes whose rate is limited by diffusion and which apparently occur in almost every collision.

The values of k_1 proved to be sensitive to the presence of neutral salts and the pH. They decrease on addition of salts and strong acids[103–105,110]. The study of the effect of the acidity of the medium made it possible to refine the mechanism of reaction (26). The new mechanism[110] includes two stages: reversible ionisation in which the amine molecule does not initially lose its bond with the proton being eliminated:

$$R_3NH^+ \ldots (HOH)_n \underset{k_-}{\overset{k_+}{\rightleftarrows}} R_3N \ldots (HOH)_m + \overset{+}{H}(OH_2)_{n-m} \tag{26a}$$

and the exchange of water molecules between the hydration shell of the amine and the bulk of the solvent:

$$HOH \ldots NR_3 + H\overset{*}{O}H \overset{k_H}{\rightarrow} HOH + R_3N \ldots H\overset{*}{O}H \ . \tag{26b}$$

Reaction (26a) alone does not lead to the exchange of protons bound to the nitrogen as long as reaction (26b) does not occur. In an acid medium the first reaction plays the role of a pre-equilibrium stage and the rate of exchange is determined by stage (26b). The kinetic equation for the overall process is of the form[104]:

$$R = k_+ [R_3NH^+] \frac{k_H}{k_H + k_- [H^+]} \ .$$

When the acidity is fairly high, $k_H \ll k_-[H^+]$ and

$$R = \frac{k_+ k_H [R_3NH^+]}{k_-[H^+]} = \frac{K_A k_H [R_3NH^+]}{[H^+]} \qquad (26c)$$

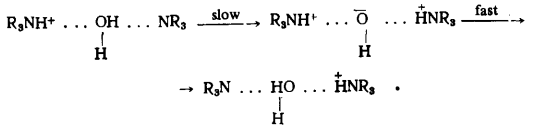
i.e. under certain conditions the rate of exchange is inversely proportional to the concentration of hydrogen ions. The consistency of the exchange kinetics with the equations quoted above implies that in very acid media the amine remains hydrated. When allowance is made for the hydration of the proton, it becomes clear that not less than two water molecules participate in reaction (26a)[110].

The values of k_H which can be found by Eqn. (26c) are of great interest, since these are the rate constants for the dissociation of the hydrogen bond between amines and water. They are listed in Table 3 together with the reciprocal quantities (τ_H), which define the average lifetime of the hydrogen bonds. The data in Table 3 suggest that τ_H is not determined by the basicity of the amine alone but also by steric factors on which depends the ease of the mutual approach of the amine and water and also other characteristics of the structure of the amines.

Table 3. Dissociation rate constants (k_H) and average lifetimes (τ_H) of the hydrogen bonds $R_3N...HOH$ at 25°C.

R_3N	$k_H \cdot 10^{-10}$, s^{-1}	$\tau_H \cdot 10^{11}$, s	$K_A \cdot 10^{10}$
NH_3	50	0.2	5.68
CH_3NH_2	8	1.25	0.242
$(CH_3)_3N$	1.1	9	1.57
$(C_2H_5)_3N$	0.38	26.3	0.155
CH_3NHCH_2COOH	0.8	12.5	30

In contrast to the values of K_A, k_3 (Table 2) decreases steadily from ammonium to trimethylammonium ions, which Loewenstein and Meiboom[42] suggest is caused mainly by steric hindrance. The ratio k_4/k_3 decreases steadily in the same series. The constants k_4 are correlated with K_A: the rate of reaction (29) increases as the acidity of the ammonium ions falls. This relation breaks down only for trimethylammonium ions, probably due to steric hindrance. The mechanism of reaction (29) was examined in detail by Grunwald and Kromhout[99]. Table 2 shows that reactions (26) are so slow that proton transfer from ammonium ions to water cannot ensure the occurrence of the rapid reactions (29). Therefore it was suggested that the rate is limited by proton transfer from the water in the hydration shell of the alkylammonium ions to the amine molecules in the hydrogen-bonded complexes:



$$R_3NH^+ \ldots \underset{\underset{H}{|}}{OH} \ldots NR_3 \xrightarrow{\text{slow}} R_3NH^+ \ldots \underset{\underset{H}{|}}{\bar{O}} \ldots \overset{+}{H}NR_3 \xrightarrow{\text{fast}} R_3N \ldots \underset{\underset{H}{|}}{HO} \ldots \overset{+}{H}NR_3 \; . \qquad (30)$$

The electrostatic field of the cation promotes the slow stage of reaction (30), since it increases the acidity of water by several powers of ten. The field is almost identical for different ammonium ions. Therefore, when the substituents are not unduly bulky, the rate of reaction is determined by the basicity of the amine, which explains the experimental data.

Meiboom[26] revised mechanism (30). He investigated the kinetics of proton exchange in the system trimethylammonium chloride–trimethylamine–water enriched in oxygen-17 as a function of the concentration of water and showed that reaction (30) involves only one water molecule. Water molecules may participate also in reactions of type (27).

The temperature variation of the rate of exchange between ammonium salts and water has been investigated by several workers[100,105,106,110]. In the first study it was found for NH_4^+ and $(CH_3)_3NH^+$ ions that the activation energies of reactions (28) and (29) are close to zero. This result appears to be doubtful, since the activation energy for the reaction between the H_3O^+ and OH^- ions, whose rate is limited by diffusion, is 2–3 kcal mole^{-1}.[51,52]

In a later investigation[105] the plausible value $E = 3.3$ kcal mole^{-1} was obtained for the exchange involving $(CH_3)_3NH^+$ via mechanism (29). The activation energy for reaction (26) with NH_4^+ ions proved to be $E = 12.2$ kcal mole^{-1}. Since the enthalpy change is 12.4 kcal mole^{-1}, one must assume that the activation energy for the reverse process

$$NH_3 + H_3O^+ \rightarrow NH_4^+ + H_2O$$

is close to zero, which is consistent with its very high rate (see above).

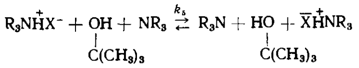
Several studies have been made of proton exchange between aminoacids and polypeptides on the one hand and water on the other in an acid medium. The mechanisms of the exchange processes involving glycine[111], sarcosine[109], glycylglycine[112], triglycine[113], and ammonium salts proved to be similar.

In contrast with acetamidinium salts[114] only the reaction of type (27) is significant. This was explained by the low acid dissociation constant of the ion $[CH_3C(NH_2)_2]^+$ which keeps the concentration of the amidine so low that reactions of type (28) and (29) scarcely occur.

Interesting results were obtained by comparing the proton exchange of ammonium salts in water and other solvents[115]. The changes in the kinetics and mechanism of the exchange could be observed as a function of the properties of the solvents and the structure of the salts. These data are of general importance in understanding the effect of the solvent on the mechanism of protolytic reactions.

In methanol[116–119], which like water has a high dielectric constant ($D = 33.7$ at 20°C), the mechanism of the exchange is similar to mechanism (26)–(29) and the mechanisms of the individual processes are only slightly different from those in water, as can be seen from a comparison of the data in Tables 2 and 4.

In contrast, in t-butyl alcohol, which has a much lower dielectric constant ($D = 12.5$ at 25°C), the mechanism of the exchange is different and the rate of the process is much lower[120–122]. The reason for the differences is that in this solvent ammonium salts exist in the form of ion pairs[123] and not free (solvated) ions. Under these conditions, processes of type (29) play the main role in the exchange, but they involve ion pairs and not free ions:



$$R_3N\overset{+}{H}X^- + \underset{\underset{C(CH_3)_3}{|}}{OH} + NR_3 \overset{k_5}{\rightleftarrows} R_3N + \underset{\underset{C(CH_3)_3}{|}}{HO} + \bar{X}\overset{+}{H}NR_3 \; . \qquad (29a)$$

Table 5 presents the experimental data and the ratios of the rate constants for reactions (29) and (29a). It shows that methylammonium salts differ sharply from trimethylammonium salts. The ratio k_4/k_5 for the former is close to 25 and depends little on the nature of the X^- anion, while for the latter the ratio varies from several thousand to several hundred and depends significantly on X^-. The difference is probably due to the fact that the single hydrogen atom at the nitrogen in $(CH_3)_3N^+HX^-$ molecules is linked to the anion by a strong hydrogen bond, which lowers the rate of exchange by mechanism (29a) and to a greater extent with increasing strength of this bond. In $CH_3NH_3^+X^-$ only one hydrogen atom is linked to the anion and the other two form hydrogen bonds with the solvent and undergo exchange at a much higher rate, which depends little on the nature of the anion.

Table 4. Rate constants for the proton exchange of ammonium salts in methanol at 24°C.

Ammonium ion	k_1, s^{-1}	$k_{-1} \times 10^{-10}$, litre $mole^{-1}$ s^{-1}	$k_4 \times 10^{-8}$, litre $mole^{-1}$ s^{-1}	$K_A^* \cdot 10^{10}$
p-$CH_6H_4NH_3^+$	$2.9.10^3$	1,04	0.81	2800
$(CH_3)_3NH^+$	0.6	0.5	3.25	1.2
2-Picoline.H^+	$9.1 \cdot 10^3$	1.2	2.89	7580
4-Picoline.H^+	$10.6 \cdot 10^3$	1.2	3.44	8830
2,4-Lutidine.H^+	$1.32 \cdot 10^3$	0.97	2.97	1360
2,6-Lutidine.H^+	$1.15 \cdot 10^3$	0.75	0.85	1530

* K_A was measured in methanol at 25°C.

In anhydrous acetic acid solution (D = 6.2 at 25°C) ammonium salts also form ion pairs and not free ions. The exchange reactions probably take place in two stages of type (26a) and (26b):

$$R_3N\overset{+}{H}\overset{-}{O}Ac \rightleftarrows R_3N \ldots HOAc \quad , \qquad (26d)$$

$$AcOH \ldots NR_3 + H\overset{*}{O}Ac \overset{k_6}{\rightleftarrows} AcOH + R_3N \ldots H\overset{*}{O}Ac \quad , \qquad (26e)$$

where reaction (26d) differs from (26a) in that the proton transfer takes place within an ion pair. The analogy with the dissociation and exchange processes in water is confirmed by a parallelism between the enthalpies and entropies of acid dissociation of ammonium ions in water and the corresponding activation parameters for proton exchange between ammonium salts and acetic acid. The experimental data[124-126] are presented in Table 6.

Table 5. Rate constants for the proton exchange between ammonium salts and t-butyl alcohol at 35°C.

R_3NH^+	X^-	$k_5 \times 10^{-5}$, litre $mole^{-1}$ s^{-1}	k_4/k_5
$(CH_3)_3NH^+$	Cl^-	1.1	3500
$(CH_3)_3NH^+$	Br^-	5.3	740
$(CH_3)_3NH^+$	$CH_3C_6H_4SO_2O^-$	7.0	560
$CH_3NH_3^+$	Cl^-	260	23
$CH_3NH_3^+$	$CH_3C_6H_4SO_2O^-$	240	25

These data show that the values of k_6 for acetate salts depend on the acid dissociation constants of ammonium ions in water (K_A). They are almost proportional to the K_A, in accordance with the above exchange mechanism which includes an ionisation stage. Of its two stages, stage (26e) is probably rate-limiting[124,125]. Table 6 shows that the rate of exchange greatly depends on the anion. In accordance with mechanism (26d)–(26e), the rate for salts with the same cation proved to be proportional to the basicity of the anion in acetic acid. Similar results were obtained in a study on the proton exchange of NN-dialkylanilinium salts in acetic acid[127].

In some cases the solvent alters the rate of exchange, while the mechanism and the components undergoing exchange remains the same. Thus the reaction between NH_4^+, H_2O, and NH_3 in water is faster by two powers of ten than in liquid ammonia, probably because water has a lower dielectric constant[98].

Table 6. Rate constants for the proton exchange between ammonium salts and acetic acid at 25°C.

R_3NH^+	X^-	k_6, s^{-1}	$K_A \cdot 10^{10}$
NH_4^+	CH_3COO^-	6080	5.69
$CH_3NH_3^+$	CH_3COO^-	230	0.238
$(CH_3)_3NH^+$	CH_3COO^-	945	1.58
$(HOCH_2)_3CNH_3^+$	CH_3COO^-	41000	84.0
NH_4^+	$C_6H_2(NO_2)_3O^-$	30	
NH_4^+	CCl_3COO^-	2	
NH_4^+	Cl^-	too low for measurement by NMR method	
$CH_3NH_3^+$	Cl^-		
$(CH_3)_3NH^+$	Cl^-		

In several studies the kinetics and mechanisms of protolytic reactions with participation of carboxylic acid hydrazides[128] and amides[43,129] were investigated. For example, it was established that in an aqueous solution of N-methylacetamide at pH 5 the PMR spectrum consists of a singlet due to C-methyl protons, a doublet due to N-methyl protons, a singlet due to water, and a broad line due to the amide hydrogen. It was found from the form of the doublet that the half-life of the exchange exceeds 1 s. On increasing or decreasing the pH, the N-methyl doublet is converted into a single line and the water singlet becomes broader, which is evidence that both acids and alkalis catalyse the exchange. The following reaction mechanisms have been proposed:

$$CH_3{-}CONHCH_3 + OH^- \overset{k_1}{\rightleftarrows} (CH_3{-}CON{-}CH_3)^- + H_2O \quad ,$$

$$CH_3{-}CONHCH_3 + H_3O^+ \overset{k_2}{\rightleftarrows} (CH_3{-}CONH_2CH_3)^+ + H_2O \quad ; \qquad (31)$$

$k_1 = 5.2 \times 10^6$ litre $mole^{-1}$ s^{-1} at 21°C and $k_2 = 3.8 \times 10^2$ litre $mole^{-1}$ s^{-1} at 23°C. The activation energy for the acid-catalysed exchange is in the range 14–16 kcal $mole^{-1}$.[130,131]

In a strongly acid solution the doublet structure of the signal due to the N-methyl protons persists in the presence of dioxan which retards the exchange. This observation shows that protonation involves mainly the oxygen atom, since the protonation of the nitrogen atom would convert the signal of the N-methyl protons into a triplet. The competition of reaction (31) with the protonation of the oxygen atom accounts for the relatively small value of k_2.

The protonation of amides at the oxygen atom was confirmed in a number of studies[132-134]. In the first of these the reaction of formamide, acetamide, and their NN-dimethyl derivatives with fluorosulphonic acid was investigated and it was found that at low temperatures a new line due to the $=C\overset{+}{O}H$ group appears in the spectrum.

Thioamides and sulphonamides are also protonated at the sulphur or oxygen atom. Thiourea and *N*-methylthiourea in fluorosulphonic acid give rise to diprotonated forms[135]. Data have been obtained from the protonation of sodium sulphamate[136].

It is noteworthy that NMR is the only reliable procedure for the investigation of the mode of protonation of acid amides and their analogues.

IV. PROTON EXCHANGE IN HYDROGEN FLUORIDE

Liquid hydrogen fluoride contains the ions HF_2^- and H^+ which are formed by the mechanism

$$2\,HF \rightleftarrows HF_2^- + H^+ \ .$$

The concentration of protons increases in the presence of BF_3 and when the system contains water, H_3O^+ ions appear:

$$HF + H_2O + BF_3 \rightleftarrows H_3O^+ + BF_4^- \ .$$

In this case the PMR spectrum consists of a single peak at room temperature and two peaks, due to HF and H_3O^+, below −50°C. The merging of the peaks on warming was explained[137] by the following proton exchange reaction:

$$H_3O^+ + HF_2^- \rightleftarrows H_2O + 2\,HF \ .$$

Its rate constant proved to be close to 10^{11} litre $mole^{-1}$ s^{-1} and the temperature coefficient was found to be small. In view of the closeness of the above values to the diffusion-limited rate constant for the reaction of hydrogen and hydroxide ions in water, it was suggested that there is an analogy also between the exchange mechanisms, the following scheme being suggested:

$$H_2\overset{+}{O}H \ldots FH \ldots F^- \rightarrow H_2O \ldots HF \ldots HF \ .$$

Possibly not one but several hydrogen fluoride molecules are involved in this reaction.

V. PROTON EXCHANGE IN PH AND SH GROUPS

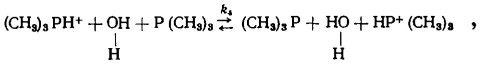
We have emphasised more than once the effect of the acidity of the reactants in protolytic reactions and of the strength of the hydrogen bonds formed by them on the rate of proton transfer. However, so far, it has been impossible to separate the roles of these factors, since for many compounds of a particular type they vary in parallel. Such an estimate can be made by comparing the rates of proton exchange in a series of analogous nitrogen- and phosphorus-containing compounds and hydroxy- and mercapto-derivatives, since the replacement of nitrogen by phosphorus and of oxygen by sulphur increases the acidity but lowers the strength of hydrogen bonds. Therefore the study of exchange in PH and SH groups is of particular interest. The available data are fairly scanty, but they nevertheless allow certain definite conclusions.

A detailed study has been made of proton transfer from PH bonds in aqueous solutions of trimethylphosphonium ions[138]. In an acid medium (pH < 6) the rate of exchange is low and the PMR spectrum consists of a septet due to the hydrogen atom in PH, a double doublet due to methyl hydrogen atoms, resulting from spin–spin coupling with the PH proton and with ^{31}P, and a single line due to water. With increase of the pH, the rate of reaction rises and the septet merges into a very broad singlet, the signal due to the methyl protons is converted into a broadened doublet, and the water line is also slightly broadened. Analysis of the form of the methyl signal led to the determination of the overall rate of exchange involving trimethylphosphonium ions and the rate of the processes with participation of water could be found from the width of the water signal. Reaction mechanisms analogous to those adopted for ammonium salts were proposed:

$$(CH_3)_3PH^+ + H_2O \overset{k_1}{\rightrightarrows} (CH_3)_3P + H_3O^+ \ , \tag{32}$$

$$(CH_3)_3PH^+ + OH^- \overset{k_2}{\rightleftarrows} (CH_3)_3P + H_2O \ , \tag{33}$$

$$(CH_3)_3PH^+ + P(CH_3)_3 \overset{k_3}{\rightleftarrows} (CH_3)_3P + HP^+(CH_3)_3 \ , \tag{34}$$



$$(CH_3)_3PH^+ + \underset{\substack{|\\H}}{OH} + P(CH_3)_3 \overset{k_4}{\rightleftarrows} (CH_3)_3P + \underset{\substack{|\\H}}{HO} + HP^+(CH_3)_3 \ , \tag{35}$$

but the values of k_3 and k_4 were not determined separately.

Table 7. Rate constants for the proton exchange of $(CH_3)_3\overset{+}{N}H$ and $(CH_3)_3\overset{+}{P}H$ in water at 22°C.

$(CH_3)_3\overset{+}{X}H$	k_1, s^{-1}	k_2, litre $mole^{-1}$ s^{-1}	$(k_3 + k_4)$ litre $mole^{-1}$ s^{-1}	pK_A
$(CH_3)_3\overset{+}{P}H$	7.9	$4.6 \cdot 10^7$	$1.2 \cdot 10^2$	8.8
$(CH_3)_3\overset{+}{N}H$	4.7	$<10^{11}$	$3.4 \cdot 10^8$	9.8

The corresponding exchange rate constants for trimethylammonium and trimethylphosphonium ions in water are compared in Table 7. These data cannot be explained in terms of the acid–base properties of the ions undergoing exchange. Thus the higher value of k_1 for $(CH_3)_3PH^+$ is consistent with its higher acidity, but it remains obscure why k_2 for this species is a thousand times lower than for $(CH_3)_3NH^+$ although trimethylphosphonium ions behave as proton donors also in reaction (33). The authors accounted for the relative values of the combined constants $k_3 + k_4$ by the fact that in reaction (35), as in reaction (29), the rate is limited by proton transfer from water to the phosphine. However, it is still not clear why a difference between the basicities of the amine and phosphine by only one power of ten causes an enormous change in $k_3 + k_4$ (by six powers of ten).

On the other hand, the data in Table 7 can be explained if it is postulated that the ratio of the rates under consideration is determined by the ratio of the strengths of the hydrogen bonds. For phosphorus, these bonds are much weaker than for nitrogen and one must suppose that they are particularly weak in those cases where the phosphorus atom behaves as a proton acceptor. This in fact accounts for the lowering of k_2 and the even greater lowering of $k_3 + k_4$ on passing from ammonium to phosphonium ions. However it still remains obscure why k_1 increases slightly under these conditions.

A comparison, similar to that carried out above, cannot be made for dimethylphenylphosphonium ions in methanol[116], since their nitrogen-containing analogue has not been investigated. One can only assert that reactions of types (34) and (35) are much slower with these ions than with ammonium salts, which is consistent with the much weaker proton-accepting character of phosphorus in hydrogen bonds.

The exchange in SH bonds has been investigated on a somewhat larger scale. The study of phenylmethanethiol showed[139] that the rate of reaction is proportional to the concentration of the alkaline or acid catalyst. On this basis, the following mechanisms have been proposed for the exchange:

$$\mathrm{C_6H_5CH_2SH_2^+ + C_6H_5CH_2SH \overset{k_1}{\rightleftarrows} C_6H_5CH_2SH + C_6H_5CH_2SH_2^+}\ , \qquad (36)$$

$$\mathrm{C_6H_5CH_2SH + C_6H_5CH_2S^- \overset{k_2}{\rightleftarrows} C_6H_5CH_2S^- + C_6H_5CH_2SH}\ ; \qquad (37)$$

$k_1 = 1.35 \times 10^2$ litre mole^{-1} s^{-1} and $k_2 = 6 \times 10^5$ litre mole^{-1} s^{-1}. The uncatalysed process is so slow that its rate cannot be determined by the NMR method.

The rate of exchange of protons in the SH group of 2-mercaptoethanol has been studied[140]. The PMR spectrum of a solution of this substance in carbon tetrachloride consists of a triplet due to the thiol hydrogen, a quartet due to S–CH$_2$, a triplet due to O–CH$_2$, and a singlet due to OH. The spectrum retains the same form in an acidified aqueous medium, but in a neutral solution or solutions made alkaline with sodium acetate the SH triplet and the OH singlet merge into a common signal. Analysis of these changes as a function of the catalyst concentration, taking into account the acid–base equilibrium constants in the system, made it possible to determine (at 27°C) the rate constants for the uncatalysed exchange ($k_0 = 32$ s^{-1}) and the reactions catalysed by acetate ions ($k = 2 \times 10^3$ litre mole^{-1} s^{-1}). The equilibrium constant for the reaction

$$\mathrm{HOCH_2CH_2SH + CH_3COO^- \rightleftarrows HOCH_2CH_2S^- + CH_3COOH}$$

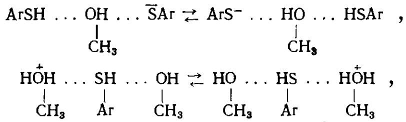
was found and the rate constant for the process

$$\mathrm{HOCH_2CH_2S^- + CH_3COOH \rightarrow HOCH_2CH_2SH + CH_3COO^-}\ ,$$

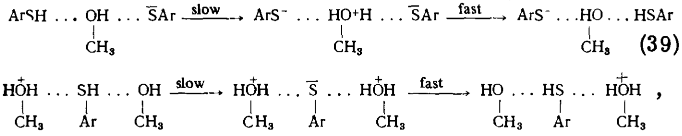
was calculated to be 10^8 litre mole^{-1} s^{-1}. The absence of the acid catalysed proton exchange in the SH group of 2-mercaptoethanol was explained by the low basicity of the thiol group.

It is interesting to compare the above data with the results for alcohols, for example it is instructive to compare k_1 and k_2 from Eqns. (36) and (37) with k_4 and k_2 from Eqns. (9) and (7) (Table 1). The comparison shows that the rate of exchange in SH groups is smaller by several powers of ten than in OH. We explained this difference by the lower strength of SH...S hydrogen bonds compared with OH...O. This interpretation was confirmed in the present author's studies[141,142] of proton exchange of thiophenols.

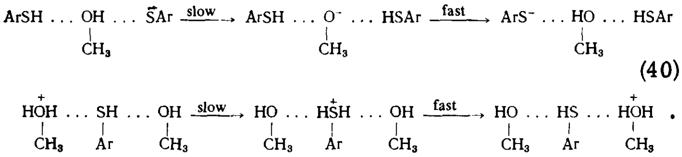
A study was made of the exchange between a series of thiophenols and methanol catalysed by hydrogen chloride or sodium methoxide. The rate of reaction was found to be proportional to the concentration of the thiophenol, alcohol, and the catalyst. It increased (and the activation energy fell) in parallel with the acidity on introducing electron accepting substituents into the thiophenol nucleus. For *para*- and *meta*-substituted compounds, a linear relation was observed between the activation energy and the logarithm of the rate constants for the exchange in alkaline and acid media (E_B, E_A, lgk_B, and lgk_A), on the one hand, and Hammett's σ constants, on the other, the values of ρ in the correlation equations proving virtually identical in both series. These data confirmed the exchange mechanism. Three most probable mechanisms were considered, in which the reactants were combined by hydrogen bonds into a single reaction complex:



$$\mathrm{ArSH}\ldots\underset{\mathrm{CH_3}}{\mathrm{OH}}\ldots\overline{\mathrm{S}}\mathrm{Ar}\rightleftarrows\mathrm{ArS^-}\ldots\underset{\mathrm{CH_3}}{\mathrm{HO}}\ldots\mathrm{HSAr}\ , \qquad (38)$$
$$\underset{\mathrm{CH_3}}{\mathrm{H\overset{+}{O}H}}\ldots\underset{\mathrm{Ar}}{\mathrm{SH}}\ldots\underset{\mathrm{CH_3}}{\mathrm{OH}}\rightleftarrows\underset{\mathrm{CH_3}}{\mathrm{HO}}\ldots\underset{\mathrm{Ar}}{\mathrm{HS}}\ldots\underset{\mathrm{CH_3}}{\mathrm{H\overset{+}{O}H}}\ ,$$



$$\mathrm{ArSH}\ldots\underset{\mathrm{CH_3}}{\mathrm{OH}}\ldots\overline{\mathrm{S}}\mathrm{Ar}\xrightarrow{\text{slow}}\mathrm{ArS^-}\ldots\underset{\mathrm{CH_3}}{\mathrm{HO^+H}}\ldots\overline{\mathrm{S}}\mathrm{Ar}\xrightarrow{\text{fast}}\mathrm{ArS^-}\ldots\underset{\mathrm{CH_3}}{\mathrm{HO}}\ldots\mathrm{HSAr} \qquad (39)$$
$$\underset{\mathrm{CH_3}}{\mathrm{H\overset{+}{O}H}}\ldots\underset{\mathrm{Ar}}{\mathrm{SH}}\ldots\underset{\mathrm{CH_3}}{\mathrm{OH}}\xrightarrow{\text{slow}}\underset{\mathrm{CH_3}}{\mathrm{H\overset{+}{O}H}}\ldots\underset{\mathrm{Ar}}{\overline{\mathrm{S}}}\ldots\underset{\mathrm{CH_3}}{\mathrm{H\overset{+}{O}H}}\xrightarrow{\text{fast}}\underset{\mathrm{CH_3}}{\mathrm{HO}}\ldots\underset{\mathrm{Ar}}{\mathrm{HS}}\ldots\underset{\mathrm{CH_3}}{\mathrm{H\overset{+}{O}H}}\ ,$$



$$\mathrm{ArSH}\ldots\underset{\mathrm{CH_3}}{\mathrm{OH}}\ldots\overline{\mathrm{S}}\mathrm{Ar}\xrightarrow{\text{slow}}\mathrm{ArSH}\ldots\underset{\mathrm{CH_3}}{\mathrm{O^-}}\ldots\mathrm{HSAr}\xrightarrow{\text{fast}}\mathrm{ArS^-}\ldots\underset{\mathrm{CH_3}}{\mathrm{HO}}\ldots\mathrm{HSAr} \qquad (40)$$
$$\underset{\mathrm{CH_3}}{\mathrm{H\overset{+}{O}H}}\ldots\underset{\mathrm{Ar}}{\mathrm{SH}}\ldots\underset{\mathrm{CH_3}}{\mathrm{OH}}\xrightarrow{\text{slow}}\underset{\mathrm{CH_3}}{\mathrm{HO}}\ldots\underset{\mathrm{Ar}}{\mathrm{H\overset{+}{S}H}}\ldots\underset{\mathrm{CH_3}}{\mathrm{OH}}\xrightarrow{\text{fast}}\underset{\mathrm{CH_3}}{\mathrm{HO}}\ldots\underset{\mathrm{Ar}}{\mathrm{HS}}\ldots\underset{\mathrm{CH_3}}{\mathrm{H\overset{+}{O}H}}\ .$$

The data showing the acceleration of the exchange with increasing acidity of thiophenols contradict mechanism (40), which requires the opposite relation, but are consistent with mechanism (39). The choice between the latter and mechanism (38) was made on the basis that only reactions (39) explain the observed equality of the values of ρ in the correlation equations, since only in mechanism (39) is the slow exchange stage the same in both alkaline and acid media, namely proton transfer via the hydrogen bond in the SH...OH dimers. Hence it was concluded that there should be a quantitative relation between the kinetic parameters of the exchange and the thermodynamic characteristics of the hydrogen bond. Such a relation does indeed exist.

Table 8. Kinetic parameters of the proton exchange between thiophenols and methanol and the thermodynamic parameters of the hydrogen bonds between thiophenols and acetone.

ArSH	Proton exchange				Hydrogen bond		
	k_B (27°), litre mole^{-1} s^{-1}	k_A (27°) litre mole^{-1} s^{-1}	E_B, kcal mole^{-1}	E_A, kcal mole^{-1}	K (27°), mole fraction^{-1}	$-\Delta H$, kcal mole^{-1}	$-\Delta S$, e.u.
p-Methoxythiophenol	$4.2 \cdot 10^3$	$1.2 \cdot 10^2$	9.0	12.5	2.3	2.6	7.1
p-Thioxylenol	$3.3 \cdot 10^3$	—	8.3	—	2.1	2.9	8.2
Tetraline-2-thiol	$5.5 \cdot 10^3$	—	8.5	—	2.6	2.8	7.8
p-Thiocresol	$5.8 \cdot 10^3$	$1.7 \cdot 10^2$	8.2	12.0	2.6	2.9	7.8
Thiophenol	$14.0 \cdot 10^3$	$2.8 \cdot 10^2$	7.5	11.0	2.9	3.2	8.6
p-Chlorothiophenol	$28.3 \cdot 10^3$	$7.8 \cdot 10^2$	6.3	10.0	3.3	3.8	10.0
3,4-Dichlorothiophenol	$112.0 \cdot 10^3$	$33.3 \cdot 10^2$	5.5	8.5	4.5	4.1	10.4

We used NMR to investigate[143] the thermodynamics of hydrogen bond formation between acetone and the same series of thiophenols for which the exchange had been investigated and found a linear relation between E_B and E_A, on the one hand, and the enthalpy of formation of the hydrogen bond ΔH, on the other, and also between k_B and k_A, on the one hand, and the association constants K, on the other. It is significant that this relation holds also for *ortho*-substituted thiophenols. The kinetic and thermodynamic data obtained in these studies are compiled in Table 8.

The total set of results shows that the characteristics of the hydrogen bond formed by sulphur play a decisive role in the kinetics and mechanism of proton exchange of thiophenols. The weakness of these bonds explains, in particular, the relatively high activation energies and the low rates of exchange (much lower than in the phenols–methanol systems[75]). The proton-accepting power of sulphur is apparently much weaker. This hypothesis accounts for the observation that the exchange involving thiophenol in an acid medium does not take place by mechanism (40) in which sulphur serves as a proton acceptor, in contrast to the exchange involving phenols, which takes place by reaction (20), analogous to mechanism (40). We may recall that in the case of hydrogen bonds formed by phosphorus the proton-accepting character of phosphorus is apparently much weaker than that of nitrogen.

VI. EXCHANGE IN C–H GROUPS.

Rapid proton exchange in C–H bonds of hydrocarbons and their derivatives takes place only in catalysis by bases and only in those cases where the acidity of the hydrogen is particularly enhanced. Like the other exchange processes examined here, these reactions probably take place in hydrogen-bonded complexes. Hydrogen bonds are less typical for carbon, which explains the rare occurrence of rapid exchange in C–H groups.

Several studies have been made on substituted acetylenes $R-C\equiv CH$.[144,145] It was found that with $R = C_6H_5$, CH_2CH_2OH, CH_2OCH_3, $C(CH_2)_2OCH_3$, $C(CH_3)_2OH$, and $CH(OC_2H_5)_2$ the rate of base-catalysed exchange with aqueous t-butyl alcohol is proportional to the concentrations of the substrate and the catalyst; the logarithm of the rate constants varies linearly with σ^*. The mechanism can be represented as follows:

$$R-C\equiv CH + OH^- \rightleftarrows R-C\equiv C^- + H_2O\ .$$

A study was also made of the exchange in compounds with $R = SC(CH_3)_3$, OCH_3, $C(CH_3)_3$, $SCH=CH_2$ and $OCH=CH_2$ catalysed by $(CH_3)_4NOH$.[146] The rate proved to be a maximum for sulphur-containing substances and a minimum for t-butylacetylene, and is lower the higher the dielectric constant of the solvent. These data were explained by the fact that only in compounds containing sulphur is there conjugation of the type

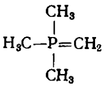
$$\overline{C}\equiv C-SR \leftrightarrow :C=C=\overline{S}R\ ,$$

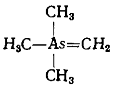
which stabilises the anion, lowers the energy of the transition state for the reaction, $R-C\equiv C^{-\delta}...H...OH^{-\delta}$, and increases the rate of exchange. The transition state is less solvated than OH^- ions, which in fact explains the decrease of the exchange rate with increasing dielectric constant of the solvent.

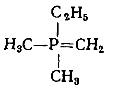
In certain systems a rapid exchange was observed between the hydrogen in C–H groups and carbanions. Thus it has been established[147] that the rate constants for the reaction between dimethyl sulphoxide and Na^+ or $Li^+CH_3SOCH_2^-$ (determined from the change in the form of the ^{13}C satellites of the signal due to the CH_3 group) are 12 and 7 litre $mole^{-1}\ s^{-1}$ respectively at 37°C.

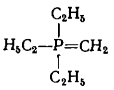
In another study[148] it was shown by a double resonance method that the rate of exchange between fluorene and 9-fluorenyl-lithium in dimethyl sulphoxide solutions at 38°C is characterised by the constant $k = 0.5$ litre $mole^{-1}\ s^{-1}$. These results are inconsistent with the much higher rate of exchange in the analogous system comprising 9-methylfluorene and the 4,5-methylenephenanthryl anion[149] observed in a very dilute dimethyl sulphoxide solution by the stop-flow method. The difference is probably due to self-association of the organometallic compound in concentrated solution.

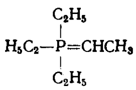
Rapid proton exchange was observed recently in phosphoranes and their analogues. Thus at room temperature the PMR spectra of the pure compound (I) or its benzene solution show doublets due to the methyl and methylene protons (the splitting is caused by interaction with the ^{31}P nuclei), but the rapid exchange induced by heating deprives the hydrogen atoms of their individual characteristics, which leads to a broadening of the signals, smearing out of the doublet structure, and merging of the signals into a singlet at a temperature above 100°C. In the presence of proton-donating compounds, for example traces of an alcohol, the singlet is observed even at room temperature[150,151]. A similar behaviour was noted for compounds (II)[152] and (III)–(V)[153]. In the latter compounds only the α-hydrogen atoms become indistinguishable. Variation of the form of the signal of the $\equiv P=CHR$ group with temperature was observed also for compounds having the general formula (VI) with R = H, CN, $CO(CH_2)_2C_6H_5$, $COCH_3$, $COOCH_3$, or CHO,[154] it too was explained by rapid proton exchange

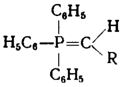

$H_3C-\underset{CH_3}{\overset{CH_3}{P}}=CH_2$
(I)


$H_3C-\underset{CH_3}{\overset{CH_3}{As}}=CH_2$
(II)


$H_3C-\underset{CH_3}{\overset{C_2H_5}{P}}=CH_2$
(III)


$H_5C_2-\underset{C_2H_5}{\overset{C_2H_5}{P}}=CH_2$
(IV)


$H_5C_2-\underset{C_2H_5}{\overset{C_2H_5}{P}}=CHCH_3$
(V)


(VI)

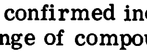
The mechanisms of the above processes were investigated in several studies[154–156], the authors concluded that the exchange takes place between phosphoranes and catalytic amounts of phosphonium salts present in the solutions and formed by the interaction of the phosphorane with proton-donating molecules:

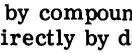
$$\begin{aligned} &(a)\quad R_3\overset{+}{P}-\overset{-}{C}R_2 + HX \rightarrow [R_3\overset{+}{P}-CR_2H]X^-\ , \\ &(b)\quad R_3\overset{+}{P}-\overset{-}{C}R_2 + [R_3\overset{+}{P}-CR_2H]X^- \rightleftarrows [R_3\overset{+}{P}-CR_2H]X^- + R_3P^+-\overset{-}{C}R_2\ . \end{aligned} \qquad (41)$$

This mechanism explains the catalysis of the exchange by proton-donating compounds mentioned above. It is confirmed by the inhibition of the reaction by bases, which decompose the phosphonium salts.

The rapid exchange by mechanism (41) probably explains the broadening of the signal due to the methylidyne hydrogen in the PMR spectra of the sulphoranes (VII) and (VIII)[156]:


(VII)


(VIII)

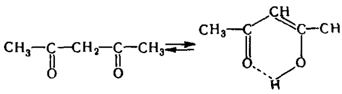

(IX)

$[(CH_3)_3\overset{+}{S}=O]X^-$.
(X)

Recently rapid exchange was observed in dimethyloxosulphonium methylide (IX).[157] It makes all the hydrogen atoms in this substance indistinguishable in solutions even at a temperature as low as −30°C. The exchange is probably catalysed by impurities. One cannot exclude the possibility that it proceeds by a mechanism analogous to mechanism (41) and is catalysed by compounds of type (X). This hypothesis is confirmed indirectly by data[158] for the rapid proton exchange of compounds of type (X) in aqueous alkaline solutions.

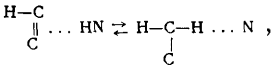
We may note that reactions of type (41b) constitute acid–base interactions. Their rate is high because the ylide structure of phosphorane and their analogues leads to high basicity of the methylene hydrogen and the positive charge at the phosphorus, arsenic, or sulphur atom increases the acidity at the hydrogen at the adjacent carbon atom.

An interesting case of proton exchange in CH groups associated with the tautomerism of acetylacetone has been investigated[159,160]. The PMR spectrum of pure acetylacetone shows individual signals corresponding to the enol and keto-forms; however, in the presence of diethylamine the equilibrium

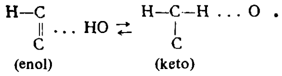


is displaced towards the formation of the enol and a common signal for the protons in OH, NH, and =CH– appears in the spectrum. To explain the involvement of the enolic methylidine hydrogen in the proton exchange, mechanisms were proposed with the intermediate participation of the keto-tautomer (only the atoms or groups between which protons migrate are indicated):

$$\text{O—H} \ldots \text{N} \rightleftarrows \text{O} \ldots \text{H—N}\ , \tag{42}$$



$$\underset{\text{C}}{\overset{\text{H—C}}{\|}} \ldots \text{HN} \rightleftarrows \text{H—}\underset{\overset{|}{\text{C}}}{\text{C}}\text{—H} \ldots \text{N}\ , \tag{43}$$



$$\underset{\substack{\text{C}\\ \text{(enol)}}}{\overset{\text{H—C}}{\|}} \ldots \text{HO} \rightleftarrows \underset{\substack{|\\ \text{C}\\ \text{(keto)}}}{\text{H—C—H}} \ldots \text{O}\ . \tag{44}$$

We may note that reaction (44) represents the usual keto-enol transformation.

Special experiments showed that the exchange in =CH– is much slower than in OH and NH. This is consistent with the finding that the hydrogen-bond bridges with participation of π-bond electrons are usually weaker than those formed with participation of unshared electron pairs.

VII. CERTAIN GENERAL PROBLEMS OF PROTON EXCHANGE

In this section we shall give a general account of the role of hydrogen bonds in the mechanism of proton exchange and of the nature of the reaction complexes by which the exchange takes place; we will also examine certain considerations concerning the acidity of compounds with SH and PH bonds, which we proposed when comparing the data for the rate and mechanism of proton exchange.

The entire information presented in the review and probably all other published data are consistent with the hypothesis that in rapid exchange reactions the protons always migrate along hydrogen bonds and the ease of such migration is greater the stronger the bonds. Some time ago this hypothesis enabled Brodskii[161] to give a general treatment of the vast experimental data for hydrogen isotope exchange, to devise a classification for such data which has since been generally adopted, and to explain why hydrogen bound to atoms with non-bonding electron pairs is involved in the exchange. Using this hypothesis, Miklukhin[162,163] predicted the variation of the rate of hydrogen isotope exchange (and proton exchange) with the strength of the hydrogen bonds in reaction complexes. These predictions were later confirmed experimentally (see Section V). The hypothesis explains the usually observed parallel variation of the rate of exchange and the acidity of the protons being exchanged by the fact that the acidity and the strength of the hydrogen bonds vary in the same sense in series of related compounds. It also explains the higher rates of exchange between ions of opposite sign, frequently noted above, compared with the exchange between an ion and a molecule, or between neutral molecules, since the hydrogen bonds between ions of different signs are stronger than in the other two cases. It can also explain the rapid exchange in C–H bonds (see Section VI). This exchange is observed only in the system comprising compounds with highly acid hydrogen atoms and a strong base (X) with unshared electron pairs or π electrons. Probably isotope exchange in such systems takes place via hydrogen bonds of the type C–H...X. We may recall finally that in certain cases (see Sections II and V) a linear relation was established between the activation energy for proton exchange and the strength of hydrogen bonds. Thus, there are good reasons for the belief that rapid proton exchange always takes place via hydrogen-bonded reaction complexes.

The nature of these complexes was investigated only in rare cases and as a rule remains unknown. Thus the cyclic structures for these complexes proposed in many investigations of uncatalysed exchange processes are usually unsupported by any evidence. The number of members of the ring (4, 6, 8 and above) is also chosen arbitrarily since in the majority of cases the number of molecules participating in the slow reaction step is unknown.

In the interpretation of the mechanisms of reactions of different types cyclic complexes are sometimes preferred to open-chain complexes because the former can ensure a higher rate of reaction (see, for example, Syrkin[15]). We may note, however, that, for the formation of hydrogen-bonded cyclic complexes in the rapid exchange processes in which we are interested, it is necessary that each molecule forming part of the complex should be capable of behaving simultaneously as a hydrogen donor and acceptor. This condition does not as a rule hold in catalysed exchange, since the acid catalyst blocks the free electron pairs and frequently leads to the loss of acceptor capacity by the molecule, while the base usually leads to the conversion of molecules into ions, which lack labile hydrogen. Thus many of the very rapid catalysed proton exchange reactions undoubtedly involve open-chain complexes. We suggest that one cannot exclude the possibility that many uncatalysed exchange reactions also proceed via open-chain complexes.

In Section V it was already stated that the low rate and the relatively high activation energy of proton exchange in the PH and SH groups compared with NH and OH can be accounted for by the low strength of the hydrogen bond formed by phosphorus and sulphur. Generalising the findings, one can postulate, following Miklukhin[163], that the exchange in AsH, SbH, SeH, and TeH should be even slower and the activation energy should be still higher.

We have also noted (see Section V) that the properties of the hydrogen bond formed by sulphur and phosphorus determine the mechanism of the exchange involving mercapto-compounds and phosphonium salts and that the proton-accepting functions of sulphur and phosphorus are probably even weaker (compared with oxygen and nitrogen) than their proton-donating functions. We suggest that these characteristics of the hydrogen bond are responsible also for the acid properties of mercapto-compounds and phosphonium salts. The greater weakness of hydrogen bonds formed by sulphur and phosphorus compared with oxygen and nitrogen usually results in the retardation of both the forward and reverse reactions in the acid–base equilibrium of the type

$$\text{X—H} \ldots \text{B} \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} \text{X}^- \ldots \text{HB}^+\ .$$

This is because, as already stated above, the proton-accepting functions of sulphur and phosphorus are very much weaker. As a result, the acid dissociation constants $K = k_1/k_{-1}$ prove to be higher than for the corresponding oxygen- and nitrogen-containing substances.

This treatment is probably of general validity. It explains, for example, the higher acidity of phosphines compared with amines and the increase of the acidity in the series

$$H_2O < H_2S < H_2Se < H_2Te \text{ and } HF < HCl < HBr < HI\ .$$

Evidently this approach to the problem of acidity is applicable only in those cases where the hydrogen in the X–H bonds has partial positive charge sufficient for the formation of the hydrogen bond X–H...B.

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Pisarzhevskii Institute of
Physical Chemistry, Academy
of Sciences of the Ukrainian SSR,
Kiev

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Application of Flash Photolysis in the Study of the Triplet State of Organic Substances

A.K.Chibisov

Flash photolysis is a relaxation method for the investigation of the mechanism of rapid photochemical reactions. The fundamental design and constructional features of spectroscopic apparatus for flash photolysis have been examined. Considerable attention has been devoted to the description of the sources for flash photolysis. The application of flash photolysis in the study of triplet states of organic substances in solutions is considered. The results obtained for the quantum yields and the triplet-triplet absorption spectra of aromatic hydrocarbons, carbonyl compounds, dyes, and pigments have been presented. The mechanisms and the kinetics of the deactivation of triplet states, the quenching mechanisms, and the role of the triplet state in photochemical reactions have been discussed.
The bibliography includes 197 references.

CONTENTS

1. INTRODUCTION

The study of excited electron states in chemical and biological processes constitutes an extremely urgent task. Primary photochemical reactions are known to take place with participation of both excited singlet and triplet states. Terenin[1] and Lewis and coworkers[2-4] put forward and justified experimentally the hypothesis that the transition from the excited singlet to the triplet state is due to the inversion of the spin of the optically excited electron. The longer lifetimes of triplet molecules (10^{-3}–10^{-4} s) compared with those in the excited singlet state (10^{-8}–10^{-9} s) in solutions are responsible for the dominant role of triplet states in the majority of photochemical reactions.

Until comparatively recently the sole source of direct information about triplet states of polyatomic molecules were data on the spectra and decay of phosphorescence[5]. Since most substances are not phosphorescent in liquid solutions, i.e. under conditions where diffusion processes take place, there was no information about triplet states of substances in solution. With the appearance of pulse excitation methods and in particular the method of flash photolysis† it became possible to follow directly processes involving the population and deactivation of the triplet states of substances in condensed and gaseous phases.

Recently many papers have been published on the triplet states of organic substances in solutions investigated under conditions of intense flash photolysis. Therefore it has become necessary to give a systematic account of the information and the properties of triplet states and their role in primary photochemical processes. The available reviews[6-8] by no means fully reflect the data on the physicochemical properties of the triplet states of organic substances. The present review deals exclusively with the results obtained in the study of the triplet states of organic substances by the method of flash photolysis. The aim of the review was also to illustrate the scope of the method of flash photolysis in the investigation of intermediate short-lived products of rapid reactions.

2. METHOD OF FLASH PHOTOLYSIS

Flash photolysis is one of the relaxation methods employing powerful brief light pulses which act on the given substance to give rise to a considerable non-equilibrium concentration of metastable states. The relaxation of the system to the initial or a new equilibrium state is "followed" from the absorption spectrum or some other characteristic recorded over a period of time after the pulse initiation.

Pulse illumination is achieved as a result of a pulse discharge, preferably in an inert gas (xenon, argon, and krypton)[9]. The source of the electrical energy of the flash ($E = CU^2/2$) is a battery of high-voltage condensers of capacity C (μF) charged to a potential U (kV). One or several gas-discharge flash tubes connected in series or in parallel serve as a source of the flash. The flash source connected by heavy leads to the battery of condensers constitutes the electrical circuit.

In the design of apparatus for flash photolysis much attention has been devoted to the electrical circuit and particularly to the flash source. The requirements which must be met by the source reduce to minimum duration and selectivity of the emission and also to maximum light yield. The electrical discharge in the circuit is oscillatory or shows simple decay depending on the relation between the resistance R, the inductance L, and the capacitance C of the circuit elements. When the relation $R = 2\sqrt{L/C}$ holds, the critical damping conditions are achieved, the duration of the emission τ is then a minimum which is most suitable for photoexcitation. A decrease of τ is obtained by lowering L and C ($\tau \propto \sqrt{LC}$). However, one must bear in mind that the compensation of the electrical energy of the flash on lowering C by increasing U is restricted by the load factor

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† In the Russian literature this method is also referred to as pulse photolysis, pulse photoexcitation, and pulse spectroscopy.

($F \propto CU^4$), which determines the duration of the serviceability of the flash tubes. For electrical circuits with a low value of C (several microfarads), the duration of τ is determined largely by the self-inductances of the flash tubes. The inductance L of a circuit consisting of two series-connected elongated flash tubes (interelectrode distance 20 cm; 250 nH) connected to a condenser (5 μF; 6 nH) by a low-inductance circuit of the "sandwich" type (length 100 cm; 8 nH) is 264 nH.[10] The duration of the flash in this version $\tau = 2\pi\sqrt{LC}$ (according to the current) is 7.2 μs at $E = 1000$ J. The reduction of τ to 1.8 μs is achieved using a coaxial design for the flash tubes with $L = 6$ nH.[11]

Ultrashort (10^{-7}–10^{-12} s) light pulses are obtained by employing a self-contracting (the Z-pinch effect) pulse discharge ($\tau = 2 \times 10^{-7}$ s, $E = 4850$ J)[12] or lasers operating under giant pulse conditions[13–15].

In order to determine the time resolution of the spectrophotometric apparatus with flash photolysis, it is necessary to consider the flash duration τ_{light} in contrast to τ_{current}. Due to the afterglow recombination process $\tau_{\text{light}} \geq \tau_{\text{current}}$. For $\tau_{\text{current}} = 5$ μs, the duration of the recombination afterglow τ_{light} may reach 150 μs (for 0.1 of the peak light amplitude) depending on the type of gas employed, the pressure, and the wavelength of the emission. The duration of afterglow can be reduced by increasing the internal surface area of the flash tube[16], by decreasing the length of the mean free path of the excited molecules[17], and by introducing quenching gases (N_2 and O_2).[18,19]

In the practical application of flash photolysis, flash lamps filled with both inert and molecular gases (O_2, N_2, and H_2) and their mixtures have found the greatest use[18–20]. Depending on the type of gas and its pressure (5 mm–10 atm‡), the spectral distribution of the pulse emission changes appreciably[21–23]. The emission maximum shifts towards the ultraviolet part of the spectrum when the energy of the flash increases as a result of the increase in U.[24] The application of flash lamps filled with various gases in combination with narrow-band light filters interposed between the source of radiation and the test object ensures the selectivity of excitation.

The number of quanta n emitted by the flash lamp during the flash depends on E, the type of gas, and the wavelength of the emission. According to actinometric measurements, $n = 1 \times 10^{20}$ quanta per flash in the range 220–440 nm at $E = 3000$ J ($\tau_{0.1} = 9.5$ μs; tube filled with O_2 at 20 mmHg).[19] With such high light intensity, the molecules of the light-absorbing substance (10^{-5}–10^{-6} mole litre^{-1}) undergo repeated (10^2–10^3) excitation during a single light pulse. A high concentration of intermediate, for example triplet, photoexcitation products is thereby achieved. Thus 100% population of the phosphorescent triplet level (5×10^{-7} mole litre^{-1}) is attained when an aqueous solution (0.01 N NaOH) of the dye is irradiated by a flash with $E = 6000$ J [25] (the probability of the transition to the triplet state is about 0.05)[26]. The high concentration of the intermediates generated by the photon excitation permits the use of spectroscopic methods for their recording and identification.

For semiquantitative measurements of the intermediate products of a reaction initiated by a light pulse, a spectrographic method of recording, described in the first version of the flash photolysis apparatus[27], is employed. Fig. 1 shows schematically the positions of the principal constructional elements of the flash photolysis apparatus with spectrographic recording[10]. The flash initiating the photochemical reaction is produced by the discharge of a high-voltage condenser (*1*) via two cylindrical flash lamps connected in series (*4*). The lamps are connected to the condenser via low-inductance leads (*2*) of the "sandwich" type. The flash is initiated by an electric pulse applied to the trigger (*3*) (a thyratron, ignitron, etc.). The test object is put in a cuvette (*5*) and is initially excited by light from photolysis flash lamps (*4*). The absorption spectrum of the intermediate product is "instantaneously" (about 10^{-6} s) recorded with the aid of a low-power monitoring flash lamp (*6*) and a spectrograph (*7*). The absorption spectrum of the intermediates is photographed an arbitrarily fixed delay time $\Delta\tau$ after the initiation of the excitation.

A series of absorption spectra of the intermediates are obtained in repeated measurements with variable delay times $\Delta\tau$. The change in the blackening of the photographic plate, which serves as a receiver of the radiation of the monitoring source, is proportional to the change in the optical density of the solution of the test substance, provided that the degree of blackening and the exposure are linearly related. The use of the spectrographic method for the recording of intermediates is valid for substances whose absorption spectra show fine (for example vibrational–rotational) structure. In this case the application of photoelectric recording requires many repetitions of the irradiation of the substance by light pulses, which frequently leads to its decomposition. In this respect the spectrographic method of recording is convenient for the study of the mechanism of irreversible photochemical processes.

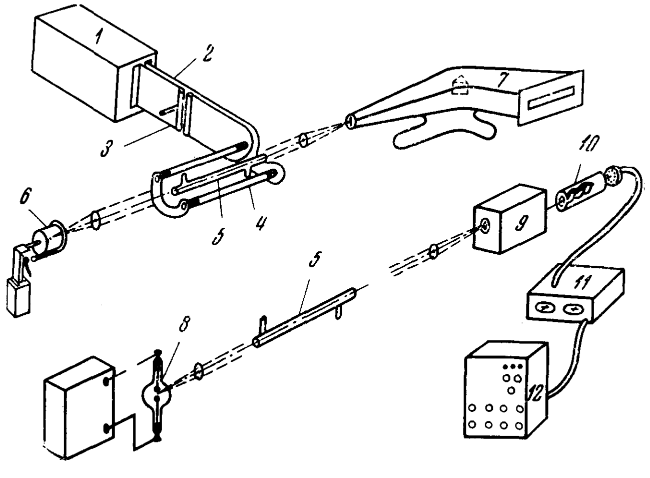

Figure 1. Diagram of flash photolysis apparatus[10] (for explanation, see text).

For accurate measurements of concentrations, the extinction coefficients of intermediates, and the kinetics of their reactions, the more sensitive photoelectric method of recording is employed. Photoelectric detectors cover a much wider range of wavelengths compared with the photographic plate, which in turn yields more information about short-lived products of photochemical reactions. Fig. 1 also shows schematically the positions of the principal elements of a flash photolysis apparatus with photoelectric

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‡ For spherical flash lamps.

recording. In this version the monitoring flash lamp (*6*) is replaced by a source of continuous radiation (*8*)—an incandescent lamp or an ultrahigh pressure arc lamp filled with xenon or mercury. The spectrograph (*7*) is replaced by a monochromator (*9*) with a photomultiplier cell (*10*), a power source (*11*), and an oscilloscope (*12*). The spectral changes under the influence of the flashes from the photolysis lamp are recorded "point by point", the monochromator being set before each flash to a fixed wavelength in the relevant wavelength range.

The differential resolving power (on the basis of the change in the optical density ΔD) of the flash photolysis apparatus with photoelectric recording is determined by the level of fluctuation interference (noise) of the recording system. An increase of the signal-to-noise ratio is achieved by employing the maximum possible illumination of the photocathode of the photomultiplier by the continuous monitoring source, by using a low supply voltage for the photomultiplier, and with the aid of electric filters (*RC*) which limit the high frequency components of the transmitted signal[28-30]. CAT's combined with a source of pulse photoexcitation and operating under stroboscopic conditions have been employed recently to increase the signal-to-noise ratio[29,31]. When the illumination of the reaction system is repeated many times, the signal-to-noise ratio increases by a factor of $\sqrt{n}$, where n is the number of exciting light pulses.

As well as the above two methods for the recording of the absorption spectra of intermediates, fast scanning spectroscopy is employed[32-35]. In this method the absorption spectrum of the intermediates is scanned at a high speed with simultaneous oscilloscopic recording of the spectrum. In the single-beam high-speed spectrometer with a rotating system of three mirrors (optical accelerator) the range 400–1100 nm is scanned over a period of 4×10^{-5} s.[34]

The majority of the measurements of the absorption spectra of the intermediates have been made with flash energies in the range 100–1000 J. Approximate calculations show that an energy of 1000 J is sufficient for most photochemical studies[36]. As already mentioned, the time resolution of the flash photolysis apparatus is determined by the duration of emission from the photochemical flash source. The limiting rate constants for rapid reactions may be estimated from the resolution time of the apparatus and its sensitivity. For a first-order reaction, the maximum rate constant k_1 is estimated as $k_1 \simeq 10^5$ s^{-1} when the duration of the flash $\tau_{0.5}$ is several microseconds. For a second-order reaction, for example a reaction between radicals, $k_2 = \epsilon l \tau_{0.5}^{-1} \Delta D^{-1}$ is found from the relations $k_2 = \tau_{0.5}^{-1} C^{-1}$ and $\Delta D = \epsilon C l$, where ϵ is the extinction coefficient of the intermediate product (radical), C its concentration, and l the thickness of the absorbing layer (in the direction of the probing beam). For $l = 10$ cm, $\Delta D = 0.1$, and $\tau_{0.5} = 10^{-5}$ s, we have $k_2 = 10^7 \epsilon$. Consequently the maximum value is $k_2 = 10^{11}$ litre mole^{-1} s^{-1} when $\epsilon = 10^4$ litre mole^{-1} cm^{-1}.[36]

The reaction intermediates may be recorded in ways other than from absorption spectra. The charged species (ions) generated by the light pulse can be recorded from the change in electrical conductivity[37]; free radicals can be recorded using ESR spectra[38].

However, in the practical application of flash photolysis, the spectroscopic method for recording intermediate products, and in particular triplet states, has found the greatest use. In principle, this method can be used to solve two problems: the elucidation of the structure of intermediates from their absorption spectra, and of the mechanism and kinetics of the transformation of intermediates in rapid reactions.

3. QUANTUM YIELD OF THE TRIPLET STATE

Many molecules of aromatic hydrocarbons, carbonyl compounds, dyes, and pigments are effectively converted into the triplet state in liquid and solid solutions under the action of flash photolysis. The possibility of directly observing the population and deactivation processes of triplet states is determined, on the one hand, by the relatively long lifetime of triplet molecules and, on the other hand, especially by the capacity of triplet molecules to absorb from the triplet level (the triplet–triplet absorption spectrum). The last factor is a consequence of the transitions between states of the same multiplicity being allowed and constitutes the foundation of the spectroscopic recording of triplet molecules using pulse illumination.

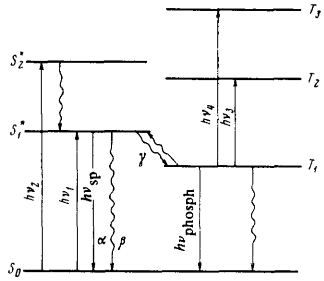

Figure 2. Schematic representation of the energy levels of the molecule: S_1^* and S_2^*—excited singlet levels; T_1, T_2, and T_3—excited triplet levels; for other explanations, see text.

The energy of the lowest excited singlet state is known to be degraded by several processes including fluorescence, non-radiative degradation, and transition to the triplet state[39-42]. Fig. 2 shows schematically the positions of the energy levels of the molecules, where α, β, and γ denote the probabilities of transitions giving rise to fluorescence (α), non-radiative degradation (internal conversion) (β), and transition to the triplet state (γ). There are simple relations between the probability of the γ transition, the quantum yield Φ_T in the formation of the triplet state, and the lifetime τ of the molecules in the S_1^* state: $\Phi_T = \gamma/(\alpha + \beta + \gamma)$ and $\Phi_T = \gamma\tau$. Using flash photolysis, it is possible to find Φ_T by the following two procedures. The first, the direct determination of $\Phi_T = C_\gamma / C_a = \Delta D / (\epsilon_T - \epsilon_S)\theta C_0 l$, is based on the direct determination of the concentrations of the triplet molecules C_γ and the molecules C_a excited by the light pulse[26,43-45]. ΔD is the change in optical density on formation of the triplet state, $\epsilon_T - \epsilon_S$ the difference between the extinction coefficients of the molecules in the triplet and singlet stage respectively, θ the fraction of light quanta absorbed by the molecules of the substance at an initial concentration C_0, and l the thickness of the absorbing layer. The expression for θ is $\theta = \int I_f(\nu) R(\nu) [1 - I_M(\nu)] d\nu / \int I_f(\nu) R(\nu) d\nu$, where I_f and I_M are the fractions of the light pulse transmitted by the light filter and the substance respectively and R is the relative light yield of the flash excitation source[26]. The accuracy of such determinations of Φ_T could be within 20–30%.[46]

The second method for the determination of Φ_T[47,48] is based on the perturbation by heavy atoms of the spin-orbital coupling in the molecule[49]. The effect of heavy or paramagnetic atoms in one molecule leads to an increase of the probability of the transition to the triplet state of another[50] and the quenching of the fluorescence[51]. Thus in the presence of heavy atoms the relative yield F/F^0 of fluorescence falls with a parallel increase of the yield D_T/D_T^0 of the triplet molecules of the substance. The quantitative relation between the two processes is expressed by $F^0/F = (D_T F^0/D_T^0 F - 1)(1 + k_1/k_2)\Phi_T + 1$, where k_1 and k_2 are the rate constants for the quenching process:

$$S_1^* + Q \rightarrow S_0 + Q \quad , \tag{1}$$

$$S_1^* + Q \rightarrow T_1 + Q \quad . \tag{2}$$

Bromobenzene[47], potassium and sodium iodide and bromide, p-iodophenol, bromocyclohexane, p-dibromobenzene[52], and also gaseous xenon[48], etc. are used as heavy-atom quenching agents Q. Table 1 presents a number of values of Φ_T determined by one of the two methods. It shows that the values of Φ_T for xanthene dyes (fluorescein, eosin, and erythrosine) increase sharply on introduction of a heavy atom (bromine and iodine) into the fluorescein molecule. This is due to the effect of the heavy atom bound chemically to the molecular skeleton on the probability of transition to the triplet state[55].

Table 1. The quantum yields Φ_T of the transition to the triplet state determined by the method of flash photolysis.

Object	Solvent (20°C)	Φ_T	Refs.
Anthracene	liquid paraffin	0.58 ± 0.10	26
		0.75	47
9-Methylanthracene	liquid paraffin	0.44	47
9-Phenylanthracene	ethanol	0.51 ± 0.02	52
1,2,5,6-Dibenzanthracene	3-methylpentane	1.03 ± 0.16	26
Pyrene	ethanol (95%)	0.38 ± 0.02	48
Phenanthrene	3-methylpentane	0.70 ± 0.12	26
Fluorescein	water, pH 9	0.05 ± 0.02	26
	water, pH 12	0.08	53
6-Hydroxy-9-phenylfluorescein	water, pH 12	0.02	53
Dibromofluorescein	water, pH 9	0.49 ± 0.07	26
Eosin	water, pH 9	0.71 ± 0.10	26
Erythrosin	water, pH 9	1.07 ± 0.13	26
Chlorophyll a	ether	0.64	44
Chlorophyll b	ether	0.88	44
Phaeophytin a	–	0.3 ± 0.1	45
Mesoporphyrin	–	0.3 ± 0.1	45
Zn-mesoporphyrin	–	0.28 ± 0.1	45
Al-etioporphyrin	ethyl iodide (77°K)	0.8	54

A knowledge of Φ_T and the fluorescence quantum yield Φ_{fl} permits the determination of $\Phi_{n.d}$ for non-radiative degradation of many of the compounds listed in Table 1. Thus for pyrene[48] and also anthracene and its derivatives[47,52], $\Phi_T + \Phi_{fl} = 1$, which indicates the absence of a non-radiative degradation process. A value of $\Phi_{n.d}$ close to zero was also observed for xanthene dyes[44], chlorophylls[44,45], and etioporphyrins[57]. An appreciable contribution (⩾ 50%) of non-radiative degradation to the deactivation of the excited singlet state was observed for mesoporphyrins[45] and 6-hydroxy-9-phenylfluorescein[3]. In the latter case $\Phi_{n.d} = 0.8$, while for fluorescein $\Phi_{n.d} \simeq 0.1$.[53] The difference between the values of $\Phi_{n.d}$ for the two compounds indicated above, which differ by the charge of the carboxy-group (in an alkaline solution), is due to the structure-forming effect of water molecules (solvent), which lowers the probability of the deformation of the molecular skeleton and hence of non-radiative degradation[41,53].

The values of Φ_T listed in Table 1 and determined indirectly, for example from the sensitisation of the *cis–trans* isomerism[56], are in good agreement with one another.

4. TRIPLET-TRIPLET ABSORPTION

In 1953 Porter and Windsor[58] observed the appearance in the spectrum of anthracene in hexane of a short-lived triplet absorption at 398 and 420 nm under the influence of pulse illumination. Subsequently the same workers[59] recorded the absorption spectra of the triplet molecules of 32 substances including aromatic hydrocarbons, ketones, and other compounds. The triplet–triplet absorption spectrum arises as a result of the absorption of light quanta by triplet molecules ($T_1 \xrightarrow{h\nu_3} T_2$; $T_1 \xrightarrow{h\nu_4} T_3$; etc., Fig.2). Fig. 3 shows the absorption spectra of the triplet states of condensed aromatic hydrocarbons ranging from benzene to pentacene. The triplet–triplet absorption of benzene was observed only in a solid matrix at 77°K[60], while the spectra of the triplet absorption of naphthalene, anthracene, naphthacene, and pentacene were measured at room temperature in liquid solution[59]. The wavelengths of the triplet absorption maxima of certain aromatic hydrocarbons (anthracene and its derivatives, naphthalene and its derivatives, naphthacene, pentacene, phenanthrene, chrysene, pyrene, rubrene, and others) have been given in a number of papers[59,61–65].

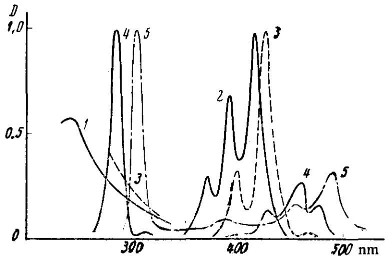

Figure 3. Triplet–triplet absorption spectra: *1*) benzene; *2*) naphthalene; *3*) anthracene; *4*) naphthacene; *5*) pentacene.

An important characteristic of absorption spectra is the oscillator strength f,[66] which is related to the experimental extinction coefficient ϵ: $f = 4.32 \times 10^{-9} \int \epsilon(\nu) d\nu$. The ϵ_T for a triplet–triplet absorption is determined in several ways. One of them is based on the fact that the transition of a molecule to the triplet state is accompanied by the depletion of the singlet S_0 level. This method of determination of ϵ_T is convenient for those substances whose singlet–singlet and triplet–triplet absorption spectra do not overlap.

The degree of attenuation (decolorisation) of the singlet absorption band under the influence of pulse illumination is a measure of the concentration of triplet molecules. In this case $\epsilon_T^{\lambda_2} = \epsilon_S^{\lambda_1}(\Delta D^{\lambda_2}/\Delta D^{\lambda_1})$, where λ_1 and λ_2 correspond to the maxima in the singlet and triplet absorption. In the case of overlapping singlet–singlet and triplet–triplet absorption spectra, ϵ_T is found from the variation of ΔD with flash energy E. The limiting value ΔD^0, which is independent of E, corresponds to 100% conversion into the triplet state[25,67]. ϵ_T can also be estimated from the kinetic data for the deactivation of the triplet molecule. In this case one finds experimentally the relative rate constant for triplet–triplet annihilation: $\varphi = k/\epsilon_T$.[34] The rate constant k is usually close to the diffusion constant $k_D = 8RT/3000\eta$, where η is the viscosity of the medium[68]. Consequently $\epsilon_T = 8RT/3000\eta\varphi$. The values of ϵ_T for certain aromatic hydrocarbons found by one of the above methods and also the values of the calculated oscillator strength f are listed in Table 2. The high extinction coefficient ϵ_T for the triplet–triplet absorption of aromatic hydrocarbons is evidence of a high probability of the transitions $T_1 \rightarrow T_2$, $T_1 \rightarrow T_3$, etc. According to the literature[59,71], T_1, T_2, T_3, T_4, and T_5 are identified with the states ${}^3B^+_{2u}$, ${}^3A^-_{1g}$ (lower), ${}^3B^-_{1g}$ (lower), ${}^3B^-_{1g}$ (upper), and ${}^3A^-_{1g}$ (upper) respectively. The positions of the excited triplet levels T_2, T_3, etc. are found from the positions of the lower triplet levels T_1 for polyacenes[2,50,72] and triplet–triplet absorption data[59]. The experimental values of T_2, T_3, T_4, and T_5 proved to be in good agreement with calculation[71].

Table 2. Extinction coefficients ϵ_T for triplet–triplet absorption and their oscillator strengths f for aromatic hydrocarbons.

Object	Solvent 20°C)	ϵ_T, litre mole^{-1} cm^{-1}	f	λ, nm	Refs.
Benzene	65% isopentane + 35% 3-methylpentane*	⩾1600	—	≃240	0
Naphthalene	liquid paraffin	10 000	0.06	415	59
	cyclohexane	22 600	—	412	9
	3:1 ethanol – methanol**	45 000	—	413	70
Anthracene	liquid paraffin	71 500	0.4	424	59
	hexane	46 000	—	420	63
	cyclohexane	57 200	—	420	9
	3:1 ethanol – methanol**	90 000	—	425	70
Naphthacene	liquid paraffin	52 600	0.4	460	59
	liquid paraffin	8000	0.05	312	59
	liquid paraffin	195 000	0.9	285.5	59
Pentacene	hexane	205 000	2.4	490	59
	hexane	630 000	2.0	305	59

* Measurements at 77°K.

** Measurements at 113°K.

The measurement of the triplet–triplet absorption spectra of aromatic compounds containing heteratoms, for example ketones, and also dyes and pigments, is in many cases more difficult than the measurement of the triplet spectra of aromatic hydrocarbons. In contrast to aromatic hydrocarbons, the flash photolysis of many hetero-compounds yields both triplet and intermediate products (radicals, ions, isomers, etc.) as a result of the photo-excitation of the molecules. In many cases the absorption spectra of the intermediates are very similar to the triplet absorption spectra; moreover, radicals may be formed as a result of the reaction of triplet molecules with those of the medium, which leads to a considerable shortening of the lifetimes of the triplet states. Therefore, in order to identify the triplet absorption spectra, certain auxiliary procedures (triplet–triplet transfer, the method of matrix isolation, phosphorescence, etc.) are employed.

The absorption spectrum of the intermediate in the flash photolysis of benzophenone in liquid paraffin, identified as of the triplet type, was first reported by Porter and Windsor[59]. However, subsequently on the basis of data for the triplet–triplet energy transfer in the system benzophenone–naphthalene, it was shown[73] that the spectrum of the intermediate product of benzophenone is due to a ketyl radical and not to the triplet state. Probably the most reliable observations of the triplet state of benzophenone are reported by Bell and Linschitz[74] and by Melhuish[75]. Using a flash source with a duration of several microseconds, they observed the appearance of a short-lived (10^{-5} s) absorption in the photoexcitation of benzophenone in benzene[74]. Comparative data for the spectra of the triplet state of benzophenone and its ketyl radical were obtained using a poly(methyl methacrylate) matrix[75]. The difficulty of recording the spectrum of the triplet absorption of benzophenone is caused, on the one hand, by the short lifetime of the triplet in solution (10^{-5}–10^{-7} s[76–79]) and, on the other hand, by the similarity of the spectra of the triplet state of benzophenone and the ketyl radical. The short lifetime of the triplet state of benzophenone is due to its high reactivity for abstraction of hydrogen atoms from the molecules of the medium[74], and also to the quenching of the benzophenone triplet state by the photochemical reduction products[80]. Qualitatively analogous results were obtained from benzaldehyde and acetophenone[81]. The triplet states of carbonyl derivatives of naphthalene (naphthaldehyde, acetonaphthone, and naphthyl phenyl ketone) are less reactive in solutions in respect of photochemical reduction. This is indicated indirectly by the low quantum yield of the conversion into pinacols observed on irradiation in isopropyl alcohol[82]. For example, 2-acetonaphthone is not photochemically reduced in secondary alcohols[83]. This made it possible to record the triplet absorption spectrum of 2-acetonaphthone in benzene with a maximum at 430 nm[84]. Measurements have also been made of the triplet absorption spectra of certain aromatic alcohols. The maximum in the triplet absorption of 1-naphthol in benzene was observed at 390 nm[84] and that of 2-naphthol in water at 432 nm[85] and in a gelatine film at 443 nm[86].

The lower triplet level of aromatic hetero-compounds may be n,π^*, or π,π^*, or CTS (the charge-transfer state) depending on the nature of the substituents in the aromatic ring (amino-, hydroxy-, methoxy-groups, etc.) and the medium (hydrocarbons or solvents tending to form hydrogen bonds). For p-aminobenzophenone, the lower triplet level in isopropyl alcohol is CTS (T_1) and in cyclohexane n,π^*[87] (see Section 7 of this review).

The triplet absorption spectra of dyes have been investigated in less detail compared with aromatic hydrocarbons and oxygen-containing compounds. As in the case of aromatic ketones, the triplet molecules of dyes are capable of reversible electron-transfer reactions in the absence of external electron donors or acceptors[25]. In many cases this leads to the masking of the triplet absorption spectra of dyes by those of radicals. Moreover, in view of the tendency of dye molecules towards the formation of dimers and more complicated association complexes, triplet absorption measurements must be made in dilute dye solutions (10^{-6}–10^{-7} M). In order to detect triplet molecules at a low concentration, highly sensitive flash photolysis apparatus is necessary.

The study of the triplet states of dyes using their absorption spectra is important in elucidating the mechanism of the sensitising action of dyes. Measurements have been made of the triplet absorption spectra of individual examples of xanthene[25,88–91], acridine[92], phenazine[93,94], thiazine[95–99], and polymethine[100] classes§. Fig. 4 presents the triplet absorption spectra of phenosafranine in aqueous solution at different pH; Table 3 lists the wavelengths λ_{max} of the maximum triplet–triplet absorption and the extinction coefficient ϵ_T for certain dyes. The dyes listed in Table 3 are characterised by an intense $S_0 \rightarrow S_1^*$ absorption band in the visible part of the spectrum. The transition to the triplet state is accompanied by a weakening of the $S_0 \rightarrow S_1^*$ band. Acridine Orange in triethylamine solution is an exception[92]. In the triplet state there are a number of transitions, $T_1 \rightarrow T_2$, $T_1 \rightarrow T_3$, etc., which appear experimentally as several triplet absorption bands usually located at the short-wavelength and long wavelength limits of the singlet absorption. A change in the pH of the medium leads to a displacement of the triplet absorption bands as a result of the shift of the acid–base equilibrium of the triplet molecule.

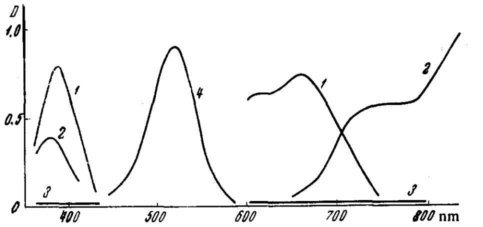

Figure 4. Triplet–triplet absorption spectra of phenosafranine in aqueous solution; *1*) pH 3–5; *2*) pH 5–7; *3*) pH 12; *4*) singlet–singlet absorption spectrum of phenosafranine at pH 7.[94]

The triplet absorption spectra of pigments of the type of chlorophyll and also porphyrins and phthalocyanines have been investigated in greater detail than those of dyes. This is due to the important role of chlorophyll as a sensitiser in the primary photosynthetic process. The triplet absorption spectra of chlorophylls a and b have been measured in a number of studies[67,101–110] on solutions of the pigment in various solvents (benzene, toluene, pyridine, ether, and others) with different flash energies (ranging from hundreds to several thousand joules) and in different excitation wavelengths ranges (blue and red). The principal findings in these investigations are that the triplet absorption spectrum of the pigments is independent of the exciting wavelength (blue or red), that the extinction coefficient is high ($\epsilon_T \simeq 10^4$ litre mole^{-1} cm^{-1}; π,π^* triplet absorption), and the triplet level of chlorophyll is readily populated (a high quantum yield Φ_T). The triplet absorption spectrum of chlorophyll is presented in Fig. 5; this shows that the most intense triplet absorption band of chlorophyll is located in the blue-green region; then in the region of the first transition $S_0 \rightarrow S_1^*$ (645 nm) the extinction coefficient $\epsilon_T^{645} \ll \epsilon_S^{645}$. This latter finding may be used to determine the "yield of triplet molecules per flash" and to find the values of ϵ_T. A triplet absorption with a maximum in the blue-green part of the spectrum is characteristic also of metal-free analogues of chlorophylls—phaeophytins a and b[67,102,104,108–110], chlorophyllin a[111], methyl chlorophyllide a[112], phaephorbide a + b[112], bacteriochlorophyll[107], and also certain porphyrins[102,104,107,113,114], and magnesium-phthalocyanine[104,113,115,116].

Table 3. The values of λ_{max} and ϵ_T for the triplet–triplet absorption of dyes.

Dye	Medium	λ_{max}, nm	ϵ_T, litre mole^{-1} cm^{-1}	Refs.
Fluorescein	H_2O, pH 12	520; >950	$8 \cdot 10^3$ (520 nm)	25
	H_2SO_4, 0.1 M	470	$9 \cdot 10^3$ (470 nm)	88
	H_2SO_4 .9 M	650	$7 \cdot 10^3$ (650 nm)	88
Eosin	H_2O, pH 7.2	410	—	91
	H_2O, pH 5.4	459; 540	$4.4 \cdot 10^4$ (459) nm	89
Erythrosine	H_2O, pH 9	—	$(2.6 \pm 0.7)10^4$ (526 nm)	26
Acridine Orange	acetic acid	≈650	—	92
Safranine T	H_2O, pH 9	380; 750; >850	—	93
	H_2O, pH 5	390; 650; 720	—	93
Thionine	H_2O, pH 8	690; 760	$9 \cdot 10^3$ (760 nm)	96
	H_2O, pH 1	375; 655	1.510^4 (655 nm)	96
Methylene Blue	H_2O, pH 7	420; 780; 800; 870	—	97
	H_2SO_4, 0.1 *N*	280; 375	—	97
Methylene Green	H_2O, pH 9	410; 760; 790 >840	$1.5 \cdot 10^4$ (840 nm)	99
Novomethylene Blue	H_2O, pH 9	420; 780; >840	$4 \cdot 10^3$ (840 nm)	100

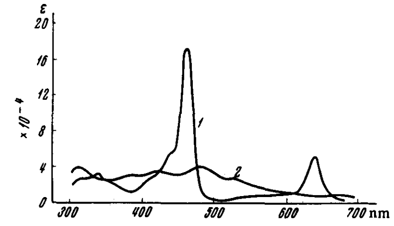

Figure 5. Triplet–triplet (curve *2*) and singlet–singlet (curve *1*) absorption spectra of chlorophyll b in benzene[106].

Study of the triplet–triplet absorption spectra of tetrapyrrole pigments made it possible to determine the effect of the structure of the molecule on triplet–triplet transitions. Even very considerable changes in the structure of pigments[46] have little effect on the nature of the triplet spectrum. The triplet absorption spectra of pigments are diffuse, differing significantly from the characteristic singlet–singlet absorption spectra. Moreover the triplet absorption spectra of chlorophylls are very similar to those of short-lived radicals—intermediate products of the photochemical oxidation-reduction reactions of chlorophylls[108,117] which makes it difficult to interpret the experimental results unambiguously using only spectroscopic data. In the latter case data for the kinetics of the deactivation of triplet states are valuable.

In many studies[108,118] the effect of "impurity" amounts of water on the spectroscopic properties of the triplet

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§ Phthalocyanine dyes will be examined below together with pigments.

state of chlorophyll was investigated, and it was shown that the introduction of traces of moisture to a carefully dried solution of chlorophyll in toluene leads to an increase of the "yield of triplets per flash". The results did not confirm the hypothesis[119] that polar compounds affect the relative probabilities of fluorescence and the transition of chlorophyll to the triplet state. The familiar effect of the "activation" of the fluorescence of carefully dried solutions of chlorophyll in hydrocarbons (for example 3-methylpentane) in the presence of polar compounds[120,121] could not be explained by a decrease of the quantum yield Φ_T. The "activation" of the fluorescence of chlorophyll has been explained by the inversion of the positions of the n,π^* and π,π^* excited singlet levels[122,123]. To account for the results quoted by the present author[108] and Livingston[118], one must suppose firstly that the non-radiative degradation of energy in the n,π^* state is several times faster than the transition to the triplet state and secondly that the lifetime of the molecules in the π,π^* triplet state is much longer than in the n,π^* state. The latter assumption is probably unsound[40]. A more soundly based explanation of the observed effect has been put forward by Evstigneev et al.[124] and by Amster and Porter[125], who state that the absence of the fluorescence of chlorophyll in dried solutions is caused by the dimerisation of the pigment molecules. The introduction of moisture into the chlorophyll solution leads to the formation of monosolvates of the pigment as a result of the deaggregating effect of the water molecules and hence an increased concentration of "normal" (fluorescent) chlorophyll molecules.

In a number of studies measurements have been made of the triplet absorption spectra of retinene (the *trans*-form), which is one of the components of the visual pigments. A triplet–triplet absorption of retinene has been recorded in methanol[126,127], methylcyclohexane[128], toluene[129], and hexane[129] with a maximum at 440–450 nm. A triplet absorption was not observed for a solution of retinene in water containing 1% of digitonin or in 1 : 1 methanol–water mixtures. The quantum yield of the transition of retinene to the triplet state in methylcyclohexane decreased on addition of methanol to the solution, which is due to the formation of a complex between triplet retinene and methanol[128]. The triplet state of retinene is populated as a result of a transition from the n,π^* excited singlet level. The presence of water in the retinene solution leads to a change in the relative positions of the n,π^* and π,π^* excited singlet levels, accompanied by a decrease of the probability of the transition to the triplet state.

In connection with the postulated importance of the triplet state of chlorophyll in primary photosynthetic processes[130–132], repeated attempts have been made to detect the triplet–triplet absorption of chlorophyll *in vivo*[133,134]. Flash photolysis of photosynthetically active chloroplasts leads to eight types of spectral changes caused by electron and ion migration[135]. However, the triplet–triplet absorption spectrum of chlorophyll in photosynthesising organisms has not so far been observed. The likely explanation may be an effective transfer of energy from excited chlorophyll molecules to photochemically active centres[136]. The short-lived (about 10^{-5} s) absorption at 520 nm, observed on flash illumination of the cells of the alga *Chlorella*, was interpreted as due to the triplet state of carotenoids[137,138] as a result of energy transfer through triplet states with participation of chlorophyll. The triplet absorption spectrum of chlorophyll was observed only for chloroplasts[134] disrupted by surface-active substances (digitonin) and also for artificially isolated chlorophyll–protein complexes[139] and monomolecular layers of chlorophyll deposited on a glass support in the presence of aliphatic acid salts[140].

5. KINETICS OF THE DEACTIVATION OF TRIPLET STATES

The study of the mechanism and kinetics of the deactivation of triplet states is based on the direct measurement of the rate of decay of the triplet–triplet absorption bands. Numerous kinetic measurements of the decrease of the intensity of the triplet absorption of aromatic hydrocarbons, dyes, and pigments in a liquid solution have shown that the rate of deactivation of triplet molecules obeys the general equation

$$-\frac{dT}{dt} = k_1T + k_2T^2 + k_3TS \;, \qquad [1]$$

where

$$k_1 = k_0 + \sum_i k_{Q_i}Q_i \qquad [2]$$

in accordance with the following deactivation processes:

$$T \to S \;, \qquad (0) \quad (k_0)$$

$$T + T \to S^* + S \;, \qquad (2) \quad (k_2)$$

$$T + S \to S + S \;, \qquad (3) \quad (k_3)$$

$$T + Q_i \to S + Q_i \;, \qquad (i) \quad (k_{Q_i})$$

where k_0 is the rate constant for the unimolecular deactivation, k_2 the rate constant for triplet–triplet annihilation, k_3 the rate constant for the self-quenching process, and k_{Q_i} the rate constant for the quenching of the triplet state by extraneous (impurity) molecular quenching agents Q_i.

The unimolecular reaction [reaction (0)] includes the following deactivation processes: phosphorescence (k_{phosph}), non-radiative degradation ($k_{\text{n.r}}$), and delayed fluorescence ($k_{\text{r.fl}}$)[¶]. The first two processes are shown schematically in Fig. 2 by straight and wavy arrows between T_1 and S_0 and the third is represented by a wavy arrow directed from T_1 to S_1^* and is due to the thermal excitation of the triplet molecule with its transition to the S_1^* level. Thus the expression for k_0 is written in the form $k_0 = k_{\text{phosph}} + k_{\text{n.r}} + k_{\text{r.fl}}$. In liquid solutions at room temperature the majority of complex molecules do not phosphoresce. The effect of heavy atoms on the spin–orbit coupling has been used[62] to elucidate the relation between the radiative and non-radiative degradation of the energy of the triplet state. On the basis of the dependence of k_0 and k_{phosph} on the nature of the heavy atom in the anthracene and its derivatives (anthracene, 9,10-dichloroanthracene, and 9,10-dibromoanthracene), it was concluded that the non-radiative degradation process makes a considerable contribution to the kinetics of the unimolecular deactivation of the triplet state.

The quenching of the triplet state by impurity molecules competes with unimolecular non-radiative degradation (according to Eqn. [2]) and is responsible for the discrepancies in the experimental values of k_1 (see Table 4). The minimum value of k_1 listed in Table 4 is closest to k_0. The constant k_0 may be determined in several ways. One of these is based on the Arrhenius relation between k_1 and temperature:

$$k_1 + k_0 + A\,\exp(-\Delta E/RT)[Q].$$

[¶] This type of fluorescence is also called delayed fluorescence of the first kind[41].

As the temperature or the viscosity of the medium changes, k_1 is altered due to the largely variable contribution by k_{Q_i}. The rate of deactivation of the triplet state is measured at different temperatures[145,146,149–151] and k_0 is found from the temperature variation of k_1.[150] Another procedure is based on measurements in a solid matrix where there are virtually no diffusion-dependent quenching processes. Thus the values of k_0 for anthracene in a polystyrene film[86] and in a poly(methylmethacrylate) matrix[152] are respectively 38 s^{-1} and 54 s^{-1}.

Table 4. The rate constants k_1 for the deactivation of the triplet state of anthracene.

Solvent	k_1, s^{-1}	Refs.	Solvent	k_1, s^{-1}	Refs.
Acetone	14 000 ± 3000	59	Hexane	350	63
Hexane	13 000	142	Glycerol	180 ± 20	59
Hexane	11 900 ± 1500	141	Hexane	160	146
Cyclohexane	8000	62	Hexane	130	145
Bromobenzene	1600	143	Tetrahydrofuran	110	146
Ethylene glycol	1300 ± 200	59	Isopentane	69	147
Cyclohexane	500	144	Glycerol	58	61
Cyclohexane	440	62	Hexane	56 ± 76	148

Since oxygen is an extremely effective quenching agent for triplet states, the rate constants for the deactivation process must be measured in a carefully degassed solution. It has been shown[148] that k_1 for anthracene in tetrahydrofuran can be reduced to 40 s^{-1} on eliminating the oxygen remaining after degassing by allowing it to react with NaK. Small (trace) amounts of vacuum grease, which inevitably contaminate the solution during the degassing process, can also behave as quenching impurities. It has been shown[153] that the use of a vacuum grease at $p \geqslant 10^{-10}$ mmHg leads to the contamination of the solvent during degassing even under conditions excluding direct contact between the grease and the solvent. Traces of oxygen can be effectively removed from aqueous solution by "washing" the latter with an inert gas (argon)[25]. However, this method is ineffective for organic solvents[106].

In a number of studies[62,74,86] it has been shown that k_1 decreases with the number of flashes (from 8000 s^{-1} for anthracene in cyclohexane after the first flash to 440 s^{-1} after the fiftieth flash[62]) owing to irreversible reactions of the triplet molecules with the residual O_2. The procedure involving repeated preliminary flash illumination of the substance ("flash purification"[74]) can also be recommended for the determination of k_0 (provided that the substance is stable under repeated flash photolysis).

The constant k_0 is almost independent of the viscosity of the medium and temperature. Thus for anthracene the k_0 measured in hexane ($\eta = 0.320$ cP) and glycerol ($\eta =$ 1499 cP at 20°C) are 45 ± 25 s^{-1} and 30 ± 3 s^{-1} respectively[145]. A decrease of temperature leads to a slight decrease of k_0. The activation energy for the non-radiative degradation of triplet anthracene in a poly(methyl methacrylate) matrix is 60 cal $mole^{-1}$.[152] The constant k_0 depends significantly on molecular structure. For example, the experimental constants $k_0 + \sum_i k_{Q_i} Q_i$ for fluorescein are 220 s^{-1} (cation, 9 M H_2SO_4), 600 s^{-1} (neutral molecule, 0.1 N H_2SO_4), 600 s^{-1} (univalent anion, pH 5.5), and 50 s^{-1} (divalent anion, 0.01 M NaOH)[25,154]. The significant differences between the rate constants obtained for the neutral molecule and the divalent anion of fluorescein are not a result of the quenching effects of impurities[154].

The quenching of the triplet states by microimpurities and also triplet–triplet annihilation and self-quenching are bimolecular deactivation processes of triplet states. Triplet–triplet annihilation is due to the interaction of two triplet molecules with transition of one of them to an excited singlet state with subsequent fluorescence†. The value of k_2 is close to the diffusion constant and amounts to 10^9–10^{10} litre $mole^{-1}$ s^{-1} for non-viscous media. The activation energy for triplet–triplet annihilation, determined from the temperature variation of the rate of deactivation of the triplet state, agrees with ΔE_η.[149,150] The rate-limiting stage of the triplet–triplet annihilation is the diffusion of triplet molecules in the medium, and therefore the lifetime of triplet molecules in the gas phase is lower than in solution (when there is no quenching by impurities)[155]. For the triplet state of anthracene in the gas phase at 140°C, $k_2 = (1.4 \pm 0.4) \times 10^{11}$ litre $mole^{-1}$ s^{-1}. The constant k_2 is close to 3.8×10^{11} litre $mole^{-1}$ s^{-1} calculated on the basis of collision theory, whence it follows that triplet–triplet annihilation is extremely effective and occurs at every collision between triplet molecules[155]. The experimental observation of delayed fluorescence as a result of triplet–triplet annihilation has been reported by Parker[156] and Kikuchi et al.,[157] who employed flash photolysis.

The self-quenching process, i.e. the deactivation of triplet molecules as a result of their interaction with non-excited molecules of the same substance, has been observed only for dyes[25,158] and pigments of the type of chlorophyll[105,109]. For triplet molecules of aromatic hydrocarbons, we have $k_3 \ll k_1 + k_2T$, and for dyes and pigments, $k_3 \simeq 10^7$–10^8 litre $mole^{-1}$ s^{-1}. It follows from Eqn. [1] that the dominant processes in the kinetics of the deactivation of triplet states immediately after the flash are non-radiative degradation and triplet–triplet annihilation (under the conditions of 100% excitation to the triplet state). The self-quenching process is observed from the instant of the regeneration of non-excited molecules and makes an appreciable contribution to the deactivation kinetics only at high initial concentrations (10^{-4} M) of the substance.

6. MECHANISMS OF THE QUENCHING OF TRIPLET STATES

Depending on the form of the decay of the concentration of triplet molecules of a given substance, static and dynamic quenching of triplet states can be distinguished. Another classification is into "physical" and "chemical" quenching of triplet states depending on the products and on the nature of the quencher. In the static quenching of triplet states a decrease of the concentration of triplet molecules ("yield per flash") is not accompanied by a change in their lifetime. Static quenching is characterised by an equilibrium between molecules unperturbed by the quenching agent and those altered under its influence (a complex with a quenching agent in the ground or excited state, aggregate, etc.) and associated with a lower quantum yield for populating the triplet state. Thus when water is added to an alcoholic solution of chlorophyll, the observed fall of the yield of the triplet molecules of the pigment is caused by a decrease in the concentration of chlorophyll monosolvates as a result of the shift of the monomer–dimer equilibrium towards dimers.

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† This type of delayed fluorescence is also called fluorescence of the second kind[41].

Dynamic quenching of the triplet state occurs in the collisions between triplet molecules and those of the quenching agent and is accompanied by a decrease of the lifetime of the triplets. Such quenching can yield the original molecules in the ground or excited state (physical quenching) or intermediate products, for example free radicals, ions, etc. (chemical quenching). Physical quenching processes include triplet–triplet and triplet–singlet energy transfer, paramagnetic quenching, quenching by heavy atoms, etc; among chemical quenching processes, one may include quenching by oxygen‡, by electron donors and acceptors, by transition metal ions, etc.

Table 5. Variation of the rate constants $k_{D,A}$ for the triplet–triplet energy transfer over a distance ΔE between a donor and an acceptor[162].

Donor	Acceptor	Solvent	$k_{D, A}$, litre $mole^{-1}$ s^{-1}	ΔE, cm^{-1}
Diacetyl	1,2-benzanthracene	benzene	$3.0 \cdot 10^9$	3200
Benzophenone	naphthalene	benzene	$2 \cdot 10^9$	3100
Triphenylene	naphthalene	hexane	$1.3 \cdot 10^9$	2200
Phenanthrene	1-iodonaphthalene	hexane	$7.0 \cdot 10^9$	1100
Phenanthrene	1-bromonaphthalene	hexane	$1.5 \cdot 10^8$	900
Phenanthrene	naphthalene	hexane	$2.9 \cdot 10^6$	300
Naphthalene	phenanthrene	hexane	$2 \cdot 10^4$	—300

Triplet–triplet transfer was first observed in sensitised phosphorescence at low temperatures[159,160]. In liquid solutions the quenching of the phosphorescence by energy transfer was observed for diacetyl[161]. Triplet–triplet transfer between an energy donor (D) and acceptor (A) (which do not phosphoresce in liquid solutions) is accompanied by the quenching of the triplet state of D and the appearance of the triplet absorption spectrum of A. Measurements with different triplet energy donors and acceptors, including aromatic hydrocarbons[162–165], carbonyl compounds[73,84,166], and pigments[167–170] established in the first place that the effectiveness of the energy transfer (the rate constant $k_{D,A}$ for the quenching of the triplet donor) depends on the distance ΔT between the triplet levels of the energy donor and acceptor and in the second place that a diffusion mechanism obtains in the triplet–triplet transfer in liquid solutions. Table 5 lists the values of ΔT and $k_{D,A}$ for various triplet energy donor–acceptor pairs. It follows from the data in Table 5 that the rate constant for the transfer is close to the diffusion constant (10^9–10^{10} litre $mole^{-1}$ s^{-1}) when $\Delta T \geqslant 1000$ cm^{-1}. The decrease of $k_{D,A}$ for smaller ΔT is probably due to the reverse energy transfer (from the acceptor triplet to the donor triplet)[171,172]. Using triplet–triplet transfer, the positions of the triplet levels in a number of non-phosphorescing compounds have been determined by flash photolysis. The positions of the triplet levels of *trans*-stilbene (17 500 cm^{-1}), *cis*-stilbene (20 200 cm^{-1})[164], phaeophytin a (> 11 300 cm^{-1})[169], thionine (13 640 cm^{-1})[173], and others have been estimated on the basis of the correlation between $k_{D,A}$ and ΔT for various acceptor (the position of the triplet level unknown)–donor (the position of the triplet level known) pairs. Triplet energy transfer combined with flash photolysis is used also to elucidate the role of excited singlet and triplet states in photochemical reactions. By comparing the yields of products of a reaction initiated in one case by direct and in another by sensitised (transfer via triplet states) excitation, the important role of the triplet state of anthracene in the reaction with carbon tetrachloride in bromobenzene was demonstrated[163]. Using triplet–triplet transfer, evidence was obtained proving the participation of triplet and ground singlet tetramethylbenzoquinone molecules in the formation of semiquinone radicals in alcohol[174,175]. The participation of the triplet states was also demonstrated in the photochemical reduction of 2-acetophenone by tributyltin[84], the photochemical reduction of benzophenone by isopropyl alcohol[73,166], the photochemical oxidation of chlorophyll a by *p*-benzoquinone[169,170], etc.

The heavy atom effect (the "external" and "internal" effects of the heavy atom) on spin–orbital coupling in molecules increases the probability of forbidden intercombination transitions and consequently leads to a shortening of the lifetime of triplet molecules. The internal effect of the heavy atom has been demonstrated[62] in the kinetics of the deactivation of the triplet states of anthracene and its dichloro- and dibromo-derivatives. On passing from anthracene to 9,10-dichloroanthracene and 9,10-dibromoanthracene, the deactivation rate constant k_0 increases from 110 s^{-1} to 23 000 s^{-1}. The external effect of the heavy atom is shown in the quenching of the triplet state of safranine T by potassium iodide (quenching constant 1.0×10^8 litre $mole^{-1}$ s^{-1})[93] and also of the triplet state of anthracene and its phenyl and methyl derivatives by bromobenzene[47]. The inhibiting effect of potassium iodide in the photochemical reduction of riboflavine has also been explained by the quenching of the triplet state of riboflavine by potassium iodide[176].

In a number of studies[105,142,177] it was observed that transition metal ions with paramagnetic properties are capable of quenching triplet states§. However, since Porter and Wright[142] did not find a correlation between the quenching rate constant and the magnetic susceptibility of transition metal ions, the shortening of the lifetime of triplet molecules in the presence of ions cannot be accounted for solely by "paramagnetic" quenching. On the basis of the effect of water on the rate constant for the quenching of the triplet states of anthracene and porphyrins (tetraphenylporphin and its zinc derivative) by Ni^{2+}, Co^{2+}, and Cu^{2+} ions[177] and also the effect of the ligand in the Ni^{2+}, Co^{2+}, and Cu^{2+} complexes of ethylenediamine, ethylenediaminetetra-acetate, pyridine, *o*-phenanthroline, and others[182,183], it was suggested that the quenching is due to the formation of a charge-transfer complex (CTC) between the excited molecule and the quenching agent. The excited complex $(S.MX_n)^*$ may be deactivated via the following pathway:

$$\begin{tikzcd}[column sep=small] T + MX_n \arrow[r] & (S \cdot MX_n)^* \arrow[r] \arrow[d] & S + MX_n^*, \\ & (S \cdot MX_n) \arrow[r] & S + MX_n. \end{tikzcd} \tag{4}(k_4)$$

Measurements of the rate of quenching of the triplet state by oxygen showed that the quenching rate constant is close to the diffusion constant. Probably diffusion is the rate-limiting step for the quenching of the triplet states by oxygen only in moderately viscous media. In very viscous media, for example solid matrices at 77°K, the presence of O_2 at a concentration of 10^{-4} M does not affect the rate

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‡ Quenching by oxygen can also be classified as physical quenching owing to the paramagnetic properties of O_2.

§ Quenching by oxygen which is paramagnetic, has been demonstrated for aromic hydrocarbons[59,63,142,143], dyes[25,89,96,178–180], and pigments[181].

of deactivation of triplet states[152]. The current view on the mechanism of the deactivating effect of oxygen involves paramagnetic quenching[142] and energy transfer from the triplet molecule to O_2 [1] and also the formation of a moloxide—the labile product of the addition of O_2 to the excited molecule[41]. At the same time it has been shown[25,178] that the quenching of the triplet state of fluorescein by oxygen leads to one-electron oxidation of the dye:

$$T + O_2 \rightarrow \dot{R}^+ + O_2^{\dot{-}}, \qquad (5)(k_5)$$

which takes place simultaneously with physical quenching:

$$T + O_2 \rightarrow S + O_2 . \qquad (6)(k_6)$$

The rate constants k_5 and k_6 are respectively[25,178] $k_5 = 1 \times 10^7$ litre mole^{-1} s^{-1} (pH 2.0), $k_5 = 1.4 \times 10^8$ litre mole^{-1} s^{-1} (pH 12.0), $k_6 = 1.2 \times 10^9$ litre mole^{-1} s^{-1} (pH 2.0), and $k_6 = 1.7 \times 10^9$ litre mole^{-1} s^{-1} (pH 12.0). Physical quenching is independent of the acidity of the medium, while chemical quenching is negligible in an acid medium (triplet cation of fluorescein) and increases with the pH (neutral triplet molecules and triplet anions).

As shown above in the discussion of the kinetics of the deactivation of triplet states, the rate of depletion of the triplet level depends on the rate of bimolecular triplet–triplet annihilation and self-quenching processes. Formally, these processes can also be regarded as quenching of the triplet state as a result of the collision of the triplet molecule with another such molecule or a ground state molecule (k_2 or k_3). In many cases the quenching of a triplet molecule by another triplet molecule or a ground state molecule leads to the formation of radicals produced by electron transfer and therefore quenching may be classified as being of the chemical type:

$$T + T \rightarrow R^{\dot{-}} + \dot{R}^+, \qquad (7)(k_7)$$

$$T + S \rightarrow R^{\dot{-}} + \dot{R}^+. \qquad (8)(k_8)$$

Table 6. The rate constants for the quenching of the triplet state by electron donors and acceptors.

Object	Medium	Quenching agent.	$k_9 + k_{11}$ litre mole^{-1} s^{-1}	k_9, litre mole^{-1} s^{-1}	$k_{10} + k_{12}$, litre mole^{-1} s^{-1}	k_{10}, litre mole^{-1} s^{-1}
Fluorescein	H_2O[185]	ethylenediamine tetra-acetate	$1.5 \cdot 10^5$	—	—	—
Fluorescein	H_2O[185]	Fe^{III} ethylenediamine tetra-acetate	—	—	$8 \cdot 10^8$	$1 \cdot 10^8$
Fluorescein	H_2O[25]	*p*-phenylenediamine	—	$5 \cdot 10^9$	—	—
Eosin	H_2O[158]	$K_3Fe(CN)_6$	—	—	$2.5 \cdot 10^8$	$1.5 \cdot 10^8$
Eosin	H_2O[89]	phenol	$1.5 \cdot 10^5$	—	—	—
Chlorophyll a	pyridine[187]	ascorbic acid	$\approx 10^4$	—	—	—
Chlorophyll a	ethanol[188]	methylviologen	—	—	$2.0 \cdot 10^9$	—
Phaeophytin a	ethanol[189]	phenylhydrazine	$3.0 \cdot 10^7$	—	—	—
Phaeophytin a	ethanol[189]	Methyl Red	—	—	$1.7 \cdot 10^8$	—

Reactions (7) and (8) were observed in aqueous solutions of xanthene[25,88,158,185], thiazine[91,98,186], and phenazine[93] dyes. The constants k_7 and k_8 were determined from the rate of accumulation of the radicals $R^{\cdot}$ and R^+. For fluorescein (pH 12), in particular, $k_7 = 6 \times 10^8$ litre mole^{-1} s^{-1} and $k_8 = 5 \times 10^7$ litre mole^{-1} s^{-1}.[25] The results show that electron transfer is most probable between two triplet molecules.

The quenching of triplet state by electron donors or acceptors is a consequence of a photochemical oxidation–reduction reaction with participation of triplet molecules. However, the quenching of the triplet state of the reducing agent (DH_2) or the oxidising agent (A) does not always lead to the formation of radical-ions:

$$T + \mathrm{DH}_2 \rightarrow R^{\dot{-}} + \dot{\mathrm{D}}\mathrm{H}_3^+, \qquad (9)(k_9)$$

$$T + \mathrm{A} \rightarrow \dot{R}^+ + \mathrm{A}^{\dot{-}}. \qquad (10)(k_{10})$$

Chemical quenching of triplet molecules [reactions (9) and (10)] is accompanied by physical quenching, revealed experimentally by an inconsistency between the rate of quenching of the triplet state and the rate of accumulation of $R^{\cdot}$ and R^+:

$$T + \mathrm{DH}_2 \rightarrow S + \mathrm{DH}_2 , \qquad (11)(k_{11})$$

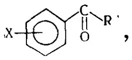
$$T + \mathrm{A} \rightarrow S + \mathrm{A} . \qquad (12)(k_{12})$$

Table 6 lists the rate constants for the quenching of the triplet molecules of dyes and pigments by various electron donors and acceptors. The mechanism of the quenching of triplet states by donors and acceptors is likely to include the formation of charge-transfer complexes as an intermediate stage in electron transfer. For instance, the probability of the conversion of charge-transfer complexes into radical-ions in the quenching of the triplet state of eosin by potassium hexacyanoferrate(III) is 0.6. [158]

7. PROPERTIES OF TRIPLET STATES AND THEIR ROLE IN PHOTOCHEMICAL REACTIONS

In contrast to the excited singlet state, a molecule in the triplet state is paramagnetic, which suggests that the triplet and phosphorescent states are identical[3,4]; this is supported by data on the kinetics of phosphorescence and photomagnetism[190]. Together with the optical properties of triplet molecules, the paramagnetic properties of triplet states are responsible for the ability of triplet molecules to absorb microwave radiation (ESR spectrum)[191].

Apart from the spectroscopic and kinetic properties and the characteristics of triplet states discussed above, triplet molecules exhibit a definite affinity for protons (the acid–base properties of triplets). The proton affinity of a molecule in an excited state may differ significantly from the affinity in the ground state. In a number of studies[192,193] this effect was investigated for aromatic acids and bases in terms of the changes in the absorption and fluorescence spectra with the acidity of the solvent. It was shown that aromatic acids dissociate in the excited singlet state over a period less than 10^{-9} s. The change in pK is then about 6. The measurements designed to determine pK_T for molecules in the triplet state by flash photolysis reveal a significant difference between pK_S (for the excited singlet state) and pK_T[85,194] together with a similarity between pK_g (for the ground singlet state) and pK_T. Similar values of pK_g and pK_T were obtained for a number of alcohols, acids, and amines[85,194]. However, for dyes of the thiazine (Methylene Blue, Methylene Green, Novomethylene Blue, Azur) and azine (safranine and phenosafranine) classes, pK_g differs from pK_T by more than 6 units[93,94,98,100,186]. Consequently the proton affinity of thiazine and azine dyes in the triplet state differs significantly from the affinity in the ground and excited singlet states.

The properties and reactivity of molecules in the triplet state depend in many respects on the distribution of electron density on excitation. For aromatic carbonyl compounds of the type  $X-C_6H_4-C(=O)-R$, the lower excited triplet state (T_1) may be n,π^*, or π,π^*, or the charge-transfer state (CTS)[87]. A characteristic feature of the n,π^* triplet state of carbonyl compounds is a high quantum yield γ of the reaction involving the abstraction of a hydrogen atom from alcohols, hydrocarbons, and related compounds ($\gamma = 1$), which ultimately yields pinacols and also the occurrence of addition to the double bond of olefins and other unsaturated compounds[195], Moreover, the n,π^* triplet level is characterised by a short-lived phosphorescence in the solid matrix at 77°K (10^{-3} s)[196], a small singlet–triplet splitting (< 3000 cm^{-1}), and a deficiency in electron density at the oxygen atom of the carbonyl group ($>C=\overset{+\delta}{O}$) [87]. The appreciably lower reactivity of the π,π^* triplet state is shown by a low quantum yield of the pinacol formation reaction ($\gamma = 0.1$). The π,π^* triplet level is then characterised by a greater singlet–triplet splitting (10 000 cm^{-1}) and also by the absence of an electron deficiency at the carbonyl group ($>C=O$) [87]. Thus the reactivity of molecules in the triplet state, and in particular of carbonyl compounds, depends on the distribution of electron density in the lower triplet state.

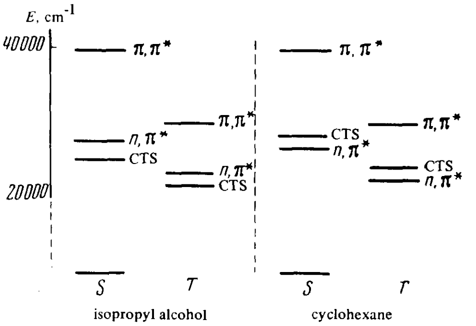
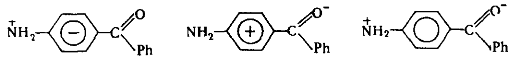


Figure 6. Schematic energy level diagram for p-aminobenzophenone in isopropyl alcohol and in cyclohexane[195].

The electron density distribution depends in turn on the nature of the substituents (X, R) and the effect of the solvent. For substituted benzophenones (R = C_6H_5 and X = a halogeno-, phenyl-, amino-, hydroxy-, and methoxy-groups in the *meta*- and *para*-positions), the quantum yield γ depends on the nature and positions of the X substituents and also on the polarity of the solvent. For benzophenone and also its *para*-substituted halogen derivatives, $\gamma \simeq 1$ (isopropyl alcohol, cyclohexane), which shows that the T_1 state is of the n,π^* type. *m*- and *p*-phenylbenzophenones have a low quantum yield of the pinacol-formation reaction ($\gamma = 0.1$) owing to the inversion of the positions of n,π^* and π,π^* triplet levels, the lower triplet level being π,π^*. The introduction of electron-donating (amino- and hydroxy-groups) substituents in the *para*-position of benzophenone leads to a variation of γ with the solvent. For amino- and hydroxy-derivatives of benzophenone, a long-wavelength absorption due to a charge-transfer state together with $n\rightarrow\pi^*$ and $\pi\rightarrow\pi^*$ transitions was observed[195]. For p-aminobenzophenone, with the CTS configuration,



$\gamma = 0.00$ in isopropyl alcohol but in a non-polar solvent (cyclohexane) $\gamma = 0.02$. Similarly, for p-hydroxybenzophenone an increase of γ from 0.02 (isopropyl alcohol) to 0.9 (cyclohexane) was observed. The increase in γ on passing from a polar to a non-polar solvent is due to the reversal of the CTS and n,π^* triplet levels (Fig. 6).

Using direct or sensitised (triplet–triplet energy transfer) flash photolysis, the involvement of triplet molecules of organic and biologically important substances in many photochemical reactions has been demonstrated experimentally. Much information on the chemistry of triplet states has also been obtained by non-pulse excitation methods[197]. There is no doubt that the triplet state participates in various photochemical reactions but one must bear in mind that the real pathway of a photochemical reaction is not determined solely by the reactivity of the excited state. A significant factor which determines the primary photochemical step is the excitation conditions (pulse or stationary conditions and the density and duration of emission), the effect of the environment [the presence of extraneous molecules (additives) and the nature of the solvent], etc. In a consideration of the real pathway of a photochemical reaction involving excited singlet or triplet molecules, one must bear in mind the probability of transition to the triplet state, the lifetime in the triplet level, and also the concentration of the reacting (excited) molecules.

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The method of flash photolysis is undoubtedly one of the powerful modern procedures for the investigation of rapid reactions initiated by light. The applications of this method in the study of triplet states discussed above illustrate one of the possibilities of flash photolysis in the study of photochemical and photobiological processes. The present state of the experimental technique permits a considerable extension of the scope of the method in the investigation of the properties of the primary products formed under the action of radiation on matter (pulse radiolysis, lasers). This constitutes a stimulus for intensive research in the chemistry of excited states, short-lived products, and rapid processes.

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Vernadskii Institute of
Geochemistry and Analytical
Chemistry, USSR Academy
of Sciences, Moscow

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Cationic Boron Complexes

O.P.Shitov, S.L.Ioffe, V.A.Tartakovskii, and S.S.Novikov

The review deals with studies on an interesting class of boron compounds constituting a very rapidly developing field at the boundary between inorganic and "organoelemental" chemistry.
The bibliography includes 189 references.

CONTENTS

I. INTRODUCTION

The chemistry of cationic boron complexes[†] began with the work of Diltey, who obtained in 1906 the first boronium cations by the interaction of β-diketones with boron trichloride[1].

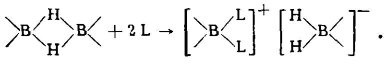
In the last decade, after the work of Parry and coworkers[2-9] who determined the structure of "diammoniate of diborane", this field in boron chemistry has developed extensively.

A number of fundamental monographs[10-21] dealing with various aspects of boron chemistry have now been published. In the first place mention must be made here of the books by Mikhailov[17], Zhigach[19], Steinberg[15], and Muetterties[18]. These monographs contain isolated data on the methods of synthesis and the properties of boronium salts but they do not provide complete information about these compounds. Moreover, in recent years many new results have accumulated, which have not been reviewed anywhere. This review gives a compilation of the literature on the cationic boron complexes up to the middle of 1969.

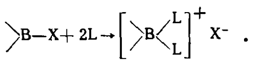
II. PREPARATION OF CATIONIC BORON COMPLEXES

The methods of preparation of numerous boron complexes with a wide variety of structures may be divided into four principal groups.

1. Asymmetric cleavage of boranes by Lewis bases:

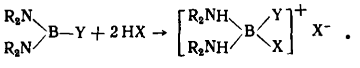


2. Conversion of substituted boranes under the action of amines:



[†] Boron complexes with boron as the central atom of the cation are called cationic boron complexes or boronium salts. In the present review both terms are used.

3. Addition of hydrogen halides to aminoboranes:



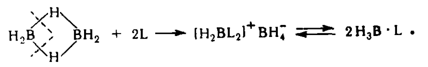
$$\begin{matrix}R_2N\\R_2N\end{matrix}\!>\!B-Y+2HX\rightarrow\left[\begin{matrix}R_2NH\\R_2NH\end{matrix}\!>\!B\!<\!\begin{matrix}Y\\X\end{matrix}\right]^+X^-\ .$$

4. Reaction of boranes with aminoboranes at elevated temperatures:

$$2L\cdot BH_3+B_2H_6\rightarrow[H_2BL_2]^+X^-\ .$$

1. ASYMMETRIC CLEAVAGE OF BORANES BY LEWIS BASES

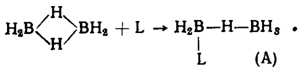
At the present time there exist two views on the mechanism of the formation of cationic boron complexes by the reaction of Lewis bases with diborane. According to Beachley[22], at a low temperature bases always cause an asymmetric cleavage of diborane and the cationic boron complexes can rearrange to the corresponding aminoboranes when the latter are thermodynamically more stable at a given temperature:



(1)

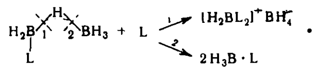
However, Shore and Parry[3] and also Inoue and Kodama[23] showed that in liquid amines and in ether there is no equilibrium between cationic boron complexes and the corresponding aminoboranes.

According to another view[5,24] the reaction of diborane with Lewis bases begins with the dissociation of one bridge bond and the formation of an intermediate product (A):



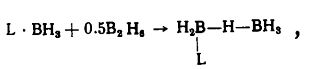
(2)

The nature of the final compound is determined by the mode of dissociation of the three-centre bond $H_2B-H-BH_3$ as a result of the attack by a second molecule of the base on product (A):



(3)

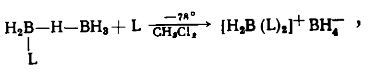
The mode of attack depends both on the structure of the reactants and on the reaction temperature. In many cases the reaction can proceed via both pathways simultaneously. This mechanism of the formation of boronium salts was confirmed by the preparation of compounds of type (A) in the tensimetric titration of aminoboranes by diborane at −78°C in methylene chloride[24,25]:



$$L\cdot BH_3+0.5B_2H_6\rightarrow \underset{\displaystyle L}{\underset{|}{H_2B}}-H-BH_3\ , \qquad (4)$$

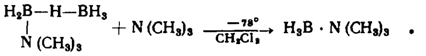
where L = NH_3, CH_3NH_2, or $N(CH_3)_3$. The presence of H_2B and BH_3 groups in these compounds was established by ^{11}B NMR spectroscopy‡.

The addition of a second mole of the amine leads to compounds indicated below:



$$\underset{\displaystyle L}{\underset{|}{H_2B}}-H-BH_3+L\xrightarrow[CH_2Cl_2]{-78°}[H_2B(L)_2]^+BH_4^-\ , \qquad (5)$$

where L = NH_3 or CH_3NH_2;



$$\underset{\displaystyle N(CH_3)_3}{\underset{|}{H_2B}}-H-BH_3+N(CH_3)_3\xrightarrow[CH_2Cl_2]{-78°}H_3B\cdot N(CH_3)_3\ . \qquad (6)$$

Thus the same products were obtained in reactions (5) and (6) as in the reaction between diborane and an excess of the corresponding amine at a low temperature.

It is interesting to note the effect of the degree of methylation of amines on the proportions of the final products in the reaction with diborane. Whereas in the reaction with ammonia[28-32] the boronium salt is mainly formed§, in the reaction with trimethylamine the product was exclusively a neutral complex[39]. Methylamine and dimethylamine[22,23,39] form mixtures of both possible compounds, with the boronium salt predominating in the first case and the neutral complex in the second:

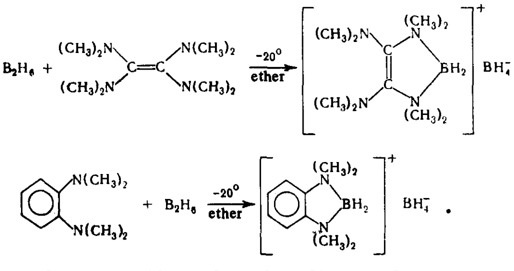
$$B_2H_6+2NH_3\rightarrow[H_2B(NH_3)_2]^+BH_4^-\ , \qquad (7)$$

$$B_2H_6+2(CH_3)_nNH_{3-n}\rightarrow\{H_2B[NH_{3-n}(CH_3)_n]_2\}^+BH_4^-+(CH_3)_nNH_{3-n}\cdot BH_3\ ,$$

$$(n=1-2)$$

$$B_2H_6+2N(CH_3)_3\rightarrow 2(CH_3)_3N\cdot BH_3\ .$$

Apparently the cleavage of the intermediate (A) is determined mainly by steric factors. This is confirmed by Wiberg's data[40] on the synthesis of boronium salts in the reaction of tertiary diamines with diborane:



(8)

The ease of preparation of such salts has been explained by the formation of a sterically favourable cyclic system[14].

Other Lewis bases can also react with diborane via mechanism (2)–(3) with formation of cationic boron complexes. In a tensimetric study of the reaction of diborane with dimethyl sulphoxide in methylene chloride at −78°C, McAchran and Shore[41] showed that in this case a boronium salt is formed:

$$B_2H_6+2(CH_3)_2SO\rightarrow\{H_2B[OS(CH_3)_2]_2\}^+BH_4^-\ . \qquad (9)$$

The formation of the hydrated ion BH_2^+ has been postulated in the reaction between diborane and 8 N hydrochloric acid at −70°C:[42,43]

$$B_2H_6+2H^++4H_2O\rightarrow 2[H_2B(H_2O)_2]^++2H_2\ . \qquad (10)$$

The cation may be formed as a result of the asymmetric cleavage of diborane by water¶:

$$B_2H_6+2H_2O\rightarrow[H_2B(H_2O)_2]^+BH_4^-\ . \qquad (11)$$

On the basis of the electrical conductivity of diborane solutions in tetrahydrofuran (THF) and diglyme, Brown and Wallace[44] and Mikhailov et al.[45] concluded that the corresponding cationic boron complexes exist in such

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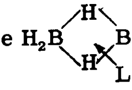
‡ Eastham[26] suggests that compounds (A) have the structure  i. e. the diborane molecule is linked to the ligand by a π-bond formed by a free orbital of diborane and the electron pair of the amine. However, this structure was rejected on the basis of tracer atom studies and the determination of the heats of reaction[27].

§ For the structure of "diammoniate of diborane" $[H_2B(NH_3)_2]^+BH_4^-$, see the appropriate literature[2-9,28,33-38].

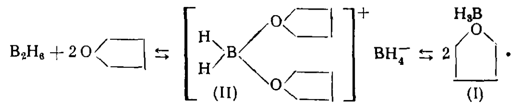
¶ However, one cannot exclude also other mechanisms of this reaction, for example:

$$B_2H_6+2H_2O\rightarrow 2H_3B\cdot H_2O\ ,$$

$$2H_3B\cdot H_2O+2HCl\rightarrow 2H_2BCl\cdot H_2O+2H_2\ ,$$

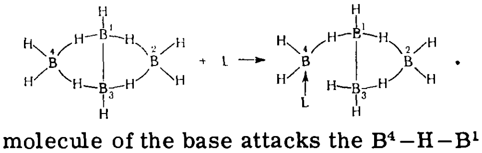
$$2H_2BCl\cdot H_2O+2H_2O\rightarrow 2[H_2B(H_2O)_2]^+Cl^-\ .$$

solutions. Mikhailov et al.[45] believe that in a tetrahydrofuran solution of diborane there is an equilibrium between the neutral complex (I) and the cationic boron complex (II):



(12)

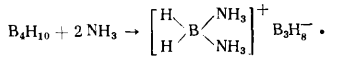
Apart from diborane, higher boranes can also undergo asymmetric cleavage by Lewis bases. The mechanism of the reaction of tetraborane with Lewis bases is similar to that of the cleavage of diborane and consists in the dissociation of one of the bridge bonds in the first stage of the reaction[46]:



(13)

A second molecule of the base attacks the B^4-H-B^1 bond, which is ruptured with the formation of the cation $(H_2BL_2)^+$ and the anion $B_3H_8^-$ (asymmetric cleavage) or the complexes $H_3B.L$ and $B_3H_7.L$ (symmetrical cleavage).

Stock et al.[47], who investigated the reaction of tetraborane with ammonia, concluded that its products are unstable compounds with the compositions $B_4H_{10}.4NH_3$ and $B_4H_{10}.2.5NH_3$. However, Kodama and Parry[48,49] showed that the product of the reaction of an ethereal solution of tetraborane with ammonia at −78°C is diammineboronium octahydrotriborate:


$$B_4H_{10} + 2NH_3 \rightarrow \left[\begin{matrix}H\\H\end{matrix}{>}B{<}\begin{matrix}NH_3\\NH_3\end{matrix}\right]^+ B_3H_8^- . \quad (14)$$

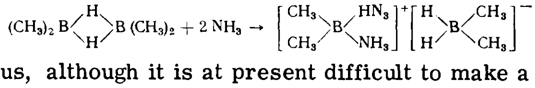
Schaeffer et al.[50] detected by ^{11}B NMR spectroscopy the anion $B_3H_8^-$ in solutions of tetraborane in tetrahydrofuran at −53°C, which is evidence of the formation of the boronium salt:

$$B_4H_{10} + 2C_4H_8O \rightarrow [H_2B(OC_4H_8)_2]^+ B_3H_8^- . \quad (15)$$

However, they did not detect the corresponding cation $[H_2B(OC_4H_8)_2]^+$.

These data are somewhat inconsistent with earlier studies, where it was found that the reactions of tetraborane with amines, ethers, or dialkyl sulphides lead exclusively to the formation of products of the symmetrical cleavage of tetraborane[51-53].

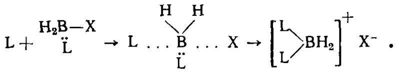
Moews and Parry[54] described the asymmetric cleavage of tetramethyldiborane by ammonia at −78°C†:


$$(CH_3)_2B{<}\begin{matrix}H\\H\end{matrix}{>}B(CH_3)_2 + 2NH_3 \rightarrow \left[\begin{matrix}CH_3\\CH_3\end{matrix}{>}B{<}\begin{matrix}HN_3\\NH_3\end{matrix}\right]^+ \left[\begin{matrix}H\\H\end{matrix}{>}B{<}\begin{matrix}CH_3\\CH_3\end{matrix}\right]^- . \quad (16)$$

Thus, although it is at present difficult to make a reliable *a priori* prediction of the structure of the final products of the reaction of boranes with Lewis bases, the published data makes it possible to follow fairly clearly the effect of the structure of the reactants on the process.

2. THE CONVERSION OF SUBSTITUTED BORANES UNDER THE ACTION OF AMINES

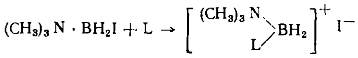
The reaction of substituted boranes with bases is the most widely used method for the synthesis of cationic boron complexes. In most cases the formation of such complexes by this method may be regarded as nucleophilic substitution by the base of an electronegative substituent X at the boron atom, probably via an S_N2 mechanism[56-58]:


$$L + \underset{L}{H_2B-X} \rightarrow L\ldots\overset{H\ H}{\underset{L}{B}}\ldots X \rightarrow \left[\begin{matrix}L\\L\end{matrix}{>}BH_2\right]^+ X^- . \quad (17)$$

In many cases in the presence of bulky substituents in the amine–borane molecule or when charged intermediate species may be stabilised, one cannot exclude also the possibility of a reaction by an S_N1 mechanism. This possibility was discussed by Ryschkewitsch and coworkers[59], who investigated the reaction of $(CH_3)_3N.BH_2I$ with methylpyridines and also by Nöth et al.[56] in the case of pyridine-chloroborane, for which there is a possibility of the formation of a cation stabilised by mesomerism. However, in a later study of Nainan and Ryschkewitsch[58] the ionisation of iodoboranes in non-polar solvents and the formation under these conditions of boronium salts by an S_N1 mechanism was fully excluded.

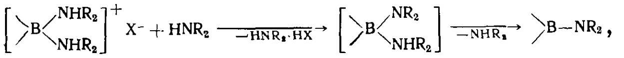
In the synthesis of boronium salts via mechanism (17) it is necessary to take into account a number of factors which influence the stability of boronium salts under the reaction conditions: (1) the dimensions and nature of the anion; (2) the steric and electronic effects of the substituents at the boron atom; (3) the structure of the bases.

An increase in the size of the anion leads to considerable stabilisation of the boronium salt. Thus, when trimethylamine-iodoborane was used instead of trimethylamine-chloroborane[56,58,60], it was possible to obtain boronium salts containing tertiary aliphatic amines in the cation:

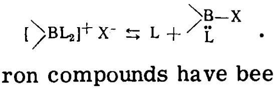

$$(CH_3)_3N \cdot BH_2I + L \rightarrow \left[\begin{matrix}(CH_3)_3N\\L\end{matrix}{>}BH_2\right]^+ I^- , \quad (18)$$

where L = $(CH_3)_3N$, $(C_2H_5)_3N$, or 4-methylpyridine.

The salts formed by the anions of weak acids (SR^-) are stable only in the presence in the cation of relatively small ligands[61]. An increase of the bulk of the substituents at the boron atom or the heteroatom of the base leads to a decrease of the stability of the boronium cation, the decomposition of which in the reaction may be represented by two mechanisms: (1) in the case of primary and secondary amines the final reaction products may be aminoboranes:


$$\left[{>}B{<}\begin{matrix}NHR_2\\NHR_2\end{matrix}\right]^+ X^- + HNR_2 \xrightarrow{-HNR_2\cdot HX} \left[{>}B{<}\begin{matrix}NR_2\\NHR_2\end{matrix}\right] \xrightarrow{-NHR_2} {>}B-NR_2 , \quad (19)$$

where R = H, alkyl, or aryl; (2) in the case of tertiary amines we believe that there is a possibility of the regeneration of the initial complex:


$$[{>}BL_2]^+ X^- \rightleftarrows L + \underset{L}{{>}B-X} . \quad (20)$$

A number of boron compounds have been used to synthesise cationic boron complexes by the substitution method: (a) complexes of halogenoboranes with Lewis bases; (b) amine-boranes; (c) mercaptoboranes and their amine complexes; (d) aryl-, alkyl-, amino-, and alkoxy-boron halides; (e) boron trihalides BX_3 (X = Cl, Br, I, or F).

a. Preparation of Boronium Salts from Complexes of Halogenoboranes with Lewis Bases

Nöth and coworkers[56,62-64] observed in a study of the reaction of ether and amine complexes of chloroboranes

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† This reaction was investigated for the first time by Schlesinger et al.[55], but they did not establish the composition and the structure of the reaction product.

with amines that the latter takes place with formation of boronium salts‡:

$$H_2BCl\cdot OR_2+2\,L\rightarrow\left[H_2B\begin{smallmatrix}\diagup L\\ \diagdown L\end{smallmatrix}\right]^+Cl^-+R_2O;\ H_2BCl\cdot L+L'\rightarrow\left[H_2B\begin{smallmatrix}\diagup L'\\ \diagdown L\end{smallmatrix}\right]^+Cl^-,\qquad(21)$$

where L and L′ = NH_nR_{3-n} (n = 1–2) or C_5H_5N.

Ryschkewitsch and coworkers[58–60,66] obtained boronium salts containing various tertiary amines in the cation:

$$L\cdot BH_2I+L'\rightarrow\left[H_2B\begin{smallmatrix}\diagup L\\ \diagdown L'\end{smallmatrix}\right]^+I^-\ ,\qquad(22)$$

where L = R_3N (R = CH_3 or C_2H_5) or pyridine and L′ = substituted pyridines, quinoline, or *NN*-dimethylaniline.

Douglass et al.[67] isolated boronium salts with alkyl substituents at the boron atom:

$$R'R''B\cdot I\cdot NC_5H_5+C_5H_5N\rightarrow[R'R''B\,(NC_5H_5)_2]^+I^-\ ,\qquad(23)$$

where R′ = 1,1,2-trimethylpropyl and R″ = H or R′ = R″ = cyclohexyl.

It has also been observed that the bis(pyridine)boronium cation is formed when pyridine-iodoborane is refluxed in an ether–benzene solution at 40°C.[68] The authors quote the following reaction mechanism:

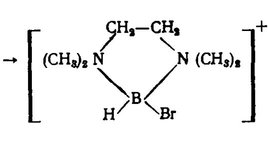
$$\begin{gathered}C_6H_5N\cdot BH_2I+(C_2H_5)_2\,O\rightarrow[C_5H_5NBH_2O\,(C_2H_5)_2]^+\,I^-,\\ [C_5H_5NBH_2O\,(C_2H_5)_2]^++I^-\rightarrow C_5H_5N\cdot BH_2OC_2H_5+C_2H_5I\ ,\\ C_5H_5N\cdot BH_2OC_2H_5\leftrightarrows C_5H_5N+H_2BOC_2H_5\ ,\\ C_5H_5N\cdot BH_2I+C_5H_5N\rightarrow[(C_5H_5N)_2\,BH_2]^+\,I^-\ .\end{gathered}\qquad(24)$$

The preparation of cationic boron complexes containing in the cation alkylthio-groups linked directly to the boron atom has been described[69]:

$$\begin{gathered}(CH_3)_3\,N\cdot BH_2SCH_3+BH_2I\cdot N\,(CH_3)_3\rightarrow\left[(CH_3)_3\,NBH_2\overset{CH_3}{\overset{|}{S}}BH_2N\,(CH_3)_3\right]^+I^-,\\ (CH_3)_3\,NBH_2SCH_3+(CH_3)_3\,N\cdot BH_2\overset{CH_3}{\overset{|}{S}}BH_2I\rightarrow\left\{\left[(CH_3)_3\,NBH_2\overset{CH_3}{\overset{|}{S}}\right]_2BH_2\right\}^+I^-,\end{gathered}\qquad(25)$$

and also the synthesis of boronium salts with polyfunctional bases[70,71], tertiary amines, phosphines, arsines, sulphides[72], and their oxides[73].

A monobrominated boronium cation was obtained by the reaction of trimethylamine-dibromoborane with *NNN′N′*-tetramethylethylenediamine[72]:



$$(CH_3)_3\,N\cdot BHBr_2+(CH_3)_2\,NCH_2CH_2N\,(CH_3)_2\rightarrow\left[(CH_3)_2\overset{CH_2-CH_2}{N\quad\ \ N}(CH_3)_2\ \text{(ring via }\underset{H\ \ Br}{B}\text{)}\right]^+Br^-.\qquad(26)$$

b. Preparation of Boronium Salts from Amine-boranes

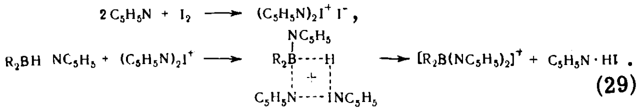
Douglass[74,75], who investigated the reaction of amine complexes of borane or its derivatives with iodine in an excess of the amine isolated cationic boron complexes:

$$RBH_2\cdot L+I_2+2\,L\rightarrow[RBHL_2]^+\,I^-+L+HI\cdot L\ ,\qquad(27)$$

where (a) R = phenyl or cyclohexyl and L = C_5H_5N and (b) R = H and L = $(CH_3)_3N$ or C_9H_7N. Initially a two-stage reaction mechanism was proposed: in the first stage an amine complex of iodoborane is formed and is then converted further into a boronium salt under the influence of the excess amine:

$$\begin{gathered}RBH_2\cdot L+I_2+L\rightarrow RBHI\cdot L+HX\cdot L\ ,\\ RBHI\cdot L+L\rightarrow[RBHL_2]^+\,I^-\ .\end{gathered}\qquad(28)$$

However, further study of the reaction[67] showed that amine-boranes containing bulky substituents at the boron atom do not react with iodine in the excess amine. Therefore Douglass suggested another mechanism with a four-membered transition complex:



$$\begin{gathered}2\,C_5H_5N+I_2\longrightarrow(C_5H_5N)_2I^+\,I^-,\\ R_2BH\ \ NC_5H_5+(C_5H_5N)_2I^+\longrightarrow\left[\begin{matrix}&NC_5H_5&\\ &R_2B\cdots H&\\ &C_5H_5N\cdots INC_5H_5&\end{matrix}\right]^+\longrightarrow[R_2B(NC_5H_5)_2]^++C_5H_5N\cdot HI\ .\end{gathered}\qquad(29)$$

This mechanism agrees better with the experimental data, since it is known that cyclic transition states are very sensitive to steric factors.

Ryschkewitsch[76] obtained dipyridineboronium salts by the reaction of sodium borohydride or trimethylamine-borane with iodine in the presence of an excess of pyridine. The author believes that the formation of the dipyridineboronium cation from sodium borohydride may be represented by the following sequence of reactions:

$$\begin{gathered}BH_4^-+I_2+2\,C_5H_5N\rightarrow C_5H_5N\cdot BH_3+C_5H_5NH^++2\,I^-,\\ BH_4^-+C_5H_5NH^+\rightarrow C_5H_5N\cdot BH_3+H_2\ ,\\ C_5H_5N\cdot BH_3+I_2+C_5H_5N\rightarrow(C_5H_5N)_2\,BH_2^++C_5H_5NH^++2\,I^-\ .\end{gathered}\qquad(30)$$

The author concludes from the measurements of the rates of reaction of deuterated and normal trimethylamine-borane with iodine that the rate-determining stage of the reaction [Eqn. (31)] is hydride transfer from trimethylamine-borane to iodine:

$$H_3B\cdot N\,(CH_3)_3+I_2+2\,C_5H_5N\rightarrow[H_2B\,(NC_5H_5)_2]^+\,I^-+(CH_3)_3\,N\cdot HI\ .\qquad(31)$$

A similar boronium cation is formed when trimethylamine-borane is refluxed with mercury(I) chloride in pyridine[76].

Borane complexes with phosphorus and arsenic derivatives can also be introduced into the Douglass reaction[70]:

$$(CH_3)_3\,SiCHL\cdot BH_3+I_2+N\,(CH_3)_3\rightarrow\{(CH_3)_3\,N\cdot BH_2CH\,[Si\,(CH_3)_3]\,L\}^+\,I^-,\qquad(32)$$

where L = $P(CH_3)_3$ or $As(CH_3)_3$.

$$(C_6H_5)_3\,PCH_2BH_3+I_2+N\,(CH_3)_3\rightarrow[(CH_3)_3\,NBH_2CH_2P\,(C_6H_5)_3]^+\,I^-.$$

c. Preparation of Boronium Salts from Mercaptoboranes

Mikhailov and coworkers[61,77] showed that in the reaction of trimers of alkylthioboranes with primary amines bis-(alkylamine)boronium mercaptides are formed regardless of the proportions of the reactants:

$$(RSBH_2)_3+6\,RNH_2\rightarrow3\,[H_2B\,(NH_2R)_2]^+\,SR^-\ ,\qquad(33)$$

where R = CH_3, C_2H_5, or n-C_4H_9. When the reaction is carried out with higher amines in the presence of benzyl chloride, bis(alkylamine)boronium chlorides are formed:

$$(RSBH_2)_3+R'NH_2+3\,C_6H_5CH_2Cl\rightarrow3\,[H_2B\,(NH_2R')_2]^+\,Cl^-+C_6H_5CH_2SR\ ,\qquad(34)$$

where R = CH_3, C_2H_5, or n-C_4H_9 and R′ = iso-C_3H_7, n-C_3H_7, iso-C_4H_9, n-C_4H_9, t-C_4H_9, n-C_5H_{11}, n-C_6H_{13}, or $C_6H_5CH_2$.

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‡ Nöth and coworkers[56] initially isolated the boronium salts as side products in the reduction of benzoyl chloride by the complexes $H_3B.NH_2R$ (R = CH_3, n-C_3H_7, or t-C_4H_9). The formation of these salts may be represented by the following equations[17]:

$$\begin{gathered}C_6H_5COCl+H_3B\cdot NH_2R\rightarrow H_2BCl\cdot NH_2R+C_6H_5CHO\ ,\\ C_6H_5CHO+H_3B\cdot NH_2R\rightarrow C_6H_5CH_2OBH_2+RNH_2\ ,\\ H_2BCl\cdot H_2NR+RNH_2\rightarrow[H_2B\,(NH_2R)_2]^+\,Cl^-\ .\end{gathered}$$

The authors proposed two schemes for the formation of bis(alkylamine)boronium chlorides without giving preference to either. The first is a modification of Nöth's method, based on the use of a halogenoborane as the initial component:

$$\begin{gathered} {}^1/_3\,(RSBH_2)_3 + 3\,R'NH_2 \rightarrow RSBH_2\cdot NH_2R', \\ RSBH_2\cdot NH_2R' + C_6H_5CH_2Cl \rightarrow ClBH_2\cdot NH_2R' + C_6H_5CH_2SR, \\ H_2BCl\cdot NH_2R + RSBH_2\cdot NH_2R' \rightarrow [H_2B(NH_2R')_2]^+Cl^- + {}^1/_3\,(RSBH_2)_3. \end{gathered} \tag{35}$$

The second scheme presupposes the partial conversion in ether of alkylamine-alkylthioborane into bis(alkylamine)-boronium mercaptide, which then reacts further with benzyl chloride:

$$\begin{gathered} 2\,R'NH_2\cdot BH_2SR \leftrightarrows [H_2B(NH_2R')_2]^+SR' + RSBH_2, \\ [H_2B(NH_2R')_2]^+SR^- + C_6H_5CH_2Cl \rightarrow [H_2B(NH_2R')_2]^+Cl^- + C_6H_5CH_2SR. \end{gathered} \tag{36}$$

We believe that the second scheme [Eqn. (36)] is less likely, because, as stated above[5,23], complexes of amine-boranes and their boronium salts are probably not interconverted in ether.

Cationic boron complexes are also formed when hydrogen chloride and halogeno-derivatives of hydrocarbons react with dimethylamine-alkylthioborane complexes[78,79]:

$$2\,RSBH_2\cdot NH(CH_3)_2 + R'X \rightarrow \{H_2B[NH(CH_3)_2]_2\}^+X^- + RSR' + {}^1/_3\,(RSBH_2)_3, \tag{37}$$

where R = CH_3 or C_2H_5, H′ = CCl_3, $CHBr_2$, C_2H_5, $C_6H_5CH_2$, or H, and X = Cl or Br. Similar reactions take place with pyridine-alkylthioboranes under the action of carbon tetrachloride:

$$2\,RSBH_2\cdot NC_5H_5 + CCl_4 \rightarrow [H_2B(NC_5H_5)_2]^+Cl^- + {}^1/_3\,(RSBH_2)_3 + RSCCl_3. \tag{38}$$

Only the amine complexes of halogenoboranes and dialkyl sulphides were isolated in the reactions of trialkylamine-alkylthioboranes with halogeno-derivatives of hydrocarbons[79]:

$$RSBH_2\cdot NR''_3 + R'X \rightarrow R''_3N\cdot BH_2X + RSR'. \tag{39}$$

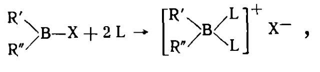
However, later a boronium salt was also obtained[80]:

$$(CH_3)_3N\cdot BH_2SCH_3 + CH_3I \rightarrow [(CH_3)_3NBH_2S(CH_3)_2]^+I^-. \tag{40}$$

Evidently, the formation of boronium salts in all the examples quoted takes place via mechanism (35).

d. Preparation of Boronium Salts from Alkyl-, Aryl-, Amino-, and Alkoxy-boron Halides

Many cationic boron complexes were synthesised by Mikhailov and coworkers[78,81-86] in a study of the reaction of diaryl- and dialkyl-boron halides with amines:



$$R'R''B{-}X + 2\,L \rightarrow [R'R''BL_2]^+X^-, \tag{41}$$

where R′ and R″ = alkyl or aryl, X = Cl, or Br, and L = amine.

Similar boronium salts were also obtained by Nöth[63,87,88] and other investigators[89,90] by mixing the reactants in an inert solvent (ether, benzene, pentane) at room or a lower temperature.

It is noteworthy that one can undoubtedly include among the boronium salts also the ternary complexes of dibutylboron chloride and bromide with pyridine, $(C_4H_9)_2BX.2C_5H_5N$ (X = Cl or Br), [91] and a group of complexes of alkoxyarylboron chlorides[92-94], alkoxyboron dichlorides[95-97], and dialkoxyboron dichlorides[98] with two moles of pyridine, the preparation of which was reported by Gerrard, Lappert, and coworkers.

Diphenyl-(αα′-dipyridyl)boronium chloride was obtained in 50% yield by refluxing diphenylboronic acid or its 2-aminoethyl ester with αα′-dipyridyl in 5 *N* solution of hydrochloric acid for 2–3 h: [89]

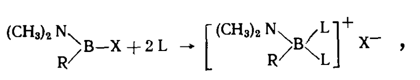
$$(C_6H_5)_2BOR + (NC_5H_4)_2 + HCl \rightarrow [(C_6H_5)_2B(NC_5H_4)_2]^+Cl^-, \tag{42}$$

where R = H or $OCH_2CH_2NH_2$.

A unique case of the synthesis of a cationic boron complex from borate has been described[98]:

$$(C_6H_5O)_3B + NH_3 \rightarrow [(C_6H_5O)_2B(NH_3)_2]^+OC_6H_5^-. \tag{43}$$

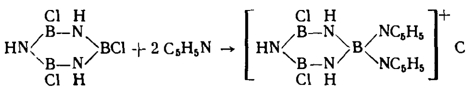
It proved possible also to obtain boronium salts by the reaction of aminoboron halides with amines[89,99]:



$$(CH_3)_2N(R)B{-}X + 2\,L \rightarrow [(CH_3)_2N(R)BL_2]^+X^-, \tag{44}$$

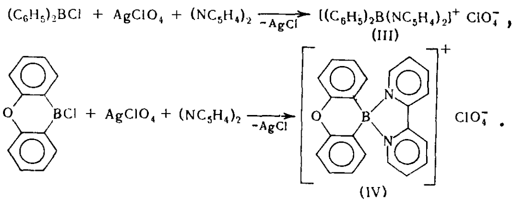
where R = $(CH_3)_2N$ or Cl, X = Cl, and L = pyridine, 4-$CH_3C_5H_4N$, or αα′-dipyridyl.

An unusual boronium salt is formed in the reaction of *B*-trichloroborazine with pyridine[99]:



(45)

The boronium salts (III) and (IV) were synthesised by Davidson and French by the reaction of a stoichiometric amount of αα′-dipyridyl with an equimolar mixture of diphenylboron chloride or 10-chloro-9-hydroxy-10-bora-anthracene with silver perchlorate in nitromethane[100,101]:



$$(C_6H_5)_2BCl + AgClO_4 + (NC_5H_4)_2 \xrightarrow[-AgCl]{} [(C_6H_5)_2B(NC_5H_4)_2]^+ClO_4^-,$$

(III)

(IV)

(46)

They showed[100,101] that, depending on the amount of αα′-dipyridyl taken, diphenylboron chloride forms 1 : 1 and 2 : 1 complexes, to which ionic structures are attributed:

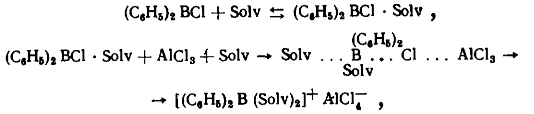
$$[(C_6H_5)_2B(NC_5H_4)_2]^+Cl^- \quad [(C_6H_5)_2B(NC_5H_4)_2]^+[Cl_2B(C_6H_5)_2]^-.$$

On the basis of the conductivities of $(C_6H_5)_2BCl$, $AlCl_3$, and $(C_6H_5)_2Br-AlCl_3$ solutions in nitrobenzene and also the ultraviolet spectra of these systems in ethyl methyl ketone, Davidson and French[102] believe that the boronium cation $(C_6H_5)_2B^+$, isoelectronic with the diphenylmethylcarbonium cation $(C_6H_5)_2CH^+$, is formed from $(C_6H_5)_2BCl$ in ionising solvents in the presence of ionic additives.

However, Moodie and coworkers[103], having analysed the ^1H NMR spectra of the products of the reaction of diphenylboron chloride and silver perchlorate in sulpholane, concluded that in solution the $(C_6H_5)_2B^+$ ion is coordinated to two solvent molecules and is therefore a boronium cation $[(C_6H_5)_2B\,(\text{sulpholane})_2]^+$.

Armstrong and Perkins[104] arrived at a similar conclusion in view of the agreement between the electronic transition calculated by the Pariser–Parr–Pople method with the absorption observed in the ultraviolet spectrum of the diphenylboron cation.

Thus Davidson and French's conclusion that the $(C_6H_5)_2B^+$ ion is present must be evidently regarded as erroneous and the appreciable increase of the conductivity of the diphenylboron chloride solution in nitrobenzene following the addition of aluminium chloride may be accounted for by the formation of a cationic boron complex according to the following mechanism:



$$(C_6H_5)_2BCl + Solv \leftrightarrows (C_6H_5)_2BCl \cdot Solv, \qquad (47)$$

$$(C_6H_5)_2BCl \cdot Solv + AlCl_3 + Solv \rightarrow Solv \ldots \underset{Solv}{\overset{(C_6H_5)_2}{B}} \ldots Cl \ldots AlCl_3 \rightarrow$$

$$\rightarrow [(C_6H_5)_2B(Solv)_2]^+ AlCl_4^-,$$

where Solv = $C_6H_5NO_2$.

Mikhailov and coworkers[45] observed that ethereal solutions of certain diarylboron chlorides [$(C_6H_5)_2BCl$, (o-$CH_3C_6H_4)_2BCl$, (p-$CH_3C_6H_4)_2BCl$, (α-$C_{10}H_7)_2BCl$, and $(C_4H_9)_2BCl$] conduct electricity and explain this phenomenon by the existence in ether of an equilibrium between organoboron chlorides and the corresponding boronium salts:

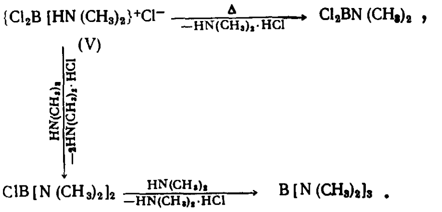
$$R_2BCl + 2(C_2H_5)_2O \leftrightarrows \{R_2B[O(C_2H_5)_2]_2\}^+ Cl^-. \qquad (48)$$

However, Moodie et al.[103] demonstrated by ^1H NMR spectroscopy that the cation of the boronium salt $\{(C_6H_5)_2B[O(C_2H_5)_2]\}^+ClO_4^-$ § is insufficiently stable and is fully decomposed in several hours via the following mechanism:

$$\{(C_6H_5)_2B[O(C_2H_5)_2]_2\}^+ \rightarrow (C_6H_5)_2BOC_2H_5 + (C_2H_5)_3O^+. \qquad (49)$$

e. Preparation of Boronium Salts from Boron Trihalides

A number of cationic boron complexes have been obtained by the reaction of boron trihalides with amines. The reaction consists of many stages and the final products depend on many factors[105-111]. Thus Nöth et al.[112] showed in a study of the reaction of boron trichloride with dimethylamine that the aminolysis of boron trichloride proceeds via a stage involving the formation of a boronium salt—dichlorobis(dimethylamine)boronium chloride (V) and dimethylaminoboron dichloride is formed only in the thermal decomposition of (V) in the course of aminolysis:

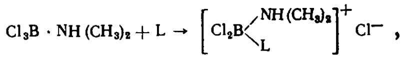


$$BCl_3 \xrightarrow{HN(CH_3)_2} Cl_3B \cdot HN(CH_3)_2 \xrightarrow{HN(CH_3)_2}$$

$$\begin{tikzcd}
\rightarrow \{Cl_2B[HN(CH_3)_2]\}^+Cl^- \arrow[r, "\Delta", "-HN(CH_3)_2\cdot HCl"'] \arrow[d, "HN(CH_3)_2"', "-2HN(CH_3)_2\cdot HCl"] & Cl_2BN(CH_3)_2, \\
ClB[N(CH_3)_2]_2 \arrow[r, "HN(CH_3)_2", "-HN(CH_3)_2\cdot HCl"'] & B[N(CH_3)_2]_3.
\end{tikzcd} \qquad (50)$$

(V)

Boronium salts containing various amines in the cation have been prepared by the reaction of dimethylamine–boron trichloride with amines in ether or benzene[112,113]:



$$Cl_3B \cdot NH(CH_3)_2 + L \rightarrow \left[Cl_2B\begin{matrix}NH(CH_3)_2\\L\end{matrix}\right]^+ Cl^-, \qquad (51)$$

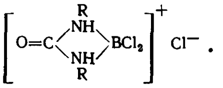
where L = NH_3, iso-$C_3H_7NH_2$, $C_4H_9NH_2$, $(CH_3)_2NH$, $(C_2H_5)_2NH$, $N(CH_3)_3$, pyridine, or 4-methylpyridine.

When trimethylamine-boron tribromide was refluxed with 3-chloropyridine, a boronium salt were also isolated: $[Br_2B(NC_5H_4Cl)_2]^+Br$.[114] Similar salts were obtained by the action of amines on solutions of boron trihalides in benzene or chloroform[115-118]¶:

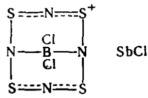
$$BX_3 + 2L \rightarrow [X_2BL_2]^+X^-, \qquad (52)$$

where (a) X = Cl or Br and L = $NH(CH_3)_2$, RNH_2, or C_5H_5N and (b) X = I and L = C_5H_5N.

On the basis of conductimetric data, Greenwood and Robinson[120] attributed an ionic structure to the adducts formed by the reaction of boron trichloride with urea derivatives:



We may mention that the infrared spectrum of the compound isolated in the reaction between $SbCl_5$ and the adduct of sulphur nitride and boron trichloride corresponds very closely to the structure of a boronium salt[121]:



A similar cationic boron complex was detected in a study of BCl_3–$SbCl_5$–CH_3CN phase diagrams at 25°C:[122]

$$BCl_3 + SbCl_5 + 2CH_3CN \rightarrow [Cl_2B(CH_3CN)_2]^+SbCl_6^-. \qquad (53)$$

Analysis of the spectroscopic characteristics and conductimetric data for solutions of boron trichloride and tribromide in acetonitrile led Schmulbach and Ahmed[123,124] to the conclusion that the ion pairs $[(CH_3CN)_2BX_2]^+BX_4^-$ exist in solution. However, the authors' conclusion probably requires confirmation. The same workers[125] suggest that the boronium cation $[I_2B(CH_3CN)_2]^+$ is formed on dissolution of $(C_2H_5)_4NBI_4$ in acetonitrile:

$$(C_2H_5)_4NBI_4 \xrightarrow{CH_3CN} (C_2H_5)_4N^+ + [I_2B(CH_3CN)_2]^+ + 2I^-. \qquad (54)$$

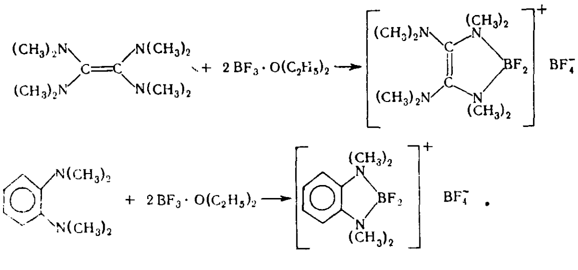
The formation of a boronium cation was postulated in the synthesis of arylboron halides from aromatic hydrocarbons and boron trichloride in the presence of aluminium and aluminium trichloride[126,127]:

$$ArH + BCl_3 \rightarrow ArH \cdot BCl_3 \xrightarrow{AlCl_3} ArHBCl_2^+ AlCl_4^-, \qquad (55)$$

$$ArHBCl_2^+ \rightarrow ArBCl_2 + H^+,$$

$$3H^+ AlCl_4^- + Al \rightarrow {}^3/_2 H_2 + 4AlCl_3.$$

The sole example of the preparation of cationic boron complexes from boron trifluoride is the reaction of boron trifluoride-ether with tertiary diamines[40,128]:



(56)

The majority of investigators assume a covalent structure for the boron trihalide complexes with amines: $R_{3-n}H_nN \rightarrow BX_3$. However, in a number of studies ionic structures were attributed to the amine complexes of boron trichloride:

$$[R_{3-n}H_nNBCl_2]^+Cl^- \quad [(R_{3-n}H_nN)_2BCl_2]^+BCl_4^-.$$

Thus the formation of an ionic complex in the dimethylamine–boron trichloride system was suggested by Brown and Osthoff[111], who concluded on the basis of a study of the vapour pressure of dimethylamine–boron trichloride that the following equilibrium exists in the gas phase:

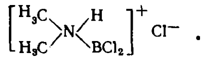
$$(CH_3)_2NH \cdot BCl_3 \leftrightarrows (CH_3)_2NBCl_2 \cdot HCl \leftrightarrows (CH_3)_2NBCl_2 + HCl. \qquad (57)$$

---

§ It is noteworthy that Mikhailov and coworkers[45] considered salts with the anion Cl^-, while boronium salts with the anion ClO_4^- are as a rule more stable[67].

¶ It is interesting that, in an ^1H NMR spectroscopic study of solutions of boron trihalides in pyridine derivatives in the temperature range between −50° and +35°C, the formation of boronium salts was not observed[119].

This observation enabled them to formulate the structure of amine-borane also in the form of the salt



The reaction of this complex with iron(III) chloride, which leads to the formation of $[Cl_2BNH(CH_3)_2]^+FeCl_4^-$, may be regarded as a confirmation of the ionic structure[129]. Moreover, dimethylamine–boron trichloride is readily hydrolysed in aqueous silver nitrate with formation of AgCl, this being in sharp contradiction with the behaviour of trimethylamine-boron trichloride, which is difficult to hydrolyse and which does not react with $FeCl_3$. At the same time the low conductivity of solutions of this complex in chloroform indicates a non-ionic structure[130].

Gerrard et al.[131] suggested that complexes of boron trichloride with aliphatic secondary amines be regarded as dichlorobis(dialkylamine)boronium tetrachloroborates:

$$[Cl_2B(NHR_2)_2]^+\ BCl_4^- ,$$

where $R = CH_3$ or iso-C_4H_9. This hypothesis is based on an analysis of the infrared spectra of these compounds, which contain absorption bands characteristic of the BCl_2 group and also frequencies corresponding to the anion BCl_4^-.

In a study of the viscosity and conductivity of melts of boron trichloride complexes with pyridine and piperidine over a wide range of temperatures, Greenwood and Wade[132] concluded that these complexes dissociate into ions to the extent of approximately 1%. On this basis, the following equilibrium between covalent and ionic forms was proposed:

$$2\,BCl_3 \cdot NC_5H_x \leftrightarrows [Cl_2B(NC_5H_x)_2]^+\,BCl_4^- , \qquad (58)$$

where $x = 5$ or 11.

The infrared spectra of the solid complex of pyridine with boron trichloride and its solutions in benzene[132] and also the ^{11}B NMR spectra of complexes of pyridine with BX_3 (X = Cl or Br) in acetonitrile and methylene chloride correspond to the covalent structure $C_5H_5N.BX_3$.[118,123] Boronium salts with ether ligands in the cation were synthesised by Mikhailov and coworkers[115–117] by the reaction of iron(III) or tin(IV) chloride with ethereal solutions of boron trichloride:

$$BCl_3 + 2\,L + FeCl_3 \xrightarrow{-70^\circ} [Cl_2BL_2]^+\ FeCl_4^- , \qquad (59)$$

where $L = (C_2H_5)_2O$ or C_4H_8O;

$$2\,BCl_3 + 4\,C_4H_8O + SnCl_4 \xrightarrow{-70^\circ} [Cl_2B(OC_4H_8)_2]_2^+\ SnCl_6^{2-} .$$

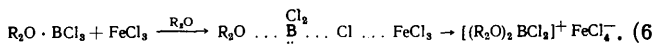
The results of this reaction and also the determinations of the molecular weights of boron trihalide-ether compounds in ether by Singer's method† and the capacity of ethereal solution of boron trihalides to conduct electricity led to the conclusion[45] that in ether there is an equilibrium between the neutral complex (VI) and the boronium salts (VII) and (VIII):

$$\underset{(VI)}{X_3B \cdot O(C_2H_5)_2} + (C_2H_5)_2O \leftrightarrows \underset{(VII)}{\{X_2B[O(C_2H_5)_2]_2\}^+}\,X^- \xrightleftharpoons{BX_3 \cdot O(C_2H_5)_2}$$

$$\rightarrow \underset{(VIII)}{\{X_2B[O(C_2H_5)_2]_2\}^+\,BX_4^-} , \qquad (60)$$

where X = Cl, Br, or F.

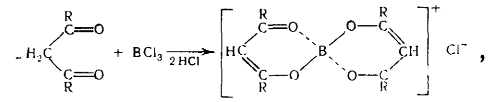
However, these results can be accounted for also from other standpoints. For example, the conductivity of the complex of boron trifluoride with anisole was explained by Pechalin and Panchenko by the formation of a charge-transfer complex[133]. Fratiello et al.[134] observed that ethereal solutions of the complexes $BCl_3.OC_4H_8$ and $BBr_3.O(C_2H_5)_2$ are unstable and therefore their conductivity may be caused by the presence of decomposition products. Moreover, the NMR spectra of the ether complexes of boron trihalides, which always contain one ^{11}B signal and one signal corresponding to each of the protons in the ether bound in the complex, are also inconsistent with the presence of ionic structures[134]. Bearing in mind the results of Fratiello et al.[134], structures of the type $[(R_2O)_2BX_2]^+X^-$ for the ether complexes of boron trihalides can be rejected altogether. The reaction of ethereal solutions of boron trichloride with Lewis acids need not necessarily be accompanied by their ionisation but may involve an S_N2 mechanism:



$$R_2O \cdot BCl_3 + FeCl_3 \xrightarrow{R_2O} R_2O \ldots \overset{Cl_2}{\underset{\ddot{R}_2O}{B}} \ldots Cl \ldots FeCl_3 \rightarrow [(R_2O)_2BCl_2]^+\,FeCl_4^- . \qquad (61)$$

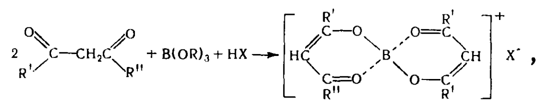
All these findings show that the problem of the existence of an equilibrium in ethereal solutions of boron trihalides cannot be regarded as finally solved.

Boron trichloride may react with β-diketones to form cationic boron complexes. Diltey in fact obtained in 1906 the first cationic boron complexes precisely by this reaction[1]:



(62)

where $R = CH_3$ or C_6H_5. Subsequently the method was improved by Barabas et al.[135] and extended to other β-diketones:



(63)

where $R' = R'' = CH_3$ or C_6H_5, R = H or n-C_4H_9, and X = Cl or ClO_4^-.

Cationic chelate complexes of boron containing tropone derivatives as ligands were synthesised by Muetterties and coworkers[136–142] by the reaction between the tropone derivatives and BBr_3 in chloroform or methylene chloride:

$$BBr_3 + 2\,T \xrightarrow[-HBr]{} [BT_2]^+\,Br^- , \qquad (64)$$

where T = tropolone, thiotropolone, or the lithium salt of *NN*-dimethylaminotroponimine and *N*-methylaminothiotropone.

In the case of tropolone the chelate complexes of boron can be obtained from boric acid and tropolone in aqueous solution in the presence of inorganic acids.

3. PREPARATION OF CATIONIC COMPLEXES BY THE ADDITION OF HYDROGEN HALIDES TO AMINOBORANES

The reaction of aminoboranes with hydrogen halides was investigated in greatest detail by Nöth and coworkers[63,87,143–147], who established that the reaction can lead to two different products, the structure of the compound depending mainly on the nature of the substituents at the boron atom. In the presence of bulky substituents,

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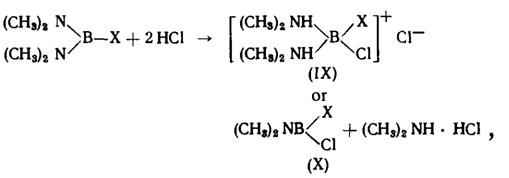
† The molecular weights determined for the other compounds of boron trichloride, trifluoride, and tribromide exceed the values for the neutral complexes by 50, 40, and 20% respectively[45].

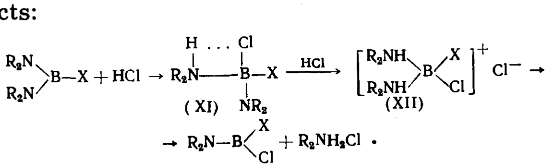
aminoborane derivatives are formed, but when the substituents are small the products are boronium salts:



(IX) or (X) (65)

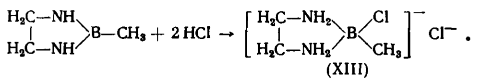
where in compound (IX) X = H, CH_3, C_2H_5, C_6H_5, Cl[‡], F, or $N(CH_3)_2$ and in compound (X) X = C_3H_7, C_4H_9, $Si(CH_3)_3$, $Si(C_6H_5)_3$, $B[N(CH_3)_2]_2$, or $N(C_2H_5)_2$.

The mechanism of the reaction of aminoboranes with hydrogen chloride probably consists in the addition of HCl to the B–N bond of the aminoborane with formation of compound (XI). Subsequent addition of a second HCl molecule leads to the formation of the boronium salt (XII), the cation of which is unstable in the presence of bulky substituents and decomposes with formation of substitution products:



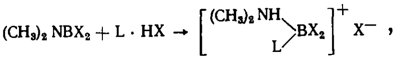
(XI) (XII) (66)

The reactions of hydrogen chloride with aminoboranes have been investigated in a number of studies. Thus, the preparation of the cationic boron complex (XIII) by the reaction of *B*-methyldiazaboroline with hydrogen chloride has been described[148]:



(XIII) (67)

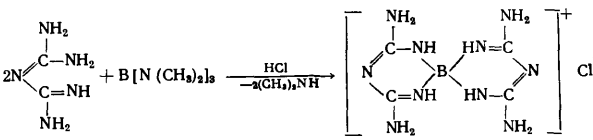
Mikhailov and coworkers[115–117] showed that the reaction of dimethylaminoboron dihalides with amine hydrogen halides in chloroform leads to the formation of boronium salts:



(68)

where X = Cl or Br and L = $(CH_3)_2NH$ or C_5H_5N.

The cationic boron complex (XIV) was synthesised by the reaction of biguanidine with tris(dimethylamino)borane in boiling pyridine followed by treatment with 0.5 *N* hydrochloric acid[149]:

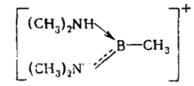


(XIV) (69)

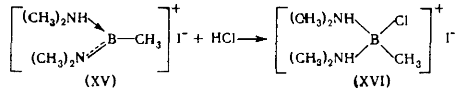
The unusual behaviour of hydrogen iodide in relation to aminoboranes is noteworthy. In contrast to the reactions with hydrogen chloride and bromide, methyl bis(dimethylamino)borane combines in toluene with only one mole of hydrogen iodide forming the insoluble complex (XV):

$$[(CH_3)_2N]_2B{-}CH_3 + HI \rightarrow \underset{(XV)}{[(CH_3)_2N]_2B{-}CH_3 \cdot HI} \,. \qquad (70)$$

On the basis of infrared spectroscopic data, Nöth and coworkers[145] attribute to (XV) the structure

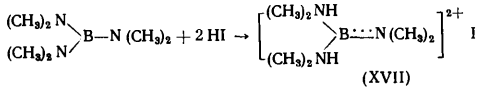


in which the cation is stabilised by the formation of a π-bond between the boron and nitrogen atoms. Additional confirmation of this structure is provided by the reaction of (XV) with hydrogen chloride, which leads to the formation of the boronium salt (XVI) and the disappearance from the infrared spectrum of the 1576 cm^{-1} absorption band characteristic of the B...N bond:



(XV) (XVI) (71)

Hydrogen iodide reacts similarly also with tris(dimethylamino)borane:



(XVII) (72)

The structure of compound (XVII) is based on infrared spectroscopic data.

4. INTERACTION OF BORANES WITH AMINE-BORANES AT ELEVATED TEMPERATURES

One of the general methods for the preparation of cationic boron complexes is the reaction proposed by Miller, Muetterties, and coworkers[70,138,140,150] between borane complexes and 'onium salts at an elevated pressure and a temperature in the range 100–180°C:

$$L\cdot BH_3 + L\cdot HX \rightarrow [H_2BL_2]^+X^- + H_2\,. \qquad (73)$$

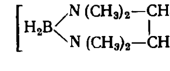
A wide variety of boronium salts have been synthesised by this method, containing in the inner sphere of the cation amines, phosphines, arsines, and dialkyl sulphides and with various acid residues as the anions. Equivalent amounts of a base and an acid may be employed instead of the 'onium salts.

Cationic boron complexes are also obtained by the reaction of borane–base complexes with diborane or higher boranes at 100–250°C: [138,151–155]

$$L\cdot BH_3 + B_2H_6 \rightarrow [H_2BL_2]^+X^- \qquad (74)$$

where X = $B_{12}H_{12}^{2-}$, $B_{12}H_{11}L^{1-}$, etc. and L = $(CH_3)_3N$, $(CH_3)_3P$, $(CH_3)_3As$, or $(CH_3)_2S$.

Boronium salts containing the cation



are formed when adducts of pentaborane(9) with *NNN'N'*-tetramethylethylenediamine (TMED) and B_4H_8.TMED are decomposed at 140–150°C.[156]

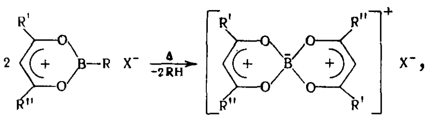
Beachley, who investigated the pyrolysis of the amine complexes of borane both in the presence of bis(methylamine)boronium chloride and in its absence, isolated boronium salts with cations containing several boron atoms[157,158]:

$$\begin{gathered} H_3B\cdot NH(CH_3)_2 + [H_2B(NH_2CH_3)_2]^+Cl^- \,|\, \xrightarrow[20\ h]{110°} \\ \rightarrow [CH_3NH_2BH_2NHCH_3BH_2NH_2CH_3]^+Cl^- + H_2 + [H_2BN(CH_3)_2]_2 , \\ H_3B\cdot NH_2CH_3 + [H_2B(NH_2CH_3)_2]^+Cl^- \xrightarrow[19\ h]{85°} \\ \rightarrow [CH_3NH_2BH_2NHCH_3BH_2NH_2CH_3]^+Cl^- + H_2 + \\ + \underset{(XVIII)}{[CH_3NH_2BH_2NHCH_3BH_2NHCH_3BH_2NH_2CH_3]^+Cl^-} + H_3B_3N_3(CH_3)_3\,. \end{gathered} \qquad (75)$$

[‡] It is interesting to note that Weiberg and Schuster[109] described a product with the same composition more then 30 years before the work of Nöth.

The same products were obtained on partial pyrolysis of 1,3,5-trimethylcyclotriborazane in the presence of methylamine hydrochloride. The structure of the boronium salt (XVIII) was proposed by Beachley on the basis of infrared and ^{1}H NMR spectroscopic data.

The preparation of bis(1,3-diketonato)boronium salts by the decomposition of 1,3-dioxaborinium salts at 100°C both in the solid state and in inert solvents (toluene and acetonitrile) has been described[159,160]:


(76)

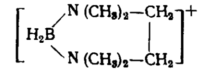
where X = Cl^- or ClO_4^-, R = C_6H_5, R′ = CH_3 or C_6H_5, and R″ = CH_3 or C_6H_5.

5. OTHER METHODS OF PREPARATION

A method for the synthesis of boronium salts with the composition $[H_2BL_2]^+X^-$, where L = tertiary amine, phosphine, or nitrile and X^- = ClO_4^- or BF_4^-, consisting in the treatment of borohydrides or amine-boranes with triphenylmethyl perchlorate or fluoroborate in the presence of bases, has been patented[161,162]:

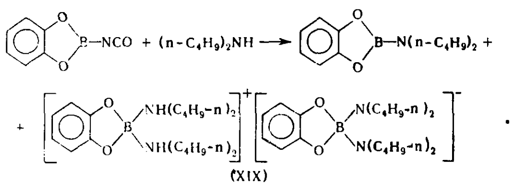
$$(C_6H_5)_3CBF_4 + (CH_3)_4NBH_4 + 2C_5H_5N \xrightarrow[CH_3CN]{-55^\circ} [H_2B(NC_5H_5)_2]^+BF_4^- + (C_6H_5)_3CH + (CH_3)_4NBF_4 \,. \qquad (77)$$

The acid hydrolysis of the adducts of pentaborane(9) with TMED and B_4H_8.TMED leads to the formation of the cation



in quantitative yield. The same cation is obtained by the hydrolysis of the adducts under neutral conditions[156].

After allowing two moles of dibutylamine to react with one mole of 2-isocyanato-1,3,2-benzodioxaboronate, Lappert and coworkers[163] isolated a complex with the composition $C_{22}H_{41}O_2N_2B$, which proved to be resistant to pyrolysis and alcoholysis. On the basis of infrared spectroscopic data, the structure of a boronium salt (XIX) was attributed to the complex:

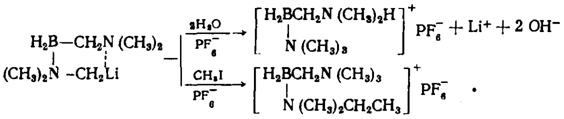

(XIX) (78)

The boronium salts $[C_5H_5NBH_2N(CH_3)_3]^+I^-$ and $\{[(CH_3)_3NBH_2]_2SCH_3\}^+I^-$ were isolated after treating $H_3BN(CH_3)_2CH_2SCH_3$ with methyl iodide and pyridine or with methyl iodide and water respectively[80].

The preparation of ionic compounds of boron (the authors regard them as boronium salts) by the reaction of trimethylamine-dimethylaminomethylborane with ethyl bromoacetate or hydrogen chloride has been described[71,164]:

$$(CH_3)_3N\cdot BH_2CH_2N(CH_3)_2 + HCl \xrightarrow{PF_6^-} [(CH_3)_3NBH_2CH_2N(CH_3)_2H]^+PF_6^- \,. \qquad (79)$$

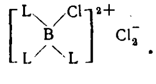
Similar compounds are also formed in the methylation with methyl iodide or in the hydrolysis of the lithio-derivative of borane (XX):[71,164]


(XX) (80)

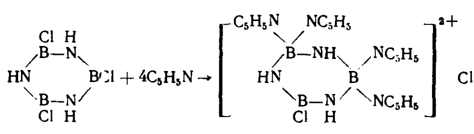
Di- and Tri-valent Cationic Complexes of Boron

The data presented above show that considerable advances have been achieved in the development of methods for the synthesis of singly charged cationic boron complexes. Until recently almost nothing was known about cationic boron complexes with charges greater than +1. The first mention of this class of compound dates back to 1951 when Sowa[165] reported the preparation of a series of boronium cations with charges ranging from +1 to +3. However, he did not prove the structure of these compounds. Only in the last three years has a series of papers appeared on the preparation of doubly and triply charged cationic boron complexes in which the structural data for the compounds are confirmed by the results of elemental analyses, infrared spectra, and conductimetric data.

When boron trichloride reacts with various primary, secondary, and tertiary amines in benzene, complexes with the composition $BCl_3.3L$ (L = amine) are obtained[166-168]; the structure of a divalent cationic complex was attributed to them:

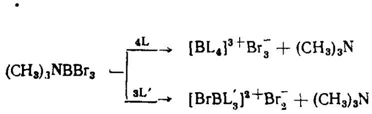


Similar complexes were prepared by the reaction of *B*-trichloroborazine and diethylaminoboron dichloride with an excess of pyridine in benzene or petroleum ether at 0°C:[99]


(81)

$$(C_2H_5)_2NBCl_2 + 3C_5H_5N \rightarrow [(C_2H_5)_2NB(NC_5H_5)_3]^{2+}Cl_2^- \,.$$

Tri- and divalent boron complexes were synthesised by refluxing $(CH_3)_3N.BBr_3$ with an excess of pyridine or its derivatives[114]:


(82)

$$(CH_3)_3NBBr_3 \xrightarrow{4L} [BL_4]^{3+}Br_3^- + (CH_3)_3N$$
$$(CH_3)_3NBBr_3 \xrightarrow{3L'} [BrBL'_3]^{2+}Br_2^- + (CH_3)_3N \,,$$

where L = 4-ethylpyridine and L′ = pyridine or 3-bromopyridine.

It is noteworthy that the complexes $3C_5H_{10}NH.BBr_3$ and $3(C_6H_5)_2NH.BBr_3$ obtained in reactions of boron tribromide with aromatic and cyclic amines and also the complexes $[(CH_3)_2N]_3B.3HI$ and $3(CH_3)_2NH.BCl_3$ should probably be regarded as divalent cationic boron complexes[112,145,169].

A divalent cationic complex has been synthesised by the reaction of tris-2,4,6-trichlorophenyl borate with ammonia[98]:

$$(Cl_3C_6H_2O)_3B + 3NH_3 \rightarrow [Cl_3C_6H_2OB(NH_3)_3]^{2+}[Cl_3C_6H_2O]_2^- \,. \qquad (83)$$

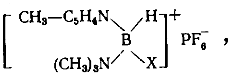
III. PHYSICAL PROPERTIES OF CATIONIC BORON COMPLEXES

Cationic boron complexes are crystalline substances. Most of them are insoluble in hydrocarbon solvents, carbon tetrachloride, and ethers. Boronium salts with small anions (Cl^-, NO_3^-, SO_4^-, etc.) are hygroscopic. They dissolve appreciably in halogenohydrocarbons (chloroform, methylene chloride, and dichloroethane), acetonitrile, acetone, alcohols, and water§, some salts crystallising as hydrates from the last solvent[89,150]. The water of hydration is readily eliminated by drying in a vacuum over phosphorus pentoxide or by recrystallisation from acetonitrile or chloroform. Boronium salts with large anions (PF_6^-, $B_{12}H_{12}^{2-}$, etc.) are much less soluble in organic solvents and water.

The boronium salts isolated from reactions in chloroform or carbon tetrachloride frequently contain between 0.2 and 0.9 mole of the solvent[75,76,136].

The saltlike nature of the cationic complexes of boron is confirmed by their capacity to conduct electricity in aqueous solutions[89,114], organic solvents[56,99,102,125,145], or amines[54]. The ionic structure of diammineboronium chloride $[H_2B(NH_3)_2]^+Cl^-$ and "diammoniate of tetraborane" $[H_2B(NH_3)_2]^+B_3H_8^-$ was also confirmed by X-ray diffraction data[170-172]. The molecular weights of these complexes have been determined in liquid ammonia[49,173,174].

Cationic boron complexes with an asymmetric boron atom should exist in optically active forms. After a number of unsuccessful attempts[135,150] optically active cationic complexes were isolated[60,66,175]:



where X = Cl or Br.

NMR Spectra of Cationic Boron Complexes

The ^{11}B NMR spectra of cationic boron complexes with 2 BH bonds consist of triplets with intensity ratios of 1 : 2 : 1 and J_{BH} constants in the range 90–120 Hz, [39,40,58-60,67,72,75,76,150,176,177] and the spectra of cations with only one BH bond consist of symmetrical doublets with J_{BH} = 134–160 Hz.[60,66,67,150]. The spectrum of bis(trimethylphosphine)-boronium consists of a quintet (0.5 : 4.4 : 5.5 : 4.4 : 0.5).[150] The ^1H NMR spectra of various cationic boron complexes have also been described[40,58-60,66,67,69-73,76,88,103,128,135,147,150,151,178].

Infrared and Ultraviolet Spectra of Cationic Boron Complexes

In the infrared spectra of boronium salts of the type $[H_2BL_2]^+X^-$ (where L is a Lewis base) there is a doublet in the region of 2380–2600 cm^{-1} associated with the stretching vibrations of the BH bonds. It is symmetrical for bisarsine and bisphosphine cations and asymmetric for bisamine cations, the band with the lower intensity lying at higher wavelengths. The frequencies due to the deformation vibrations of the BH_2 group are in the region of 1065–1170 cm^{-1}. In the deuterium-substituted cation $[D_2BL_2]^+$ the stretching and deformation vibration frequencies of the BD_2 group are displaced to 1900–1760 and 915 cm^{-1} respectively. In the region of 2430–2600 cm^{-1} cations of the type $[HB(R)L_2]^+$ have a singlet with a much lower intensity than the doublet of the BH_2 group[22,23,40,56-59,67,69-76,143,150,158].

The Raman spectra of diammineboronium and bis(dimethyl sulphoxide)boronium borohydrides each have two bands associated with the BH_2 group (2371–2315 and 2437–2422 cm^{-1} [8,41]).

The infrared spectra of the boronium salts $(R'R''BL_2)^+X^-$ containing various substituents at the boron atom (R′ and R″ = halogen, alkyl, aryl, etc.)[40,54,67,88,90,99-101,114,123,128,144,145,163], the infrared spectra of Diltey's complexes[135,159,178,179], and the ultraviolet spectra of various boronium cations[40,59,76,101,102,104,114,118,135,179] have been described.

IV. CHEMICAL PROPERTIES OF CATIONIC BORON COMPLEXES

The chemical reactions of cationic boron complexes can be divided into three groups.

1. Reactions with breakdown of the boronium salt (pyrolysis, hydrolysis, alcoholysis, and reactions with bases).

2. Reactions involving changes in the boronium cation but not resulting in its breakdown (substitution reactions and ligand exchange reactions).

3. Reactions of the anions of the boronium salts.

1. REACTIONS WITH BREAKDOWN OF THE BORONIUM SALT

a. Thermal Stability and Pyrolysis of Boronium Salts

The thermal stability of boronium salts depends both on the nature of the ligand and the substituents at the boron atom in the cation and on the nature and dimensions of the anions. Mikhailov[46] quotes the following series of bases bound in a complex with boron in terms of decreasing stability of the boronium cations: diamines > amines > phosphines > arsines > ethers > sulphides. Within the limits of each of the above types of bases, the stability of the boronium cation is determined mainly by steric factors. For example, for amine ligands it is possible to establish the following series in terms of decreasing thermal stability of boronium salts[56]:

$$[(C_6H_5)_2B\,(NH_3)_2]^+Cl^- > [(C_6H_5)_2B\,(NH_2CH_3)_2]^+Cl^- > \{(C_6H_5)_2B\,[HN\,(CH_3]_2\}^+Cl^- .$$

While diammineboronium borohydride is stable up to 80°C, the borohydrides of bis(methylamine)boronium and bis(dimethylamine)boronium are stable at room temperature only in a vacuum[10,23].

The stability of boronium salts is appreciably influenced also by the dimensions of the substituent at the boron atom, the stability as a rule decreasing with increase in the size of the substituent. Thus ethylbis(dimethylamine)boronium chloride decomposes at room temperature and methylbis(dimethylamine)boronium remains unchanged at the same temperatures in the absence of moisture[145].

The dimensions and the nature of the anion also have a significant effect on the thermal stability of the salts. The boronium salts formed with the anions of weak acids are stable only when small ligands are present in the inner sphere of the cation (NH_3, CH_3NH_2).[61] Boronium salts with anions of strong acids are distinguished by greater stability. While the boronium salt $[(CH_3)_2B(NH_3)_2]^+[H_2B.(CH_3)_2]^-$ decomposes at 10°C, its chloride is stable under

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§ The solubilities of a number of boronium salts in water have been determined[90].

the same conditions[54]. When salts with strong acid anions and bulky ligands are formed, the dimensions of the anion become of decisive importance for their stability, since small anions are capable of displacing the ligand from the cation at elevated temperatures:

$$[H_2BL_2]^+Cl^- \xrightarrow{\Delta} H_2BCl \cdot L + L \, , \tag{84}$$

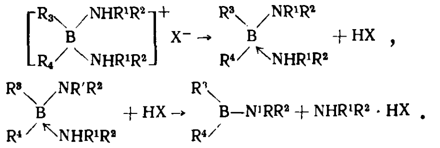
On the other hand, large anions ($B_{12}H_{12}^{2-}$, PF_6^-) permit the synthesis of stable boronium salts with ligands such as trimethylamine, ethyldimethylamine, triethylamine, and 2,6-dimethylpyridine[58,59,140,150].

Two types of thermal transformations are characteristic of boronium salts, depending on the nature of the ligand. The pyrolysis of boronium salts with tertiary amines as ligands and small anions leads to the displacement of the amine from the inner sphere of the cation by the anion and formation of complexes of the amine with boron derivatives[138,140,150,180]:

$$\{H_2B[N(CH_3)_3]_2\}^+X^- \xrightarrow{125-195^\circ} H_2B{-}X \cdot N(CH_3)_3 + N(CH_3)_3 \, , \tag{85}$$

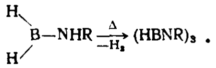
where X = Cl, Br, or N_3.

Another type of thermal transformation is characteristic of boronium salts containing primary and secondary aliphatic amines in the cation. When these salts are heated, aminoboranes and derivatives of cycloborazanes and borazines are produced, and their formation may be represented by the following equations:


(86)

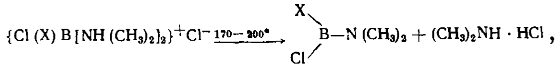
(XXI)

When R^3 and R^4 = C_nH_{2n+1}, C_6H_5, or Cl, the pyrolysis stops at this stage. When $R^1 = R^3 = H$, the product (XXI) may cyclise with formation of cycloborazanes $(H_2BNHR)_3$ or undergoes further reactions leading to borazine derivatives:



$$H_2B{-}NHR \xrightarrow[-H_2]{\Delta} (HBNR)_3 \, . \tag{87}$$

This mechanism may be illustrated by the examples of the reactions of boronium salts on heating quoted below. The wide melting point range of the boronium salts $\{Cl(X)B[NH(CH_3)_2]_2\}^+Cl^-$ can probably be accounted for by their partial decomposition on heating. This reaction, which leads to the formation of aminoboranes, occurs smoothly at 170–200°C:[63,88,112,143–145]



$$\{Cl(X)B[NH(CH_3)_2]_2\}^+Cl^- \xrightarrow{170-200^\circ} X(Cl)B{-}N(CH_3)_2 + (CH_3)_2NH \cdot HCl \, , \tag{88}$$

where X = H, Cl, Br, CH_3, or C_6H_5.

It is noteworthy that the introduction of bulky substituents linked to boron into the cation of the boronium salt leads to a lowering of the temperature at which the transformation takes place[81,84]:

$$[(C_6H_5)_2B(NH_2R)_2]^+Cl^- \xrightarrow{200-250^\circ} (C_6H_5)_2B{-}NHR + RNH_2 \cdot HCl \, , \tag{89}$$

where R = CH_3, C_2H_5, or iso-C_4H_9;

$$[(p\text{-}CH_3C_6H_4)_2B(NH_2R)_2]^+Cl^- \xrightarrow{150-170^\circ} (p\text{-}CH_3C_6H_4)_2BNH_2 + RNH_2 \cdot HCl \, ,$$

where R = C_2H_5 or iso-C_4H_9.

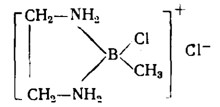
The decomposition of the salts $[H_2B(NH_2CH_3)_2]^+X^-$ and $[CH_3NH_2BH_2NHCH_3BH_2NH_2CH_3]^+X^-$, where X = BH_4 or Cl, at 100–125°C results in the formation of 1,3,5-trimethylcyclotriborazane and 1,3,5-trimethylborazine[157,158,181].

The pyrolysis of the "diammoniates" of diborane and tetraborane at 180–190°C leads to the formation of borazine[47,182]. *N*-Tri-n-burylborazine, bis-(n-butylamino)borane, and n-butylamine-borane were isolated in the thermal decomposition of bis-(n-butylamine)boronium ethylmercaptide[77].

A completely different type of thermal decomposition was observed on heating dicyclohexylbis(pyridine)boronium perchlorate in chloroform. This results in the formation of cyclohexene and cyclohexylbis(pyridine)boronium perchlorate[67]:

$$[(C_6H_{11})_2B(NC_5H_5)_2]^+ClO_4^- \xrightarrow{\Delta} [C_6H_{11}(H)B(NC_5H_5)_2]^+ClO_4^- + C_6H_{10} \, . \tag{90}$$

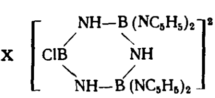
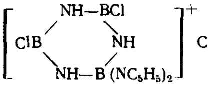
The pyrolysis of the boronium salt



at 300°C in the presence of hydrogen chloride results in the formation of methane and CH_3BCl_2 in low yields[148].

The decomposition of diphenylbis(ethyl ether)boronium[103]:

$$\{(C_6H_5)_2B[O(C_2H_5)_2]_2\}^+ \rightarrow (C_6H_5)_2B{-}OC_2H_5 + (C_2H_5)_3O^+ \tag{91}$$

and the transformation[99] on vacuum sublimation of the divalent cationic complex  $2Cl^-$ into the univalent complex  Cl^- have also been described.

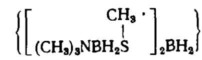
b. Hydrolysis and Alcoholysis

The hydrolysis and alcoholysis of boronium salts are the most important reactions of cationic boron complexes. It is noteworthy that the majority of boronium salts are stable in relation to water and acids but are fairly rapidly decomposed by alkalies[39,56,58,66,67,69–71,73–76,88,89,114,158]. Thus this reaction evidently reduces to nucleophilic attack on the boronium cation.

Although there has been no systematic study of the behaviour of boronium salts in hydrolysis, examination of the literature data permits the isolation of a number of factors which determine the stability of cationic boron complexes in relation to hydrolysis.

The hydrolytic stability of boronium salts is determined primarily by the basicity of the ligands in the cation. The salts become more stable with increase in the basicity of the ligands. Thus boronium cations containing thioether ligands with a relatively low basicity, $[H_2B(SR_2)_2]^+$, are readily hydrolysed by water¶.

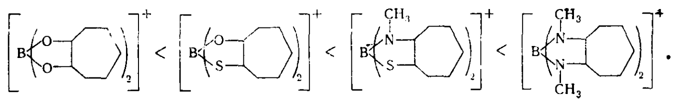
¶ However, a boronium cation containing the S–CH_3 group, $[(CH_3)_2NBH_2SBH_2N(CH_3)_3]^+$, which is resistant to acids and alkalies, has been described. Rowatt and Miller[69] explain its enhanced hydrolytic stability by the screening of the sulphur atom by $H_2BN(CH_3)_3$ groups, which are isoelectronic with the neopentyl group. The cation



in which the sulphur atom is less screened, is hydrolysed by water.

Bis(trialkylarsine)boronium salts, $[H_2B(AsR_3)_2]^+X^-$, in which the ligands are more basic, can be actually recrystallised from water, but water hydrolyses them slowly. Cations with even more basic tertiary phosphines, $[H_2B(PR_3)_2]^+$, are stable even in relation to boiling inorganic acids but are slowly decomposed in hot alkalies. Diamineboronium cations, $[H_2B(NR_3)_2]^+$, are not susceptible to the action of concentrated acids (HCl, HNO_3, H_2SO_4), and 10% alkali even on heating[70,140,150]. However, the replacement of NR_3 in the boronium cation by 4-methylpyridine leads to a sharp lowering of the hydrolytic stability of the salt[58].

An analogous variation of hydrolytic stability in relation to alkalies on passing to more basic ligands was observed by Muetterties[136-138,140-141] also for chelate cationic boron complexes:



The rate of hydrolysis of the boronium cations $[H_2BL_2]^+$, where L is a pyridine derivative, is inversely proportional to the relative strength of the base[114]. Boronium salts with weakly basic ligands such as dimethylformamide and dimethylacetamide[70] and the *N*-oxides of tertiary bases[73], exhibit an unexpectedly high stability in relation to hydrolysis.

On the basis of data for the solvolysis of a number of bis(alkylamine)boronium chlorides, Mikhailov and coworkers[183] established that, with increase in the bulk of the molecules of nitrogen-containing bases, the hydrolytic stability of the salts decreases in the series

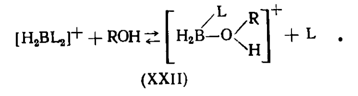
(a) $NH_3 > CH_3NH_2 > C_2H_5NH_2 > n\text{-}C_3H_7NH_2 > C_4H_9NH_2 > n\text{-}C_5H_{11}NH_2 > n\text{-}C_6H_{13}NH_2$;
(b) $NH_3 > CH_3NH_2 > (CH_3)_2NH$;
(c) $n\text{-}C_3H_7NH_2 > iso\text{-}C_3H_7NH_2$;
(d) $n\text{-}C_4H_9NH_2 > iso\text{-}C_4H_9NH_2 > t\text{-}C_4H_9NH_2$.

Bulky or electronegative substituents at the boron atom reduce the hydrolytic stability of boronium salts[54,56,61,112]. Thus the stability of salts of the type $\{(Cl)XB[NH(CH_3)_2]_2\}^+ . Cl^-$ decreases with increase in the bulk of the substituent X in the following sequence[88,143,147]: $H > F > Cl \sim C_6H_5$.

The nature of the anion of the boronium salt probably also influences its hydrolytic stability. Boronium salts with anions of weak acids $[(CH_3)_2BH_2^-, SR^-]$ are fairly readily hydrolysed[23,151], while the anions of strong acids, particularly large anions ($B_{12}H_{12}^{2-}$, PF_6^-), increase the hydrolytic stability of the salts[140,150].

The hydrolytic stability of the cationic boron complexes depends on the magnitude of the positive charge of the cation and decreases as it is diminished[114].

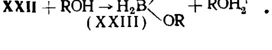
The mechanism of the hydrolysis of boronium salts is still obscure. According to the data of Mikhailov and coworkers[46,183], in the first stage of the solvolysis of the boronium salts $(H_2BL_2)^+Cl^-$ (where L are primary and secondary aliphatic amines) one amine molecule is replaced by water or an alcohol molecule:



$$[H_2BL_2]^+ + ROH \rightleftarrows \underset{\text{(XXII)}}{\left[H_2B\overset{L}{\diagup}\!\!-O\begin{smallmatrix} R \\ H \end{smallmatrix} \right]^+} + L \quad . \qquad (92)$$

(XXII)

The mixed cation (**XXII**) formed dissociates at the O–H bond with formation of a neutral complex of the hydroxy- or alkoxy-borane:

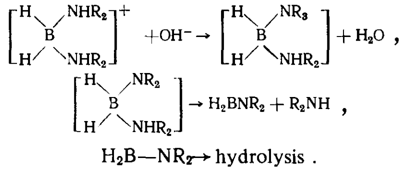


$$\textbf{XXII} + ROH \rightarrow \underset{\text{(XXIII)}}{H_2B}\begin{smallmatrix} L \\ OR \end{smallmatrix} + ROH_2^+ \quad . \qquad (93)$$

Compounds of type (**XXIII**) are solvolysed at a high rate with evolution of hydrogen.

The mechanism shows that the possibility of the displacement of the ligand in the first stage is determined both by the basicity of the hydrolysing agent and the strength of the boron–ligand bond. On the other hand, the ease of the acid-catalysed dissociation of the cation (**XXII**) in the second stage depends both on the nature of the amine incorporated in it and on the basicity of the medium. In addition, the rate of alcoholysis decreases with increasing bulk of the alcohol molecule.

In the alkaline hydrolysis of the boronium salts $(H_2BL_2)^+X^-$ (where L are primary or secondary amines), one cannot of course exclude the possibility of the reaction of the hydroxide ion with NH protons:

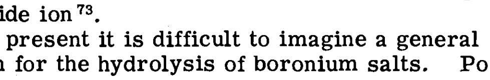


(94)

However, this last mechanism has been questioned by Mikhailov et al.[117]

Muetterties[140,150] proposed a different mechanism for the alkaline hydrolysis of boronium salts with the cations $[H_2BL_2]^+$ (where L = PR_3, AsR_3, or SR_2), according to which the initial stages of the process involves the attack by the hydroxide ion on the positively charged heteroatom of the ligand.

It is interesting to note that in certain cases there is a possibility of a nucleophilic attack by the hydroxide ion also on an atom more remote from boron[136,137]. In the alkaline hydrolysis of the boronium cation with tropolone molecules as ligands in a medium containing $H_2^{18}O$, tropolone becomes enriched in oxygen-18 to an extent corresponding to 50% of the possible maximum. On this basis, Muetterties suggests that the initial stage of the hydrolysis consists in the attack by the OH^- ion not on the central boron atom but on the carbon atom linked to oxygen:



(95)

An analogous mechanism of hydrolysis was proposed for the boronium cation $[(CH_3)_3NBH_2O \leftarrow P(CH_3)_3]^+$:

$$[(CH_3)_3NBH_2O \leftarrow P(CH)_3]^+ + OH^- \rightarrow (CH_3)_3NBH_2O \leftarrow \overset{OH^-}{\overset{\vdots}{P}}(CH_3)_3 \xrightarrow{-H^+} (CH_3)_3NBH_2O^- + PO(CH_3)_3 . \qquad (96)$$

This reaction is of third order: of first order with respect to the boronium cation and of second order with respect to the hydroxide ion[73].

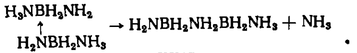
Thus at present it is difficult to imagine a general mechanism for the hydrolysis of boronium salts. Possibly the reaction mechanism varies with the type of hydrolysing agent and the nature of the boronium salt.

c. Effect of Bases on Boronium Salts Containing Amines as Ligands

A number of communications have been published on the preparation of aminoboranes or their polymerisation products by reaction of strong bases with cationic boron complexes. Probably the reactions can be described in all cases by a general mechanism including as the first stage the elimination by the base A^- of a proton from the amine in the boronium cation:

$$[H_3NBH_2NH_3]^+ + A^- \rightarrow HA + \underset{(XXIV)}{H_3NBH_2NH_2}\ , \qquad (97)$$

where A^- is the base [$C{\equiv}CH^-$, NH_2, H^-, NH_2R (R = H or alkyl)]. The ammine-aminoborane (**XXIV**) formed dimerises with loss of an ammonia molecule:

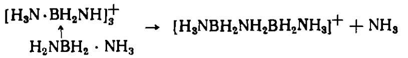


$$\begin{matrix} H_3NBH_2NH_2 \\ \uparrow \\ H_2NBH_2NH_3 \end{matrix} \rightarrow \underset{(XXV)}{H_2NBH_2NH_2BH_2NH_3} + NH_3\ . \qquad (98)$$

The ammine-aminoborane (**XXV**) formed or the product of its further condensation may cyclise with elimination of an NH_3 molecule:

$$H_3N(BH_2NH_2)_n \rightarrow (H_2BNH_2)_n + NH_3\ . \qquad (99)$$

Another pathway for the formation of cycloborazanes $(H_2NBH_2)_n$ includes attack on the boron atom in the diammineboronium cation by the ammine-aminoborane (**XXIV**):



$$\underset{(XXIV)}{\begin{matrix} [H_3N\cdot BH_2NH]_3^+ \\ \uparrow \\ H_2NBH_2\cdot NH_3 \end{matrix}} \rightarrow \underset{(XXVI)}{[H_3NBH_2NH_2BH_2NH_3]^+} + NH_3\ . \qquad (100)$$

The boronium cation (**XXVI**) can be lengthened by mechanism (98) quoted above with transfer of a proton to the base A^- [reaction (97)] or can cyclise with loss of an ammonia molecule according to reaction (99).

The examples below illustrate the formation of aminoboranes in the reaction of boronium salts with bases. Sodium acetylide reacts with diammineboronium borohydride forming aminoboranes in two different modifications, one of which is cyclotriborazane (n = 3):[185]

$$[H_2B(NH_3)_2]^+BH_4^- + NaC{\equiv}CH \xrightarrow{NH_3\,(liq.)} (H_2BNH_2)_n + NaBH_4 + CH{\equiv}CH + NH_3\ . \qquad (101)$$

Cycloborazanes with the composition $(H_2BNH_2)_n$, where n = 2, 3, or 5, were synthesised by the reaction of sodamide with diammineboronium borohydride[184]:

$$[H_2B(NH_3)_2]^+BH_4^- + NaNH_2 \xrightarrow{NH_3\,(liq.)} (H_2BNH_2)_n + NaBH_4 + 2NH_3\ . \qquad (102)$$

The "diammoniate of diborane", which is stable in dry ether at room temperature, decomposes rapidly in the presence of small amounts of ammonia with formation of a polymeric aminoborane[3]:

$$[H_2B(NH_3)_2]^+BH_4^- + NH_3 \xrightarrow{(C_2H_5)_2O} (H_2BNH_2)_n + H_3B\cdot NH_3 + H_2\ . \qquad (103)$$

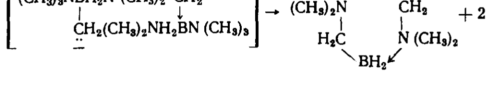
Probably bis(ethylamine)boronium ethylmercaptide decomposes similarly in ether under the influence of traces of an amine[61]:

$$[H_2B(NH_2C_2H_5)_2]^+SC_2H_5^- \xrightarrow{H_2NC_2H_5} H_2BNHC_2H_5 + C_2H_5SH + C_2H_5NH_2\ . \qquad (104)$$

The reaction of bis(trimethylamine)boronium chloride with sodium hydride[186] and butyl-lithium[164] and also the reactions of a number of boronium salts with metallic sodium[2,50,54] take place with initial elimination of a proton from the nitrogen atom or from the alkyl group of the amine.

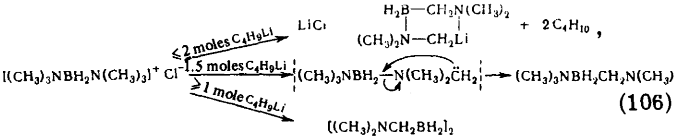
The reaction with sodium hydride gives rise to a six-membered boron-containing heterocycle in 5% yield. The formation of this product may be represented by the following mechanism

$$[(CH_3)_3NH_2BN(CH_3)_3]^+Cl^- + NaH \rightarrow NaCl + H_2 + [(CH_3)_3NBH_2N(CH_3)_2\ddot{C}H_2^{\ominus}]\ ,$$



(105)

In the reaction with butyl-lithium a number of products are formed depending on the proportions of the reactants[71,164]:



(106)

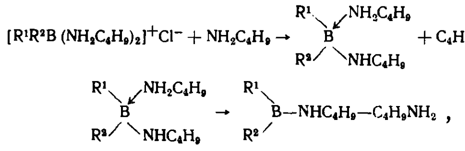
The reactions of the boronium salts $[H_2B(NH_3)_2]^+X^-$ and $[(CH_3)_2B(NH_3)_2]^+[H_2B(CH_3)_2]^-$ with sodium in liquid ammonia lead to the formation of aminoboranes†[2,49,54]:

$$[H_2B(NH_3)_2]^+X^- + Na \xrightarrow{NH_3\,(liq.)} H_2NBH_2 + NH_3 + NaX + {}^1/_2H_2\ ,$$

where $X^- = Cl^-$, Br^-, BH_4^-, or $B_3H_8^-$:

$$[(CH_3)_2B(NH_3)_2]^+[H_2B(CH_3)_2]^- + Na \xrightarrow{NH_3\,(liq.)} Na[H_2B(CH_3)_2] + (CH_3)_2B{-}NH_2 + NH_3 + {}^1/_2H_2\ . \qquad (107)$$

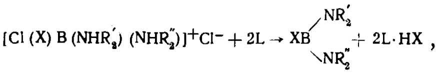
Boronium salts with substituents at the boron atom can also decompose under the influence of amines with formation of aminoboranes[84,86]:



(108)

where (1) $R^1 = R^2 = p\text{-}CH_3C_6H_4$ and (2) $R^1 + R^2 = (CH_2)_6$.

It is noteworthy that hexamethylenebis(n-butylamine)-boronium chloride does not react either with CH_3NH_2 or $(C_2H_5)_3N$. Unfortunately there is no explanation in the literature[86] of this phenomenon. At the same time it is known that dichlorobis(dialkylamine)boronium chloride[112] and chlorophenylbis(dimethylamine)boronium chloride[88] decompose smoothly under the influence of $(C_2H_5)_3N$ and $(CH_3)_2NH$:



$$[Cl(X)B(NHR'_2)(NHR''_2)]^+Cl^- + 2L \rightarrow XB\begin{matrix} \diagup NR'_2 \\ \\ \diagdown NR''_2 \end{matrix} + 2L\cdot HX\ , \qquad (109)$$

where X = Cl or C_6H_5 and L = $(C_2H_5)_3N$ or $(CH_3)_2NH$.

It is also noteworthy that reactions of a different type, leading to a transformation of the boronium cation, have also been described. Thus the complex $Cl_3B.3NH(CH_3)_2$, which is evidently the divalent cationic boron complex $\{ClB[NH(CH_3)_2]_3\}^{2+}Cl^-$, is converted by triethylamine into the univalent boronium salt $\{Cl_2B[NH(CH_3)_2]_2\}^+Cl^-$.[112]

d. Oxidation of Boronium Salts

Boronium salts containing tertiary amines as ligands are extremely resistant to oxidation. They remain unchanged under the action of oxidising agents such as Ag^+, Cu^{2+}, Hg^+, and Au^{3+} salts, potassium dichromate, and 30% hydrogen peroxide solution. Even "aqua regia" at 100°C does not decompose the cation $[H_2B(NR_3)_2]^+$ but merely converts it into the monochloro-derivative $HB(Cl)B(NR_3)_2$.[58,140,150,164] Cases of the oxidation of boronium salts by potassium permanganate[58,128] and trimethylamine-*N*-oxide[106] have been described.

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† In these reactions the acidic protons of ammonia serve as a source of hydrogen. This was confirmed by Parry and coworkers[6] in a study of the reaction of various deutero-derivatives of the "diammoniate of diborane" with sodium in liquid ammonia.

e. Reduction of Boronium Salts

Very few examples of the reduction of boronium salts are known at present. The preparation of borazanes by the reaction of $LiBH_4$ with $[H_2B(NH_2R)_2]^+Cl^-$ has been reported[4,56,62]. The only product isolated in the reduction of $[(CH_3)_2B(NH_3)_2]^+Br^-$ by hydrogen at 120°C and a pressure of 3200 atm proved to be ammonium bromide[54].

The reduction of a cationic boron complex containing tropolone as a ligand has been described

$$[(C_7H_5O_2)_2B]^+Br^- \xrightarrow{BH_4^-} (C_7H_6O_2)\,B\,(O_2C_7H_5)\ . \tag{110}$$

Bis-(*NN*-dimethylaminotropolonimine)boronium bromide is reduced similarly by lithium aluminium hydride:

$$[(C_9H_{11}N_2)_2B]^+Br^- \xrightarrow{LiAlH_4} (C_9H_{12}N_2)\,B\,(C_9H_{11}N_2)\,. \tag{111}$$

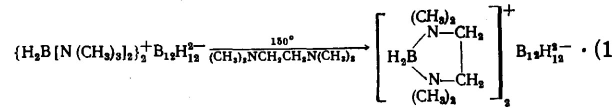
Both these boronium cations are resistant to polarographic reduction[136,140].

2. REACTIONS IN THE CATION

a. Ligand Exchange Reactions

The ligands in the boronium cation may be displaced by stronger bases without decomposing the complex. Miller and Muetterties[140,150] quote the following series of bases arranged in order of decreasing ease of exchange of the ligand in boronium salt cations: sulphides ≫ arsines > phosphines > amines > diamine. The electron-donating properties of these bases increase in the same sequence.

The steric effects of the substituents in the bases also have a significant effect on the possibility of the displacement of ligands from the cation. For example, substitution of dimethyl sulphide in $\{H_2B[S(CH_3)_2]_2\}^{2+}B_{12}H_{12}^{2-}$ by trimethylamine, *αα'*-dipiridyl and *NN*-dimethylpiperazine is rapid at room temperature, while *N*-methylpiperidine and ethyldimethylamine are incapable of displacing dimethyl sulphide. The displacement of tertiary amines by diamines takes place at an elevated temperature (up to about 150°C):

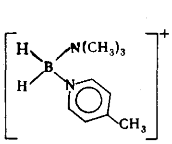


· (112)

Muetterties suggests that the first stage of the reaction is dissociation

$$[H_2B\,(NR_3)_2]^+ \rightleftarrows [H_2BNR_3]^+ + NR_3\,, \tag{113}$$

because the formation of the transition state by an S_N2 mechanism is unlikely owing to steric hindrance. However, the absence of the racemisation of the optically active boronium cation



both at room temperature and at 100°C throws doubt on the possibility of the reversible dissociation of one of the ligands at the boron atom[66].

Examples of the substitution of trimethylamine in the cation by pyridine or its derivatives at 100–110°C have been described[58]. A weak base (4-acetylpyridine) proved to be incapable of displacing a molecule of trimethylamine from the cation on refluxing in benzene for 4 h.[58] It is interesting to note that the trimethylamine, a comparatively strong base, does not displace pyridine *N*-oxide from the boronium cation at 50°C.[73]

The exchange of primary and secondary amine ligands in boronium salts with small anions (Cl^-, BH_4^-) takes place under mild conditions[54]. Thus the cations $[H_2B(NH_2CH_3)_2]^+$ and $\{H_2B[NH(CH_3)_2]_2\}^+$ undergo ligand exchange reactions on dissolution in liquid ammonia or liquid amines[23]

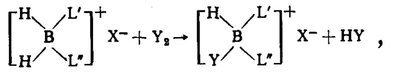
$$\begin{tikzcd}
{[H_2B(NH_2CH_3)_2]^+Cl^-} \arrow[rr, shift left, "(CH_3)_2NH\ (liq.)"] \arrow[dr, "NH_3\ (liq.)"'] & & {\left\{H_2B[HN(CH_3)_2]_2\right\}^+Cl^-\ .} \arrow[ll, shift left, "CH_3NH_2\ (liq.)"] \arrow[dl, "NH_3\ (liq.)"] \\
& {[H_2B(NH_3)_2]^+Cl} &
\end{tikzcd} \tag{114}$$

Since in these salts the amine is not dissociated from the boronium cation at a low temperature, one may assume that here the ligand exchange reactions have an S_N2 mechanism.

The attempts to substitute the ligand in di- or trivalent boronium cations by other amines led to the decomposition of the products or the recovery of the initial compounds[114].

b. Hydrogen Substitution Reactions in the Cation $[H_2BL_2]^+$

When chlorine or bromine is allowed to act on solutions of the boronium salts $[H_2BL_2]^+X^-$ in water[138,140,150,154] or methylene chloride[60,66], one hydrogen atom linked to boron is replaced by halogen. However, the chlorination in water is slow even at 90°C:



(115)

where X = I or Cl and Y = Cl or Br.

When the boronium salts $[H_2B(NR_3)_2]^+Cl^-$ are acted upon by reactants such as "aqua regia", NCl_3, and SF_5Cl, the monochloro-substituted cations $[H(Cl)B(NR_3)_2]^+$ are formed.

The iodination of boronium salts does not take place either with iodine or iodine monochloride. In the latter case at 80°C both hydrogen atoms are replaced by chlorine:

$$\{H_2B\,[N\,(CH_3)_3]_2\}^+Cl^- \overset{ICl}{\rightarrow} \{Cl_2B\,[N\,(CH_3)_3]_2\}^+. \tag{116}$$

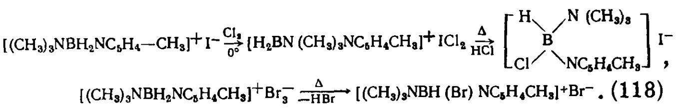
When fluorine in a stream of nitrogen is passed through an aqueous solution of $\{H_2B[N(CH_3)_3]_2\}^+$ at 0°C, the mono- and di-fluorinated cations $\{(F)HB[N(CH_3)_3]_2\}^+$ and $\{F_2B.[N(CH_3)_3]_2\}^+$ are obtained. Fluorination in the presence of chloride ions gives the mixed cation $\{Cl(F)B[N(CH_3)_3]_2\}^+$.

Peroxydisulphuryl fluoride substitutes both hydrogen atoms in the boronium salt cation:

$$\{H_2B\,[N\,(CH_3)_3]_2\}^+PF_6^- \xrightarrow{S_2O_6F_2} \{(FSO_3)_2B\,[N\,(CH_3)_3]_2\}^+PF_6^-\,. \tag{117}$$

Miller and Muetterties suggest that the above reactions have a radical mechanism. However, on the basis of data for the chlorination of the boronium salt $[(CH_3)_3NBH_2NC_5.H_4CH_3]^+I^-$ in methylene chloride at a low temperature and in the absence of light, Ryschkewitsch and Garrett[66] suggest that the mechanism of the halogenation of boronium cations consists in the electrophilic attack on the BH bond by a halide molecule.

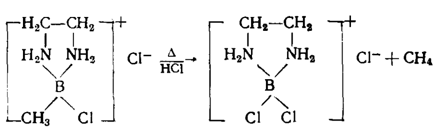
Halogeno-substituted cations are obtained also on heating boronium polyhalide salts[66]:



$$[(CH_3)_3NBH_2NC_5H_4{-}CH_3]^+I^- \xrightarrow[0^\circ]{Cl_2} [H_2BN(CH_3)_3NC_5H_4CH_3]^+ICl_2 \xrightarrow[HCl]{\Delta} \left[\begin{matrix} H & & N(CH_3)_3 \\ & B & \\ Cl & & NC_5H_4CH_3 \end{matrix}\right] I^- ,$$

$$[(CH_3)_3NBH_2NC_5H_4CH_3]^+Br_3^- \xrightarrow[-HBr]{\Delta} [(CH_3)_3NBH(Br)NC_5H_4CH_3]^+Br^- . \quad (118)$$

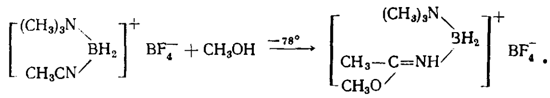
The substitution by chlorine of a methyl group bound to the boron atom in a cationic complex on heating the latter with hydrogen chloride has also been described. However, the reaction conditions and the properties of the final product have not been indicated[148]:



(119)

The reaction of $[(CH_3)_3NBH_2N(CH_2)_2CH_2SCH_3]^+$ with hydriodic acid results in the formation of $\{[(CH_3)_3N]_2BH_2\}^+$.[70]

It is noteworthy that the reactions of the cations in boron complexes containing only amine molecules in the cation as ligands have now been described. The sole exception appears to be the reactions with methyl alcohol of the boronium salt (XXIX) containing acetonitrile as a ligand[187]:



(XXIX)

(120)

3. REACTIONS OF BORONIUM SALT ANIONS

Reactions involving the exchange of the anions in boronium salts are widely used to identify these compounds and to modify their properties. Thus when diammineboronium borohydride was treated with ammonium chloride or bromide in liquid ammonia, diammineboronium chloride and bromide were obtained[2]:

$$[H_2B(NH_3)_2]^+BH_4^- + NH_4X \rightarrow [H_2B(NH_3)_2]^+X^- + NH_3BH_3 + H_2 , \quad (121)$$

where X = Cl or Br.

When ethereal or aqueous solutions of hydrogen halides (HCl, HBr) react with boronium salts containing the anions BH_4^-,[2,3,22,41] $B_3H_8^-$,[49] and $H_2B(CH_3)_2^-$,[54] the corresponding halides are obtained. The reverse reaction—the replacement of the chloride ion by the borohydride ion—was achieved by allowing sodium borohydride to react with boronium chloride salts in liquid amines[23,158]:

$$[H_2BL_2]^+Cl^- + NaBH_4 \xrightarrow[-45^\circ-(-78^\circ)]{L(liq.)} [H_2BL_2]^+BH_4^- + NaCl , \quad (122)$$

where $L = CH_3NH_2(CH_3)_2NH$;

$$[CH_3NH_2BH_2NHCH_3BH_2NH_2CH_3]^+Cl^- + NaBH_4 \xrightarrow[-30^\circ]{CH_3NH_2}$$

$$\rightarrow [CH_3NH_2BH_2NHCH_3BH_2NH_2CH_3]^+BH_4^- + NaCl .$$

The mercaptide ion is replaced by the chloride ion when boronium mercaptides are treated with hydrogen chloride[61] or benzyl chloride[61,79]. Boronium halides are converted into the corresponding perchlorates on treatment with ammonia or metal (Ag^+, K^+, and Na^+) perchlorates both in water and in organic solvents[67,74-76,90,100,101,103,135]. Hexafluorophosphates[58-60,67,70-73,76,80,114,136,139,141,150,151], hexafluoroarsenite salts[58,66,114], and tetraphenylborate salts[56,58,59,89] are precipitated when aqueous or alcoholic solutions of boronium halides are acted upon by the corresponding ammonium, sodium, and potassium salts.

Boronium chlorides react with the chlorides of iron[56,78,88,115,116,135,143-145,158], aluminium[56,135], tin[1,83,116,135], antimony[63,135], gold[1,150,152], platinum[1,145], zinc, cadmium, and mercury[1,58,66,188], forming salts with complex anions. Treatment of alcoholic solutions of boronium salts containing the anions $FeCl_4^-$ and $SnCl_6^{2-}$ with 70% perchloric acid leads to the formation of the corresponding perchlorates[135] and in reactions of KPF_6 or $NaB(C_6H_5)_4$ with boronium salts having the anions BF_4^- and BH_4^-, the hexafluorophosphates or tetraphenylboronates are formed[40,128].

When ion-exchange resins or the reactions of boronium chlorides with silver oxide in water are employed, the products are cationic complexes of boron containing hydroxide ions and behaving as strong bases. When these complexes were acted upon by acids, boronium salts with different anions were synthesised[89,150,152,155,180]. Boronium salts containing the anions $B_9H_{14}^-$, Br^-, I^-, I_3^-, Br_3^-, N_3^-, $SSP(SH_3)_2^{2-}$, NO_3^-, HSO_4^-, $C(SCN)_4(NH_3)_2^-$, $(NC)_2C{-}CHC{-}(CN)_2^-$, etc. have also been obtained by exchange reactions[58,136,150,189]. Several reactions of boronium salts involving transformations in the anion have been described too. When SO_2 is passed through an alcoholic solution of bis-(1,3-diketonato)boronium di-iodoiodate, the corresponding iodide was obtained[135]. A quantitative conversion of boronium salts with the anions I_3^-, Br_3^-, and I_2Cl^- into the corresponding halides takes place when they are treated with $Na_2S_2O_5$, acetone, or an olefin[66]. The reaction of difluoro[tetrakis(dimethylamino)ethylene]boronium tetrafluoroborate with phenylmagnesium bromide results in the formation of the tetraphenylboronate of the cation[40].

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Zelinskii Institute of
Organic Chemistry,
USSR Academy of
Sciences, Moscow

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Advances in the Chemistry of 1,2,5-Thiadiazoles and 1,2,5-Selenadiazoles

V.G.Pesin

Published information on 1,2,5-thiadiazoles, 1,2,5-selenadiazoles, their derivatives, and fused systems formed by these heterocycles is summarised. A list of 322 references is included.

CONTENTS

I. INTRODUCTION

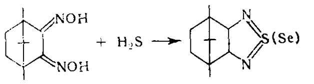
Although benzo- and naphtho-1,2,5-thia- and -selenadiazoles were described by Hinsberg in 1889,[1-4] no interest was taken in this group of compounds for more than sixty years. In 1950 the Reviewer and his coworkers began systematic investigations in this field[5]. Papers by other workers soon appeared, mainly devoted to the study of fused 1,2,5-thia- and -selena-diazole ring systems. Research in this field has been stimulated also by the discovery, among 1,2,5-thia- and -selena-diazole derivatives, of compounds which show promise of practical application in various fields. Research on monocyclic derivatives of these heterocycles began only in 1958.

Although an imense amount of information has now been accumulated on the chemistry of 1,2,5-thia- and -selena-diazoles, it has not been examined systematically or critically, apart from a short review of two or three pages[6]. The present survey covers the literature to 1968 inclusive.

II. MONOCYCLIC 1,2,5-THIADIAZOLES AND 1,2,5-SELENADIAZOLES

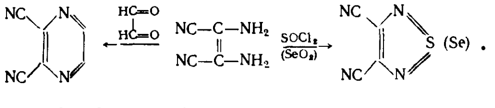
1. Synthesis

Until quite recently it proved impossible to synthesise monocyclic 1,2,5-thia- or -selena-diazoles from aliphatic compounds. The preparation of bornylene-1,2,5-thiadiazole by treating β-camphorquinone dioxime with hydrogen sulphide[7]

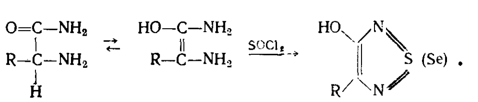


suggested that monocyclic 1,2,5-thiadiazoles might be obtained from aliphatic dioximes. However, neither dimethylglyoxime[8] nor cyclohexane-1,2-dione dioxime[9] reacts with hydrogen sulphide under similar conditions. Yet phosphorus pentasulphide or boiling sodium sulphide solution dehydrates the dioximes to the corresponding oxadiazoles. Only dimethylglyoxime has been isolated from the action of potassium sulphide on diacetyldimethylglyoxime in boiling alcohol[10].

It seemed obvious that difficultly accessible alkenediamines would be necessary for the synthesis of monocyclic 1,2,5-thiadiazoles by treatment with thionyl chloride. This was confirmed by the synthesis of the 3,4-dicyanothiadiazole from thionyl chloride and the tetramer of hydrogen cyanide[10]†, and of the selenium analogue by conducting the reaction with selenium dioxide[10]:



Drawing a further analogy with the synthesis of pyrazine derivatives, Collins and other workers[12-15] obtained hydroxy-derivatives of 1,2,5-thiadiazole from amides of α-amino-acids or their nitriles‡:

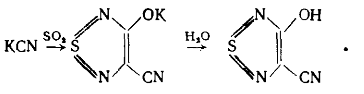


The cyclising agents used were thionyl chloride[14], sulphinylaniline[15], and sulphur monochloride[17]. Use of the *NN*-diphenylamide of sulphurous acid in a nitrogen atmosphere has been claimed[14] instead of thionyl chloride. Weinstock and his coworkers have established[16,17] that 1,2,5-thiadiazole and its derivatives are easily formed by reaction between sulphur monochloride and aliphatic compounds containing an N–C–C–N chain. Sulphur dichloride has also been employed in this reaction[18-20]. Sulphur dibromide yields bromo-derivatives of thiadiazole[18].

Thiadiazole derivatives have been obtained also by the action of sulphur dichloride on diethyloxalimide[21] or cyanogen[22].

The synthesis from sulphur nitride S_4N_4 and aliphatic compounds is of theoretical interest[23,24].

A fundamentally different method is the reaction between potassium cyanide and sulphur dioxide[19,25-28]:



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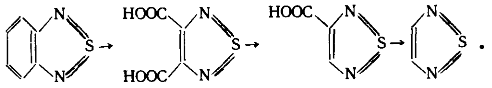
†Replacement of thionyl chloride by glyoxal yielded 2,3-dicyanopyrazine[11].

‡Replacement of thionyl chloride by a 1,2-diketone gave hydroxypyrazines[16].

1,2,5-Selenadiazole, unknown until recently, has been obtained by the reaction between ethylenediamine and selenium monochloride [29,30,32]. Higher yields of this compound and its mono- and di-methylated derivatives have been synthesised from ethylenediamine (or propylenediamine), dimethylglyoxime, and selenium dioxide [30-32].

A method of obtaining monocyclic 1,2,5-thiadiazoles and 1,2,5-selenadiazoles which is of practical importance is the degradation of fused ring systems incorporating these heterocycles. In benzo-1,2,5-thiadiazole (I) the benzene ring is less resistant than the thiadiazole ring to the action of oxidants. This permits the oxidative cleavage of (I) to 1,2,5-thiadiazole-3,4-dicarboxylic acid, which is converted by successive decarboxylation into the monocarboxy-acid and then into unsubstituted 1,2,5-thiadiazole [9,10,33-40]:

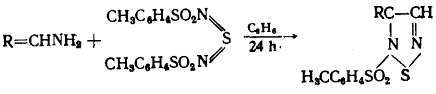

(I)

The pyrimidine ring in pyrimido-1,2,5-thia(and selena)-diazoles is readily cleaved by basic or acidic reagents under mild conditions [41-46], with the formation of various derivatives of 4-amino-1,2,5-thia(or selena)diazole-3-carboxylic acid.

Hydrogenated 1,2,5-thiadiazoles. Michaelis [47] and more recently Shew [10] made unsuccessful attempts to obtain di- and tetra-hydro-1,2,5-thiadiazoles by treating ethylenediamine and its *NN'*-diethoxycarbonyl derivative with thionyl chloride; indeterminate results were obtained by the action of thionyl chloride on *NN'*-diethoxycarbonyl- and -dibenzoyl-vinylenediamines under various conditions [10].

1,2,5-Thiadiazolidines are obtained by treating ethylenediamines with sulphur dichloride [48]. According to Peyron [49] such thiadiazolidines and also benzothiadiazolines can be obtained by the successive action of chlorine and sodium sulphide on *NN'*-diacylethylenediamines or *NN'*-diacyl-*o*-phenylenediamines. Attempts to reproduce this synthesis and also to obtain similar heterocycles by treating dipotassium ethylenediamine-*NN'*-ditoluene-*p*-sulphonate with sulphur monochloride, sulphur dichloride, or thionyl chloride were also unsuccessful [9].

A synthesis of 1,2,5-thiadiazolines by the cycloaddition of alkeneamines to "sulphodi-imides" has been described recently [50]: e.g.



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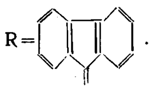
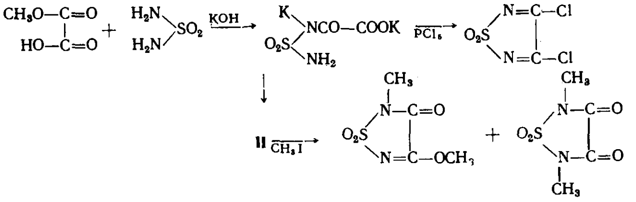


1,2,5-Thiadiazolidine 1,1-dioxide ("ethylenesulphamide") has been synthesised in good yield from ethylenediamine and sulphuric diamide under various conditions [51,52]. Dehydro-derivatives of this compound have been obtained by the reaction of sulphuric diamide with α-dicarbonyl compounds [53-57].

Wen [21], studying the structure of a product of the oxidation of benzo-1,2,5-thiadiazole by potassium permanganate, obtained the dipotassium salt of *N*-sulphamoyloxamic acid by the reaction of sulphuric diamide with methyl oxalate in the presence of caustic potash, and from it the disilver salt (II). He obtained two isomeric thiadiazolidine dioxides by the action of methyl iodide on this latter salt. With phosphorus pentachloride the dipotassium salt gave 3,4-dichloro-1,2,5-thiadiazole 1,1-dioxide, in which the chlorine atoms were so labile that they could easily be replaced by amino- and alkoxy-groups by known methods.



2. Properties

1,2,5-Thiadiazole (m.p. −50.1°, b.p. 94°C) is distinguished by great thermal stability (it remains unchanged when heated to 360°C [1,19]), and resists the action of acids, alkalis, and oxidants, but not reductants. It is an extremely weak base, its salts being easily hydrolysed by water [35]. The hydrochloride, nitrate, and picrate cannot be prepared; the sulphate and chlorate are extremely unstable [35]. It forms complex compounds with mercury chloride and silver nitrate [35] (analogy with pyrazine) [58].

1,2,5-Thiadiazole is extremely inert to electrophilic substitution and addition. It does not react with bromine either on irradiation or in the presence of iron(III) bromide [9,10]. It does not undergo the Friedel–Crafts reaction§.

Deuterium exchange takes place only in the presence of heavy-metal salts, but the ring then undergoes reductive cleavage with the evolution of hydrogen sulphide. Deuteration has been achieved by means of orthophosphoric acid under extremely severe conditions (in sealed tubes at 250°C for 37 h [35]). Deuteration has been effected also by decarboxylating mono- and di-carboxylic acids of 1,2,5-thiadiazole in which the carboxy-groups has previously been deuterated.

Nucleophilic substitution, on the other hand, takes place quite easily. For example, 1,2,5-thiadiazole itself is immediately aminated by sodamide. 3-Amino-1,2,5-thiadiazole has been obtained also by a different method [13,59].

The above results indicate the electron-acceptor character of the heterocycle, which is confirmed by various reactions of 1,2,5-thiadiazole derivatives. For example, the 3-methyl compound reacts similarly to 2-methyl- and 2,5-dimethyl-pyrazines with *p*-dimethylaminobenzaldehyde [60]. A 3-chloro-substituent is highly labile, and has enabled 3-sulphanilamido-derivatives to be prepared [18,61,62]. A 3-hydroxy-group has a well developed phenolic character [15], and 3-cyano-4-hydroxy-1,2,5-thiadiazole is a stronger acid than acetic [19]. They form salts with lithium, copper, and silver. These compounds are not acylated by acetic anhydride, benzoyl chloride, or toluene-*p*-sulphonyl chloride; nor can the hydroxyl be replaced by a mercapto-group or chlorine [15,19].

The electron-acceptor influence of the thiadiazole ring is especially clearly developed in the inertness of chlorine

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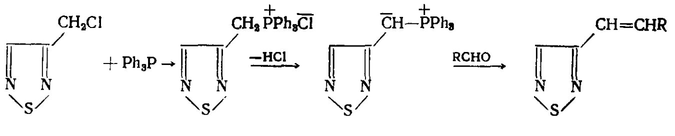
§However, 3-amino-1,2,5-thiadiazole undergoes halogenation in acetic acid at 20°C. [278] (Note added in proof.)

in chloromethyl and 1′-chloroethyl derivatives. These compounds do not react with aqueous silver nitrate even on boiling. On the other hand, 3-α-chlorobenzyl-1,2,5-thiadiazole yields a precipitate of silver chloride and the corresponding carbinol even when shaken in the cold[60]. In this case the intermediate carbonium cation is probably stabilised by interaction with the π-electron cloud of the benzene ring. This effect is prevented in the first two cases by the acceptor influence of the heterocycle.

It has recently proved possible[63] to detach chlorine from chloromethylthiadiazole by the action of a stronger nucleophilic reagent—triphenylphosphine:



where R = Ar, Het.

Many papers have been published on reactions, in which the ring is preserved, of 1,2,5-thia- and -selena-diazole derivatives containing various substituents in the side-chain[10,13,19,21,25,26,35-39,42,43,59-66]. In fused benzo-systems the thiadiazole ring is stable to the action of oxidising agents[9,10,21,33,34,36-40,67], but the heterocyclic ring may, depending on the conditions, be cleaved on oxidation with permanganate[9,10,19,21,25,33-40]. One of the products of the oxidation of benzo-1,2,5-thiadiazole with permanganate has a cyclic structure according to Shew[10], whereas Wen[21] has attributed the acyclic structure KOOC.CO.NK.SO_2NH_2 to the same compound. Ross[19] assumes that both compounds are formed by permanganate oxidation.

The thiadiazole ring is not stable towards reducing agents. Either reductive cleavage occurs or else the ring is not affected at all depending on the derivatives, the reductant, and the conditions. For example, 1,2,5-thiadiazole-3,4-dicarboxylic acid remains unchanged on hydrogenation (with palladium–carbon)[37]; 3-hydroxy-1,2,5-thiadiazole, when boiled with 50% alcohol in the presence of Raney nickel, undergoes fission with the formation of diethylaminoacetamide[19]. 3-Cyano-4-hydroxy-1,2,5-thiadiazole is only partly cleaved by sodium in alcohol (hydrogen sulphide is evolved), and is unaffected by sodium tetrahydroborate[19]. Other examples are known in which the thiadiazole ring is stable towards reduction by metal hydrides[60]. The thiadiazole ring is cleaved by sodium hydrogen sulphite, which readily attacks electron-deficient carbon atoms[25].

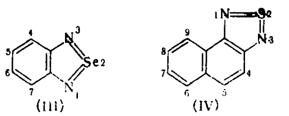
1,2,5-Selenadiazole and its methyl derivatives are cleaved by hydrogen sulphide[30,31], being reduced to the corresponding alkylenediamines and elementary selenium. 1,2,5-Selenadiazole is unaffected by treatment either with 14% NaOD in D_2O (at 60°C for 5 days) or 15% D_2SO_4 in D_2O (at 50°C for 40 min). Alkaline or ammoniacal hydrogen sulphide solution converts 3,4-dimethylselenadiazole into tetramethylpyrazine. 3,4-Diphenylselenadiazole is stable to the action of hydrogen sulphide; with sodium in alcohol it undergoes reductive cleavage to form 1,2-diphenylethylenediamine[32].

III. BENZO-1,2,5-THIADIAZOLES AND BENZO-1,2,5-SELENADIAZOLES

Many systems are now known in which these heterocycles are fused to other rings. The benzo-ring systems have been most thoroughly investigated, and the pyrimido- and naphtho-derivatives to a less extent.

1. Synthesis

The main method for synthesising benzo-1,2,5-thiadiazole (I) and benzo-1,2,5-selenadiazole (III) derivatives is the cyclisation of *o*-diamines. It was in this way that Hinsberg[1-4] first obtained (I), (III), and naphtho[1,2-*c*]-[1,2,5]-thiadiazole (IV) by treating *o*-phenylenediamines and 1,2-naphthylenediamines with concentrated sulphurous acid or with sodium hydrogen sulphite (in sealed tubes at 180–200°C for 8 h). Study of Hinsberg's reaction has shown that it can be conducted under milder conditions: several derivatives of (I) have been obtained in yields up to 40% by passing sulphur dioxide into solutions of *o*-diamines in dimethylformamide[68].



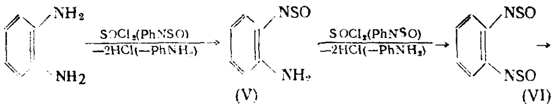
Weinstock[9] synthesised (I) in ~60% yield by heating *o*-phenylenediamine with sodium metabisulphite in ethylene glycol at 140°C for 6 h. It has been shown recently[69,70] that benzo- and naphtho-1,2,5-thiadiazoles are formed in almost theoretical yields when sulphur dioxide is passed into solutions of *o*-diamines in dichloromethane with triethylamine as catalyst.

Michaelis and his coworkers[71,72] used thionyl chloride as cyclising agent. When pyridine or triethylamine is present to combine with the hydrogen chloride formed, the reaction takes place rapidly (within a few minutes instead of many hours) and with almost quantitative yields[73-75].

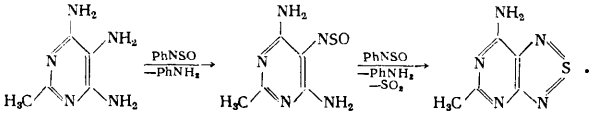
These results disprove the statement[76,77] that 4-nitro-1,2-phenylenediamine is less active than the 3-nitro-isomer in forming a thiadiazole ring.

Since thionyl chloride cannot be used for the cyclisation of *o*-diamines in which the benzene ring is substituted by hydroxyl, carboxyl, sulpho, and other groups, a study has been made of the reaction of diamines with sulphinylaniline[73-75,78,79], which Michaelis[71] had used for the preparation of (I). This reaction takes place exceptionally easily with various aromatic and heterocyclic diamines and their salts, in almost theoretical yield.

With both thionyl chloride and sulphinylaniline the reaction involves the intermediate formation of *o*-sulphinylaminoaniline (V) and *NN′*-disulphinyl-*o*-phenylenediamine (VI):[9,80]

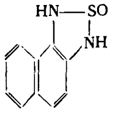


From the products of the reaction of 4,5,6-triamino-2-methylpyrimidine with sulphinylaniline Shealy and Clyton[81] isolated 4,6-diamino-2-methyl-5-sulphinylaminopyrimidine, which is converted by sulphinylaniline into 7-amino-5-methylpyrimidothiadiazole:



Beecken[70] has shown that *o*-arylenediamines and 1,2-naphthylenediamine react with sulphinylaniline to give high yields of the corresponding *o*-disulphinylamines.

The use of *p*-sulphinyltoluenesulphonamide instead of sulphinylaniline produces a similar effect[82].



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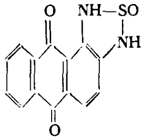
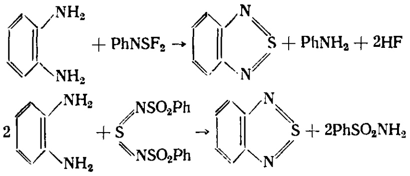


(VIII)

Dietz[83] isolated the sulphurous diamide (VII) from the products obtained by the reaction of 1,2-naphthylenediamine with sulphinylaniline. It has recently been shown[84] that the action of alkali on 6,11-dihydro-6,11-dioxoanthra[1,2-*c*]-[1,2,5]-thiadiazole at 20°C yields the analogous diamide (VIII), which, depending on the experimental conditions, can be converted into the original thiadiazole, into the *o*-diamine, or into a mixture of the two.

Thus the mechanism of the formation of (I) from *o*-arylenediamines and thionyl chloride involves the intermediate formation of an *o*-sulphinylaminoarylamine, an *o*-disulphinylaminoarene, and a cyclic sulphurous diamide.

Benzothiadiazole (I) is formed also by the use of "sulphinylaniline difluoride"[85] or *NN'*-diphenylsulphonyl-"sulphur di-imide":[86]



Derivatives of (I) are obtained by the action of sulphur monochloride on *o*-phenylenediamines or *o*-nitroanilines[87].

Schrage and Hitchings[88] obtained 7-amino-5-chloropyrimido[4,5-*c*]-[1,2,5]-thiadiazole by the action of sulphuryl chloride on 4,5,6-triamino-2-methylthiopyrimidine, but the reaction was complicated by several side-reactions. A method consisting in fusing 4-amino-5-nitrosopyrimidines with thiourea, which yields pyrimido-1,2,5-thiadiazoles, is of theoretical interest[89]. These compounds can also be synthesised[90-92] from *o*-aminonitrosopyrimidines and sodium thiosulphate.

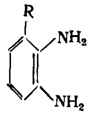
A fundamentally new method was proposed by Weinstock[9]: he synthesised naphtho-1,2,5-thiadiazole by the action of sulphur nitride S_4N_4 on 1- or 2-naphthylamine. 1,8-Naphthylenediamine yields 9-aminonaphthothiadiazole. Attempts to extend this method to aniline and other amines were unsuccessful.

Benzo-1,2,5-thiadiazole oxide was presumably obtained by the action of sulphur dichloride on *o*-benzoquinone dioxime[93]; however, it could not be obtained by treating the latter or benzofuroxan with hydrogen sulphide, sulphinylaniline, or phosphorus pentasulphide[8,93]. Unsuccessful attempts have been made[3,8,93] to replace oxygen in benzo- and naphtho-furazans by sulphur by means of various sulphurising agents.

A general method for obtaining the selenium analogues is to treat *o*-diamines with selenium dioxide[1,4,94-99]. Since this reaction takes place readily and also gives high yields, it can be used for the identification of *o*-diamines[94,99].

2. Properties

Synthesis of the polycyclic derivatives (I) and (III) from *o*-diamines is restricted by the relative inaccessibility of the latter. The preparation of many of them, in particular 1,2,3-derivatives of the type



(IX)

presents considerable difficulties. Therefore substitution in (I) and (III) is of considerable interest for preparation purposes.

(*a*) Electrophilic Substitution

Nitration. Benzothiadiazole can be nitrated as readily as can benzene (with nitric acid of density 1.35 at 0°C) to give a 95% yield of 4-nitrobenzothiadiazole[75,100,101].

The fact that the nitro-group enters the 4-position shows that the greatest electron density is located on carbon atom 4(7) and that the electron cloud is drawn towards the heterocycle. However, the acceptor effect of the latter is relatively small, since it hardly impedes the reaction at all, and is shown only in the orientation of the nitro-group [position 5(6) is less reactive]. But even this effect is considerably weakened or completely absent in the nitration of derivatives of (I) containing donor substituents (methyl, methoxy, hydroxy) at position 4.

The nitration of 5-methylbenzothiadiazole gives 94% yield of the 4-nitro-derivative. Under similar conditions 4-methylbenzothiadiazole yields a mixture of the 5- and 7-nitro-derivatives in the proportions 35 : 65,[98,102] which indicates that the influence of the methyl group predominates over that of the heterocycle. Similar proportions of *ortho* and *para* substitutions (but with the *ortho*-isomer predominating) are observed in the nitration of toluene.

The presence of two methyl groups—at positions 5 and 6—has little effect on the direction of nitration by a nitrating mixture: the 4-nitro-derivative is formed exclusively, and is converted into the 4,7-dinitro-compound on further nitration with a mixture of sodium nitrate and sulphuric acid. It is also formed in 96% yield directly from 5,6-dimethylbenzothiadiazole[103,104].

4-Acetamidobenzothiadiazole, as well as its 5(6)-mono- and 5,6-di-methyl derivatives, is easily nitrated at position 7; 5-acetamidobenzothiadiazole is readily nitrated at position 4.[105]

Stronger electron donors, such as alkoxyl and hydroxyl, weaken the influence of the heterocycle on the orientation of nitration[102,106]. Thus 4-ethoxybenzothiadiazole yields equal quantities of the 5- and 7-nitro-derivatives, which indicates that in this case these positions in the benzene ring have closely similar electron densities. On nitration with excess of nitric acid the reaction product is the 4-ethoxy-5,7-dinitro-derivative (in almost quantitative yield).

Under these conditions 4-hydroxybenzothiadiazole gives only the 5-nitro-derivative (in 95% yield), which on subsequent nitration is converted into the 5,7-dinitro-compound. Hence a 4-hydroxy-group completely suppresses the electron-acceptor effect of the thiadiazole ring and produces maximum electron density at position 5.

The nitration of 5-hydroxy- and 5-ethoxy-benzothiadiazole gives almost quantitative yields of the corresponding 4-nitro-derivatives[106,107]. In the case of the 4-hydroxy-5-methyl compound nitration yields the 7-nitro-derivative exclusively[108].

Bromomethyl derivatives of (I) are more difficult to nitrate[109]. Under the usual conditions for the nitration of aromatic compounds 5-bromomethylbenzothiadiazole gives a 58% yield of the 4-nitro-compound; a quantitative yield of this compound can be obtained by using fuming nitric acid. Under these conditions the 4-bromomethyl derivative is nitrated at position 7 in almost quantitative yield. A 4-cyanomethyl group exerts an analogous orientating effect[109]. The presence of chlorine atoms in the side-chain of toluene has a similar retarding influence on nitration.

In the nitration of a 4-halogenobenzothiadiazole the nitro-group goes mainly to position 7. Only the use of more severe conditions (a mixture of sodium nitrate and sulphuric acid at 100°C) makes it possible to obtain the 5,7-dinitro-derivatives[104,110]. The 5-halogeno-derivatives are nitrated at position 4, and the 4,6-dihalogeno-compounds at position 7. Both mononitro-products undergo further nitration by a mixture of sodium nitrate and sulphuric acid to the 4,7- and 5,7-dinitro-compounds respectively. The 7-nitro-derivative is obtained from a 4-halogeno-5-methyl compound[104,111].

The accumulation of halogen substituents in the benzene ring of (I) strongly deactivates it to attack by the nitronium cation. The 4,5- and 4,7-dihalogeno-compounds are nitrated at positions 7 and 5 respectively with comparative difficulty, especially in the latter case. When the 4,5,7-trihalogeno-compounds are nitrated under similar conditions, the nitro-group enters the vacant 6-position. Depending on the nitrating agent the 5,6-dihalogeno-compounds yield either 4-mono- or 4,7-di-nitro-derivatives[103,104,112,113]. Two nitro-groups can be introduced into the *ortho* (5,6) positions by the action of sodium nitrate in sulphuric acid on 4-halogeno-7-methyl compounds. Under similar conditions 4- and 5-nitrobenzothiadiazoles are converted into the same 4,6-dinitro-derivative.

Both 5-methyl-4-nitro- and 5-methyl-6-nitro-derivatives are nitrated to the 4,6-dinitro-compound. The 4-methyl-5-nitro- and 4-methyl-7-nitro-isomers are likewise nitrated to the 5,7-dinitro-product[98,102].

Benzo-1,2,5-selenadiazole (III) and its many derivatives are easily nitrated under the usual conditions for aromatic compounds, the yields being high and often close to theoretical[97,98,102,114-120]. Substitution is oriented in the same way as in the corresponding thia-analogues. Nitration of unsubstituted (III) gives a 98% yield of the 4-nitro-derivative[115]. A 97% yield of a mixture of the isomeric 5- and 7-nitro-derivatives in the proportions 45 : 55 is formed from the 4-methyl compound. With identical substituents in positions 5 and 6, a mixture of sodium nitrate and sulphuric acid, depending on the nature of the substituents, either gives mono- or di-nitrobenzoselenadiazole or does not nitrate the compound at all (as e.g. in the case of the 5,6-dinitro-compound).[120]

All the nitrobenzothiadiazoles and nitrobenzoselenadiazoles obtained can be reduced to the corresponding amines, which appear in high yields in the former case[98,103,104,106,110,111,121], but in considerably lower yields in the latter case[98,115,122], owing to the lower resistance of the selenadiazole ring to the action of reducing agents (e.g. degradation under the influence of hydriodic acid[123]).

Sawicki and Carr[114] showed that the nitro-group in 5-methyl-4-nitrobenzoselendaiazole activates the adjacent methyl group, which is evident in the condensation of the latter with benzaldehydes.

Nitrosation. Like 1- and 2-naphthols, 4- and 5-hydroxybenzothiazoles are easily nitrosated, the nitroso-group entering positions 5 and 4 respectively[106,107]. The 4-hydroxy-5-methyl compound is nitrosated at position 7. Thus the nitrosation of hydroxy-derivatives of (I) proceeds similarly to their nitration[106]. From a study of the nitrosation of 5-hydroxybenzothiazole Efros and his coworkers concluded[96] that the nitroso-group in the 5-hydroxy-4-nitroso-derivative possesses no hydroxyimino-function. This conclusion is inconsistent with the behaviour of the 4-hydroxy-5-nitroso- and 5-hydroxy-4-nitroso-derivatives under the conditions of the Bucherer reaction[124], which indicates that these compounds can exist in the tautomeric quinone oxime form. The hydroxynitroso-derivatives of (I) are easily reduced to the amines[107,124].

Azo-coupling. The 4- and 5-amino- and 4- and 5-hydroxy-derivatives of benzothiazole are readily coupled with diazonium salts to form the 7- and 4-azo-derivatives respectively[90,105,122,125-127]. If position 7 in the 4-hydroxy-derivative is occupied by methyl or methoxyl, the azo-group enters position 5.[127,128] This is the way in which azo-coupling occurs in the naphthalene series.

Halogenation. Chlorination and bromination in the benzothiadiazole series do not always take place in the same way, which can be explained only by the difference in the nature of the halogens. The catalytic effect of heterolysis of the interatomic bond in the molecule is less necessary for bromine than for chlorine. This is evident in the fact that, in the bromination of benzothiadiazole, electrophilic substitution takes place equally readily in the presence and in the absence of a catalyst. Bromine differs from chlorine in showing no tendency to add to benzothiadiazoles [except in the bromination of (I) itself].

Catalysed chlorination of benzo-1,2,5-thiadiazoles[110,111,131-135]. The chlorination of (I) was first studied by Efros and his coworkers[76], who concluded that this compound was incapable of addition and that no reaction took place in the absence of a catalyst. They reported also that benzothiadiazole is chlorinated in the presence of iron to the 4,7-dichloro-derivative having m.p. 57.5°C. These data were later found to be incorrect[129,130], when a 91% yield of this compound was obtained with m.p. 182°C. Further rise in temperature to 190–200°C yields successively 4,5,7-trichloro- and 4,5,6,7-tetrachloro-benzothiadiazole. Under similar conditions the 4,7-dibromo-compound is chlorinated to the 4,7-dibromo-5,6-dichloro-derivative[112].

Methyl group present at positions 4 and 5 have hardly any effect on the direction of the chlorination of melts in the presence of iron, when di- and tri-chlorinated derivatives are mainly formed. Only from the 4-methyl compound is it possible to isolate the 7-monochloro-derivative. The coincident orientating effects of heterocycle and substituents in 5,6-dimethylbenzothiadiazole result in the occurrence of chlorination under milder conditions (not only in the melt but also in acetic acid), with the formation mainly of the 4,7-dichloro-derivative. In acetic acid 4,5,6,7-tetrachlorotetrahydrobenzothiadiazole has also been isolated.

If an electron-withdrawing substituent (nitro, sulpho) is present at position 4 in benzothiadiazole, its strong deactivation of the benzene ring probably results initially in its displacement by chlorine, after which catalytic chlorination takes place in the usual way[134]. These substituents are also readily replaced by chlorine under similar conditions in nitro- and sulpho-derivatives of naphthalene and benzene.

5-Nitrobenzothiadiazole is catalytically chlorinated at position 7, as a consequence of concerted orientation by the heterocycle and by the nitro-group [134].

Uncatalysed chlorination of benzo-1,2,5-thiadiazoles. Like naphthalene, benzo-1,2,5-thiadiazole is chlorinated exothermically in chloroform, carbon tetrachloride, or dichloroethane at 60°C or in the melt at 80–90°C, four chlorine atoms being added. Alcoholic alkali eliminates two molecules of hydrogen chloride from the adduct with the formation of 4,7-dichlorobenzothiadiazole [112,129,130]. In acetic acid, chlorination gives a mixture of the tetrachloro-adduct and the substituted 4,7-dichloro-derivative. The latter is the sole product if chlorination is conducted in formic acid [133].

Neither a 4- or 5-methyl group, a 4-ethyl group, nor a 5-methoxy-group prevents the addition of four chlorine atoms under the conditions given above for (I). Alcoholic alkali splits off hydrogen chloride from the tetrachloro-adducts, converting them respectively into 4,6-dichloro-7-methyl (or ethyl)- and 4,7-dichloro-5-methyl (or methoxy)-benzothiadiazole [98,112,113]. The chlorination of 4- and 5-methylbenzothiazole in acetic acid yields in both cases a mixture of the tetrachloro-adduct and a monosubstituted product (at positions 7 and 4 respectively). Only monosubstitution takes place in formic acid.

The action of excess of sulphuryl chloride on 4- and 5-methylbenzothiadiazole yields only the corresponding 7- and 4-monochlorinated compounds. Nor do two methyl groups at positions 5 and 6 have any significant effect on the direction of chlorination [133], which occurs similarly to that of monomethyl derivatives. In the melt four chlorine atoms are added, but in acetic acid a mixture of this adduct and the dichlorinated dimethyl compound is formed.

The presence of amino, hydroxyl, and alkoxycarbonyl groups activates (I) towards chlorinating agents [78,79,111,136,137], and the reactions occur under milder conditions. The action of chloramine or sulphuryl chloride in chloroform or in acetic acid on 5-hydroxy- or 5-amino-benzothiadiazole results in the entry of chlorine at position 4. Chlorination of 4-amino-, 4-hydroxy-, and 4-methoxycarbonyl-benzothiadiazole under the same conditions yields 5,7-dichlorobenzothiadiazole: it proves impossible to limit the process to monochlorination.

Thus the heterocycle does not influence the direction of the chlorination of (I), substituents in the benzene ring being of decisive importance. The activating effect of substituents on position 5 falls in conformity with the decrease in nucleophilic character in the sequence $NH_2 > OH \gg CH_3$.

Bromination of benzo-1,2,5-thiadiazoles. Bromination results *only* in substitution, independently of the presence or the absence of a catalyst (contrast to chlorination). This can be explained by the different characters of these halogens.

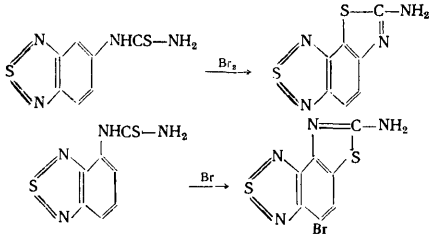
The action of excess of bromine on molten benzothiadiazole in the presence of reduced iron yields almost exclusively the 4,7-dibromo-derivative. With an equimolecular quantity of bromine under the same conditions about half the initial compound remains unchanged, and the above dibromo-derivative is accompanied by a minute amount of 4-bromobenzothiadiazole [131]. As with chlorination, the process cannot in practice be limited to monosubstitution.

In the absence of a catalyst four bromine atoms are added [112,129,130]. Subsequent treatment with alcoholic alkali yields 4,7-dibromobenzothiadiazole.

Bromination is considerably facilitated by the presence of methyl, hydroxyl, or an amino-group. The 4- and 5-methyl derivatives are brominated in the melt: the former at position 7 and in the side-chain (homolytically), and the latter to 4,7-dibromobenzothiadiazole [98]. When the reaction is conducted in the presence of reduced iron, only substitution in the benzene ring takes place, with the formation respectively of the 7-bromo- and the 4,7-dibromo derivatives [131-133].

Molten 5,6-dimethylbenzothiadiazole is brominated quantitatively to the 4,7-dibromo-derivative. In acetic-acid solution either the same product or the 4-monobromo-derivative is obtained depending on the quantity of bromine [133]. The latter product is formed also by replacing the amino-group in the 4-amino-5,6-dimethyl derivative by means of the Sandmeyer reaction. Amino-, hydroxy-, and methoxycarbonyl-benzothiadiazoles are brominated with the same orientation as in chlorination [78,78,111,136,137]. The thiocyanation of 4- and 5-amino-derivatives occurs similarly [78,79,131].

Acylated amines of (I) are brominated similarly to the amino-derivatives. The bromination of 5-thioureidobenzothiadiazole in chloroform yields 7-aminothiazolo-[5,4-*d*]benzothiadiazole; however, bromination of the isomeric 4-thioureido-compound under similar conditions results in cyclisation accompanied by the entry of bromine into the benzene ring [78,79,131].



5-Bromo- and 4,6-dibromo-benzothiadiazoles are brominated to the 4,5,7-tribromo-derivative [132]. 4- and 5-Nitrobenzothiadiazoles do not react with boiling bromine in the presence of iron.

Halogenation of benzo-1,2,5-selenadiazoles. Substitution alone occurs in the chlorination of benzo-1,2,5-selenadiazole, with formation of the 4,5,6,7-tetrachloro-derivative [98]. The 4-methyl compound, molten or dissolved in carbon tetrachloride, dichloroethane, or acetic acid, is chlorinated at position 7; in formic acid the 5,7-dichloro-derivative is also obtained. The 5-methyl compound is converted into the 4-chloro-, 4,7-dichloro-, and 4,6,7-trichloro-derivatives respectively in carbon tetrachloride, dichloroethane, or acetic acid, in the melt, and in formic acid. Sulphuryl chloride in carbon tetrachloride converts the 4- and 5-methyl compounds into the 7- and 4-chloro-derivatives respectively. The chlorination of benzoselenadiazole in the presence of silver sulphate in concentrated sulphuric acid yields a mixture of the 4-chloro- and 4,7-dichloro-derivatives [119]. The latter compound is formed also from the 4-chloro-derivative under similar conditions; 5-chlorobenzoselenadiazole gives the 4,5-dichloro-derivative [119].

Thus, in contrast to the thia-analogues, benzoselenadiazole is unable to add chlorine. In its derivatives, also, the reactivities of positions 4–7 are more alike than in the thia-analogues, in which substitution takes place preferentially at positions 4 and 7. All this provides evidence of the more aromatic character of (III) compared with (I), probably resulting from the better ability of selenium than of sulphur to transmit conjugation.

As with chlorination, bromination produces only substitution in the benzene ring of (III).[98,119] In the presence of silver sulphate in concentrated sulphuric acid the 4,7-dibromo-derivative is formed[119]. The action of bromine on the molten 4- and 5-methyl compounds produces resinification[98]. In acetic acid the 4-bromo-7-methyl and the 4-bromo-5-methyl and 4,7-dibromo-5-methyl derivatives are formed respectively[98].

In the presence of silver sulphate in concentrated sulphuric acid, crystalline iodine acts on benzoselenadiazole to give a low yield of a mixture of the 4-iodo- and 4,7-di-iodo-derivatives[119].

Sulphonation. Benzo-1,2,5-thiadiazoles are more difficult than naphthalenes to sulphonate. Under sufficiently severe conditions (17% oleum at 150°C for 1 h) a 78% yield of the 4-sulphonic acid is obtained from (I).[76,138,139] The use of 22% oleum raises the yield to 90%, when a minute amount of the 4,7-disulphonic acid also separates[140]. Under similar conditions benzo-1,2,5-selenadiazole gives an 83% yield of its 4-sulphonic acid[119] (or a 71.5% [141]). The isomeric 5-sulphonic acid of (III) is obtained[140] by the Hinsberg reaction[4].

4- and 5-Methylbenzothiadiazoles are sulphonated more easily (with 20% oleum at 110°C for 2 h), high yields of the 7- and 4-sulphonic acids respectively being obtained[142]. The use of chlorosulphuric acid instead of oleum gives the corresponding sulphonyl chlorides. The 4-sulphonyl chloride can also be obtained directly from benzothiadiazole and chlorosulphuric acid (in the presence of thionyl chloride[143]) or by the action of phosphoryl chloride on the corresponding sulphonic acid[135,136].

Hydroxy- and amino-benzothiadiazoles are sulphonated under milder conditions. Only the 5,7-disulphonic acids are formed by the 4-hydroxy- and 4-amino-derivatives[138,139].

Thus in the presence of an active electron donor position 5 readily undergoes electrophilic attack, as is observed in halogenation and nitration. No influence of the heterocycle is apparent.

On chlorination sulpho-groups in benzothiadiazoles are replaced by chlorine. Bromination of 5-hydroxybenzothiadiazole-4-sulphonic acid yields the 4-bromo-5-hydroxy-derivative. Benzothiadiazole-4-sulphonic acid can also be converted into the 4-chloro-derivative under similar conditions, but the yield does not exceed 5–8% owing to oxidative degradation[141]. In this respect the properties of naphthalenesulphonic acids are repeated by sulphonic acids both of benzothiadiazoles and of benzoselenadiazoles.

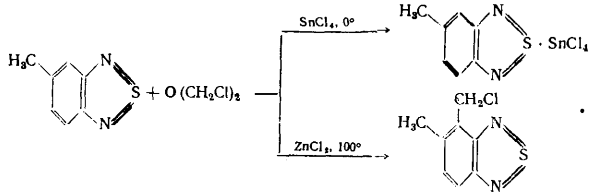
(*b*) Alkylation and Acylation at Carbon and Nitrogen

Chloromethylation. Conditions usual in the aromatic series have been applied to study the chloromethylation of benzothiadiazole and its derivatives. Attempts to chloromethylate (I) itself by the combined action of hydrogen chloride, paraformaldehyde, and zinc chloride were unsuccessful[144,145]. Negative results were obtained also when bischloromethyl ether was used in the presence of zinc chloride hydrate[146]. Only by the action of bischloromethyl ether in the presence of aluminium chloride[147,148] has it been possible to obtain 4,7-bischloromethylbenzothiadiazole (in 76% yield). The process cannot be restricted to monosubstitution even when a double excess of benzothiadiazole is used[147,148].

Chloromethylation does not take place with bischloromethyl ether in the presence of electron-donor compounds, e.g. in dimethylformamide or with a considerable excess of paraformaldehyde or hexamethylenetetramine. In the presence of a minute amount of paraformaldehyde¶ the main product is 4,7-bischloromethylbenzothiadiazole. If bischloromethyl ether prepared as in Ref. 150† is used, a mixture of the 4-chloromethyl and 4,7-bischloromethyl derivatives is formed, the ratio of which cannot be controlled[147,148,151,152].

The above results suggest that chloromethylation, in both benzothiadiazoles and aromatic compounds, is especially sensitive to the slightest changes in the reaction conditions, which cannot always be rationally taken into account.

Chloromethylation is facilitated by the introduction of an electron-donor substituent into the benzothiadiazole molecule. Thus 4- and 5-methyl compounds and the corresponding methoxy-derivatives react readily with paraformaldehyde and hydrogen chloride in the presence of zinc chloride as catalyst if the reaction is conducted in acetic acid[144]. With bischloromethyl ether the process depends[145] on the nature of the catalyst and on the temperature:



The 4-chloromethyl-5-methyl derivative is formed also with chlorosulphuric acid (at 100°C for 9 h) or aluminium chloride (at 65°C for 2 h) as catalyst, the yield being ~60%.

4-Methylbenzothiadiazole is chloromethylated at position 7 in the presence of chlorosulphuric acid, or with formation of the 5,7-disubstituted product in the presence of aluminium chloride[151]. The 5-methyl compound is chloromethylated under more severe conditions and with a lower yield than in the case of the 4-methyl compound.

Entry of a chloromethyl group is still more facilitated by the presence of a second methyl group in the benzene ring. The 4,5-dimethyl compound is chloromethylated at position 7, and the 5,6-isomer forms the 4,7-disubstituted product exclusively[135,151].

4- and 5-Chlorobenzothiadiazoles are not chloromethylated by bischloromethyl ether in the presence of chlorosulphuric acid. By using a more vigorous catalyst—aluminium chloride—it has proved possible[148] to introduce a chloromethyl group at positions 7 and 4 respectively. Nitrobenzothiadiazoles are not chloromethylated even in the presence of active catalysts under severe conditions.

When heated above 70°C with bischloromethyl ether in the presence of chlorosulphuric acid, unsubstituted benzo-1,2,5-selenadiazole is decomposed with the separation of selenium[153]. Aluminium chloride as catalyst forms a complex after 5 min, but on prolonged heating a 85–90°C small yields can be isolated of either the 4-mono- or the 4,7-bis-chloromethyl derivative depending on the extent of contamination of the initial bischloromethyl ether with paraformaldehyde[149,150].

¶Present in bischloromethyl ether prepared as in Ref. 149.

†Contaminated with a considerable quantity of paraformaldehyde.

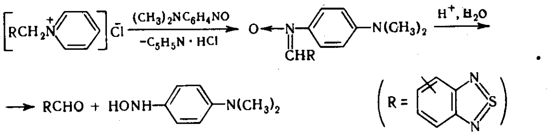
The methyl derivatives are more easily chloromethylated[153]. With bischloromethyl ether slightly contaminated with paraformaldehyde[149] 5-methylbenzoselenadiazole forms in the presence of chlorosulphuric acid the 4-chloromethyl-5-methyl compound. Under similar conditions bischloromethyl ether containing a considerable amount of paraformaldehyde gives a mixture of all three possible isomers—the 4-, 6-, and 7-chloromethyl-5-methyl derivatives (Ref. 150). The 4-methyl compound gives predominantly the 4-chloromethyl-7-methyl derivative, independently of the paraformaldehyde content of the bischloromethyl ether.

The 4- and 5-chloro-derivatives of benzoselenadiazole are more difficult to chloromethylate than are their thia-analogues under the same conditions. Processes involving degradation of the heterocycle predominate.

The chlorine in chloromethyl derivatives of benzothiadiazole and benzoselenadiazole is readily replaced by hydroxyl, alkoxyl, cyano, thiocyano, and amino: *o*- and *p*-methyl groups in chloromethylated benzothiadiazole facilitate, whereas chlorine impedes, nucleophilic substitution of the chloromethyl chlorine[140,144,145]. This shows an analogy with the behaviour of nuclear-substituted benzyl chlorides. However, the acceptor character of the heterocycle has hardly any effect.

The behaviour of chloromethylbenzothiadiazole has been studied under the conditions of the Sommelet reaction, which is employed for the synthesis of aldehydes. The acceptor influence of the heterocycle is not apparent in the preparation of the hexamethylenetetramine salt from the 4-chloromethyl-7-methyl compound. However, hydrolysis of the salt results in a low yield of the aldehyde. Similarly, the 4-formyl-5-methyl compound has been obtained in insignificant yield[144] by decomposition of the corresponding hexamethylenetetramine salt with very dilute hydrochloric acid.

Under the conditions of the Kröhnke reaction[113,147,148,154] chloromethylbenzothiadiazoles are converted fairly smoothly into aldehydes. This reaction, unlike the Sommelet reaction, is favoured by electron-accepting substituents. *p*-Nitrosodimethylaniline reacts with 1-benzothiadiazol-4′-ylmethylpyridinium chloride or the corresponding 4′,7′-dipyridinium salt in the presence of piperidine or a solution of caustic soda as catalyst to form the corresponding nitrones, acid hydrolysis of which gives high yields of 4-formyl- and 4,7-diformyl-benzothiadiazoles respectively[113,147,148]:



The resulting formyl derivatives were converted into the corresponding acids by means of hydrogen peroxide or silver oxide.

The mobility of the chlorine in a chloromethylated benzothiadiazole is unaffected by a *para*-methyl group, whereas the yield of aldehyde obtained by the Kröhnke reaction is considerably diminished by an *ortho*-methyl group, apparently because of steric hindrance. With *N*-methylformamide and phosphoryl chloride 4- and 5-methoxybenzothiadiazoles give the 4-formyl-7-methoxy- and 4-formyl-5-methoxy-derivatives respectively[144].

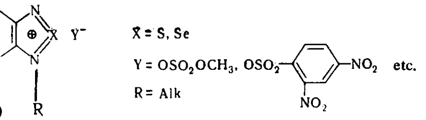
Friedel—Crafts reaction. This accompanies chloromethylation conducted in the presence of aluminium chloride, but it often plays the main part. Chloromethyl derivatives of benzothiadiazole and benzoselenadiazole do not under the Friedel–Crafts reaction with the initial heterocycles. Unsubstituted 1,2,5-thiadiazole behaves similarly in the presence of aluminium chloride[60]. This is consistent with the fact that methyl- and acetamido-benzothiadiazoles do not undergo the Friedel–Crafts reaction[151]. The probable reason is the electron-acceptor influence of the heterocycle.

Raising the temperature in the reaction of benzothiadiazole with alkyl bromides and iodides merely results in decomposition of the alkyl halides.

A relatively smooth reaction is obtained with acetic anhydride, whose interaction with aluminium chloride is not so exothermic as that of alkyl and acyl halides. This enables the process to be conducted at 130–140°C without resinification. However, the Friedel–Crafts reaction is then extremely slow[151].

Benzothiadiazole derivatives are themselves able to act as electrophilic reagents in the Friedel–Crafts reaction: e.g. benzothiadiazole-4-carbonyl chloride reacts with benzene in the presence of aluminium chloride to give an almost quantitative yield of the 4-benzoyl derivative[151].

N-Alkylation. Hinsberg[1,4] did not succeed in obtaining quaternary salts of benzothiadiazole and benzoselenadiazole, nor their 5-methyl derivatives, even by heating them with alkyl iodides at 160°C. Recently Nunn and Ralph[155] have accomplished alkylation of the unsubstituted benzo-compounds in high yields by means of dialkyl sulphates and substituted benzenesulphonates. They established that the products consisted only of mono-quaternary ammonium salts of the type



(X)

The selenadiazole ring is more easily quaternised, and the resulting adduct is more stable (e.g. to hydrolysis), than with the thia-analogue.

All the quaternary salts obtained can be converted into halides, thiocyanates, perchlorates, and other salts by double decomposition.

Quaternary salts are obtained also by the reaction between *o*-aminodiphenylamine hydrochloride and selenous acid[156].

Alkylation and acylation of amino- and hydroxy-derivatives. Hydroxylated benzothiadiazoles and benzoselenadiazoles are stronger acids than the corresponding phenols and naphthols; the amines are weaker bases than the corresponding anilines and naphthylamines. Thus the pK_a of 4- and 5-hydroxybenzothiadiazoles are 7.86 and 8.16 respectively (the corresponding value for phenol is 9.99, and those for the naphthols 9.83 and 9.91); values of pK_b for 4- and 5-aminobenzothiadiazoles and aniline are respectively 11.3 and 9.4.[76,157,158] However, this has little effect on the reactivities of the hydroxy- and amino-derivatives of benzothiadiazole and benzoselenadiazole, which are close to those of naphthols and naphthylamines‡. They undergo all the reactions characteristic of the latter, in particular diazotisation, azo-coupling, alkylation, etc.

A detailed study of the hydroxyethylation of aminobenzothiadiazoles has been made in connection with the synthesis of compounds of presumed cytotoxic activity.

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‡Polymorphism is observed in hydroxylated benzothiadiazoles[159].

Since the mechanism of the hydroxyethylation of amines involves addition of the amine to a carbonium ion, the basic strength of the amine plays an important part in the reaction. This is less vigorous with the 4- and 5-amines than with aniline, since they are less basic, as mentioned above[76,157,158]. On treatment with oxiran in acetic acid they form only the monohydroxyethylamino-derivatives[118].

Methyl substituents *ortho* and *para* to the amino-group promote high yields of the bishydroxyethylamino-derivatives. Interchanging methyl and amino between positions 4 and 5 has no significant influence on the reaction. With the 7-methyl-4-amine, on the other hand, bishydroxyethylation can be effected only in a considerable excess of methanol, owing to the stronger interaction of the substituents[118].

4-Amino-5-methylbenzoselenadiazole undergoes this reaction under the same conditions as its thia-analogue, with the formation of bishydroxyethylated products.

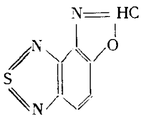
Hydroxyethylated benzothiadiazoles and benzoselenadiazoles can be converted by known methods into the corresponding chloroethylamino-derivatives. An interesting synthesis[160] is that of the thiadiazole analogue of the well known antitumorigenic preparations—*o*- and *p*-sarcolysin.

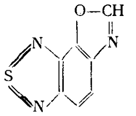
Alkylation of 4- and 5-aminobenzothiadiazoles with chloroacetic acid[161] yields the corresponding carboxymethylamino-derivatives.

On alkylation with alcohols in the presence of sulphuric acid, hydroxylated benzothiadiazoles behave like naphthols (phenols do not undergo this reaction), being converted into the corresponding alkoxy-derivatives[107], which are obtained also by alkylation with alkyl halides in the presence of alkoxides. Chloroacetic acid in the presence of alkali yields an *O*-carboxymethylated derivative. The alkylation of halogenated 4-hydroxy-derivatives with chloroacetic and with bromoacetic esters in the presence of sodium ethoxide gives 4-ethoxycarbonylmethoxy-derivatives containing halogen in the benzene ring[113,136,137].

Many studies have been made (e.g. Refs. 75, 76, 78, 79, 97, 98, 100, 101, 103, 105, 107, 108, 110, 115, 122, 134, and 162–164) of the acylation of amino- and hydroxybenzothia- and -selena-diazoles. The reactions are conducted under the usual conditions for aromatic amines and phenols, the heterocycles having no appreciable effect.

4-Amino-5-hydroxy- and 5-amino-4-hydroxy-benzothiadiazoles, like *o*-aminophenols, react with orthoformic ester to give oxazole derivatives[106,107]





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Aminobenzothiazoles react with thiocyanic acid and with aryl isothiocyanates to form the corresponding thiourea derivatives[5,78,79,131].

Thus the substituent preferentially enters position 4(7) in electrophilic substitution of benzothiadiazoles and benzoselenadiazoles, as in the naphthalene series. The activating effect of substituents on the reactivity of position 5(6) increases regularly in the sequence—$CH_3 \ll OCH_3 < OH \leqslant NH_2$.[5] The influence of substituents on the reactivity of the benzene ring is qualitatively similar to analogous effects in the benzene series[5].

(*c*) Homolytic Substitution

Among homolytic substitutions in the benzo-1,2,5-thiadiazoles a detailed study has been made of bromination with *N*-bromosuccinimide. The latter does not act on (I) in boiling carbon tetrachloride, in dimethylformamide, or in the melt at 95–100°C.[5,161] Only aluminium chloride or 50% sulphuric acid catalyses this reaction, when the 4,7-dibromo-derivative is the main product[5,161]. On chlorination with chlorosuccinimide under similar conditions the process can be restricted to monosubstitution by using a threefold excess of benzothiadiazole (yield up to 20%[112]).

Benzene, too, is brominated by *N*-bromosuccinimide only in the presence of a Lewis acid. On the other hand, naphthalene, anthracene, and phenanthrene are brominated in carbon-tetrachloride solution in the absence of a catalyst. These comparisons indicate that benzothiadiazole is strongly aromatic in comparison with, for example, naphthalene. The isomeric 4- and 5-methylbenzothiadiazoles, like 1- and 2-methylnaphthalenes, are brominated by *N*-bromosuccinimide (in carbon tetrachloride, without a catalyst) in the side-chain[109,113,165]. Toluene is not brominated under these conditions. Chlorine in the benzene ring of (I) has no significant effect on the reaction. Under similar conditions to the above, 4,6-dichloro-7-methylbenzothiadiazole gives after 24 h 85% of the 7-bromomethylated compound[113].

The presence of a nitro-group in the benzene ring prevents homolytic bromination, which in the case of e.g. the 4-methyl-7-nitro-compound occurs only in the presence of benzoyl peroxide and under ultraviolet irradiation[109]. The isomeric 5-methyl-4-nitro-derivative is difficult to brominate under the same conditions; the presence of a brominated product has been detected only by thin-layer chromatography[166].

N-Bromosuccinimide (in carbon tetrachloride with benzoyl peroxide) smoothly brominates 4- and 5-carboxyethylbenzothiadiazoles[166] in the β-position with respect to the carboxyl, the yields being respectively 94% and 79%. The 4-chloromethyl-5-methyl compound is brominated under the same conditions as the corresponding carboxyethyl derivative, bromine entering the unsubstituted methyl group[145,151].

Bromine present in alkyl derivatives of benzothiadiazole readily undergoes nucleophilic substitution, which enables various derivatives to be obtained which are of interest for biological testing, in particular amino-acids and their *NN*-bis-2-chloroethyl derivatives[109,113,160,165,167–169].

(*d*) Nucleophilic Substitution

The thiadiazole ring, which has a weakly electron-acceptor character, favours nucleophilic substitution in a benzene ring fused to it. Nitro-derivatives of benzo-1,2,5-thiadiazole containing *ortho*- and *para*-halogen are easily substituted on treatment with nucleophilic reagents (alkoxides, amines, etc.[108,113,116,168–170]).

It is noteworthy that *o*- and *p*-halogenonitrobenzenes and 2,4-dibromonitrobenzene do not react with potassium thiocyanate under analogous conditions. This confirms the activating effect of the heterocycle in (I). The reactions of benzothiadiazole derivatives with other weak nucleophiles—ammonia, diethyl thiophosphate salts—reveal similar effects of the heterocycle[171,172].

An apparent anomaly is evident in the reaction of 4,6-dichloro-7-nitrobenzothiadiazole with ammonia in boiling ethylene glycol or in molten phenol, when only one chlorine atom is replaced by an amino-group (at position 6, *ortho* to the nitro-group). This shows the relatively weak influence of the heterocycle, which is insufficient to activate two positions in the benzene ring. For this purpose, however, it is sufficient to introduce a second nitro-group: the action of ammonia on the 4,6-dichloro-5,7-dinitro-compound yields the 4,6-diamino-derivative.

As is to be expected, the nature of the halogen which is replaced has no significant influence on the course of nucleophilic substitution in the benzo-1,2,5-thiadiazoles. No departures from the above rules are observed in the reactions of the halogeno-nitro-derivatives with other amines and hydrazines[118].

The activating effect of the heterocycle on the mobility of chlorine atoms is clearly revealed[173] by the example of 4- and 5-chlorobenzo-oxa(thia, selena)diazoles, which react with sodium methoxide in methanol at 130°C with quantitative formation of the corresponding methoxy-derivatives. The nucleophilic substitution of chlorine is a second-order reaction, the rate for the 5-chloro-derivatives increasing in the sequence—$O \gg Se > S$—and for the 4-chloro-derivatives in the sequence—$O > Se \gg S$.[173]

The thia- and selena-diazole rings have an activating influence and make the halogen mobile also in the fused pyrimido-systems[174]. Shealy and his coworkers[42-45,81] report enhanced mobility of substituents in position 7 of pyrimidothiadiazoles. An unsuccessful attempt has been reported[175] to prepare hydroxybenzothiadiazoles by alkaline fusion.

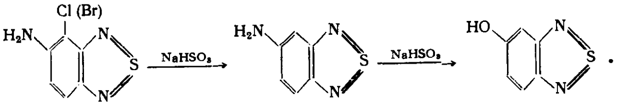
The similarity of benzothiadiazole and benzoselenadiazole to naphthalene, which is evident in several reactions, is clearly shown in the direct amination of the nitro-derivatives by hydroxylamine in alkaline medium[116,176,177]. Nitronaphthalenes undergo a similar reaction. 4- and 5-Nitrobenzo-thiadiazoles and -selenadiazoles yield the 5-amino-4-nitro- and 4-amino-5-nitro-derivatives respectively. Nitrobenzene is not aminated under these conditions, which clearly indicates the electron-acceptor character of the heterocycle. Dinitrobenzothiadiazole and also the isomeric methyl-nitro-compounds in which the position *ortho* to the nitro-group is unsubstituted undergo this reaction, but unsubstituted benzothiadiazole and benzoselenadiazole do not. The latter two compounds can be directly aminated by hydroxylamine sulphate in concentrated sulphuric acid[178].

Wen[179] found that 5-formylbenzothiadiazole reacts with nitromethane (in alkaline-alcoholic medium with subsequent acidification) to produce the 5-(1-hydroxy-2-nitro)-ethyl derivative.

(*e*) Amino- and Hydroxy-benzothiadiazoles in the Bucherer Reaction

Sodium hydrogen sulphite solution acts on 4- and 5-aminobenzothiadiazoles to form the corresponding hydroxy-derivatives in yields of 62.5% and 50% respectively. The presence of a methyl group in the benzene ring considerably diminishes the yields of hydroxy-derivatives[175,180].

Monohalogenated amino-derivatives behave differently under the conditions of the Bucherer reaction. Thus 5-amino-4-chloro(or bromo)benzothiadiazole eliminates halogen, perhaps[175] owing to its reduction:



The reverse conversion of hydroxy- into amino-compounds has been accomplished in the case of the 4- and 5-hydroxy-derivatives[124,127].

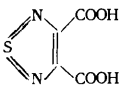
A mechanism has been suggested for the Bucherer reaction in the benzo-1,2,5-thiadiazoles which is analogous to that for naphthalene derivatives. It has been confirmed by the isolation, from the products of the reaction of isomeric hydroxy-nitroso-derivatives with sodium hydrogen sulphite, of the corresponding tetrahydro-oxonaphthalenesulphonic acids[124]. It has been stated[96] that 5-hydroxy-4-nitrosobenzothiadiazole does not react with sodium hydrogen sulphite, and hence does not undergo the Bucherer reaction.

(*f*) Oxidation of Benzothiadiazoles and Benzoselenadiazoles

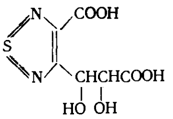
Hinsberg[1] observed that benzothiadiazole is slowly oxidised by acid potassium permanganate, but he did not isolate the oxidation products. Later he noted[67] that this heterocycle is not oxidised by 30% hydrogen peroxide in acetic acid at 100°C. It has been shown recently[113] that under these conditions the 4,6-dichloro-7-ethylthio- and -7-*p*-chlorophenylthio-derivatives are converted into 27% yields of the corresponding sulphones, the heterocycle being unaffected. Nor is benzoselenadiazole oxidised by 30% hydrogen peroxide[97] under the above[67] conditions.

Perbenzoic acid in chloroform does not oxidise benzothiadiazole. Peracetic acid completely decomposes the organic part of the molecule. This occurs also in the oxidation of the 5-methyl-, 5-chloro-, and 4,7-dichloro-derivatives, ammonium sulphate and glycollaldehyde being detected among the reaction products[33,34]. Ammonium sulphate has been isolated also from the action of hydrogen peroxide on 1,2,5-thiadiazole[9].

Ozonisation of benzothiadiazole yields the dialdehyde of thiadiazole, 1,2,5-thiadiazole-3,4-dicarboxylic acid (XI),[33,34] and glyoxal (analogy with naphthalene).



(XI)



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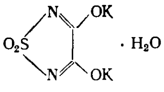
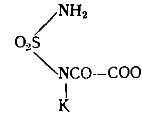


(XIII)



(XIV)

Among the products isolated from the oxidation of benzothiadiazole by aqueous potassium permanganate at 50–60°C were the acids (XI) and (XII) and also a compound of the presumed structure (XIII).[10,36] According to Wen[21] this compound (XIII) has the structure (XIV). His arguments suggest that this is probably closer to the truth. However, the experimental (synthetic) and spectral data which he cites are not inconsistent with the structure (XIII). The acid (XI) has been obtained also by the oxidation of 5-methyl-[37] and 4-nitro-benzothiadiazole[9] by aqueous potassium permanganate. The 4,7-dichloro-derivative is quite stable under these conditions, but is oxidised by alkaline potassium permanganate[33,34].

Benzothiadiazole and benzoselenadiazole are unaffected by a chromic mixture at 100°C. Resistance to oxidation is weakened by the presence of donor substituents in the ring. Under certain conditions it is possible to oxidise several benzothiadiazole derivatives and preserve the structure of the heterocycle. For example, the 4-amino-7-hydroxy-6-methyl and 4,7-diamino-5-methyl compounds are oxidised by a chromic mixture to the 5-methyl-4,7-dioxo-derivative of benzothiadiazole[108], which is a heterocyclic analogue of vitamin K_3.

The dibasic acid (XI) can be obtained in good yield by heating benzothiadiazole with chromium trioxide in sulphuric acid; under the same conditions benzoselenadiazole is completely decomposed[38-40]. A lower yield of

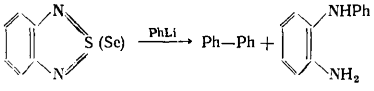
(XI) is formed by the oxidation of mono- and di-methyl derivatives of (I) under the same conditions. The oxidation of 5-bromobenzothiadiazole gives the 4,5-dibromo-derivative as well as the acid (XI). The 5-chloro-, 4,7-dichloro-, 4,7-dibromo-, 4-nitro-, and 5-nitro-derivatives are almost completely resistant to oxidation under these conditions.

The stability towards oxidising agents of benzothiadiazoles containing electron-acceptor substituents has enabled several carboxylated derivatives to be obtained[142].

Comparison of the behaviour of benzo-1,2,5-thiadiazoles and naphthalene on oxidation by chromic acid indicates that the benzene ring in the former is more stable than one of the naphthalene rings, whereas the tendency of derivatives of the latter to be oxidised to quinones is not so characteristic of compounds of the benzothiadiazole series.

(*g*) Reduction

The thiadiazole ring is extremely unstable towards reducing agents. Lane and Williams[181,182] established that phenyl-lithium reduces benzothiadiazole and benzoselenadiazole with fission of the heterocycle:



Several workers have shown[10,19,23,25,26,60] that the stability of the thiadiazole ring to the action of sodium in alcohol and also of various metal hydrides depends on the nature of the substituents in the ring. Shealy and his coworkers[42-45,81] studied the reactions of pyrimido-1,2,5-thiadiazoles, and found that both lithium tetrahydroaluminate and hydrogen sulphide reduce the heterocycle with the formation of *o*-diamines of the pyrimidine series.

The reductive cleavage of the thiadiazole ring by the action of zinc or tin in acids with the formation of aromatic or heterocyclic *o*-diamines provides a convenient method for preparing many of them, including those which are difficultly accessible by other methods[183-188].

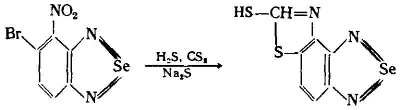
It has been established also that, in the reductive cleavage of fused thiadiazoles, the stability of the heterocycle is increased by the accumulation of chlorine atoms in the benzene ring[189]: 5 chloro- and 4,7-dichloro-benzothiadiazoles are quite stable towards sodium in boiling alcohol, whereas the unsubstituted compound and its methyl derivatives are cleaved under the same conditions[190]. Other workers have also reported that the behaviour of the heterocycle under these conditions depends on the nature of substituents in the benzene ring[19,23,25,26].

The thiadiazole ring in benzothiadiazol-5-ylacetic acid and its phenylisopropylamide[161,188] and also in chloromethylbenzothiadiazole[144] is stable to the action of sodium in alcohol and to Raney nickel.

The great stability of the thiadiazole ring to reducing conditions—in the presence of iron in 2% acetic acid, sodium dithionite, sodium hydrogen sulphide, sodium sulphide or disulphide, sodium sulphite, zinc in calcium chloride solution, ammoniacal hydrogen sulphide, hydrogen sulphide dissolved in sodium sulphide solution, alkaline iron(II) sulphate solution— has made it possible to reduce nitro-, nitroso-, and azo-derivatives of benzothiadiazole to the corresponding amino-compounds, and also to study the effects of other substituents and of the position of the reducible group on the reduction of the above derivatives[98,100,101,105,106,108,111,125,171,190,191].

The selenadiazole ring is still less resistant to reduction. Benzoselenadiazole derivatives are converted into *o*-diamines even by hydriodic acid or by sodium dithionite[10,123,192], which makes it possible to prepare many compounds of interest in connection with their biological activity, in particular derivatives of β-phenyl-α-alanine[193]. According to Elvidge et al.[123] the reduction of 4-nitro- and 4,6-dinitro-benzoselenadiazoles with hydriodic acid involves degradation of the heterocycle while the nitro-groups remain in the resulting phenylenediamines.

As with the thia-analogue, the sensitivity of the selenadiazole ring to reduction depends on the nature of substituents in the benzene ring. Thus hydrogen sulphide cleaves 4-amino-5-nitrobenzoselenadiazole to 1,2,3-triamino-4-nitrobenzene[116], whereas the 5-bromo-4-nitro-derivative in converted, without any destruction of the heterocycle, into selenadiazolobenzothiazole[194]:



The isomeric 4- and 5-nitrobenzoselenadiazoles behave differently towards iron in 2% acetic acid: the former is reduced to the 4-amino-derivative in 50% yield, whereas the 5-nitro-compound resinifies[115]. Under the same conditions 5-nitrobenzothiadiazole is reduced to the 5-amine[78]. This is evidence of the enhanced stability of benzoselenadiazole to reductive cleavage when a 4-nitro-group is present in the benzene ring.

Benzothiadiazoles and benzoselenadiazoles can be reduced either with potassium or cathodically to form radical-anions. These can be obtained also by reaction of the initial compounds with the dipotassium salt of the dianion of cyclo-octatetraene[195] or with the anions of propiophenone and 9,10-dihydroanthracene[196]. Electron transfer from the dipotassium salt is incomplete, the process being reversible[195]. Under similar conditions the reaction with 4- and 5-nitrobenzothiadiazole gives a quantitative yield of cyclo-octatetraene: electron transfer is complete, and no equilibrium is observed[197]. Thus the reduction of benzothiadiazole and benzoselenadiazole either with potassium or cathodically resembles that of naphthalene.

The ease of polarographic reduction increases from benzothiadiazole to benzoselenadiazole in conformity with the fall in electronegativity of the key heteroatoms and with the decrease in the dipole moment of the diazole. The final reduction product is *o*-phenylenediamine, which requires six electrons[198]. The overall process is irreversible and is regarded[199] as involving the intermediate formation of *o*-benzoquinonedi-imine.

In aprotic solvents the reduction of these compounds involves a reversible intermediate one-electron transfer with formation of the corresponding radical-anions[199-201]. The latter are stable at 20°C, and in the absence of oxygen are capable of one-electron oxidation to the original substances[196,199]. They are π-electron radicals.

(*h*) Complex formation

Several investigations have revealed the ability of benzothiadiazoles and benzoselenadiazoles to form complexes. Lane and Williams showed[202] that they are able to form molecular compounds with tetrahydroquinoxaline derivatives.

Bertini[30] noted that 1,2,5-selenadiazole and its methyl derivatives are able to form complexes with cadmium chloride. Benzoselenadiazole forms a 1 : 1 compound with palladium chloride, whose use has been suggested for the detection of palladium in the presence of platinum(IV), cobalt, nickel, and lead[203]. With a methanolic solution of benzoselenadiazole aqueous solutions of cadmium salts form insoluble complexes $Cd(III)_2X_2$, where X = Cl, Br, I, SCN, SeCN, NCO, N_3. On thermal decomposition these complexes split off one or two molecules of (III) in stages[204].

Benzothiadiazole and its 5-methyl derivative form 1 : 1 complexes with tin(IV) chloride[145,148,153]. A similar complex is formed with mercury(II) chloride under similar conditions[35]. Benzoselenadiazole derivatives under the same conditions form 2 : 1 complexes with aluminium chloride[153].

Apparently the formation of high yields of hydroxylated benzothiadiazoles and benzoselenadiazoles when the corresponding alkoxy-derivatives are heated with anhydrous aluminium chloride is also preceded by intermediate complex formation[158,164,173,205]. σ-Complexes of benzothiadiazole and its chloromethyl derivatives with aluminium chloride have been isolated in the presence of hydrogen chloride, and examined spectroscopically[5,151].

3. Relation between Structure and Reactivity of Benzothiadiazoles and Benzoselenadiazoles

There is no generally accepted structure for benzothiadiazole and benzoselenadiazole. On the one hand it has been shown[5,206] that these heterocyclic systems reproduce the most important properties of naphthalene, being fully comparable in aromatic character, and in this sense are its heterocyclic analogues. Examination of chemical, spectroscopic, and structural results for 1,2,5-thiadiazole, benzothiadiazole, benzoselenadiazole, and their derivatives indicates that the quinoid structure reported[76,96,115,122,126,207,208] for these systems is incorrect. On the contrary, all the experimental results indicate that the actual state of the benzothiadiazole and benzoselenadiazole molecules corresponds to a structure containing quadrivalent sulphur (or selenium), which forms two π-bonds by means of *pd*-hybrid orbitals.

From the similarity in the properties of 1,2,5-thiadiazole and pyrazine, and of benzothiadiazole and quinoxaline, an analogy was noticed[5,206] between the syntheses of benzothiadiazole and quinoxaline. A similar analogy has been shown[10,11,16,30-32] in the formation of derivatives of 1,2,5-thia(and selena)diazole and pyrazine. The ready conversion of aliphatic compounds into 1,2,5-thia(selena)-diazoles[10,12-32] also indicates the aromatic structure of benzothiadiazole and benzoselenadiazole.

Recently published spectroscopic and physicochemical investigations are also consistent with the above view. Strom and Russell[196] studied the electron spin resonance spectra of radical-anions of benzothiadiazole and benzoselenadiazole, and found that the acceptance of unpaired electrons by the key heteroatoms increases from sulphur to selenium. They calculated the distribution of spin density in the anion of benzothiadiazole by the LCAO-MO method to the Hückel approximation for a *d*-model (taking into account the *d*-orbitals of sulphur) and for a *p*-model. They obtained identical results in good agreement with the experimental data. A similar result has been obtained by other workers[209].

The e.s.r. spectra of the radical-anions from benzothiadiazole, benzoselenadiazole, naphtho[1,2-*c*]-[1,2,5]-thiadiazole, naphtho[2,3-*c*]-[1,2,5]-thiadiazole, and naphtho[1,8-*cd*]-[1,2,6]-thiadiazine have been interpreted[201] by the LCAO-MO method to the Hückel approximation. The experimental results agree satisfactorily with the *p*-orbital model, which also correlates adequately with the polarographic reduction of these compounds. However, the authors note that the e.s.r. spectra of the radical-anions containing conjugated sulphur are insufficient by themselves to decide the character of the nitrogen–sulphur bond in these compounds, which requires more extensive experimental data covering many other properties.

Solodovnikov and Todres[209] compared an analysis of the e.s.r. spectra of radical-anions from benzothiadiazole and benzoselenadiazole with calculations of the distribution of spin density in these anions. They concluded that the key heteroatoms in the molecules are in some way involved in conjugation. They based this conclusion also on an analysis of the electronic absorption spectra. Other workers[210] have reached the same conclusion. Comparison of the e.s.r. spectra of radical-anions of benzothiadiazole, benzoselenadiazole, and their 4- and 5-chloro-derivatives shows that the maximum density of the unpaired electron in the radical-anion of (I) is located on the α-carbon atom. Similar results have been obtained by other workers[196,211]. Thus the radical-anions of benzothiadiazole and of naphthalene are characterised by spin density distributions of the same type.

The unpaired electron densities on the $C_{(4)}$ and $C_{(5)}$ atoms are different in the anions from benzoxadiazole and from benzothiadiazole but the same in the anion from benzoselenadiazole[209]. The proton hyperfine splitting constants at positions 4 and 5 are equal in the radical-anion from benzoselenadiazole, but different in those from benzoxadiazole and benzothiadiazole[210]. These results agree well with those of chemical investigations[5,206].

Delocalisation of electrons in the benzothiadiazole and benzoselenadiazole molecules is confirmed also by the proton magnetic resonance spectra of these systems, which closely resemble one another and that of naphthalene: the heterocyclic compounds exhibit "naphthalenelike" spectra[212]. All three systems possess similar spin–spin splitting constants. The effects of substituents in the benzene ring of (I) and (III) (nitro, chloro, methyl, and amino in positions 4 and 5) on the chemical shifts are qualitatively identical with (and quantitatively closely similar to) analogous effects in the benzene series[212-214].

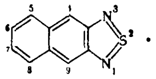
"Aromaticity" in the sense of the intensity of the ring current increases from sulphur to selenium[212].

These conclusions coincide with results of chemical experiments on the reactivity of benzothiadiazole and benzoselenadiazole[5,206]. Direct measurements of the magnetic susceptibility of these heterocyclic systems have confirmed the considerable levelling out of bonds in the heterocycle, i.e. the participation of the key atoms—sulphur and selenium—in forming the ring system of delocalised electrons[212].

It is interesting that the proton chemical shifts τ of 1,2,5-selenadiazole and 1,2,5-thiadiazole increase[32,212] from selenium (0.76) to sulphur (1.43),[29] i.e. in the opposite sequence to that following from the electronegativities of the key atoms. According to these results the selenadiazole is the most electrophilic.

Brown and Bladon[215] regard their results for the proton magnetic resonance spectra of benzothiadiazole and benzoselenadiazole as indicating that the six-membered rings are in some measure quinoid.

Ray and Narasimhan[211] have used the LCAO-MO method to calculate bond orders and lengths for 1,2,5-thiadiazole, benzothiadiazole, and naphtho[2,3-*c*]-[1,2,5]-thiadiazole (XV)



(XV)

They also calculated the π-electron density, the frontier electron density, and the localisation energy of the cation for positions 4 and 5 in (I) and positions 4–6 in (XV). Values of the spin density were computed for the radical-anion from (XV) as respectively 0.1130, 0.0413, and 0.0253 for positions 4–6 (experimental values not obtained). These workers[211] regard the calculated values as showing good agreement with corresponding experimental data where available, and also with experimental results for the reactivities and stabilities of these compounds.

The order of the N–S bond and the length of the C–N bond increase in the sequence—1,2,5-thiadiazole < (I) < (XV)—while the length of the N–S bond decreases in this sequence. These results are consistent with Cava and Schlessinger's view[216] that in the compound (XV) the sulphur is present in the quadrivalent state.

On the assumption that the sulphur is conjugated by means of *p*-orbitals Markov and Skancke[217] used the Pariser–Parr–Pople SCF MO method to calculate for the isomeric 1,2,5- and 1,3,4-thiadiazoles bond orders and lengths and π-electron charges on the sulphur, nitrogen, and carbon atoms. These workers[217] regard the calculated values as agreeing satisfactorily with certain experimental results. It must be noted that interatomic distances were not calculated for N–S, while the calculated C–C bond length diverges considerably from the observed values. Satisfactory agreement is found only for the C–N bond.

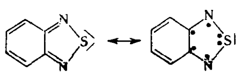
Soptrajanov[218] has shown that the enthalpy, entropy, and heat capacity increase in the sequence—1,3,4-thiadiazole, 1,2,5-thiadiazole, its deutero-analogue, and thiophen.

Calculated and experimental data relating to a quantitative estimate of the electronic structure of certain thiazoles and isomeric 1,2,5- and 1,3,4-oxa- and -thia-diazoles have been given[219], but no definite conclusions on the structure of the thiadiazoles.

Zahradnik and Koutecky[220] applied the LCAO-MO method to a comparative study of four isomeric thiadiazoles using the Longuet-Higgins model and a model which disregarded the participation of *d*-orbitals. They concluded that the limited experimental data can be interpreted better by the Longuet-Higgins model.

Kataev and Plemenkov[221] used the LCAO-MO method to the Hückel approximation to calculate the benzothiadiazole and benzoselenadiazole molecules, both with and without taking *pd*-hybridisation into account. They calculated the ionisation potentials, the $\pi-\pi^*$ transition energies, the π-moments of the molecules, the bond lengths, and the reactivity indices for both models. Comparison of calculated with experimental results showed that the actual state of these molecules corresponds to models involving *pd*-hybridisation.

The clearly defined aromaticity of (I) and (III) and the inability of their key atoms to increase their valency (to be oxidised) are consistent with another structure on the assumption that the sulphur (selenium) is involved in conjugation by the lone pair of electrons:



In this case aromaticity is achieved by the formation of a closed π*p*-electron system. In the benzenoid structure the closed system of electrons has the character $\pi(p-pd)$.[5,221]

With regard to which of these two structures represents the actual state of the molecule, the similarity of the chemical properties of benzothiadiazole and benzoselenadiazole to those of naphthalene, the similarity in the electronic spectra of benzothiadiazole and its derivatives to the typical spectra of fused aromatic compounds, the clearly defined aromatic character of benzothiadiazole and its derivatives revealed by their infrared spectra, the similarity of the proton magnetic resonance spectra of benzothiadiazole and of naphthalene, and the similarity in method of synthesis and in ultraviolet spectra between benzothiadiazole and quinoxaline, thiadiazole and pyrazine, and the similarity in the e.s.r. spectra of radical-anions from benzothiadiazole and from naphthalene—all these facts agree well with an aromatic, benzenoid structure for benzo-1,2,5-thiadiazole and benzo-1,2,5-selenadiazole.

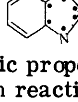
This conclusion is further confirmed by comparing benzothiadiazole and benzoselenadiazole with their oxygen analogue—the little studied benzofurazan. On nitration the nitro-group enters position 4, but the reaction occurs with considerably greater difficulty than in the (I) and (III) series. Benzofurazan readily adds four bromine atoms under normal conditions, is considerably less stable to oxidants, acids, and alkalis, and is more stable to reduction than are the thia- and selena-analogues. The reductive cleavage of benzofurazan by phenyl-lithium also takes place differently from that of (I) and (III).[181,182]

The ultraviolet spectrum of benzofurazan differs markedly from that of benzothiadiazole § and is displaced 30 nm to shorter wavelengths[10]. The dipole moments increase in conformity with the electronegativity of the key atoms in the sequence[223]

O > S > Se
D 4.37 1.73 0.94 .

The few experimental data give no adequate concept of the reactivity of benzofurazan. However, comparison of the properties which have been described with the corresponding properties of benzothiadiazole indicates that benzofurazan is weakly aromatic. On the whole the properties of the benzochalcogenadiazoles indicate that the sequence of increasing aromaticity (and hence diminishing "unsaturation") is—oxa < thia < selena.

Oxygen, in contrast to sulphur, is unable to expand its valency shell to ten electrons by means of *d*-orbitals. The weak aromatic properties of benzofurazan can be explained by the possibility of formation, in the planar[223–225] furazan ring, of a closed π*p*-system comprising six electrons. The structure of benzofurazan can therefore be represented by the formula



which reflects its aromatic properties.

Hence the difference in reactivity between benzofurazan and benzothiadiazole is explained by the different structures of these compounds. Since the above structure for benzofurazan is unique, it must be assumed that in benzothiadiazole and benzoselenadiazole the key heteroatom forms with the nitrogen atoms two π-bonds involving *pd*-hybrid orbitals[5,206,221].

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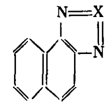
§The ultraviolet spectrum of furazan[222] also differs markedly from that of 1,2,5-thiadiazole.

IV. OTHER FUSED 1,2,5-THIADIAZOLES AND 1,2,5-SELENADIAZOLES

Naphtho[1,2-*c*]-[1,2,5]-thiadiazole (IV) and the corresponding napthoselenadiazole (XVI)

(IV, X=S)
(XVI, X=Se)



which were first obtained by Hinsberg[1,4], had not been investigated until recent years. These systems are stable towards acids, alkalis, oxidants, and heat, but are unstable towards reducing agents, which cleave the heterocycle.

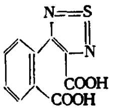
Naphthothiadiazole is nitrated as readily as is benzothiadiazole, forming predominantly the two isomeric 6- and 9-nitro-products[226,227], which can be reduced to the amino-derivatives by the action of iron in 2% acetic acid. The amines form readily hydrolysable salts, are acylated, are converted by means of the diazo-reaction into halogeno- and hydroxy-derivatives, and undergo the Bucherer reaction[226,227].

When naphthothiadiazole is chlorinated in acetic acid, either a dichloro-derivative or predominantly the 5-chloro-compound is formed, depending on the experimental conditions. The latter is obtained also by the action of sulphuryl chloride on the naphthothiadiazole. In formic acid or in the melt (in the presence of iron) chlorination occurs at position 5, and also a trichloro-derivative is formed identical with that obtained by chlorinating the 5-chloro-compound. Chlorination of molten naphthothiadiazole in the absence of iron yields an adduct—the 4,5-dichloro-4,5-dihydro-derivative[228].

Bromine acts on molten naphthothiadiazole to yield mainly the dibromo-derivative, whether in the absence or in the presence of iron[226,228]. In acetic acid the main product is the 4-bromo-compound.

Depending on the conditions and the concentration of oleum, sulphonation gives either the 4-sulphonic acid or (mainly) the corresponding disulphonic acid. Similarly, chlorosulphonation with chlorosulphuric acid gives either the 4-sulphonyl chloride or mainly the disulphonyl chloride, depending on the conditions[226,227].

The thiadiazole ring in the naphtho-compound resists oxidation by a chromic mixture: fission occurs at the $C_{(4)}-C_{(5)}$ bond, with formation of the dicarboxylic acid



The presence of electron-acceptor substituents, e.g. the nitro-group, enhances the stability of the system to oxidation. A chromic mixture or chromium trioxide in concentrated sulphuric acid produces no appreciable change in 6-nitronaphthothiadiazole: this compound is cleaved oxidatively only by an alkaline solution of potassium permanganate[226,227].

The spectrum of the radical-anion of the naphthothiadiazole has been studied[201].

Sulpho-derivatives of naphthoselenadiazole, obtained by Hinsberg's reaction, have been described[229-231].

Naphthoselenadiazole itself can, like naphthalene, be reduced by potassium or cathodically to form a radical-anion[209]. The latter is obtained also by reaction with the dipotassium salt of the dianion of cyclo-octatetraene[195] (difference from naphthalene—evidence of the electron-acceptor character of the heterocycle).

Comparison of the e.s.r. spectra of the anions of naphthoselenadiazole and benzoselenadiazole led to the conclusion that the distribution of spin density in the heterocycle probably changes little from benzologues to naphthologues[209].

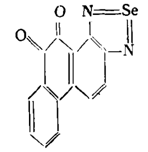
The linear naphtho[2,3-*c*]-[1,2,5]-thiadiazole (XV), which is isomeric with the above angular system (IV), was first obtained by Cava and Schlessinger[216], who showed that this compound undergoes diene synthesis with maleic anhydride and phenylmaleimide to form the corresponding adducts.

Oxidation of the linear naphthothiadiazole (XV) with potassium dichromate in acetic acid yields a heterocyclic analogue of anthraquinone, which can be reduced to a quinol of the linear naphthothiadiazole. The quinone is obtained also by cyclisation of 2,3-diamino-1,4-naphthaquinone with thionyl chloride[232,233].

Quantum-mechanical investigations of the linear naphthothiadiazole and its radical-anion have been reported[201,211].

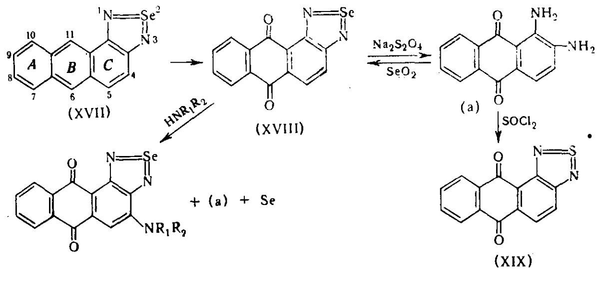
Depending on the conditions, chlorine and bromine act on the linear naphthothiadiazole to form either the 4,9-dihalogeno- or the 4,9-dihalogeno-4,9-dihydro-derivative. Chlorination with sulphuryl chloride gives a 41% yield of the 4,9-dichloro-derivative[234].

Among derivatives of phenanthrene only 10,11-dihydro-10,11-dioxophenanthro[1,2-*c*]-[1,2,5]-selenadiazole



obtained by Hinsberg's reaction, is known[235].

The same method has been used to obtain anthraselenadiazole and anthrathiadiazole, which have been subjected to several reactions[192,236-239]. Anthraselenadiazole (XVII) is oxidised by chromic acid to a quinone, which is reduced with the separation of selenium and the formation of 1,2-diaminoanthraquinone (a);[192] the latter can be converted either back into the quinone (XVIII) or into its thia-analogue (XIX):



Amines act on (XVIII) to produce partial amination of the benzene ring fused to the selenadiazole ring, the reaction being accompanied by formation of an *o*-diamine and separation of selenium[236,238].

Hydrogen or chlorine at position 4 in (XVIII) and (XIX) can be replaced by amino[237,238,240], arylthio, alkylthio, arylsulphonyl, and sulpho[239,241]. If chlorine is present at position 5, hydrogen at position 4 can also be replaced.

Chlorine at position 5 cannot undergo similar substitution. Several other reactions have been studied[241].

The above reductive opening of the selenadiazole ring has been considered[238] to involve initial addition of the amine at positions 4 and 5 of the dihydrodioxoanthraselenadiazole, after which the adduct is oxidised by the initial quinone, which is thus reduced mainly to 1,2-diaminoanthraquinone and selenium.

Nitration of the quinone (XIX) with a nitrating mixture at 50°C gives an 85% yield of a mixture of the 7- and 10-mononitro-derivatives in the proportions 1.5 : 1, which can be reduced with sodium hydrogen sulphide to the corresponding amines. Caustic soda acts on the nitro-derivatives to open the thiadiazole ring; the resulting 1,2-diaminoanthraquinones can be reduced to 1,2,5- and 1,2,8-triaminoanthraquinones[239].

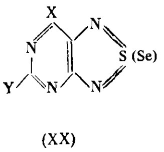
The fact that the nitro-groups enter the "outer" benzene ring A—not ring C—is explained[239] by deactivation of the latter by the thiadiazole ring, which is protonated in sulphuric acid.

A sulphurous diamide can be isolated[84] from the products of the action of alkali on the quinone (XIX) at 20°C. Both dihydrodioxoanthraselenadiazole (XVIII) and dihydrodioxophenanthroselenadiazole are equally readily cleaved by alkali to form the corresponding *o*-diamines. Fission of the selena- and thia-diazole rings by the action of alkalis on the quinone-diazoles is a convenient method for obtaining difficultly accessible derivatives of 1,2-diaminoanthraquinone[242,243].

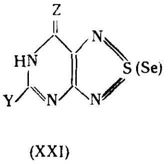
6,11-Dihydro-6,11-dioxoanthra[1,2-*c*]-[1,2,5]-thia(and selena)diazoles are chlorinated in acetic acid at position 4, but in sulphuric acid or oleum at positions 7 and 10, with the formation of 7,10-dichloro-derivatives[244].

Products in which the 1,2,5-thiadiazole and 1,2,5-selenadiazole rings have been fused with many cyclic systems—carbazoles, dibenzothiophens, dibenzoselenoles, benzothiazoles, benzoxazoles, quinoxalines, benzimidazoles, quinoline (by the Skraup synthesis from aminobenzothiadiazole)¶, pyridines, pyrimidines, pyridazine, benzo-1,2,5-thiadiazoles, and benzo-1,2,5-selenadiazoles—have now been investigated[41-45,78,79,81,88,106-108,131,174,176,245-260]. These complicated heterocyclic systems have been obtained mainly by reaction of the corresponding *o*-diamines with thionyl chloride, sulphinylaniline, or selenium dioxide. Systems containing a selenadiazole ring have been obtained also from amino- or acylamino-benzothiadiazoles and -benzoselenadiazoles by known methods[249,257,259].

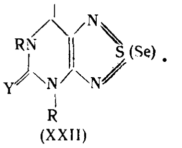
Especial interest attaches to investigations by Shealy and his coworkers[41-45,81] of several reactions of the pyrimidothiadiazole and pyrimidoselenadiazole derivatives



(XX)

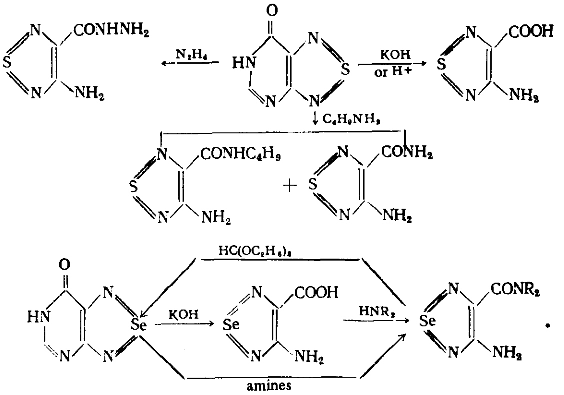


(XXI)



(XXII)

The substituents X = Cl, SH, $SCH_2C_6H_5$ in the compound (XX : Y = H) are shown to be highly mobile, and readily undergo substitution on reaction with aniline. The thiadiazole ring in (XX) is cleaved by lithium tetrahydroaluminate or by hydrogen sulphide to the corresponding *o*-diamines. Basic and acidic reagents under mild conditions open the pyrimidine ring:



V. SPECTROSCOPIC PROPERTIES OF 1,2,5-THIADIAZOLES AND 1,2,5-SELENADIAZOLES

Many workers have studied the spectroscopic characteristics of 1,2,5-thiadiazoles, 1,2,5-selenadiazoles, and their fused systems in both the ultraviolet and the infrared for the purposes both of identification and of comparison with the corresponding data for typical aromatic and heteroaromatic compounds[5,9,12,21,24,32,35,59,96,97,102,114-116,122,126,144,151,157,205,207,216,234,245-248,260-273]. The Raman spectra of the monocyclic and fused heterocycles have also been studied[264,267-269,271,272].

The ultraviolet spectra revealed a constant bathochromic shift in the absorption maximum on passing from thiadiazole and benzothiadiazole derivatives to their selenium analogues. Similarity in the character of the absorption and in the distribution of the maxima was observed in the ultraviolet spectra of benzothiadiazole and quinoxaline, and of 1,2,5-thiadiazoles and pyrazines[5,9,206]. Sawicki[248] explains the similarity of the ultraviolet spectra of several benzothiadiazole and benzoselenadiazole derivatives to those of the corresponding *o*-aminonitrobenzenes—the initial compounds for the synthesis of these heterocycles—by regarding the heterocyclic derivatives as *ortho*-substituted.

Bird and Cheeseman[270] compared the infrared spectra of benzoselenadiazole and twenty-five of its mono- and di-substituted derivatives with those of di-, tri-, and tetra-substituted benzenes. They felt that the results did not permit any conclusions to be drawn on the distribution of electron density or the fine structure of the benzoselenadiazole derivatives.

Soptrajanov and Ewing[267] made a comprehensive investigation of the vibrational spectra of 1,2,5-thiadiazole and its dideuterated derivative[267]. They gave a complete interpretation of the infrared spectra of liquid and gaseous specimens and of the Raman spectra of liquid 1,2,5-thiadiazole.

Benedetti and Bertini[271] studied the infrared spectrum over the range 4000–400 cm^{-1} of 1,2,5-selenadiazole in solid, liquid, and gaseous states and dissolved in carbon disulphide. The Raman spectrum was recorded for liquid selenadiazole. The molecule of this compound was shown to be planar, the key atoms—sulphur and selenium—being conjugated.

A satisfactory correlation has been demonstrated[200,273] between the positions of the maxima in the ultraviolet

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¶4- and 5-Aminobenzothiadiazoles also undergo the Herz reaction[252], as well as with aryl isothiocyanates[261].

absorption spectra of 4- and 5-substituted benzoselenadiazoles and benzothiadiazoles and the Hammett σ_m and σ_p constants.

A study has been made of the infrared, ultraviolet, and proton magnetic resonance spectra of two isomeric pyrido-1,2,5-selenadiazoles[260]. The proton magnetic resonance spectra were regarded[260] as indicating considerable fixation of C–C bonds in the pyridine ring.

Study of the mass spectra of benzoselenadiazole, its 5-methyl and 4,5,6-trimethyl derivatives, and phenanthro-[1,2-*c*]-[1,2,5]-selenadiazole showed[274] that, in spite of the great stability of their molecular ions M^+, the two carbon-nitrogen bonds undergo rupture on electron bombardment with the formation of ions of dehydrobenzene or its analogues. It has also been shown[275] that benzoselenadiazole is less stable to electron bombardment than is phenazine or the above phenanthraselenadiazole (it splits off hydrogen cyanide more easily).

The mass spectra of 1,2,5-thia- and -selena-diazoles have been studied also by Marquardt[35] and Weinstock et al.[29] The stability of these heterocycles towards electron bombardment is evidence of their aromatic character.

From investigation of the infrared and ultraviolet spectra of benzothiadiazole and some of its derivatives the conclusion is drawn that it represents a typical heteroaromatic system[5,206,262-265] and there are no grounds for supposing that benzothiadiazole and benzoselenadiazole have a quinoid structure.

VI. APPLICATION OF DERIVATIVES OF 1,2,5-THIADIAZOLES AND 1,2,5-SELENADIAZOLES

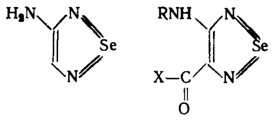
1,2,5-Thiadiazole and its benzo- and pyrimido-systems are in their way analogues respectively of pyrazine, quinoxaline, and pteridine, present in many biologically active compounds. There are indications that several derivatives of benzothiadiazole possess low toxicity[8].

The biological properties of acid derivatives of 1,2,5-thiadiazole have been investigated in detail. Hydrazides of the 3-carboxylic acid are active against *Escherichia coli*,[9] and also inhibit the action of monoamino-oxidase[276]. The *N*-phenylisopropylammonium salt of this acid has a strong stimulating action on the central nervous system and on respiration[277]. Sulphanilamides of the thiadiazole and selenadiazole series possess bactericidal activity[59,61,278-280]: thus 3-sulphanilamido-1,2,5-thiadiazole has been recommended[61,62,280] for the treatment of coccidiosis in poultry.

Several halogenated and hydroxylated 1,2,5-thiadiazoles have been found to have a bactericidal effect[12,14]. Among the above heterocyclic compounds substances have also been detected which possess insecticidal[162,163], fungicidal, herbicidal[55,56,64,65,280], antihelminthic[281-283], nematocidal[64,65], and diuretic[143] action.

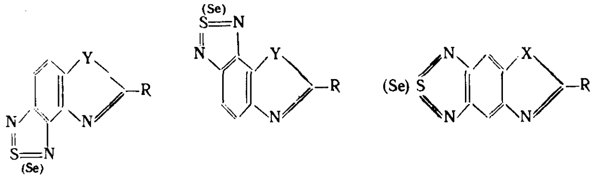
Daams, Koopman, and their coworkers have recently compared[112,113,283-285] the structure with the herbicidal and fungicidal action of chlorinated benzothiadiazoles. According to their observations the strongest herbicide is the 4,5,7-trichloro-derivative, and also the 5,7-dichloro-4-methyl compound. The latter, as well as several dichloronitrobenzothiadiazoles, exhibits high fungicidal activity. 4,5,7-Trichlorobenzothiadiazole has been proposed[286] in particular for the fight against harmful members of the fish fauna.

Several thia- and selena-diazole derivatives possess antitumorigenic activity. Shealy and his coworkers have reported[41,287] a new class of cytotoxic agents, the selenadiazoles, among which the most effective have been found to be



where R = H, Alk and X = OH, N<. Such activity is possessed also by several pyrimido-1,2,5-selenadiazoles[255,256] and their thia-analogues[249 288-290] containing hydroxy- and amino-groups in the pyrimidine ring. *NN*-Bischloroethylamino-derivatives of benzothiadiazole[5,160], including analogues of *o*- and *p*-sarcolysin, are of interest in this connection.

As mentioned above, fused thia- and selena-diazoles can be coupled with diazonium salts to form azo-dyes. Several of them show promise for industrial synthesis[205,291]. Cyanine dyes containing thia- and selena-diazole rings have been synthesised by Soviet[246,247] and Italian[245,292] chemists on the basis of the systems



(where X = S, NR; Y = O, S, Se, CH:CH, NR; and R = H, CH_3) and other fused heterocycles containing reactive methyl groups.

3-Chloro-1,2,5-thiadiazole has been claimed to possess good solvent power for certain polymers[18,61]. It is said[52] to be possible to obtain synthetic condensation resins from 1,2,5-thiadiazoline 1,1-dioxide and dialdehydes[52].

The analytical usefulness of the ability of thia- and selena-diazole derivatives to form complexes can be judged in particular from the possibility of detecting palladium in the presence of platinum(IV), nickel, cobalt, and lead by means of benzoselenadiazole[203]. It has been suggested that the ability of coloured solutions of certain derivatives of this compound, e.g. 5-(3,4-diaminophenyl)-benzoselenazole, to absorb in a certain range of the ultraviolet spectrum, should be used for analytical purposes[291,293,294]. This will permit a quantitative determination of the selenium content of benzoselenadiazole derivatives

The formation of certain derivatives—e.g. 4,5-dichlorobenzoselenadiazole, 5,5′-bibenzoselenadiazolyl—from the corresponding *o*-diamines can be used for the spectrophotometric determination of Se^{IV}.[273,295]

Dihydrodioxoanthra-thia- and -selena-diazoles can be used to obtain daylight-fluorescent colorants which show promise for practical application[296].

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Leningrad Chemical and
Pharmaceutical Institute

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Structural and Steric Factors Determining the Rate of Autoxidation of α-Methylene Groups in Alkylarenes and Alkenes

V.V.Voronenkov, A.N.Vinogradov, and V.A.Belyaev

Data on structural and steric effects in the autoxidation of alkylarenes and alkenes are summarised. Special attention is paid to the effect of steric hindrance on the rate of oxidation of an α-CH bond in various hydrocarbons—alkylbenzenes, alkylnaphthalenes, alkenes, alkylindanes, and tetrahydronaphthalenes—and data are given on the relation between their refractions, ultraviolet spectra, and rate of oxidation. The role of the molecular conformation of the hydrocarbons in the conjugation of single bonds is demonstrated, together with the effect of this conjugation on the rate of autoxidation of the α-CH bond. A list of 91 references is included.

CONTENTS

1. Introduction

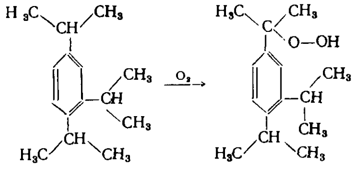
Oxidation with molecular oxygen (autoxidation) provides the basis for the large scale production of several synthetic organic products. Hence the publication of a number of reviews and monographs[1-4] on the autoxidation of hydrocarbons is not accidental. However, these works make no detailed examination of the influence of structural and steric factors on the rate of autoxidation. Yet recent investigations prove fairly convincingly[5-8] that the rate of autoxidation is determined in considerable measure by the chemical and three-dimensional structure of the molecules and by the presence of steric hindrance. Investigation of these effects is of value in understanding the mechanism of the oxidation of hydrocarbons.

2. Alkylbenzenes

The early experimental papers, which contained information on the influence of steric factors on the rate of autoxidation of alkylated aromatic compounds and their derivatives, reported investigations by Remsen[9-13] and by Ciamician and Silber[14]. Remsen noted that the ease of oxidation of a methyl group attached to an aromatic ring depends on the space occupied by the adjacent substituent. The latter workers studied the autoxidation of the isomeric xylenes, and concluded that *o*-xylene is the most resistant to oxidation, and the *para*-isomer the most unstable (the *meta*-isomer occupies an intermediate position). Mowry obtained similar results for the oxidation of the diethylbenzenes[15]. Erofeev and Chirco[16] found that the rate of autoxidation of the α-methylidyne group in *o*-cymene is half that in the *para*-isomer. Eventova and Mashkina[17] studied the oxidation of the di-isopropylbenzenes, and found that the tendency to oxidation increased in the sequence *ortho*–*meta*–*para*. The same order occurs with the cyclohexyltoluenes[18].

The spatial proximity of the adjacent alkyl groups in *o*-dialkylbenzenes is responsible not only for a decrease in the rate of oxidation of the α-methylene groups but also the formation of new oxygen-containing derivatives—α-lactones—during oxidation. Volkov and his coworkers[19-21] found that phthalans (0.2–0.3%) are formed in the earliest stages of the oxidation of *o*-alkyltoluenes and their homologues.

Thus the diminished rate of autoxidation of *o*-dialkylbenzenes and the accompanying formation of α-lactones are due to *ortho*-substitution (the "*ortho*-effect"). This effect determines the path and the rate of oxidation of other polyalkylbenzenes. Thus in the liquid-phase oxidation of 1,2,4-tri-isopropylbenzene[19,20] only the isolated isopropyl group undergoes oxidation, while the other two groups (located side by side) remain almost unoxidised:



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The use of chromatographic methods of analysis made it possible to refine quantitatively the laws of the autoxidation of polyalkylbenzenes. For example, the relative rates of reaction of isopropylbenzene, 1-isopropyl-3,4-dimethylbenzene, 1-isopropyl-2,5-dimethylbenzene, and 1-isopropyl-2,3-dimethylbenzene with tertiary peroxy-radicals were 1, 2.1, 0.92, and 0.91[21]. It is interesting that even in the early work Weissberger[22,23], who investigated the autoxidation of benzoin and its homologues, noted that the reaction velocity is greatly dependent on the nature and position of substituents in the benzene ring (Table 1).

In this case steric hindrance due to *ortho*-substitution is shown in a marked decrease in the rate of oxidation, as in the *o*-dialkylbenzenes. Here the *ortho*-effect could be assessed numerically, because, according to Weissberger[23], the autoxidation rate coefficients which would be expected in the absence of an *ortho*-effect could be calculated.

The diminished rate of autoxidation in *ortho*-substituted alkylbenzenes was explained solely by mechanical factors—repulsion of substituents or shielding of the α-carbon atom by adjacent alkyl groups[24]. This interpretation of the influence of substituents does not indicate why the *meta*-isomer, in which there is no shielding of the α-carbon atom, is oxidised just as slowly as the *ortho*-isomer. An alternative explanation was based on the mechanism of autoxidation and the geometry of the transition state for hydrocarbons[5].

Table 1. Rates of autoxidation of substituted benzoins.

$Ar^1-\overset{O}{\overset{\Vert}{C}}-CH(OH)-Ar^2$	$10k_{20}$, observed
$Ar^1 = Ar^2 =$ *o*-diethoxyphenyl	7.32
$Ar^1 = Ar^2 =$ *p*-diethoxyphenyl	29.4
$Ar^1 = Ar^2 =$ *o*-dimethoxyphenyl	20.4
$Ar^1 = Ar^2 =$ *p*-dimethoxyphenyl	36.6
$Ar^1 =$ phenyl; $Ar^2 =$ *o*-tolyl	260.0
$Ar^1 =$ *o*-tolyl; $Ar^2 =$ phenyl	29.4
$Ar^1 = Ar^2 =$ *o*-chlorophenyl	725.0
$Ar^1 = Ar^2 =$ *p*-chlorophenyl	900.0

The liquid-phase autoxidation of alkylated aromatic hydrocarbons takes place by a free-radical chain mechanism, the attack usually occurring at hydrogen attached to a carbon atom in the α-position with respect to the aromatic ring. This is explained by the relative inactivity of the peroxy-radical $ROO^{\bullet}$ in the main chain-propagation reaction.

$$ROO^{\bullet} + R'H \rightarrow ROOH + R^{\bullet} \tag{I}$$

so that it acts fairly selectively: it attacks preferentially highly reactive bonds—homolytically conjugated C–H bonds of the α-carbon atom[25,26]. The rate of homolytic detachment of hydrogen in reaction (I) is determined by the strength of the α-C–H bond and the stability of the resulting radical. The strength of the bond under attack depends substantially on its σπ-conjugation with the aromatic ring. Thus, for example, the energy of rupture of a C–H bond in methane, where there is no σπ-conjugation, is 23–24 kcal $mole^{-1}$ greater than that for a similar bond in toluene, a compound with well defined σπ-conjugation[27].

Thus decreased σπ-conjugation between the benzene ring and the α-C–H bond under attack in the alkyl group should lead to a corresponding increase in its energy, and hence to an increase in the activation energy and a decrease in the rate of oxidation[28]. The diminished reactivity of the C–H bond in *o*-dialkylbenzenes indicates weakening of its conjugation with the benzene ring and diminished polarisability of molecules of this type. This conclusion is supported by the lower molar refraction MR_D of *o*-dialkylbenzenes compared with the *para*-isomers (Table 2).

Since molar refraction is proportional to the volume of the atoms, its dimunution in *o*-dialkylbenzenes indicates that their atoms are more compactly arranged than in the molecules of the *para*-isomers[29]. This is supported by the fact that the former isomers have higher densities, refractive indices, and boiling points[30].

The compaction of the alkyl groups in *o*-dialkylbenzenes (in *o*-cymene, for example, the methyl group forces the adjacent isopropyl group out of the plane of the benzene ring) destroys the σπ-conjugation of the α-C–H bond with the benzene ring. This is apparent in a decreased polarisability, and hence a decrease in the electron mobility of *o*-dialkylbenzenes compared with the *para*-isomers[31–38]. For the same reasons changes occur in electronic (ultraviolet) absorption spectra in dialkylbenzenes[39–43].

Table 2. Molar refraction of dialkylbenzenes.

Hydrocarbon	MR_D	ΔMR_D
p-Xylene	36.02	0.25
o-Xylene	35.77	—
p-Cymene	45.34	—
o-Cymene	45.04	0.30
p-Diethylbenzene	48.82	—
o-Diethylbenzene	48.53	0.29
p-Di-isopropylbenzene	54.65	—
o-Di-isopropylbenzene	54.35	0.30

The changes occurring in the electronic spectra of benzenes as a result of introducing an alkyl group into the ring are due to displacement of the electrons of the α-C–H bonds towards the ring, i.e. to σπ-conjugation. The presence of steric hindrance in the molecule weakens the conjugation of the alkyl group with the benzene ring to a greater or lesser extent. This weakening results in a shift of the electronic spectra to shorter wavelengths accompanied by a diminution in the intensity of absorption. On the other hand, displacement to longer wavelengths with increase in intensity indicates an increase in the conjugation of the system. Such spectra are distinguished by a steep rise to high extinctions with fine structure (Fig. 1).

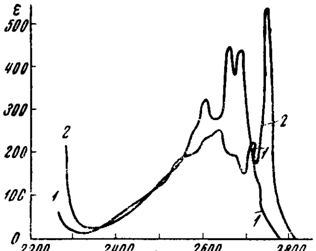
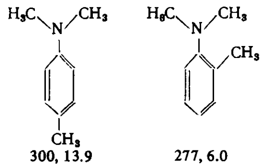


Figure 1. Ultraviolet absorption spectra of: 1) *o*-cymene; 2) *p*-cymene.

For dialkylbenzenes containing hydrogen atoms attached to the α-carbon atom the shift to longer wavelengths accompanied by increased strength of absorption occurs in the sequence—*ortho*, *meta*, *para*—as is clearly evident from Table 3. The same applies to the isomeric *NN*-dimethyl-*o*- and -*p*-toluidines[44]



300, 13.9 277, 6.0

(λ_{max} in μm, $10^{-3}\varepsilon$).

It has been remarked earlier that the dialkylbenzenes form the sequence—*ortho–meta–para*—according to their tendency to liquid-phase autoxidation. The absorption coefficients of the electronic spectra and also the exaltation of molar refraction—constants which characterise the mobility of the electrons in the dialkylbenzene molecules—increase in the same sequence. Thus there is a direct connection between the oxidisability of a C–H bond involving an α-carbon atom and its capacity for $\sigma\pi$-conjugation (electronic delocalisation): a high degree of $\sigma\pi$-conjugation between the bond and the benzene ring leads to greater oxidisability of the bond.

Table 3. Ultraviolet spectra of *o*- and *p*-dialkylbenzenes [39]*.

Compound	λ_{max}	ϵ_{max}
p-Xylene	2740	600
o-Xylene	2630	275
p-Diethylbenzene	2730	420
o-Diethylbenzene	2635	245
p-Cymene	2735	530
o-Cymene	2630	250
p-Di-isopropylbenzene	2715	370
o-Di-isopropylbenzene	2635	245

* The values of λ_{max} and ϵ_{max} for *m*-dialkylbenzenes are very close to the corresponding values for *o*-dialkylbenzenes.

This is confirmed by the kinetics of the autoxidation of dialkylbenzenes. Fig. 2 gives rate curves for the absorption of oxygen during the autoxidation of *o*- and *p*-cymenes [5], which show appreciable differences in the rates, *p*-cymene being oxidised considerably more rapidly than the *ortho*-isomer. A similar difference in rates of autoxidation is observed with a mixture of *o*- and *p*-dialkylbenzenes [45,46] and a mixture of isomeric alkylchlorobenzenes (Fig. 3). In particular the relative rate constants for the oxidation of the chloroisopropylbenzenes [6] are $k_p : k_m : k_o = 10 : 7 : 1$.

The hindrance to conjugation in *o*-diaklylbenzenes exists not only in the initial molecule but also in the transition state and in the radical. The geometry of the transition state in the autoxidation of hydrocarbons, e.g. cumene, can be represented by the scheme in Fig. 4. This shows that, during attack by the radical ROO• on the C–H bond, all three angles of the σ-bonds at the α-carbon atom change from 109° (the tetrahedral angle) to 120° in the radical, in which the three valences of the α-carbon atom are coplanar with the benzene ring. In this case maximum delocalisation of the unpaired *p*-electron is accomplished, with creation of a single "through" conjugated system covering the whole radical. A stable radical, capable of continuing the oxidation chain, is thereby formed. However, formation of a planar radical becomes difficult if *ortho*-substituents are present in the aromatic ring. Fig. 5 shows that coplanarity of the radical is impeded by overlapping of the van der Waals spheres [47,48] of the methyl and *o*-isopropyl groups, which are not directly bound to one another. In this case there is no gain in energy due to conjugation, which might have partly balanced (diminished) the energy required to break a C–H bond involving the α-carbon atom of the alkyl. For the same reason a stable radical capable of continuing the oxidation chain is not obtained.

Thus the steric hindrance ("*ortho*-effect") in the autoxidation of alkylated aromatic hydrocarbons consists essentially in destruction of the coplanarity of the system, which results in breakdown in the $\sigma\pi$-conjugation of the α-C–H bond with the benzene ring ("steric inhibition of mesomerism").

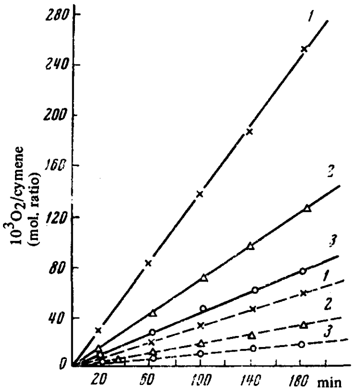


Figure 2. Rate curves for the absorption of oxygen in the presence of 4 wt. % of isopropylbenzene hydroperoxide at (°C): 1) 120; 2) 110; 3) 100. Full lines represent *p*-cymene; broken lines represent *o*-cymene.

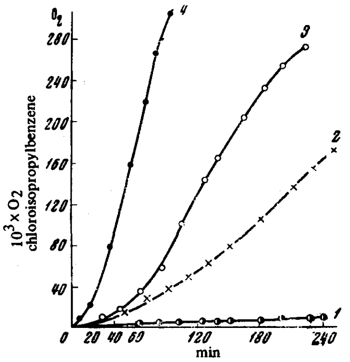
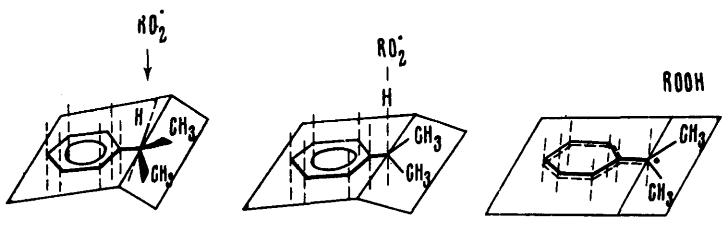


Figure 3. Effect, on rate of oxidation of chloroisopropylbenzene (with 0.6 wt. % of Na stearate + 4 wt. % of CaO at 120°C), of isomeric composition (wt. %): 1) 83 *o* + 13 *p*; 2) 34.3 *o* + 19.8 *m* + 45 *p*; 3) 23.55 *o* + 7.25 *m* + 69.2 *p*; 4) 7.42 *o* + 4.13 *m* + 88.5 *p*.

Similar conclusions were reached by Kooyman and Strang [49–51] in a study of the reactivity of α-methylene [and methylidyne (Ed. of Translation)] groups in various hydrocarbons towards the •CCl_3 radical. They found that the reactivity of the α-hydrogen atoms was greatly dependent on the coplanarity of the benzene ring and the α-carbon atom in the transition state. A quite close correlation was observed in the relative activities of •CCl_3 and ROO• radicals towards the same α-hydrogen atoms (Table 4).



initial state transition state final state—radical

Figure 4. Graphical representation of transition state in the oxidation of cumene.

The rate of autoxidation of an α-C–H bond is, of course, governed not only by the position but also by the nature of alkyl groups present in the benzene ring. Thus Russell[52], who studied the autoxidation of hydrocarbons in the presence of an initiator at 90°C, showed that (*a*) the relative rates of oxidation of cumene, ethylbenzene, and toluene were respectively 1 : 0.59 : 0.075; and (*b*) electron-donor substituents, e.g. methyl, accelerate autoxidation, whereas electron-acceptor substituents (COOH, NO_2, Cl, Br, etc.) slow it down.

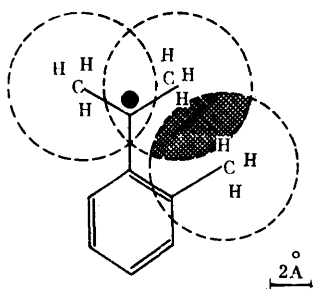


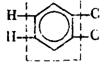
Figure 5. Effect of steric hindrance in the radical of *o*-cymene.

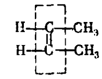
Similar results were obtained by Ingold[53], who found that the rates of autoxidation of *p*-nitrocumene, cumene, and *p*-cymene were approximately in the proportions 1 : 2 : 4. He also gave interesting data on the relative reactivities of the α-C–H bond in several alkylated aromatic hydrocarbons towards various radicals (Table 5). It is seen that the rate of abstraction of hydrogen from the α-carbon atom increases from toluene to cumene for all radicals other than ROO•. Although this radical removes hydrogen attached to the tertiary carbon atom in cumene, the rate of oxidation is lower than in ethylbenzene. A probable explanation is that the peroxy-radical formed from ethylbenzene is more active than that formed from cumene.

The autoxidation of alkylbenzenes is sensitive not only to the steric hindrance of $\sigma\pi$-conjugation in the molecule but also to such a delicate electronic effect in hydrocarbon molecules as the "alternation effect". This was shown by the work of Eventova and her coworkers[54] on the oxidation of the diphenylalkanes $C_6H_5[CH_2]_nC_6H_6$, the rates of which alternate with increase in *n*: i.e. the rate increases with an even number of carbon atoms in the polymethylene chain, but then decreases with an odd number (Table 6); this suggests that the chain is conjugated.

3. Alkenes

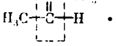
From the point of view of molecular symmetry *o*-dialkylbenzenes (I) correspond to the analogous *cis*-ethylene (I*a*)[55-60], and *para*-substituted benzenes (II) to the analogous *trans*-compounds (II*a*):





(Ia)

(II)



(IIa)

.

Table 4. Relative reactivity of hydrogen atoms in hydrocarbons towards radicals.

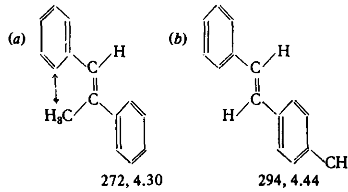
Hydrocarbon	$\cdot CCl_3$ [49,51]	ROO· [5,51]
Toluene	1	1
Isopropylbenzene	12.5	13.3
o-Cymene	1.1	1.3
p-Cymene	5.6	4.0

Table 5. Relative reactivities of hydrocarbons towards radicals.

Radical	Ethylbenzene	Cumene
$(CH_3)_3CO\cdot$	3.2	6.8
$C_6H_5\cdot$	4.6	9.7
ROO·	8.1	2.3
Br·	17.0	37.0
$Cl_3C\cdot$	50.0	260.0

In fact, the alkyl groups in *cis*-alkenes, like those in *o*-dialkylbenzenes, are squeezed together as a consequence of their proximity (Fig. 6). This results in increases in density and refractive index, rise in boiling point[30], and decrease in molar refraction in comparison with *trans*-alkenes (Table 7).

The relation between the ultraviolet spectra of *cis*- and *trans*-alkenes is similar to that between those of *o*- and *p*-dialkylbenzenes. For example, the absorption maximum of methyl-*trans*-stilbene (*a*), which exhibits "*cis*-packing" between methyl and phenyl, lies at a shorter wavelength than that of the *para*-isomer (*b*):



(λ_{max} in μm, log ε). In general *cis*-isomers have their maximum absorption at rather shorter wavelengths, and the absorption coefficient is in all cases considerably smaller than for the *trans*-forms[43].

Table 6.

No. of C atoms n = 1	2	3	4	5	6
Oxidation, % = 11.8	21.5	17.0	26.0	23.0	42.0

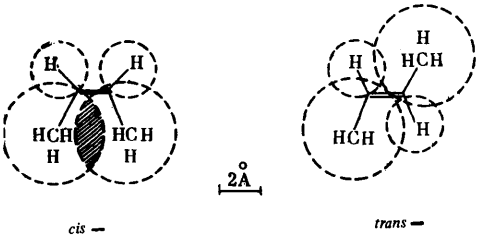
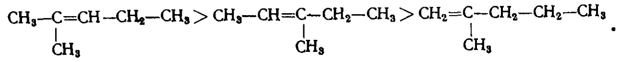


Figure 6. Interaction of atomic groupings, not directly combined together, in *cis*- and *trans*-but-2-ene.

Thus the "packing" in the *cis*-alkene molecule, like that in the *o*-dialkylbenzene molecule, destroys the coplanarity of the double bond with the trigonal α-carbon atom, thereby diminishing the degree of σπ-conjugation of the α-C—H bond. This leads to an increase in the energy of rupture of this bond compared with that of a C—H bond in *trans*-alkenes. This was shown initially in homolytic chlorination, which, like liquid-phase oxidation, has a radical-chain mechanism. Walling and Thaler[61] found that the homolytic chlorination of *trans*-but-2-ene with t-butyl hypochlorite yields 83% of *trans*-1-chlorobut-2-ene, whereas that of *cis*-but-2-ene under comparable conditions gives 65% of *cis*-1-chlorobut-2-ene. A similar difference in reactivity is apparent in the liquid-phase oxidation of isomeric *cis*- and *trans*-alkenes. The oxidation of a mixture of *cis*- and *trans*-4-methylpent-2-ene by oxygen shows[62] that the oxidisability of an α-C—H bond is considerably greater in the *trans*-alkene than in the *cis*-isomer (Figs. 7 and 8). The oxidation rate constants at 70°C were respectively 0.00385 and 0.0086 M min^{-1} for *trans*- and *cis*-forms.

Comparison of data obtained by various workers[63-67] on the autoxidation of branched alkenes clearly reveals that the oxidisability of α-methylene groups, e.g. in methylpentenes, diminishes in the sequence



$$\underset{\displaystyle CH_3}{CH_3—\overset{|}{C}}=CH—CH_2—CH_3 > CH_3—CH=\underset{\displaystyle CH_3}{\overset{|}{C}}—CH_2—CH_3 > CH_2=\underset{\displaystyle CH_3}{\overset{|}{C}}—CH_2—CH_2—CH_3 .$$

The molar refraction and the exaltation decrease in the same sequence. Nevertheless, it is evident that enhanced oxidisability of α-methylene groups is observed where the methyl and the oxidisable α-methylene group are in the *trans*-position (parallel).

Table 7. Molar refraction of *cis*- and *trans*-alkenes.

Hydrocarbon	MR_D	ΔMR_D
trans-Pent-2-ene	25.61	0.25
cis-Pent-2-ene	25.38	
trans-Hex-2-ene	25.59	0.24
cis-Hex-2-ene	29.34	
trans-Hex-3-ene	29.61	0.21
cis-Hex-3-ene	29.40	
trans-3-Methylpent-2-ene	29.96	0.25
cis-3-Methylpent-2-ene	29.71	
trans-4-Methylpent-2-ene	29.75	0.24
cis-4-Methylpent-2-ene	29.51	
p-Xylene (*trans*)	36.02	0.25
o-Xylene (*cis*)	35.77	

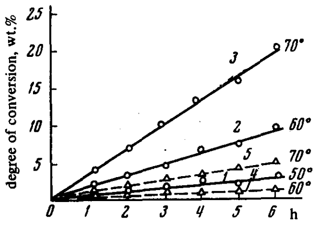
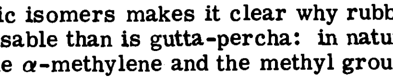


Figure 7. Variation in degree of conversion (with 0.5 mole % of 2-methylpent-2-ene hydroperoxide at 50—70°C):
1)—3) *trans*-4-methylpent-2-ene; 4, 5) *cis*-4-methylpent-2-ene.

These results, which support Nesmeyanov's conclusion[68] that the single bonds are more highly conjugated in *trans*-alkenes, make it possible to estimate the oxidisability of certain polymeric hydrocarbons, e.g. rubber and gutta-percha



Comparison of the three-dimensional structures of these two polymeric isomers makes it clear why rubber is more readily oxidisable than is gutta-percha: in natural rubber the oxidisable α-methylene and the methyl groups are in the *trans*-position, in which steric hindrance is absent; in gutta-percha, however, these two groups are in the *cis*-position, causing steric hindrance to conjugation, and hence a decrease in the reactivity of the α-methylene group.

4. Monoalkylnaphthalenes

Isomeric 1- and 2-alkylnaphthalenes differ in physical properties in the same way as *o*- and *p*-dialkylbenzenes. This is shown by their boiling points, specific gravities, refractive indices, and molecular refraction[69]. Comparison of the latter shows that the 1-isomer possess a lower refraction than their 2-analogues. Table 8 gives these data for the liquid hydrocarbons and their solutions[29].

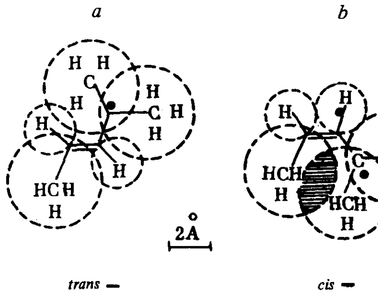


Figure 8. Radicals obtained by autoxidation of: *a*) *trans*-4-methylpent-2-ene; *b*) *cis*-methylpent-2-ene.

The diminished refraction of 1-alkylated naphthalenes in liquid and dissolved states supports the view that intramolecular factors—interaction between adjacent alkyl groups which are not directly bound to one another—are responsible for the regular variation in refraction, as in the case of *o*- and *p*-dialkylbenzenes and *cis*- and *trans*-alkenes. Fig. 9 illustrates such interaction for 1- and 2-monoalkylnaphthalenes.

Table 8. Molar refraction of 1- and 2-monoalkylated naphthalenes.

Substituent	Liquids		Solutions	
	MR_D	ΔMR_D	MR_D	ΔMR_D
2-Methyl	49.24	0.42	49.42	0.40
1-Methyl	48.82		49.02	
2-Ethyl	53.88	0.42	53.86	0.41
1-Ethyl	53.46		53.45	
2-Isopropyl	58.89	0.41	—	—
1-Isopropyl	58.48		—	
2-Butyl	63.31	0.43	—	—
1-Butyl	62.88		—	
2-Iodo	57.88	1.34	57.65	1.14
1-Iodo	56.54		56.51	

1-Alkylnaphthalenes have a lower optical exaltation as well as a lower refraction than the 2-isomers. This is all because the packing of the "*peri*-hydrogen" in 1-alkylnaphthalenes forces the adjacent $C_{Ar}-C_{Alk}$ bond out of the plane of the naphthalene ring, with a resultant breakdown in σπ-conjugation of the ring with an α-C–H bond in the alkyl group[70,71]. Thus steric hindrance to σπ-conjugation arises not only from the influence of bulky *ortho*-substituents but also from that of hydrogen in the *peri*-position with respect to the substituent in the 1-position of naphthalene. The occurrence of steric hindrance to σπ-conjugation in 1-alkylnaphthalenes is indicated also by the fact that the electronic absorption spectra of 2-alkylnaphthalenes, like those of *p*-dialkylbenzenes, possess a more intense long-wavelength maximum than do the 1-isomers.

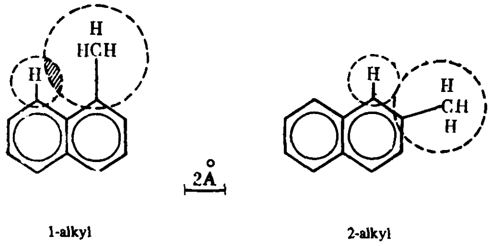


Figure 9. Interaction of unlinked groups in monoalkylnaphthalenes.

For the same reason the degree of conjugation of the unpaired *p*-electron of a new 1-alkylnaphthalene radical is lower and its stabilisation diminished, so that the radical is unable to continue the oxidation chain. This conclusion is supported by the oxidation rate curves for 1- and 2-monoalkylnaphthalenes illustrated in Fig. 10.

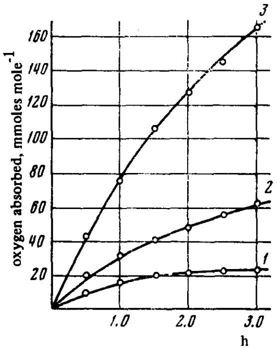
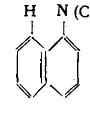


Figure 10. Variation in rate of oxidation of isopropylnaphthalene (with 0.01 wt.% of manganese resinate at 110°C) with amount (wt.%) of 1-isopropyl compound mixed with the 2-isomer: 1) 70; 2) 55; 3) 12.

It is interesting that analogous hindrance to conjugation[72] arises also in compounds of the type



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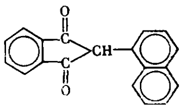
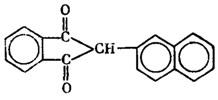
The above concepts can obviously explain also the difference in oxidisability of the tetrahydro-5(and 6)-isopropylnaphthalenes[73] and between 2-naphth-1′-ylindane-1,3-dione (*a*) and the corresponding 2-naphth-2′-yl derivative (*b*)[74].

(*a*)



(*b*)



Whereas 1-alkylnaphthalenes are less reactive in reactions involving autoxidation of an α-C–H bond in the alkyl, they are more reactive in the radical polymerisation of 1-vinylnaphthalenes. For example, 1-vinylnaphthalene polymerises about 2.5 times as fast as styrene[75]. It is interesting that the increase in reactivity in this case coincides with the increase in dissociation (the Gomberg series) of hexa-arylethanes[76] as a function of these substituents—phenyl < 2-naphthyl < 1-naphthyl—which means the alkyls having a greater steric effect on the α-carbon atom also show a greater degree of dissociation. This conclusion is supported not only by the Gomberg series but also by Theilacker and Ewald's data[77] on the dissociation of substituted hexa-arylethanes in benzene solution at 25°C (Table 9).

Table 9.

Hexa-arylethane	Degree of dissociation, %
Hexaphenylethane	2.5
Tetraphenyl-1,2-di-*o*-tolylethane	25.2
Hexa-*o*-tolylethane	90.8

The above cases of the effect of steric hindrance on rate of autoxidation in alkylated aromatic compounds and in alkenes constitute some of the most important specific examples of interaction between atoms which are not directly attached to one another in the molecule, a problem which was first formulated by Butlerov[78] and developed by Markovnikov.

The existence of such interaction is indicated by a mechanical model of the molecule. This was stated as early as 1904 by Chugaev[79]: "Chemical molecules represent a mechanism involving a known store of energy. In order to understand the action of these mechanisms, it is equally necessary to know their internal structure and the distribution of energy in them... We are indebted to organic chemistry for the first information on the nature of these mechanisms. Perhaps it is destined to make a further step and show how these mechanisms act, indicating the relation between them and the rate of chemical reactions. Is not this possibility evident in the cases of stereochemical hindrance, a large number of which are known in organic chemistry?". The above correlating data on the autoxidation of hydrocarbons confirm the validity of the ideas expressed by this remarkable Russian chemist.

5. Homologues of Indane and Tetreahydronaphthalene—Role of Molecular Conformation of Hydrocarbons in Conjugation of Single Bonds

The oxidation of homologues of indane and tetrahydronaphthalene has been studied in detail by Volkov and his coworkers[80], who have shown in particular that alkylindanes and alkyltetrahydronaphthalenes react far more readily than do the corresponding alkylbenzenes with a peroxy-radical ROO•. The difference between the rates of oxidation of these hydrocarbons is easily explained by the influence of rotational isomerism on the degree of coplanarity of the α-carbon atom with the benzene ring. In fact, the trigonal α-carbon atom lies in the plane of the ring in both the transition state and the radical of the oxidisable hydrocarbon (Fig. 4). The oxidisable α-C–H bond is then perpendicular to the plane of the ring: i.e. this bond has an axial orientation, which corresponds to the maximum degree of $\sigma\pi$-overlapping of the orbitals[81]. If this or a closely similar conformation is already present in the hydrocarbon molecule, conjugation (delocalisation of electrons) is readily accomplished, without the consumption of energy. This leads to an increase in the reactivity of the compound. Indane and its alkyl derivatives possess such a favourable conformation owing to the "rigid" fixation of the atoms of the alicyclic ring. The conformation of tetrahydronaphthalene is closely similar to that of indane. On the other hand, with e.g. di-isopropylbenzene the favourable conformation constitutes a small proportion among other conformations. In order to detach hydrogen from an α-carbon atom in di-isopropylbenzene, therefore, additional energy must be expended to bring the molecule into a coplanar condition in the transition state and in the radical (Fig. 4). Hence it follows that the autoxidation of alkylated aromatic hydrocarbons should have a higher activation energy, and hence a lower rate, than that of alkyl derivatives of indane and tetrahydronaphthalene.

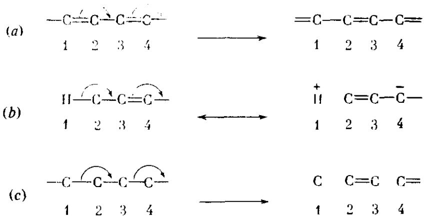
Thus Webster[82] found that the relative rates of oxidation of *m*-di-isopropylbenzene, tetrahydro-1,4-dimethylnaphthalene, and 1,1,3-trimethylindane—compounds having the same hindrance and forming tertiary radicals of similar structure—were 2 : 9 : 10. Hence indane derivatives show the highest rate of oxidation. It is interesting that the same sequence applies to the long-wavelength shift of the absorption maximum in the electronic spectra of these hydrocarbons. Since electronic spectra characterise the degree of delocalisation of electrons, it is obvious that the greatest delocalisation occurs in indane compounds.

The above oxidation results show that alkylindanes are rather more reactive than are alkyltetrahydronaphthalenes. The explanation is that the alicyclic ring of tetrahydronaphthalene is not so flat as that of indane because of its slight conformational distortion (the former has the "half chair" shape[83]), and therefore requires a definite though small additional energy to produce a favourable conformation. It is interesting to note a similar regularity in reactions involving heterolytic rupture of an α-C–H bond[84].

Numerous facts accumulated from the study of the autoxidation of alkenes and alkylarenes confirm the suggestion that conformation plays an important part in the conjugation of single bonds[85–87]. As early as 1950 Nesmeyanov[25] showed for the first time the possibility of such conjugation. He put forward the following principles for heterolytic conjugation: "The complete conjugation of two single bonds requires that they should be parallel (or nearly parallel) to one another. However, this condition is insufficient. ... It is also necessary (at least in heterolytic conjugation phenomena) that one of the conjugating σ-bonds should be of donor character and the other of acceptor character, and that they should be located *trans* to one another". This quotation shows that the first requirement for conjugation is a favourable conformation.

The same stereochemical laws apply to the homologous as to the heterolytic development of conjugation[25]. An actual case of the former is σπ-conjugation, on the stereochemistry of which several papers have been published by Nesmeyanov[88] and also by Shorygin[89,90] and their coworkers. This work shows that, whereas two single bonds are conjugated when mutually parallel, conjugation occurs between a single and a multiple bond when they are perpendicular. This clearly opposite character of the stereochemistry of the two types of conjugation obviously has the same origin: the most favourable conformation is produced, in which delocalisation of electrons can be achieved with minimum energy.

This principle of the role of a favourable conformation can be justified by fairly simple theoretical arguments. The interaction of single and multiple bonds involved in conjugation in saturated and unsaturated compounds can be represented as the displacement of electron density along a chain of atoms:



A common feature here is the formation of a new double bond 2–3. In the first case this change in electronic structure should not result in a change in the molecular conformation. In the second and third cases changes would occur in the configuration of the molecule. In particular, formation of the double bond 2–3 requires that substituents in this portion of the molecule should have a planar (or nearly planar) arrangement. If such conformation is already present, as in the dienes (*a*), electron transfer occurs freely. On the other hand, where a favourable conformation (*b*) and (*c*) must be created, additional energy is obviously needed.

In alicyclic hydrocarbon molecules the atoms may be rigidly fixed. Conjugation is therefore more clearly developed here, as is confirmed by the increased tendency of alicyclic compounds, e.g. indane and tetrahydronaphthalene, compared with alkylated aromatic compounds, e.g. isopropylbenzene, to undergo autoxidation. Data on the autoxidation of hydrocarbons indicate that the conjugation of single bonds is similar in character to that of double bonds and is due to a quantum-mechanical effect[91].

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Yaroslavl Institute of Technology

Scientific Research Institute of Monomers for
Synthetic Rubber,
Yaroslavl

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Organosilicon Derivatives of Aminoalcohols

E.Lukevics, L.Liberts, and M.G.Voronkov

The literature data and the present authors' investigations in the field of organosilicon derivatives of aminoalcohols are reviewed. The methods for the preparation, the chemical and biological properties, and the practical applications of organosilicon derivatives of aminoalcohols, in which the silicon atom is linked directly to the aminoalcohol heteroatom or via a carbon chain, are discussed.
The bibliography includes 204 references.

CONTENTS

I. INTRODUCTION

The increase of interest in the study of the properties and reactions of aminoalcohols and their derivatives is due to at least two causes: the specific biological properties and high reactivity associated with the presence of more than one functional group and the presence of competing reactive centres in their molecules. It is sufficient to mention that many aminoalcohols and their derivatives are biogenic amines playing an extremely important role in the vital processes of organisms (choline and acetylcholine). On the other hand, numerous widely employed medicinal preparations have been prepared on the basis of aminoalcohols (ephedrine, Pentaphen, Dimedrol, Novocaine, Dicaine, Spasmolytin, adrenaline, Ustimon, and others). Moreover, aminoalcohols are effective complex-forming agents and are used to remove from solutions various metal ions. Aminoalcohol complexes can be employed as models of oxidases and in all probability (after a detailed study of their biological properties) will find application in medicine.

The studies on the physical, chemical, and biological properties of organosilicon derivatives of aminoalcohols have provided valuable information about the influence of the amino-group on the strength and reactivity of the Si–O bond in aminoalkoxysilanes, about the degree of intramolecular interaction between the nitrogen atom of the aminoalkoxy-group and the silicon atom leading to the formation of a strong donor-acceptor Si ← N bond in cyclic organosilicon derivatives of triethanolamine (silatranes), and about the relation between the structure and biological activity of organosilicon derivatives of aminoalcohols, among which extremely toxic compounds have been discovered (1-arylsilatranes). The application or organosilicon derivatives of aminoalcohols as water repelling agents, hardening agents for epoxy-resins, dispersing agents, and intermediates for the synthesis of special polymers are no less important.

The results of studies in this interesting and extremely promising field of the chemistry of organosilicon compounds published up to May 1969 are reviewed in the present article.

II. ORGANOSILICON DERIVATIVES OF AMINOALCOHOLS IN WHICH THE SILICON ATOM IS LINKED DIRECTLY TO THE HETEROATOM OF THE AMINOALCOHOL

A. METHODS OF PREPARATION OF AMINOALKOXYSILANES

1. Reactions of Chlorosilanes with Aminoalcohols

When chlorosilanes and silicon tetrachloride react with ethanolamine and its *N*-substituted derivatives in the presence of hydrogen chloride acceptors, the first step is the silylation of the hydroxy-group of the aminoalcohol with formation of aminoalkoxysilanes [1-14]:

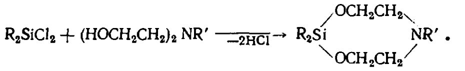
$$\geqslant\text{SiCl} + \text{HOCH}_2\text{CH}_2\text{NR}_2 \xrightarrow{+\text{B}} \geqslant\text{SiOCH}_2\text{CH}_2\text{NR}_2 + \text{B}\cdot\text{HCl}\,.$$

The reaction is carried out in chloroform [5,15], ethyl ether [5,8,9], petroleum ether [11], and benzene [13,14]. The hydrogen chloride acceptors employed are ammonia [8,15], triethylamine [5,9,10], pyridine [14], or an excess of the aminoalcohol itself [5,11,13]. Organosilicon derivatives of ethanolamine [5,8,13] and its *N*-substituted derivatives [1,9-11], 3-(α-pyridyl)propanol [10], and aminobutanols [14] have been obtained in this way.

When the reactant ratio is equimolar, the hydrogen chloride formed is bound by the aminoalkoxysilane itself, which is converted into the hydrochloride [5,7,16-20]:

$$\geqslant\text{SiCl} + \text{HOCH}_2\text{CH}_2\text{NR}_2 \rightarrow \geqslant\text{SiOCH}_2\text{CH}_2\text{NR}_2\cdot\text{HCl}\,.$$

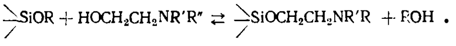
The reaction of trialkylchlorosilanes with diethanolamine takes place similarly to the reaction with monoethanolamine: in the first step both hydroxy-groups are silylated and only then also the amino-group, in the presence of an excess of the trialkylchlorosilane [5,7]. It has been noted in patents [16,19,20] that the hydrochlorides of 2-[(2′-hydroxyethyl)amino]ethoxysilanes are formed in the reactions of alkyltrichlorosilanes with diethanolamine, while the products of the reaction of silicon tetrachloride with di- and tri-ethanolamines in the presence of ammonia are polymers[15]. A cyclic compound was obtained by the reaction of dichlorodimethylsilane with *N*-ethyldiethanolamine in the presence of triethylamine[21]:



It has been pointed out[22] that a deposit is formed in the exothermic reaction of silicon tetrachloride with diethanolamine. This was attributed to complex formation via the free electron pair of the nitrogen atom and the vacant 3*d* orbitals of the silicon atom. It is surprising that the author completely fails to take into account the possibility of a substitution reaction with participation of hydroxy-groups.

2. Alcoholysis of Alkoxysilanes and Acyloxysilanes by Aminoalcohols

When alkoxysilanes are heated with ethanolamine and its *N*-derivatives with simultaneous distillation of the alcohol evolved, the corresponding aminoalkoxysilanes are formed:



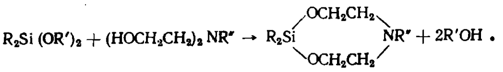
The reaction is carried out in the presence of catalytic amounts of potassium hydroxide[9], sodium methoxide[13,29], sodium aminoalkoxide[1,3,6,24], tetra-alkoxytitanium[25,26], or in the absence of catalysts[1,6,13,27-37].

For the synthesis of aminoalkoxysilanes, ethoxysilanes are most frequently employed[1-3,6,13,23-25,27-42] but methoxy-[1,9,26], n-propoxy-[33,40], isopropoxy-[33], and butoxysilanes[34,43] can also be used. Among alkoxysilanes, alkoxysilanes with three further organic substituents[3], dialkoxysilanes with two further organic substituents[1,9,23-27,31,32,37], trialkoxysilanes with one additional organic substituent[1,27,28,31,32], tetra-alkoxysilanes[13,29-31,33-36], and polyalkoxysilanes[34,38-42,44] have also been used in the reaction with ethanolamine and its *N*-substituted derivatives. In all cases all the alkoxy-groups at the silicon atom are replaced by aminoalkoxy-groups with formation of the corresponding di-, tri-, and tetra-(aminoalkoxy)-silanes. The attempts to isolate the mixed ethers from the products of the transetherification of tetraethoxysilane or tetraisopropoxysilane with ethanolamine, with the molar ratio of the reactants ranging from 1 : 1 to 1 : 3, were unsuccessful[33]. Nevertheless the reaction of tetraethoxysilane with 2-(diethylamino)ethanol (molar ratio 5 : 2) gave diethoxydi-[2-(diethylamino)ethoxy]silane[13]. Mixed aminoethoxyfurfuryloxysilanes containing between one and three furfuryloxy-groups have been obtained by the transetherification of tetraethoxysilane with a mixture of ethanolamine and furfuryl alcohol[29].

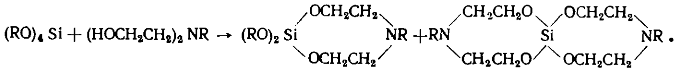
Two and three triethylsilyl groups can be introduced into the diethanolamine and triethanolamine molecules respectively by transetherification[3,6,7]:

$$n\,\mathrm{R_3SiOR} + (\mathrm{HOCH_2CH_2})_n\,\mathrm{NH}_{3-n} \rightleftarrows (\mathrm{R_3SiOCH_2CH_2})_n\,\mathrm{NH}_{3-n} + n\,\mathrm{ROH}\,. \quad n = 1\text{—}3,$$

Readily polymerised cyclic products have been obtained by the reaction of dialkoxysilanes containing two additional organic substituents with diethanolamine and its *N*-substituted derivatives[21,27,43,45-47]:



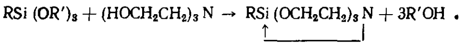
Usually ethoxysilanes are introduced into the reaction and the latter is carried out in the absence of a catalyst. However, best yields (80–86%) are achieved when dialkyldibutoxysilanes are employed in the presence of a catalytic amount of the corresponding sodium aminoalkoxide[43]. Polymers are obtained by the reaction of trialkoxysilanes containing an additional organic substituent with diethanolamine[48]. The reaction of tetra-alkoxy silanes with diethanolamine also leads to the formation of polymers[34,49]. However, in some cases it proved possible to isolate low-molecular-weight cyclic compounds[47]:



It is very probable that the intermediate acyclic compounds cyclise on distillation[13,47]:

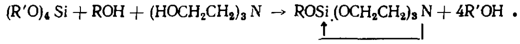
$$\mathrm{(RO)_4\,Si + 2\,(HOCH_2CH_2)_2\,NH \xrightarrow[-2ROH]{} (RO)_2\,Si\,(OCH_2CH_2NHCH_2CH_2OH)_2}\,.$$

The reaction of trialkoxysilanes containing a further organic substituent[47,50-53] and tetra-alkoxysilanes[47,50,51,53-56] with triethanolamine (1 : 1 molar ratio) does not lead to the formation of polymers but to monomeric chelate cyclic compounds—silatranes†, stabilised as a result of the presence in the molecule of the transannular coordinate bond Si ← N:



$$\mathrm{RSi\,(OR')_3 + (HOCH_2CH_2)_3\,N \rightarrow RSi\,(OCH_2CH_2)_3\,N + 3R'OH}\,.$$

When the reaction of tetraethoxysilane with triethanolamine is carried out in the presence of phenols[50,61] or carboxylic acids[50,62], the products are the corresponding 1-aryloxy- and 1-acyloxy-silatranes:



$$\mathrm{(R'O)_4\,Si + ROH + (HOCH_2CH_2)_3\,N \rightarrow ROSi\,(OCH_2CH_2)_3\,N + 4R'OH}\,.$$

In some cases the formation of acyclic[37], spirocyclic[51], and also polymeric transetherification products[51] was observed in the reaction of tetra-alkoxysilanes with triethanolamine (for other reactant ratios).

The reaction of acyloxysilanes with aminoalcohols has not been investigated at all. In only one patent[63] is there a mention of the possibility of preparing 2-aminoethoxysiloxanes from acetoxysiloxanes and ethanolamine in the presence of tetraisopropoxytitanium. Another patent[64] describes the synthesis of a polymer from diheptadecyloxydimethylsilane (partially acylated by stearic acid) and triethanolamine.

3. Reactions of Siloxanes and Siloxanols with Aminoalcohols

When a solution or a hydrogel of silicic acid is heated with ethanolamine[65-68] or 2-(diethylamino)ethanol[67], the hydroxy-groups are partially substituted by aminoalkoxy-groups, which leads to the formation of modified silica gels. The same type of exchange of hydroxy-groups for aminoalkoxy-groups can occur in the reaction of aminoalcohols with polysiloxanols having a number of other organic substituents[69]. The siloxane bond is probably not involved in these reactions. The reaction of polysesquisiloxanes $(\mathrm{RSiO_{1.5}})_x$ and polysiloxanols $[\mathrm{RSiO_{1.5-y}(OH)_{2y}}]_x$, both containing a number of other organic substituents, with aminoalcohols in the presence of potassium hydroxide on heating in an inert solvent with azeotropic distillation of water is of quite a different type. It involves the cleavage of the Si–O–Si bonds with formation of tri-[2-(dialkylamino)ethoxy]silanes having one

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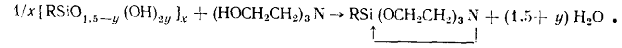
†For details of the synthesis and properties of silatranes, see the appropriate reviews[50,57-60].

further organic substituent in the case of 2-dialkylaminoethanols[1] and silatranes with one organic substituent in the 1-position in the case of triethanolamine[50,57–60,70–72]:

$$2/x\,(\mathrm{RSiO_{1.5}})_x + 6\,\mathrm{HOCH_2CH_2NR'_2} \rightarrow 2\,\mathrm{RSi(OCH_2CH_2NR'_2)_3} + 3\,\mathrm{H_2O}\ ,$$



$$1/x\,[\mathrm{RSiO_{1.5-y}(OH)_{2y}}]_x + \mathrm{(HOCH_2CH_2)_3N} \rightarrow \mathrm{RSi(OCH_2CH_2)_3N} + (1.5+y)\,\mathrm{H_2O}\ .$$

The rate of reaction increases with the degree of condensation of the initial siloxanes and also on passing from alkyl- to aryl- and vinylpolysiloxanols. Polyhydrosiloxanes substituted by a number of organic groups $(\mathrm{RSiHO})_x$ can also be employed in this reaction. Then dehydrocondensation with evolution of hydrogen takes place in the absence of the catalyst, but the addition of alkali is necessary for the cleavage of the siloxane bond[1,71].

4. Reactions of Aminosilanes with Aminoalcohols

When diaminodi-t-butoxysilane is heated with ethanolamine at 150–200°C, ammonia is evolved and di-(2-aminoethoxy)di-t-butoxysilane is formed[73]:

$$\mathrm{(RO)_2Si(NH_2)_2} + 2\,\mathrm{HOCH_2CH_2NH_2} \xrightarrow[-2\mathrm{NH_3}]{} \mathrm{(RO)_2Si(OCH_2CH_2NH_2)_2}\ .$$

The reaction of diaminodi-t-butoxysilane with *N*-alkyl- and *NN*-dialkylethanolamines and propanolamine derivatives takes place similarly. In the case of 2-diethylaminoethanol the product formed by the substitution of the 1-amino-group by a 2-diethylaminoethoxy-group was also isolated. t-Butoxytri(2-ethylaminoethoxy)silane was detected in addition to di-t-butoxydi-(2-ethylaminoethoxy)-silane in the products of the reaction of 2-ethylaminoethanol[73].

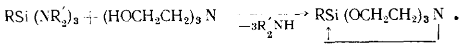
The possibility of employing triethylaminosilane for the silylation of ephedrine is mentioned (without indicating the experimental conditions) in a brief communication[74].

Diethylaminotrimethylsilane readily silylates the hydroxy-groups in mono-, di-, and tri-ethanolamines[4,6,7,75]:

$$n\,\mathrm{R_3SiNR'_2} + \mathrm{(HOCH_2CH_2)}_n\mathrm{NH}_{3-n} \xrightarrow[-n\,\mathrm{R'_2NH}]{} \mathrm{(R_3SiOCH_2CH_2)}_n\mathrm{NH}_{3-n}\ ,$$

where $n = 1$–3.

With di- and tri-ethanolamines, it is possible to achieve the successive substitution of all the hydroxy-groups by trimethylsiloxy-groups. When diethylaminosilanes $\mathrm{R}_{4-n}\mathrm{Si(NR'_2)}_n$ containing between one and three diethylamino-groups are employed in this reaction, it is possible to obtain aminoethoxysilanes containing between one and three 2-aminoethoxy- or 2-dialkylaminoethoxy-groups[5,75,76]. When $n = 2$, the reaction with diethanolamine leads to monomeric cyclic compounds (as in the reaction with dialkoxysilanes), while the reaction with triethanolamine leads to polymers. On the other hand, when $n = 3$, diethanolamine gives a polymer, and a cyclic compound (a silatrane with an organic substituent in the 1-position) is formed in the reaction with triethanolamine[75]:



$$\mathrm{RSi(NR'_2)_3} + \mathrm{(HOCH_2CH_2)_3N} \xrightarrow[-3\mathrm{R'_2NH}]{} \mathrm{RSi(OCH_2CH_2)_3N}\ .$$

5. Reactions of Silazanes with Aminoalcohols

Hexamethyldisilazane silylates the hydroxy-groups of ethanolamine[6,8,77,78] and its *N*-substituted derivatives[74,79,80], diethanolamine[77,81], triethanolamine[77], and heterocyclic aminoalcohols[79,82]. The silylation involves both trimethylsilyl groups:

$$n\,\mathrm{(R_3Si)_2NH} + 2\,\mathrm{(HOCH_2CH_2)}_n\mathrm{NR'}_{3-n} \xrightarrow[-n\,\mathrm{NH_3}]{} 2\,\mathrm{(R_3SiOCH_2CH_2)}_n\mathrm{NR'}_{3-n}\ .$$

When 1,3-dialkoxy-1,1,3,3-tetramethyldisilazanes are heated with ethanolamine, the silazane group is cleaved and ammonia is evolved. The subsequent heating of the reaction mixture with simultaneous distillation of the corresponding alkanol leads to the formation of di-(2-aminoethoxy)dimethylsilane[77]:

$$\mathrm{(R_2R'OSi)_2NH} + 4\,\mathrm{HOCH_2CH_2NH_2} \xrightarrow[-\mathrm{NH_3}]{} 2\,\mathrm{R_2Si(OCH_2CH_2NH_2)_2} + 2\mathrm{R'OH}\ .$$

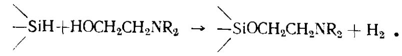
The reaction of hexamethylcyclotrisilazane and octamethylcyclotetrasilazane with ethanolamine, 2-dialkylaminoethanols, derivatives of isomeric propanolamines, and 4-amino-1-butanol leads to the formation of the corresponding di(aminoalkoxy)dimethylsilanes[6,77,79,83]:

$$\mathrm{(R_2SiNH)}_n + 2n\,\mathrm{HOCHR'(CH_2)}_m\mathrm{NR''_2} \xrightarrow[-n\mathrm{NH_3}]{} n\,\mathrm{R_2Si[OCHR'(CH_2)}_m\mathrm{NR''_2]_2},$$

where $\mathrm{R = CH_3}$, $\mathrm{R' = H}$ or $\mathrm{CH_3}$, $\mathrm{R'' = H, CH_3, C_2H_5, C_4H_9}$, or $\mathrm{(CH_2)_5}$, $n = 34$, and $m = 1$–3.

6. Dehydrocondensation of Hydrosilanes and Hydrosiloxanes with Aminoalcohols

Trialkylsilanes undergo dehydrocondensation with ethanolamine, its *N*-substituted derivatives, and 2-piperidinoethanol in the presence of sodium aminoalkoxides with formation of the corresponding aminoalkoxysilanes[1,3,6,74,84]:

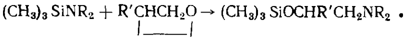


$$\mathrm{{>}SiH} + \mathrm{HOCH_2CH_2NR_2} \rightarrow \mathrm{{>}SiOCH_2CH_2NR_2} + \mathrm{H_2}\ .$$

Polyalkylhydrosiloxanes $(\mathrm{RSiHO})_n$ react vigorously with ethanolamine in the absence of catalysts[1,85–89]. When cyclotetrasiloxanes ($n = 4$) and cyclopentasiloxanes ($n = 5$) are employed, the reaction products are gels to which the structure $[\mathrm{CH_3Si(OCH_2CH_2NH_2)O}]_n$ is attributed and which are insoluble in benzene, toluene, xylene, and dioxan[88]. With higher oligomers ($n \simeq 13$–16) in which $\mathrm{R = CH_3}$, the products of the reaction with ethanolamine are also gels, which rapidly become insoluble on storage. When $\mathrm{R = C_2H_5}$ (GKZh-94), the exothermic reaction with ethanolamine involves a stage in which a rubberlike gel is formed (at 60–65°C), but on attainment of 140°C the reaction mass becomes liquid again and completely transparent. The liquid product is soluble in aromatic hydrocarbons, ether, and dioxan[87].

7. Other Methods

A number of other methods which have as yet not acquired general importance have been employed for the synthesis of individual examples of aminoalkoxysilanes with different structures. The reaction of substituted oxirans with trimethyl(diorganyl)silanes at 80°C takes place with the opening of the oxygen-containing ring by the mechanism[90]

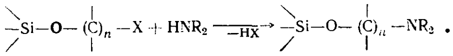


$$\mathrm{(CH_3)_3SiNR_2} + \mathrm{R'CHCH_2O} \rightarrow \mathrm{(CH_3)_3SiOCHR'CH_2NR_2}\ .$$

This apparently very simple and promising reaction cannot be used as a general method for the synthesis of aminoalkoxysilanes, since it can only be achieved when powerful electron-accepting substituents are present in the group R′ of the substituted oxiran. For example, whereas in the reaction of trimethylpiperidinosilane with trichloromethyloxiran the yield of (1-trichloromethyl-2-piperidinoethoxy)-trimethylsilane is 89% after only 1.3 h, in the reaction with chloromethyloxiran the yield does not exceed 45% even after heating for 22 h. Methyloxiran does not react at all with trimethylpiperidinosilane in a sealed tube at 80°C.[90] The rate of this reaction decreases also on passing from piperidinosilanes to diethyl- and dimethyl-aminosilanes, which is consistent with the sequence of decreasing basicity of the above amines[90].

The reaction of oxiranylmethoxysilanes with amines can also lead to the formation of aminoalkoxysilanes. In the only known example of such a reaction described in a patent[91], diethylenetriamine was employed as the amine, which led to the formation of infusible, insoluble resins.

Aminoalkoxysilanes can also be synthesised by substituting halogen atoms in halogenoalkoxysilanes by amino-groups[18]:



$$\equiv Si-O-(C)_n-X + HNR_2 \xrightarrow[-HX]{} \equiv Si-O-(C)_n-NR_2 .$$

1-Hydrosilatranes, which are very difficult to obtain by the reaction of triethoxysilane with trialkanolamines (because of the substitution at the Si–H bond), have been synthesised by the transetherification of triethoxysilane with boratranes[50,92,93]:

$$HSi(OC_2H_5)_3 + B(OCHRCH_2)_3N \rightarrow HSi(OCHRCH_2)_3N + B(OC_2H_5)_3 .$$

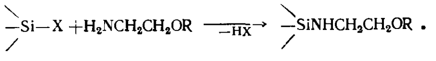
1-(triorganylsiloxy)titanatranes are obtained by the general method for the formation of the group Si–O–Ti.[94]

B. METHODS FOR THE PREPARATION OF ORGANOSILICON DERIVATIVES OF AMINOALCOHOLS CONTAINING THE Si–N BOND

The dehydrocondensation of substituted silanes $RSiH_3$ with ethanolamine and diethanolamine takes place vigorously with evolution of heat[95]. The structure of 2-hydroxyethylaminosilanes containing the Si–N bond, for example $RSi(NHCH_2CH_2OH)_3$, is attributed to the reaction products[95-99]. However, bearing in mind the comparative ease of the cleavage of the Si–N bond by alcohols[100,101] (including ethanolamine[7,75]) with formation of the Si–O bond, the structure proposed for the products of the reaction of substituted silanes with ethanolamine is very doubtful.

Also doubtful is the structure $RCH[(CH_2OH)NHSi(CH_3)_3]$ allegedly formed when di(trimethylsilyl) derivatives of the corresponding aminoacids $RCH[NHSi(CH_3)_3]COOSi(CH_3)_3$ are reduced with lithium aluminium hydride[102]. On hydrolysis of the reaction mixture with moist ether, the Si–N bond in these compounds is hardly likely to be retained. The final hydrolysis product might be formed with equal success from the *O*-derivative $RCHNH_2CH_2OSi(CH_3)_3$.

Organosilicon derivatives of aminoalcohols in which the presence of the Si–N bond has been unquestionably demonstrated have so far been synthesised from aminoethers not containing a free hydroxy-group. They have been synthesised by the reaction of aminoethers with trialkyldiethylaminosilanes[103], trialkyl-t-butylaminosilanes[103], hexamethyldisilazane[80], and substituted chlorosilanes in the presence of triethylamine[103]:



$$\equiv Si-X + H_2NCH_2CH_2OR \xrightarrow[-HX]{} \equiv SiNHCH_2CH_2OR .$$

C. METHODS FOR THE PREPARATION OF ORGANOSILICON DERIVATIVES OF AMINOALCOHOLS CONTAINING BOTH Si–O AND Si–N BONDS

Organosilicon derivatives of aminoalcohols containing both Si–O and Si–N bonds are synthesised by a number of reactions used for the preparation of aminoalkoxysilanes: by the reaction of aminoalcohols with chlorosilanes[1,5,6], dialkylaminosilanes[6,75,104], and hexamethyldisilazane[77]. The application of an excess of these organosilicon reagents leads to the formation of di- and tri-organylsilyl derivatives containing both the Si–O and the Si–N bonds. However, in many cases best results in the synthesis of these compounds are obtained on further silylation of the amino-group in individual aminoalkoxysilanes[4-7,75,77]:

$$R_3SiOCH_2CH_2NH_2 + XSiR'_3 \xrightarrow[-HX]{} R_3SiOCH_2CH_2NHSiR'_3 ,$$

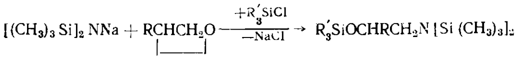
$$(R_3SiOCH_2CH_2)_2NH + XSiR'_3 \xrightarrow[-HX]{} (R_3SiOCH_2CH_2)_2NSiR'_3 ,$$

where X = Cl, $(C_2H_5)_2N$, $(CH_3)_3SiNH$, or H.

It proved possible to introduce three trimethylsilyl groups into the ethanolamine molecule by allowing diethylaminotrimethylsilane[6,75] and hexamethyldisilazane[77] to react with its di(trimethylsilyl) derivative in the presence of ammonium sulphate:

$$R_3SiOCH_2CH_2NHSiR_3 + XSiR_3 \xrightarrow[-HX]{} R_3SiOCH_2CH_2N(SiR_3)_2 .$$

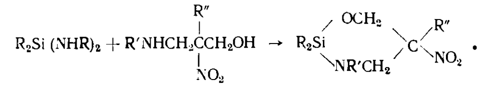
Another reaction involving the formation of *N*-[2-(trisubstituted-siloxy)ethyl]hexamethyldisilazanes (yield 65%) takes place by the mechanism[105,106]



$$[(CH_3)_3Si]_2NNa + RCHCH_2O \xrightarrow[-NaCl]{+R'_3SiCl} R'_3SiOCHRCH_2N[Si(CH_3)_3]_2 .$$

In all probability it proceeds via the cleavage of the oxiran ring by hexamethyldisilazylsodium with subsequent silylation of the intermediate alkoxide by trisubstituted chlorosilane. It is very surprising that, in contrast to trialkylchlorosilanes, chlorodimethylsilane forms in this reaction dimethylsilyldi(trimethylsilyl)amine instead of the aminoalcohol derivative[105,106].

When dimethyldi(diorganylamino)silanes react with 2-alkyl-3-alkylamino-2-nitro-1-propanol (in molar proportions of 1 : 1) in the presence of ammonium chloride, the reaction involves both the hydroxy- and the amino-group with evolution of two equivalents of the primary amine and the formation of a cyclic product[107]:



It is asserted[86,88] that the products of the reaction of polyalkyl hydrosiloxanes with ethanolamine are siloxanes containing alternating $SiOCH_2CH_2NH_2$ and $SiNHCH_2CH_2OH$ groups. This has been confirmed by the reaction with hydrogen chloride in which only half the amino-groups were bound into salts. However, bearing in mind the possibility of the reaction of compounds containing Si–N bonds with alcohols to form Si–O bonds and also the possibility of the cleavage on the Si–N bond by hydrogen chloride, more reliable evidence is required to confirm the proposed structure of the reaction products.

D. PHYSICAL PROPERTIES

The infrared[52,108] and ^1H NMR[60,109] spectra and the dipole moments[110] of silatranes have been investigated and their crystallographic parameters have been determined[111-113]. Silatranes have high dipole moments (5.3–7.1 D), greatly exceeding (by 4.6–5.8 D) the values calculated for the structure without taking into account the donor–acceptor interaction between the nitrogen and silicon atoms[110]. This demonstrates convincingly the presence in silatrane molecules $RSi(OCH_2CH_2)_3N$ of an N → Si coordinate bond the length of which in 1-phenylsilatrane is 2.193 Å.[113] The presence of the same coordinate bond was attributed without any proof to the cyclic organosilicon derivatives of diethanolamine $R_2Si(OCH_2CH_2)_2NH$.[46,47] The study of their dipole moments did not confirm this hypothesis[45].

The ^1H NMR spectra of 2-aminoethoxysilanes indicate a lowering in these compounds (compared with ethoxysilanes) of the extent of $p\pi - d\pi$ interaction between the oxygen and silicon atoms[114].

E. CHEMICAL PROPERTIES

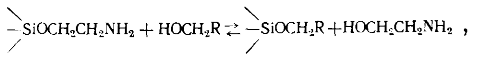
1. Hydrolysis

The hydrolysis of aminoalkoxysilanes has been little investigated. Some of them are readily hydrolysed by water[6,7,33,52]. At the same time it has been stated that compounds of the type $Si(OCH_2CH_2NR_2)_4$, where $R = C_2H_5$ or C_4H_9, are relatively stable in aqueous solution[33]. Silatranes are even more resistant to moisture and are hydrolysed with greater difficulty than the corresponding substituted triethoxysilanes[50,115]. The hydrolysis of silatranes in an aqueous medium is kinetically of first order with respect to the silatrane. The logarithms of the rate constants are linearly correlated with the σ^* constants of the substituents at the silicon atom[59].

Compounds of the type $R_3SiOCH_2CH_2NHR'$ are hydrolysed quantitatively by a 30% solution of alkali[8,116]. In contrast, *N*-[2-(trialkylsiloxy)ethyl] hexamethyldisilazanes are not hydrolysed even on refluxing with a solution of alkali, but are readily cleaved by dilute hydrochloric acid[104].

2. Alcoholysis

The alcoholysis of aminoalkoxysilanes takes place when they are heated with alcohols and the lower-boiling component of the equilibrium system is distilled off[6,7,31,33,34]:



$$(R_3SiOCH_2CH_2)_2NH + 2\,HOCH_2CH_2NH_2 \rightleftarrows R_3SiOCH_2CH_2NH_2 + (HOCH_2CH_2)_2NH\ .$$

The organosilicon derivatives of ethanolamine and diethanolamine containing both Si–O and Si–N bonds can be selectively desilylated by alkanols[5-7,117]:

$$(R_3SiOCH_2CH_2)_n\,NH_{2-n}SiR'_3 + HOR'' \rightarrow (R_3SiOCH_2CH_2)_n\,NH_{3-n} + R'_3SiOR'',$$

where $n = 1$ or 2.

The cleavage of the Si–N bond by alkanols in compounds of the silazane type takes place in the presence of a catalytic amount of ammonium phosphate[6,7,118] or traces of hydrochloric acid[105,106]. If one uses C_2H_5OD for desilylation under these conditions, an *N*-deuterated derivative is formed[6,7]:

$$R_3SiOCH_2CH_2N(SiR_3)_2 + 2R'OM \rightarrow R_3SiOCH_2CH_2NM_2 + 2R_3SiOR',$$

where M = H or D.

3. Reactions with Acids and Their Anhydrides

Aminoalkoxysilanes are fairly strong bases and can be titrated with hydrochloric acid in the presence of Methyl Red.[75] The formation of salts of aminoalkoxysilanes with inorganic[16,18-20,86,119-121] and carboxylic acids[13,16,121-123] has been noted in a number of patents. However, in only two cases[5,11] were the corresponding hydrochlorides isolated in a pure form and adequately characterised. The difficulty of obtaining the hydrochlorides of aminoalkoxysilanes can be accounted for by the ready cleavage of the Si–O bond in these compounds by hydrogen chloride[6,7,90,107]:

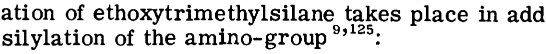
$$(R_3SiOCH_2CH_2)_n\,NH_{3-n} + (n+1)\,HCl \rightarrow n\,R_3SiCl + (HOCH_2CH_2)_n\,NH_{3-n}\cdot HCl,$$

where $n = 1$–3.

The cleavage of these compounds by acetic acid[6,7,90] and also acetic anhydride[107] and *p*-nitrobenzoyl chloride[105,106] takes place similarly. The reaction of disubstituted di-(2-aminoethoxy)silanes with the dianhydride of pyromellitic acid[26,63] and di-isocyanates[27] leads to the formation of polymers.

4. Reactions with Organosilicon Compounds

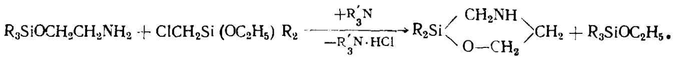
The silylation of the amino-group in aminoalkoxysilanes by chlorosilanes, aminosilanes, and silazanes was discussed in Section B, 3. Aminoalkoxysilanes are silylated by chloroalkylsilanes[5,8,116]:



In a study of the rate of reaction of various amines with (chloromethyl)dimethylethoxysilane in ethanol solution, the following series of decreasing reactivities was obtained[124]:

$$HOCH_2CH_2NH_2 > (CH_3)_3SiOCH_2CH_2NH_2 > C_3H_5NH_2 > (C_2H_5)_2NH\ .$$

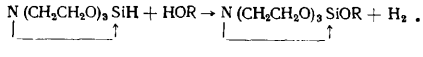
The study of the products of this reaction showed that in the presence of triethylamine intramolecular cyclisation with elimination of ethoxytrimethylsilane takes place in addition to the silylation of the amino-group[9,125]:



5. Other Reactions

Aminoalkoxysilanes with an unsubstituted amino-group are readily hydroxyalkylated by oxiran and substituted oxirans[5,27,33,34,42,126]. The reaction of aminoalkoxysilanes with alkyl iodides yielded the corresponding ammonium salts[24,75,76]. The basic properties of the nitrogen atom in silatranes are reduced so much owing to the formation of the N → Si donor–acceptor bond that they do not react with methyl iodide[50,71].

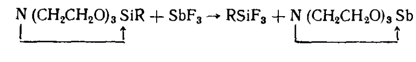
1-Hydrosilatranes undergo dehydrocondensation with alcohols and phenols in the presence of alkali metal alkoxides (phenoxides) or zinc chloride[127] and with carboxylic acids in the presence of zinc chloride[50]:



$$N(CH_2CH_2O)_3SiH + HOR \rightarrow N(CH_2CH_2O)_3SiOR + H_2\ .$$

It proved impossible to carry out the dehydrocondensation of 1-hydrosilatranes with alcohols[127] and also to use them for the hydrosilylation of olefins (cyclohexene and styrene)[93] in the presence of $H_2PtCl_6.6H_2O$.

The reaction of 1-substituted silatranes with SbF_3 involves an exchange reaction by the mechanism[128]



$$N(CH_2CH_2O)_3SiR + SbF_3 \rightarrow RSiF_3 + N(CH_2CH_2O)_3Sb\ .$$

1-Vinylsilatrane reacts with silver nitrate in aqueous solution in the presence of fluoride ions, giving a characteristic blue colour, which rapidly becomes black. It is suggested that the reaction takes place with elimination of the vinyl group from the silicon atom by silver fluoride with subsequent decomposition of the vinylsilver formed initially[128,129].

F. BIOLOGICAL PROPERTIES

Like the corresponding aminoalcohols, the majority of aminoalkoxysilanes have a depressant effect on the central nervous system. After their administration, an inhibition of respiration and motor activity and convulsions are observed. However, triethyl-[2-(diethylamino)ethoxy]-silane and tri-[2-(diethylamino)ethoxy]phenylsilane have a stimulating effect.

2-(Diethylamino)ethoxytrimethylsilane and di(diethylaminoethoxy)dimethylsilane reduce the motor activity of mice and impair the coordination of motion in doses much lower than the median lethal dose (by a factor of 12.6 and 11.3 respectively).

Derivatives of ethanolamine in the series $R_{4-n}Si(OCH_2CH_2NH_2)_n$ with $n = 1-3$ are 2–9 times more toxic than ethanolamine itself. On the other hand, derivatives of 2-dialkylaminoethanols are less toxic than the corresponding aminoalcohol $HOCH_2CH_2NR_2$ (particularly for $R = CH_3$ or C_4H_9) or their toxicity is of the same order of magnitude (for $R = C_2H_5$). The toxicity of compounds in the series $(R_3SiOCH_2CH_2)_nNH_{3-n}$, where $R = CH_3$ or C_2H_5 and $n = 1-3$, decreases markedly with increase of n. On the whole, the toxicity of organosilicon esters of aminoalkanols is low and varies in the range from 120 mg kg^{-1} for di-(2-aminoethoxy)diethylsilane to 4000 mg kg^{-1} for tri-[2-(triethylsiloxy)ethyl]amine [7,130]. 1-Alkyl- and 1-alkoxysilatranes have a low toxicity [50,57–60,131–134].

In contrast, 1-arylsilatranes are highly toxic [135]. The median lethal dose of 1-phenylsilatrane in experiments on white mice administered intraabdominally is 0.43 mg kg^{-1} [132] (0.33 mg kg^{-1} according to Voronkov [59]). Even in doses of 0.2–0.25 mg kg^{-1} 1-phenylsilatrane causes marked motor excitation of the animal accompanied by a change in the position of the tail (the Straub symptom). 1-Tolylsilatrane is even more toxic (LD_{50} = 0.20 mg kg^{-1}). [59] In contrast to warm blooded animals, 1-phenylsilatrane has completely no effect on frogs in doses up to 30–40 mg kg^{-1}. [50,132]

[2-(Dimethylamino)ethoxy]trimethylsilane methiodide exhibited a H-cholinolytic activity in experiments on the smooth muscle of the stomach ($EC_{50} = 4.5 \times 10^{-4}$). [76]

G. PRACTICAL APPLICATIONS

Aminoalkoxysilanes are used to make water repellent fabrics [15,32,53,64,136,137], leather [64], glass [16,120], paper [64], and building materials [31]. Coatings with improved adhesion to metals [27,121], coatings with satisfactory dielectric and thermal properties [26,63,64,126], and also coatings for casting moulds [38] have been obtained on their basis.

Polyaminoalkoxysiloxanes are used as surface-active substances [42] and binders for refractory materials [34,39,40,138,139].

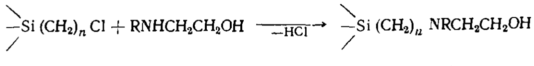
Aminoalkoxysilanes, their carboxylic acid salts, and products of their interaction with oxirans have been proposed as hardening agents for epoxy-resins [35,46,51,126], dispersing agents [13,37,119,122,123,140], viscosity-reducing agents in non-aqueous systems [13], vulcanisers [13], plasticisers [25], binders for fibre glass [53,141], and intermediates in the synthesis of polymers [26,27,53,63,126].

2,3-Di(difluoroamino)propoxysilanes can be employed as rocket fuel and as binders for solid rocket fuel [25].

III. ORGANOSILICON DERIVATIVES OF AMINOALCOHOLS IN WHICH THE SILICON ATOM IS LINKED TO THE AMINOALCOHOL HETEROATOM VIA A CARBON CHAIN

A. METHODS OF SYNTHESIS

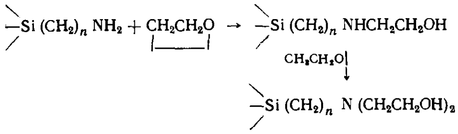
Trialkylchloroalkylsilanes silylate the amino-group of ethanolamine [2,142], 2-alkylaminoethanols [142–144], and diethanolamine [145], forming organosilicon aminoalcohols:



$$\geq Si(CH_2)_nCl + RNHCH_2CH_2OH \xrightarrow[-HCl]{} \geq Si(CH_2)_nNRCH_2CH_2OH\ .$$

The reactions of chloroalkylsiloxanes with β-(2-hydroxyethylamino)ethylamine take place similarly [146,147].

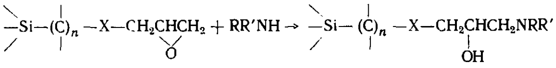
The highest yields of organosilicon aminoalcohols have been achieved in the hydroxyalkylation of organosilicon amines by oxirans [142,145,147]:



$$\geq Si(CH_2)_nNH_2 + \underbrace{CH_2CH_2O} \rightarrow \geq Si(CH_2)_nNHCH_2CH_2OH \xrightarrow{CH_2CH_2O} \geq Si(CH_2)_nN(CH_2CH_2OH)_2\ .$$

The hydroxyethylation of organosilicon anilines [149] and aminoalkylsiloxanes [150,151] is carried out similarly. Diglycidyl ether is also employed instead of oxiran [151,152]. Aminoalkylsilanes have been hydroxyethylated by ethylene chlorohydrin [144,148] and 2-chloroethyl vinyl ether [148,153].

Silicon-containing aminoalcohols are readily obtained by the reaction of silylated oxirans with ammonia [154,155] or amines [154,156–169]. Not only (oxiranylalkyl)silanes but also (oxiranylalkoxyalkyl)silanes [156,157,159,161,165,168–173] and (oxiranylalkylaminoalkyl)silanes [156,160,162] have been introduced into the reaction

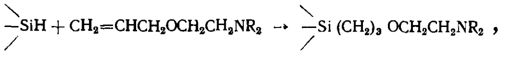


$$\geq Si-(\overset{|}{\underset{|}{C}})_n-X-CH_2\underset{O}{CHCH_2} + RR'NH \rightarrow \geq Si-(\overset{|}{\underset{|}{C}})_n-X-CH_2\underset{OH}{\underset{|}{C}}HCH_2NRR'\ ,$$

where $X = CH_2$, O, or NR″.

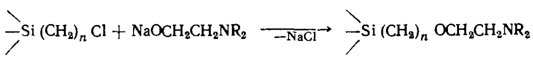
The opening of the oxiran ring of trialkyl-[β-(1-methyloxiran-1-yl]ethynyl] silanes by aliphatic amines takes place at the carbon atom directly attached to the triple bond, which leads to the formation, in contrast to (oxiranylalkyl)silanes, of primary silylated acetylenic aminoalcohols [174].

Silylated ethers of aminoalcohols have also been synthesised by the hydrosilylation of alkylene ethers of aminoalcohols by hydrosilanes and hydrosiloxanes in the presence of $H_2PtCl_6.6H_2O$: [175,176]



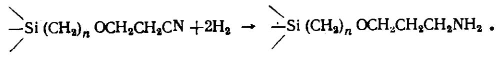
$$\geq SiH + CH_2{=}CHCH_2OCH_2CH_2NR_2 \rightarrow \geq Si(CH_2)_3OCH_2CH_2NR_2\ ,$$

by the reaction of (chloroalkyl)silanes with sodium aminoalkoxides in toluene solution [177,178]:



$$\geq Si(CH_2)_nCl + NaOCH_2CH_2NR_2 \xrightarrow[-NaCl]{} \geq Si(CH_2)_nOCH_2CH_2NR_2\ ,$$

and also by the catalytic reduction of the products of the cyanoethylation of silylated alcohols in the presence of Raney nickel [179]:



$$\geq Si(CH_2)_nOCH_2CH_2CN + 2H_2 \rightarrow \geq Si(CH_2)_nOCH_2CH_2CH_2NH_2\ .$$

Among other reactions involving the formation of silylated aminoalcohols and their ethers, mention may be made of the reduction of silylated aminoacids [180] and esters of cyanoacids [181] by lithium aluminium hydride [180] or sodium borohydride[181], the reaction of silylated diazoketones with ethanolamine[182,183], the acylation of aminoalcohols by the chlorides of trisubstituted silylbenzoic acids[184], and finally organolithium synthesis by the mechanism[185]

$$LiC_6H_4N(CH_2CH_2OLi)_2 + 3R_3SiCl \xrightarrow[-3LiCl \atop -2R_3SiOH]{+2H_2O} R_3SiC_6H_4N(CH_2CH_2OH)_2 .$$

B. CHEMICAL PROPERTIES

Silylated aminoalcohols and their ethers enter into a number of reactions common to aminoalcohols: the formation of hydrochlorides[116,142,173] and quaternary ammonium salts[143,173,175,176], esters[76,143,145], oxazolidines by reaction with aldehydes[144], oxides of aminoethers[175,176], substitution of the hydroxy-group by chlorine when acted upon by thionyl chloride[142,143], silylation by dialkylaminosilanes[5], and also coupling with diazonium salts in the case of *N*-(triorganylsilylaryl) derivatives[185].

C. BIOLOGICAL ACTIVITY AND PRACTICAL APPLICATIONS

Salts of trialkyl(aminoalkyl)silyl benzoates with organic acids and their quaternary ammonium salts have an analgesic and local anesthetic effect[184]. Many hydrochlorides of the type $[R_3SiC_6H_4COOCH_2NHR_2']Cl$ have an antibacterial activity against *S. haemolyticus* and *M. avium*.[184]

Dialkylaminoethyl esters of trimethylsilylphenylhydroxypropionic acid exhibit anticholinergic activity and some of them have a protective effect on poisoning with organophosphorus compounds[186].

The methiodides of trimethyl-[*N*-methyl-*N*-(2-acetoxyethyl)aminomethyl]silane and trimethyl-[*N*-methyl-*N*-(2-benzoyloxyethyl)aminomethyl]silane exhibit H-cholinolytic [*N*-cholinolytic ? (Ed. of Translation)], ganglion blocking, and hypotensive activity[76].

Polysiloxanes containing hydroxyethylaminoalkyl or dialkylaminoalkoxy-groups, their salts, and oxides can be used as emulsifying agents[147,175,176], surface-active substances[147], coatings for fibre glass[146,152], anticorrosion coatings for metals[150], and also for the preparation of foam plastics[187].

Polysiloxanes of the type $[CH_3Si(O)(CH_2)_4N(CH_2CH_2OH)_2]_n$ are used for the flocculation of aqueous suspensions of clays and for the binding of copper and iron ions[151].

IV. ORGANOSILICON DERIVATIVES OF AMINOALCOHOLS CONTAINING BOTH Si-O-C AND Si-Cn-N GROUPS

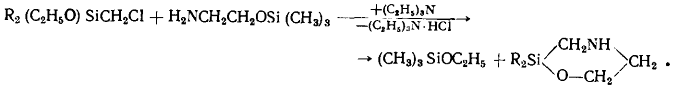
A. METHODS OF PREPARATION

Acyclic organosilicon derivatives of aminoalcohols of the type $\geqslant SiOCH_2CH_2NRCH_2Si\leqslant$, containing both Si-O-C and $Si-C_n-N$ groups have been obtained by the silylation of organosilicon aminoalcohols with trisubstituted dialkylaminosilanes[5,7] and by the silylation of trialkyl(2-aminoethoxy)silanes with chloroalkylsilanes[5,8,116]:

$$R_3SiCH_2NHCH_2CH_2OH + R_3SiNR_2' \xrightarrow[-R_2'NH]{} R_3SiCH_2NHCH_2CH_2OSiR_3 ,$$

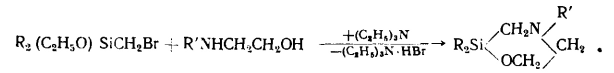
$$R_3SiOCH_2CH_2NH_2 + ClCH_2SiR_3' \xrightarrow[-HCl]{} R_3SiOCH_2CH_2NHCH_2SiR_3' .$$

If instead of trialkylchloromethylsilanes one employs alkyl(chloromethyl)alkoxysilanes of the type $(R'O)_{3-n}R_nSiCH_2Cl$, then after substitution in the amino-group intramolecular cyclisation also takes place on heating, with elimination of alkoxytrimethylsilane[9,125]‡. For example, when $n = 2$, the reaction takes place via the mechanism



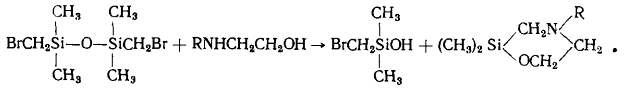
With di-(2-aminoethoxy)dimethylsilane, cyclic compounds having a similar structure are formed. Moreover, the $Si-CH_2Cl$ bond is cleaved in the initial (chloroalkyl)-silanes with further methylation of the N-H bond in the cyclic compounds formed.

When dialkyl(bromomethyl)ethoxysilanes react with 2-(*N*-organylamino)ethanols in the presence of triethylamine, substitution in the amino-group and intramolecular condensation with liberation of ethanol takes place, which also leads to the formation of 2-silamorpholine derivatives[189,192]:

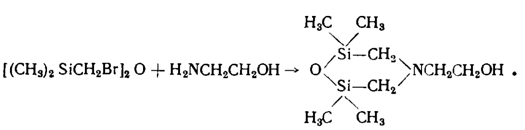


Instead of dialkyl(bromomethyl)ethoxysilanes, one may employ in this reaction also dialkyl(bromomethyl)chlorosilanes, but the yield of 2-silamorpholine derivatives is then reduced (from 62 to 37%).[192] When R′ = H, a cyclic derivative of ethanolamine could be obtained only when dimethyl(bromomethyl)chlorosilane was employed in the alkylation. On the other hand, when dimethyl(bromomethyl)ethoxysilane is used, the reaction product is the corresponding derivative of 2-(*N*-methylamino)ethanol, the formation of which has been explained by the cleavage of the $Si-CH_2Br$ bond by ethanol and the methylation of ethanolamine by the methylbromide liberated in this process[193].

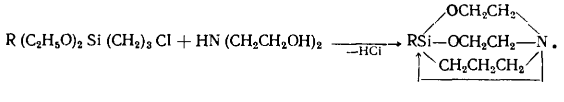
The reaction of 1,3-di(bromomethyl)-1,1,3,3-tetramethyldisiloxane with 2-(*N*-alkylamino)ethanols takes place with the cleavage of the siloxane bond[192-194]:



With ethanolamine, the product of the substitution of the amino-group, formed without the cleavage of the siloxane bond, was obtained[192,193,195,196]:



The reaction of substituted (3-chloropropyl)diethoxysilanes with diethanolamine in the presence of triethylamine leads to the silylation of the amino-group followed by intramolecular transetherification with liberation of ethanol and the formation of cyclic compounds (1-organyl-2-carbasilatranes):[4,197,198]



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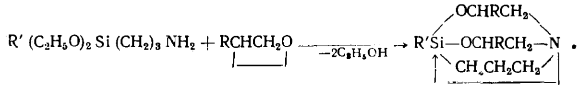
‡According to patent data[188], an acyclic substitution product was also obtained in this reaction.

Similar compounds are formed also in the reaction of alkyl-(3-aminopropyl)diethoxysilanes and of (3-aminopropyl)triethoxysilane with oxirans[198,199]:



$$R'(C_2H_5O)_2Si(CH_2)_3NH_2 + RCHCH_2O \xrightarrow[-2C_2H_5OH]{} R'Si{-}OCHRCH_2{-}N\ .$$

It has been stated that cyclisation takes place also in the case of 4-aminobutyl derivatives[199]. Other examples of this type of reaction for the synthesis of products employed in the treatment of fibre glass and for the preparation of adhesives have been described in a number of papers and patents. However, an acyclic structure is attributed to the reaction products and the possibility of cyclisation is not discussed[200-204].

B. PHYSICAL, CHEMICAL, AND BIOLOGICAL PROPERTIES

The comparatively high experimental dipole moments of 2-carbasilatranes (4.2–4.9 D), greatly exceeding the dipole moments calculated without taking into account the presence of the N → Si bond (0.2–0.8 D), indicate the presence in their molecules of a stable transannular coordinate bond N → Si.[4,7,45,198] Accordingly, they are not titrated by hydrochloric acid at room temperature and do not react with methyl iodide even on prolonged heating[198].

Intra-abdominal administration of 1-phenyl-2-carbasilatrane to white mice causes pronounced motor excitation accompanied by the Straub symptom, indicating the excitation of the spinal nervous system. When administered in doses close to the median lethal dose ($LD_{50} = 8$ mg kg^{-1}), this compound gives rise to clonicotonic convulsions[198].

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Laboratory of the Chemistry of
Organic Derivatives of the Elements,
Institute of Organic Synthesis,
Academy of Sciences of the
Latvian SSR, Riga

U. D. C. 614.449.57

Insect Chemosterilants

M.A.Bulyginskaya and M.D.Vronskikh

The review covers the literature data on the application of chemosterilants in the fight against harmful insects. The chemosterilants have been classified on the basis of their structural characteristics.
The bibliography includes 174 references.

CONTENTS

I. INTRODUCTION

The constantly rising requirement for food products to support the rapidly growing population of the earth necessitates an intensive application of chemical agents for the protection of plants in order to increase crop yields. However, large-scale application of chemical poisons has clearly shown both advantages and disadvantages of the chemical methods of combating pests. Without dealing with the undoubted advantages of this method, we shall only mention some of the problems which have arisen in consequence of the intensive application of pesticides. These include in the first place the accumulation of residual chemical poisons and their metabolites in the soil and plant, animal, and human tissues.

A progressive development of resistance to chemical poisons (in particular organic chloro-derivatives) has been noted in an increasing number of harmful species of insects and ticks (mites). The use of stable preparations with a wide spectrum of action upsets biocenotic equilibria, leads to the destruction of useful insects and ticks (mites), and gives rise to explosive multiplication of various pests.

These undesirable consequences of the large scale and intensive application of chemical poisons led to an increase of interest in many countries (particularly in the post-war years) in the biological methods of combating pests. There has been a sharp increase in publications on this question: 308 in 1955 [1] and 578 in 1958.[2] For example, in 1955 66% of all investigations in the USA were devoted to the application of insecticides and in 1967 only 21%, while the percentages of the studes dealing with biological and other specific methods were 17 and 42%.[3]

There has been a greater expansion of investigations into the ecology, biology, and dynamics of the populations of pests and entomophages and their biocenotic interactions, genetics and cytogenetics of insects, large scale cultivation of entomophages on artificial media, etc. However, it is as yet impossible to abandon the chemical methods of combating pests and employ only ecological and biological procedures. The most promising technique appears to involve a planned combination of all methods of combating pests with the maximum limitation of the use of highly toxic and stable pesticides. Such a system has been called the integral method (or the integrated system) of plant protection. Apart from taking into account the structure of agrobiocenoses, this includes the introduction of types of cultivated plants resistant to pests and disease, the prediction of the number of harmful species, and the use of selective chemical poisons, biological preparations, antibiotics, and herbicides. This programme should also incorporate the application of attractants, repellants, and chemical sexual sterilising agents, and also the breeding of entomophagous insects (or phytophagous insects in the fight against weeds) and sterile insects. The ultimate aim of integrated plant protection is the arrest or sharp reduction of the rate of "biological reconstruction", i.e. the invasion of cultivated areas by weeds, disease, and pests[4]. As regards harmful insects, this result can be achieved by methods in the following two groups: (a) by acting on the insects and the environment (destruction, modification of behaviour, destruction of natural resources); (b) by acting on hereditary properties (sexual sterilisation, introduction of harmful genes into the population)[5].

This review deals with methods of combating pests based on chemical sexual sterilisation.

Sexual sterilisation is so far the only method developed up to the stage of practical application in which the fight against pests involves influencing the hereditary properties of the species, Treatment of the population by an insecticide may be effective only when the increase of "standard mortality" is much greater than the "level of the standard birthrate". However, in accordance with the feedback principle, the temporary increase in the "rate of mortality" is countered by the insects by an increase of the "standard birthrate" and the initial population density is restored[6]. Moreover, the effectiveness of pesticides falls with decreasing population density of the pests. The fight against pests by the sterilisation method is based on another principle. The level of the "rate of mortality" remains temporarily unchanged, while the "birth rate" in the population is reduced because a definite percentage of its members are sterile—the population density will continue to decrease.

The increased interest of entomologists in the sexual sterilisation of insects can also be explained by the fact that this method introduces fundamentally new possibilities into the practice employed in combating harmful insects. Firstly, there is the high effectiveness of the method. Knipling[7] calculated the relative effectiveness of chemical methods of combating pests and of chemical sexual sterilisation. In the version where insecticides were employed (technical efficiency 95%) the insects surviving after treatment (5% of the initial population) multiplied and, possessing a biotic potential increased by a factor of five, restored towards the third generation the initial population density. In the version where a chemical sterilising agent was employed, all the insects survived but 95% became sterile.

These, by mating with one another and also with the remaining fertile individuals, deprived the latter of the possibility of multiplying. Since the sterile insects predominate in the population (19 : 1), then evidently only 5% of the cases of mating will be between fertile insects, while in all remaining cases (95%) one of the partners will be sterile. Thus only 0.25% of the individuals in the initial population will multiply. Therefore the number of insects in the succeeding generations falls sharply and towards the third is already virtually zero.

The calculations described are based on data obtained in the treatment of populations under natural conditions. Similar results are obtained when insects which have been trapped or bred under laboratory conditions are released among the natural population after treatment with the chemosterilant. It is then only necessary to maintain the required ratio between the sterile and natural insects.

Such high effectiveness permits the expectation that the population of many pests will be rapidly reduced and, in the case of some species residing in isolated centres, will be completely eradicated.

The second factor is the high specificity of the method. When the procedure involving the release of sterile insects or the application of chemosterilants in combination with sexual attractants is employed, the operation of the method is restricted to the species against which the fight is directed. The use of sexual sterilisation in combination with light traps or food attractants (or agents stimulating egg laying) reduces somewhat the specificity to group specificity but nevertheless it is still quite high and useful species of the biocenosis are not involved. The direct application of chemosterilants under natural conditions requires the utilisation of selective preparations of low toxicity, since the treatment of a natural population with chemosterilants available hitherto approaches the chemical method in the selectivity of action on the biocenosis.

Thirdly, the use of chemosterilants permits the solution of the problem of the resistance of insects to insecticides. Under laboratory conditions no difference was observed in the sensitivity to a chemosterilant of strains of the house fly resistant and susceptible to organophosphorus insecticides[8]. A similar situation was observed for spider mites[9]. Insects resistant to organic chloro-insecticides are highly susceptible to chlorine-containing chemosterilants[10]. However, experiments have shown the possibility of the development of resistance to chemosterilants also[11]. The degree of acquired resistance is relatively low and exceeds the resistance by the population sensitive to the sterilising agent by a factor of 4–5 only, while the resistance to organic chloro-insecticides increases very markedly (by a factor of hundreds and thousands)[12]. Moreover, the development of resistance in insects is accompanied by the accumulation of "small recessive genetic defects", which leads to an increase of sensitivity to the preparation after 4–5 generations[13] and the initial situation is thus restored. It is noteworthy that, when the method involving the release of sterile insects is employed, the problem of resistance to chemosterilants does not arise at all.

Fourthly, the effectiveness of the method of sexual sterilisation increases as the population density of the pest is reduced, while the effectiveness of insecticides and the majority of entomophages falls under these conditions.

Moreover, it is noteworthy that the application of this method of combating harmful insects solves the problem of the inaccessibility of the individuals for treatment, which is particularly important for certain species with a secretive mode of living. Sterile males driven by the sexual instinct seek their partners everywhere including secluded microscopic sites normally inaccessible to treatment by insecticides.

An essential condition which must be met in the method of sexual sterilisation is the retention of the normal sexual activity and normal behavioural responses in sterilised insects, which enables them to seek normal females under natural conditions and impregnate them.

In the initial experiments sexual sterilisation was achieved by irradiating insects with ultraviolet light and X-, α-, β-, and γ-rays. The success of this programme of eradication of the important pest *Cochliomyia hominivorax* Coq. in 1958–1959 over an extensive territory[14] stimulated research into methods for combating harmful species based on the release of sterile insects among natural populations. The studies carried out to discover more convenient and economical methods of sexual sterilisation of insects showed that certain chemicals give rise to phenomena in the insect organism similar in their final result to radiation-induced sterilisation, i.e. sexual sterility.

The sexual sterility of insect males can be caused by dominant lethal mutation in the sperm, aspermia, or the inactivation of the sperm. On the other hand, in females sterility may result from the suppression of ovogenesis or lethal mutations in egg cells.

The first experiments on the chemical sterilisation of insects were carried out in 1946–1947.[15-17] However, the ability of certain biologically active substances to cause hereditary changes (mutations) when acting upon organisms was noted in even earlier studies by Sakharov, Lobashev, and Smirnov in 1932–1933.[18]

Large scale research on chemosterilants was begun in 1960 in the USA and in 1961 several compounds with sterilising activity were discovered. During the next three years, more than 3000 compounds were tested, of which only about 100 preparations proved to be effective as sexual chemosterilants[19,20]. Up to the present time, the number of tested preparations has increased greatly: one laboratory in Gainsville (Florida, USA) alone tests annually 500–700 compounds in order to elucidate their sterilising activity, and Bořkovec's compilation[6] gives a list of 483 effective preparations tested on 75 insects species and 7 tick species.

The number of publications on chemical sterilisation alone increases annually in a geometrical progression and in 1967 amounted to 400 papers[21]. At present the bibliography on this subject includes more than 600 items. Several reviews of the literature on the problems of chemical sterilisation have been published: by Rukavishnikov[12,22-25], Bořkovec[6,19,26], Smith[27,28], Bertram[29], Kilgore[30], a group of authors under the editorship of La Brecque and Smith[21], and Proverbs[31].

The essential feature of the method of chemosterilants consists in the treatment of specially bred or trapped insects with specific chemical mutagenic agents (chemosterilants), followed by the release of the insects among the natural population or alternatively the natural insect population is treated at sites where it is concentrated.

However, later a distinction was drawn between chemical mutagenic and chemosterilants[32]. Many chemical mutagenic agents are sexual sterilising agents at the same time but not all chemosterilants can cause inheritable mutations or cytogenetic changes.

Chemosterilants may be defined as compounds which reduce or completely eliminate the capacity of animals for reproduction. There exist several groups of substances capable of affecting the reproductive functions of the species. The most thoroughly investigated are substances which inhibit the ovogenetic and spermatogenetic processes, destroying ripe egg cells and sperm[33,34] or causing dominant lethal mutations in the chromosomal apparatus of the sexual cells. Under these conditions, the egg cells survive and the sperm remain mobile, but the zygote dies in the early stages of development. These substances can be defined as chemosterilants in a narrow sense of the word.

In addition, there exists a group of substances which prevent mating by frightening the males away from the females or acting in a somewhat different way on the copulation process[12]. Certain compounds are capable of either eliminating or masking the odour of sexual attractans, which among insects serves as a guide in the search for a mate[12]. It may be expected that some of the substances will act on the insect organism in at least two ways. Data have been published showing that females of the codling moth treated with chemosterilants belonging to the first group or irradiated attracted males less then the untreated specimens[35,36]. Possibly, in addition to the expected effect (sexual sterilisation), chemosterilants and radiation suppressed the activity of the glands secreting the sexual attractant. Studies on these lines would be very timely, since they might provide a basis for the development of yet another method in the biological fight against harmful insects.

The inhibition of the multiplication of insects by certain chemical poisons[37] and also interference with metamorphisis and the sterility of individuals treated by the analogues of certain hormones[38,39] have been observed. However, compounds belonging to the above group (with the exception of the first) can be classified as chemosterilants, only in an extremely arbitrary sense and therefore will not be discussed in detail in the present review.

Frequently attempts at classification of chemosterilants have encountered difficulty in combining a wide variety of compounds into systems based on the similarity of differences in their structures, reactivities, or biochemical effects. In the first experiments on chemical sterilisation compounds employed in the treatment of cancer were applied[19,41-44].

An empirical relation between mitotic agents influencing the process of cell division (mitosis) and compounds with antineoplastic (antitumour) activities was established in the period between 1950 and 1960.[40] At the same time a relation was discovered between cytostatic activity and the effectiveness of these substances as chemosterilants. Although a direct correlation was not always evident, nevertheless compounds with high antineoplastic activities (TEM†. tepa, thiotepa, apholate, tretamine, and others) proved to be promising sexual sterilising agents for insects, and served as a starting point for the selection of possible chemosterilants.

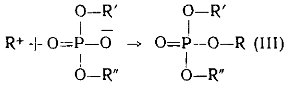
Up to 1964, in fact all the compounds effective as sterilising agents for insects were either anticancer substances or chemically related compounds[19]. Therefore we adopted (with small changes) the system employed in studies on anticancer agents for the classification of chemosterilants. Initially five categories were considered: alkylating substances, antimetabolites, radiomimetic compounds, mitotic poisons, and mixed agents[45]. This classification was partly chemical and partly biological. In addition, some overlapping of categories was noted. Later[6] the system was greatly simplifed and included only three categories: alkylating agents, antimetabolites, and compounds of a mixed type. Radiomimetic and mitotic poisons have been included in one of the above three categories.

II. ALKYLATING CHEMOSTERILANTS

Alkylation, which usually takes place when chemosterilants react with cell elements *in vivo* may be defined as the substitution of a hydrogen atom in the molecule by an alkyl group [see reaction (I)],[46,47] as the direct addition of such a group to a tertiary nitrogen atom with formation of a quaternary ammonium ion [reaction (II)], and finally as its addition to an anion, which leads to the formation of esters [reaction (III)]:[18,46]

$$R^+ + R'SH \rightarrow R'S{-}R + H^+ \quad (I)$$

$$R^+ + NR'_3 \rightarrow R'_3\overset{+}{N}{-}R \quad (II)$$



$$R^+ + O{=}\underset{\substack{|\\ O-R''}}{\overset{\substack{O-R'\\ |}}{P}}{-}\bar{O} \rightarrow O{=}\underset{\substack{|\\ O-R''}}{\overset{\substack{O-R'\\ |}}{P}}{-}O{-}R \quad (III)$$

The alkylating group R can be a hydrocarbon residue, for example the ethyl group $-CH_2CH_3$, or can contain a functional substituent, for example $-CH_2COCH_3$, $-CH_2CH_2NH_2$ (aminoalkyl), or $-CH_2CH_2COOH$.

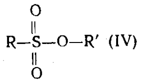
The aminoethylation reactions of nucleoprotein structures responsible for the hereditary properties of the cell (organism) in fact determine the mutagenic activity of alkylating agents[18].

Tests on compounds belonging to the following main groups of alkylating agents (Ross's classification[46]) have been described in the literature: sulphonic acid esters, dichloroethylamines (nitrogenous analogues of yperites), aziridines, halogenoalkyl ester of sulphuric acid, phosphoric acid esters, chloromethyl ethers, sulphonium and ammonium derivatives, 2-chloroethyl sulphides, ethoxides, β-lactones, diazoalkanes, and also activated derivatives of ethylene, halogenomethyl derivatives of ketones and ethers, olefins, and alcohols. The last two groups of substances (olefins and alcohols) alkylate only at a high temperature or in the presence of specific catalysts and do not operate in the living cells of the organism[6].

Sulphonic acid esters, dichloroethylamines, and ethyleneamines proved to be the most promising among alkylating chemosterilants (more than 50% of all the effective preparations belong to these groups) and they will be examined in detail. Examples of the remaining groups have been tested as sterilants on the screw-worm fly *Cochliomyia hominivorax* Coq., but largely negative results were obtained and therefore they will not be considered further.

Sulphonic Acid Esters

The alkylating activity of alkanesulphonic acid esters depends on the strength of the O–R′ bond. Alkane- and substituted alkylmethane-sulphonates (IV)



$$R{-}\underset{\substack{\|\\ O}}{\overset{\substack{O\\ \|}}{S}}{-}O{-}R' \quad (IV)$$

where $R' = CH_3$, are powerful anticancer agents[6]. The data on these compounds as chemosterilants are so far

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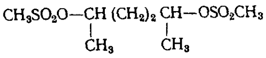
† Significance of abbreviation uncertain (Ed. of Translation).

few but some of them, for example bisulphan (V) and its dimethyl derivative (VI),

$CH_3SO_2O-(CH_2)_4-OSO_2CH_3$ (V)

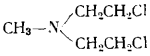


$CH_3SO_2O-\underset{CH_3}{CH}(CH_2)_2\underset{CH_3}{CH}-OSO_2CH_3$ (VI)

proved to be highly effective sexual sterilants for certain insect species, in particular beetles[6], and their toxicity is low. Certain sulphonic acid esters are effective chemosterilants for the Callitroga [screw-worm] fly. Diesters proved to be more active than monoesters as sterilants, but their toxicity is also higher[48].

Dichloroethylamines

In studies concerned with the treatment of cancer these compounds occupy a special place. A review of alkylating agents[49] tested as anticancer chemotherapeutic agents gives a list containing more than 20 000 compounds[49]. Chloroethylamines are structurally similar to yperite in which the sulphur atom has been replaced by nitrogen (VII):



$CH_3-N(CH_2CH_2Cl)_2$ (VII) .

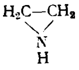
Compounds containing one 2-chloroethylamino-group ($=NCH_2CH_2Cl$) belong to single-chain yperites; compounds with a di-(2-chloroethyl)amino-group [$-N(CH_2CH_2Cl)_2$] are two-chain yperites. The presence of a number of functional groups in biological alkylating agents is regarded as an imporant property which promotes the cross-linking of chromosomes or other physiologically important cellular formations[46,50]. However, although cross-linking can sometimes account for the disproportionately high activity of polyfunctional compounds, the mechanism of the action of chloroethylamines is much more complex. Interference with metabolism (in particular of phosphorus[51]) and the inhibition of enzymes involved in the nucleic acid metabolism and also of glycolytic enzymes have been noted. This leads to the inhibition of cell division and gives rise to morphological changes in dividing chromosomes: fragmentation, mutual adhesion, the formation of bridges between chromosomes in the anaphase, and others[52].

Historically yperite derivatives have been some of the first chemical mutagenic agents discovered[15,16]. A large number of compounds of this series have already been tested as chemosterilants but only some of them showed a high effectiveness.

Nitrogenous yperite and its derivatives are effective sexual sterilants for the males of mice[53], the house fly[43], the Mexican fruit fly[54,55], and the Callitroga fly[56].

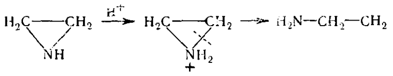
Derivatives of Aziridine

This is the most "promising" group of alkylating compounds. More than one third of the effective chemosterilants quoted in Bořkovec's compilation[6] are aziridine (ethylene imine) derivatives (VIII):



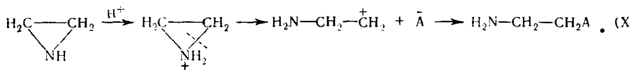
(VIII) .

The aziridine ring is responsible for the reactivity of aziridines in relation to nucleophilic agents. A characteristic property of the ring is the ease of addition of a proton to the nitrogen atom, the high reactivity of the carbon atoms, and the ease with which the ring is opened to form a chain (IX):



(IX)

The overall mechanism of the alkylation of a nucleophilic centre A by aziridine can be represented as follows [reaction (X)]:



(X)

Sulphur, nitrogen, and oxygen atoms, which usually form part of the genetic complex [see reactions (I), (II), and (III)] are most often alkylated in biological systems (S > N > O). In addition, their nucleophilic properties depend on the relative polarisability of the atom. Sulphur and nitrogen atoms, which have a high atomic weight, are more readily polarised and the compounds incorporating these elements in their molecules are powerful nucleophilic agents.

The high reactivity of alkylating compounds suggests that they can react with the majority of the substances present in each cell and containing nucleophilic groups. Such groups may be the carboxy-, phosphoryl, sulphydryl, and also amino-groups[57].

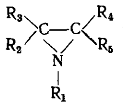
Hydroxy- and carboxy-groups of the protein complex and of aminoacids[58] and also reactive amino-groups and sulphydryl groups [see reaction (I)] should be included among biological centres capable of undergoing alkylation under mild physiological conditions (as aziridine penetrates the cell).

Carbohydrates are not as a rule alkylated, since their polar hydroxy-groups are present in an undissociated form at the physiological pH.

In contrast to glycerol esters, free aliphatic acids can be esterified on alkylation. A number of vitamins (B_1, B_6, biotin, and folic and p-aminobenzoic acids) each contain several centres undergoing alkylation. Such centres are nitrogen atoms in rings, and amino- or carboxy-groups. This accounts for the finding that not only the protein complex but also the prosthetic groups in enzymes may constitute centres sensitive to alkylation[18].

The study of a number of reactions of alkylating agents with highly purified native DNA and its components[59-61] and also with the transforming factor under mild physiological conditions[59,60] revealed the presence in DNA of several highly reactive nucleophilic centres.

The mole of an aziridine derivative consists of an active part (one or several aziridine rings) and a "carrier"—the residual component of the molecule, and can be represented schematically by formula (XI):



(XI) .

Among the aziridine derivatives investigated are compounds containing 1, 2, 3, 4, 6, and 8 alkylating rings. The increase of the sterilising activity of ethyleneimine derivatives is as a rule directly proportional to the number of aziridine rings. In investigations much attention is devoted to the problem of whether one or several aziridine groups are required for an effective chemosterilant[15,45,62,63]. Experimental data show that monofunctional derivatives are relatively ineffective as chemosterilants. Nevertheless the number of aziridine groups cannot be directly linked to the activity of the compound. For example tepa (with three aziridine groups) injected into male house flies proved to be more effective than apholate, which has six aziridine groups[64]. Moreover, the difference between the activities of difunctional and trifunctional aziridines may be much less than the difference between the monofunctional and difunctional compounds[6]. Certain diaziridines proved to be more effective than triaziridines with a similar structure[63,65,66].

The higher effectiveness of polyfunctional derivatives compared with monofunctional derivatives served as a basis for the hypothesis that polyethyleneimines can link DNA molecules in pairs and thereby bind pairs of chromosomes in the metaphase[67,68].

Examination under the microscope of the sexual cells of animals sterilised by polyfunctional compounds indeed reveals bridges between chromosomes. This is the reason for incorrect division of chromosomes among the daughter cells, which leads to genetic abnormalities and the non-viability of the daughter cells.

However, this hypothesis does not account for the mechanism of the mutagenic effect of monofunctional aziridines on mammals[50], although there is no doubt about the higher activity of polyfunctional compounds.

The sterilising activity of aziridine derivatives depends not only on the number of functional groups but also on the substitution at the carbon and nitrogen atoms of the ethyleneimine ring. The substitution of one hydrogen at a carbon atom of the aziridine ring sharply lowered the sterilising activity and the substitution of two hydrogen atoms resulted in its complete loss. Numerous reports lead to the conclusion that any substitution of hydrogen at the carbon atoms in the rings of aziridine compounds leads to a decrease of their sterilising activity on insects[19,28,45,56,63,65,69,70]. At the same time methylation is usually accompanied by a sharp lowering of the toxicity of the preparation. Substitution of one hydrogen atom lowers the toxicity of aziridine homologues by a factor of twelve in relation to rats and substitution of two atoms lowers the toxicity by a factor of twenty compared with unsubstituted aziridine[57]. This property of ethyleneimine derivatives leads to the possibility of seeking compounds whose toxicity for insects and warm blooded animals is low but which are still sufficiently effective for the purpose of sterilisation.

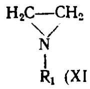
Substitution of the hydrogen atom at the nitrogen atom of the aziridine ring leads to analogous phenomena. Substitution of the hydrogen atom by aliphatic radicals lowers the toxicity of aziridine homologues in relation to rats by a factor of 10–20, substitution by aromatic groups lowers the toxicity by a factor of 40, and substitution by aliphatic-aromatic groups lowers it by a factor of 20–100 compared with unsubstituted aziridine[57]. Unfortunately, there are still insufficient data in the available literature for the analysis of the sterilising activity of such aziridine derivatives. On the other hand, acylation of aziridine (i.e. addition of an acid group to the nitrogen atom in the ring) increases the sterilising activity of the compound as well as its toxicity[28].

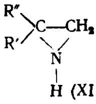
Moreover, the sterilising activity depends not only on the effective component but also on the nature of the "carrier component" of the molecule. For example, a decrease of the electronegativity of the central atom to which the aziridine groups are joined as a result of the replacement of oxygen by sulphur also lowers the sterilising activity of the compound. It must be emphasised that the substitution of hydrogen at a nitrogen atom in the "carrier component" of the molecule lowers primarily the toxicity, but has much less effect on the sterilising activity. In addition, some workers believe that the toxicity of chemosterilants is in general a function of the "carrier component" and is not closely linked to the number of aziridine groups in the molecule[48].

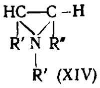
The most effective chemosterilants will probably be compounds in which aminoacids, peptides, nitrogen bases, etc. are linked to the "active component" of the molecule (aziridine ring), since natural groups apparently more readily transmit alkyl groups to cellular systems important in the vital processes of the cell and ensure their blocking. This approach has already been used in relation to compounds employed in the chemotherapy of malignant neoplasms[71].

All the aziridine derivatives already investigated can be divided (according to their chemical structure) into several groups.

C- and N-substituted derivatives of the type


(XII)


(XIII)


(XIV) .

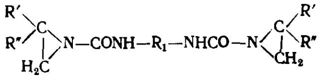
The simplest compound of this series is aziridine itself (ethyleneimine, dimethyleneimine, azacyclohexane). Experiments on the antiblastic effect of aziridines reveals its high toxicity (LD_{100} = 5 mg kg^{-1} for rats when administered intravenously). It has been established that the inhibition of the growth of tumours is achieved only on introduction of toxic (4 mg kg^{-1}) or the maximum tolerated (2.5 mg kg^{-1}) doses.

Aziridine and its homologues and also aliphatic derivatives in doses less than the maximum tolerated amounts stimulated the growth of tumours. Aromatic and aliphatic-aromatic compounds did not show this effect when administered in such doses, but some of them caused a weak inhibition of the growth of tumours. Aliphatic-aromatic ketones proved to be quite inactive in relation to sarcoma[57].

Unsubstituted aziridine showed the greatest mutagenic activity. A sharp reduction of mutagenic activity is observed in all cases of *C*- and *N*-substitution[72]. However, mutagenic activity cannot be fully identified with the sterilising activity of the compound, which involves a more complex process. Although chemosterilants without mutagenic activity exist, the majority of compounds sterilising insect males are as a rule mutagenic also.

Unsubstituted aziridine has been used to sterilise the Callitroga fly[56]. Compounds of this series are probably not very promising as chemosterilants, partly in view of their fairly high toxicity and partly because of their monofunctional nature.

Aziridine derivatives of urea (XV):


(XV) .

It has been noted that the toxicity of compounds of this type and also their antiblastic (and probably sterilising) activity falls with increase in the number of methyl groups at the carbon atoms of the aziridine ring, which constitutes yet another proof in support of the general rule (see above).

Moreover, the toxicity of many compounds with $R_1 = (CH_2)_n$ falls as the number of methylene groups is reduced. Among derivatives of this series the following chemosterilants of the house fly have been noted:

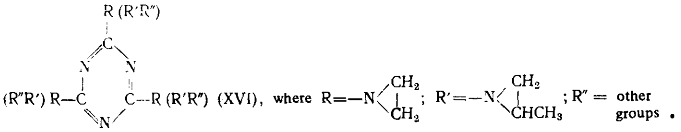
NN'-octamethylenebis(aziridine-1-carboxamide)[6],
NN'-octamethylenebis(aziridine-1-acetamide)[73],
NN'-heptamethylenebis(aziridine-1-carboxamide)[74],
NN'-pentamethylenebis(aziridine-1-carboxamide)[74],
NN'-phenylenebis(aziridine-1-carboxamide)[74],

and also chemosterilants of the Callitroga fly:

NN'-bis(aziridine-1-carboxamide)[75],
NN'-tetramethylenebis(aziridine-1-carboxamide)

and homologous compounds with 4–8 and 10 methylene groups[76]. However, aziridine derivatives have not found wide application as chemosterilants.

Aziridine derivatives of triazine (XVI):



(XVI), where R = ; R' = ; R'' = other groups .

Different derivatives may contain different combinations of the R, R', and R'' groups but an obligatory condition for these compounds is the presence of at least one aziridine group.

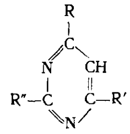
Compounds containing only one aziridine group are as a rule less toxic (LD_{100} for rats is higher by a factor of 20–100 compared with aziridine and its homologues). The presence of two aziridine groups leads to an increase of the toxicity of the preparation compared with monofunctional compounds (LD_{100} higher by a factor of only 1.5–6 compared with aziridine). Derivatives with three aziridine rings proved to be the most toxic (LD_{100} = 0.7 mg kg^{-1}).[57] The presence of various substituents instead of one or two aziridine groups (alkyl, alkoxy-, halogeno-, and others) and also of substituents at the carbon atoms of the aziridine ring likewise affects the toxicity of the compound, although the effect of these [latter? (Ed. of Translation)] substituents is much weaker than the substitution of the entire ethyleneimine group.

The cytostatic activity of aziridine derivatives as well as their toxicity depends to a considerable degree on the number of aziridine rings. It is highest for triethyleneaziridines, tretamine (TET), and methyltretamine (MeTET) and decreases progressively as the number of aziridine groups in the molecule is reduced. However, a direct correlation between toxicity and cytostatic activity is not always observed. For example, 6-benzyloxy-2,4-di-(1-aziridinyl)-*s*-triazine, which has a toxicity smaller by a factor of 20–40 than that of tretamine, is not inferior to the latter in its cytostatic activity[57].

In the series of 1-aziridinyl derivatives with amino-acid residues, the most toxic are derivatives with valine and lysine residues and the least toxic are those with glycine and alanine residues and among the latter the least toxic are compounds containing the residue of the ethyl ester of α-alanine. The introduction of an aromatic substituent into the molecule of the ethyl ester of α-alanine results in a further decrease of toxicity by a factor of two. The cytostatic activity of these compounds is less pronounced than that of tretamine and 1-aziridinyltriazines with alkyl, alkoxy, and aryl substituents[57].

Tretamine and methyltretamine are most widely used as chemosterilants[56,77-84].

Aziridine derivatives of pyrimidine (XVII):



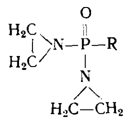
(XVII) ,

where R' and R'' are aziridine groups and R is another substituent. The nature of the R substituent has a marked influence on the toxicity of the compounds. For example, the replacement of chlorine by a methoxy-group reduces the toxicity of the preparation by a factor greater than 6.[57]

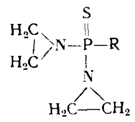
1-Aziridinyl derivatives of pyrimidine proved to be highly active. The introduction of the minimal toxic dose leads to complete disappearance of tumour tissue from male mice[57].

These compounds are of considerable interest for the purpose of sterilisation. Several preparations have been tested as chemosterilants: (a) 2,4-di-(1-aziridinyl)-6-methyl-5-nitropyrimidine (tested on *Diptera*[85,86]); (b) 4,8-di-(1-aziridinyl)pyrimido[5,4-*d*]pyrimidine[70,74]; 1-methyl-4-methylamino-1-pyrazolo[3,4-*d*]pyrimidine[56]; (d) phosphazine[*PP*-di-(1-aziridinyl)-*N*-2-pyrimidinylphosphinic amide][76,80,87]; (e) morphimide and pyrimide‡ [*PP*-di-(1-aziridinyl-*N*-6-piperidino-4-pyrimidinyl phosphinic amide and *PP*-di-(1-aziridinyl)-*N*-6-morpholino-4-pyrimidinylphosphinothioic amide], which show a high activity in tests on certain insect species and only moderate activity in tests on others[88-91].

1-Aziridinylphosphine oxides (XVIII) and sulphides (XIX):



(XVIII)



(XIX) .

This group of compounds has attracted most attention by both physicians and entomologists. The tri-(1-aziridinyl) derivatives of phosphine oxide and sulphide (tepa and thiotepa) proved to be valuable medicinal preparations and have been successfully used in the treatment of malignant tumours and a number of chemoblastoses[92].

Di-(1-aziridinyl) derivatives of phosphine oxide with aryl substituents at the phosphorus atom are as a rule less toxic than the tri-(1-aziridinyl) derivatives (tepa). However, this cannot be explained solely by the replacement of the aziridine ring, since compounds with three and four [one and two? (Ed. of Translation)] aziridine groups proved to be no less toxic than tepa. In the first case the aziridine ring is attached to the phenyl ring via a keto-group and in the second is present as the phosphoric acid diethyleneimide residue [di-(1-aziridinyl)phosphine oxide derivative (Ed. of Translation)]. This is further proof of the effect of the "carrier component" of the molecule on the properties of aziridine derivatives§.

Compounds of this group exhibit a wide variety of cytostatic effects. In their action on malignant tumours the most active compounds approach the effect of tepa, but

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‡ These are transciptions of Russian names which transliterate as morfimid and pirimid. The order of the systematic names should probably be reversed (Ed. of Translation).

§ The test in this paragraph is confused possibly owing to the omission of one or more sentences from the Russian original (Ed. of Translation).

some are much inferior and others do not show any activity at all.[57]

Di-(1-aziridinyl)phosphine oxides containing aminoacid ester residues have a low toxicity. The relations noted for the analogous derivatives of the triazine series are also shown by this group of preparations. The least toxic proved to be a compound with a glutamic ester residue (LD_{100} for mice is more than ten times higher than LD_{100} of tepa). Compounds of this series proved to be relatively inactive as antitumour agents. We were unable to find any data in the literature on the sterilising activity of preparations of this group.

Di-(1-aziridinylphosphine oxides and sulphides with heterocyclic substituents at the phosphorus atom are as a rule less toxic than tepa (approximately by a factor of 3–10) but exhibit a high antiblastic activity. For example, Dipin has become widely known in the chemotherapeutic treatment of cancer. Certain compounds of this group are known as highly effective chemosterilants, for example Phophazine and compounds with a pyrimidine ring (these were discussed above; see the aziridine derivatives of pyrimidine), Dipin (1,4-piperazinediylbis[di-(1-aziridinyl)]-phosphine oxide);[81,87] derivatives with furan and toluene rings were tested without special success[70,93,94].

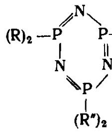
Tri-(1-aziridinyl)phosphine oxide and sulphide. As already mentioned tepa and thiotepa are most widely used in the chemotherapy of cancer. Their toxicity is fairly high but lower by a factor of 6–8 than that of unsubstituted aziridine. In entomology these compounds are known as highly active chemosterilants for a number of insects and tick species.

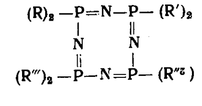
Tepa [aphoxide, tris-(1-aziridinyl)phosphine oxide] proved to be a highly effective chemosterilant for more than 25 insect species[10,56,69,83,86,95–114]. The methyl analogue of tepa (methaphoxide, metepa) is a preparation with a somewhat reduced effectiveness compared with tepa, but its toxicity is much lower; it was tested on more than fifteen insect species[56,69,94,98,101,103,106,109,111–123]. Tri-(1-aziridinyl)phosphine sulphide (thiotepa) is less toxic than tepa but its sterilising activity is weaker. It has also proved to be an effective chemosterilant for a large number of insect species[56,77–84,87–89,94,106,124–130]. The methyl analogue of thiotepa (methiotepa) has both a lower toxicity and a lower activity than the initial compound[56,85,97,106,131].

It is striking that the introduction into the metepa and methiotepa molecules of a further methyl group in place of hydrogen at a carbon atom of the aziridine ring leads to complete loss of sterilising activity[19,45,132].

The *PP*-di-(1-aziridinyl) derivatives of phosphinic and phosphinothioic amides and methyl phosphinothiolate are related to this group. These compounds have a low toxicity but nevertheless sterilise insects fairly actively even at low concentrations. *PP*-di-(1-aziridinyl)phosphinic amide proved to be a highly effective preparation for the codling moth[133]. *PP*-di-(1-aziridinyl)phosphinothioic amide is less active in relation to this insect[133]. Methyl di-(1-aziridinyl)phosphinothiolate is a highly active chemosterilant for the house fly[134].

Aziridine derivatives of the trimer (XX) and tetramer (XXI) of phosphonitrilic chloride:


(XX)


(XXI)

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The initial compounds of this series of derivatives (the trimer and tetramer of phosphonitrilic chloride) have a low toxicity. The substitution of 4, 6, and 8 chlorine atoms by 1-aziridinyl groups leads to an increase of toxicity but it still remains of the same order of magnitude as that of tepa and thiotepa and is lower by a factor of 10–20 than the toxicity of tetramine. The introduction into the molecule of piperidine, morpholine, or glycine residues in place of chlorine atoms leads to an appreciable reduction of the toxicity of the preparations[57]. Compounds with not less than four 1-aziridinyl groups exhibit a high cytostatic activity. Their reduction to two or complete replacement of 1-aziridinyl groups fully eliminates the antiblastic activity.

Several compounds of this series have been tested as insect chemosterilants: LS-152 (monomorpholinotetra-(1-aziridinyl)chlorotriphosphonitrile)[89], methylapholate[56], and apholate. The last compound proved to be highly effective and is most widely used[9,10,48,56,69,77,78,81,82,84,85,87,91,94,96,98,100,102–105,107,109,111–114,119,121,123,126,135–143]. It showed a high sterilising activity on almost 40 species of insects and ticks[21].

III. ANTIMETABOLITES

Antimetabolites are structural analogues of metabolites, i.e. substances necessary for the existence and vital activity of organisms in consequence of their decisive role in metabolic reactions (for example, vitamins, hormones, aminoacids, etc.). However, structural analogy with natural metabolites is not the only characteristic of antimetabolites.

Another important requirement which must be met by antimetabolites is metabolic antagonism[6]. Antimetabolites are interesting also because they can give rise in organisms (or in individual biological systems) to an insufficiency of the metabolite to which they are structurally related and the biological effect observed under these conditions can be removed in almost all cases or reduced by a simple increase of the concentration (dose) of the metabolite.

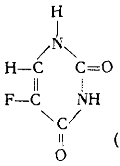
By virtue of the steric analogy, the antimetabolite competes with the metabolite and, participating together with the latter in biochemical reactions, displaces it from metabolic processes. The cell having employed antimetabolites cannot biosynthesise normal compounds (proteins, nucleic acids, and others).

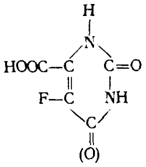
Yet another characteristic of antimetabolites is their capacity to act on females alone, particularly when administered to adult insects. The synthesis of nucleic acids in adult females is usually a prolonged process: after the emergence from the pupa, the ovaries are as a rule only partially developed, but even after the attainment of sexual maturity and mating the production of eggs continues throughout the life of the female. Since the gonads are the principal site of mitotic activity in adult insects, their specific interaction with the antimetabolite is facilitated. Immediately after the emergence from the pupa, the male has as a rule a complete set of mature spermatozoa where the formation of nucleic acids has already been completed and therefore they are more resistant to the action of antimetabolites. However, it has not been determined exactly whether antimetabolites can arrest the spermatogenesis in the males belonging to species where this process is also prolonged[19,144]. The minimum sterilising dose of the antimetabolite is low and usually smaller by a factor of 100 than that of aziridine derivatives. The toxicity of these compounds is as a rule very low and their antiblastic activity is fairly high. Moreover, it is noteworthy that the vast majority of antimetabolites are active only when administered via the intestine and only exceptionally certain preparations exhibit contact activity.

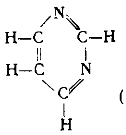
Analogues of Purine and Pyrimidine

Compounds of this series can act upon the normal cell metabolism in three ways: they can compete with a normal nucleotides for enzymes and thus prevent the regular combination of the nucleotides with nucleic acids, they can control by a feedback effect the synthesis of new nucleotides and hence nucleic acids, and finally they can be incorporated directly into newly formed nucleic acids and the latter, by losing their functional purpose, can give rise to pronounced metabolic disorders[19].

Although many analogues of purine and pyrimidine (XXIV) have already been tested, a detailed study has been made of only a few of them: 5-fluorouracil (XXII) and 5-fluoro-orotic acid (XXIII):


(XXII)


(XXIII)


(XXIV)

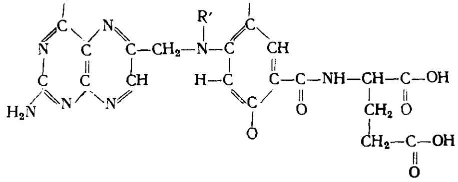
They were tested mainly on flies and mosquitoes. These compounds sterilise only the female insects[145]. 5-Fluorouracil replaces almost 50% of uracil in bacterial RNA [136] and 28–48% in TMV RNA [146] and stops their reproduction. 6-Methyluracil behaves similarly. A direct correlation has been observed between the content of 5-fluorouracil in the RNA in the eggs of the house fly and the loss of their viability[136]. It is noteworthy that in all cases the sterility was temporary and after 3–5 days was gradually eliminated[116]. 5-Fluorouracil is known as a sterilant for more than ten insect species.

5-Fluoro-orotic acid administered via the intestine proved to be effective[56,147] and the sterility was more stable—the treated females did not lay eggs. Moreover, 5-fluoro-orotic acid sterilised also males[14].

4-Amino-1-*H*-pyrazolo[3,4-*a*]pyrimidinium sulphate, which is a purine antagonist, is effective only at high concentrations[43].

Analogues of Folic Acid

Compounds of this series have a wide variety of structures and properties. More than 50 derivatives of *p*-aminobenzenesulphonamide and other sulphonamides have been tested as chemosterilants without much success[19], but the compounds bear only a very remote relation to the structure of folic acid[6] (XXV, R = OH, R′ = H):


(XXV)

On the other hand, antagonists of folic acid such as aminopterine (XXV, R = NH_2, R′ = H) and methotrexate (XXV, R = NH_2, R′ = CH_3) are highly acid sterilants for the females of numerous insect species[6,19,38,67,131,148]. It is noteworthy that the sterility caused by methotrexate is more stable—the ovaries remain undeveloped and the females do not lay eggs throughout their life[19]. Aminopterine and its sodium salt have a similar but weaker effect[10,42,148]. It is striking that the sterilising activity of these compounds can be inhibited by the introduction of an excess of folic acid[140,148].

It has been shown experimentally that aminopterin is a radiomimetic poison; it reduces the number of mitoses. Folic acid antagonists strongly inhibit the enzymes involved in the formation of folic acid and act on the synthesis of nucleic acids by inhibiting the conversion of folic acid into folinic acid and by interfering with the assimilation of the latter in the process of synthesis[26], impair cell division, and damage chromosomes[149].

Other Antimetabolites

Tests on numerous analogues of aminoacids, carbohydrates, steroids, and also aliphatic acids and hydroquinone derivatives showed that most of them are not very promising. Derivatives of hydroquinone[150], which have a low toxicity for insects and warm blooded animals, deserve mention. Among dimethylhydroquinones, 2,6-dimethylhydroquinone is the least toxic isomer. When tested, it proved to be a highly active chemosterilant for the females and males of the house fly[93].

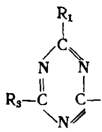
The addition of cyclopropene aliphatic acids and also of sterculic and malvalic acids to the feed lowers the egg laying capacity of chickens and the fertility of house fly females. A valuable property of these acids is their extremely low toxicity, which led some investigators[151] to suggest their inclusion as additives with certain toxic chemosterilants.

IV. COMPOUNDS OF MIXED TYPE

In recent years an increasing number of chemosterilants have appeared which are neither alkylating agents nor antimetabolite analogues. Such compounds sometimes have a structural analogy with certain of the previously described chemosterilants, but this feature alone cannot serve as a basis for their inclusion in the corresponding groups of preparations. Although the mechanism of the action of compounds of this type has as yet been little investigated, the available data suggest the existence of fundamental differences, specific for each individual group. In this section we shall consider only certain groups of the chemosterilants.

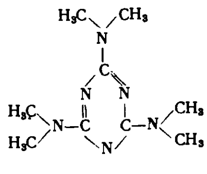
s-Triazines

Derivatives of *s*-triazine (XXVI, R_1, R_2, R_3 = H) are not alkylating agents:


(XXVI)

The substitution of any of the three hydrogen atoms in *s*-triazine by an alkyl group leads to the formation of alkyl derivatives of triazine, some of which are well known chemosterilants (see the 1-aziridinyl derivatives of triazine) and mutagenic and antiblastic agents.

Historically, the first non-alkylating *s*-triazine chemosterilants are hemel (XXVII), hexamethylmelamine (HMM), and tri-(2,4,6-dimethylamino)-*s*-triazine [XXVII, R_1, R_2, $R_3 = N(CH_3)_2$], [66] which is a structural analogue of tretamine (TET):



(XXVII)

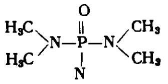
In view of the absence of aziridine rings, this compound has no alkylating properties, but it has retained the capacity to sterilise insects [66]. There exists the view that hemel is converted in animal organisms into effective chemosterilants (possibly into alkylating substances). For example, demethylation of hemel leads to the formation of formaldehyde [66]. Hemel is fairly rapidly eliminated from the insect's organism in the form of metabolities: about 50% after 5 h and about 98% after 18 h. [152]

In the last few years more than 800 derivatives of *s*-triazine were tested. Methyl-substituted melamines [XXVI, R_1, R_2, $R_3 = N(CH_3)_2$] proved to be most active chemosterilants. In this sense hemel (XXVII) may be regarded as hexasubstituted melamine. The activity of the compound increases with the number of methyl groups [131]. The substitution of one of two hydrogen atoms in the methyl groups of even penta- and hexa-methyl-substituted and *N*-propyl- and butyl-melamines leads to the loss of sterilising activity, while on their substitution by ethyl or isopropyl groups a high activity is retained by the compound. That this rule is not restricted solely to alkyl substituents, is shown by the high activity of monoacetylmelamine (XXVI, R_1, $R_2 = NH_2$, $R_3 = NHCOCH_3$), while the 2-hydroxyethyl derivative (XXVI, R_1, $R_2 = NH_2$, $R_3 = NHCH_2.CH_2OH$) and the 2-aminoethyl derivative (XXVI, R_1, $R_2 = NH_2$, $R_3 = NHCH_2CH_2NH_2$) proved to be inactive. The sterilising activity of mono-, di-, and tri-substituted derivatives is inversely proportional to the size of the substituting group. However, this rule does not apply to cyclic substituents [6,153]. Diamino-*s*-triazines with halogeno-, hydroxy-, alkoxy-, sulphydryl, and aryl groups show only a weak sterilising activity or none at all.

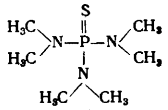
A characteristic feature of *s*-triazine derivatives is the specificity of their action: certain compounds, in particular hemel, are more effective on males than on females [62,63,66,70], but the majority of others are sterilants only in relation to females. Moreover, some of the compounds exhibit species specificity: for example, 2,4-diamino-6-(2-furyl)-*s*-triazine (XXVI, R_1, $R_2 = NH_2$, $R_3 = C_3H_3CO$) is a highly active chemosterilant of the house fly but does not have a significant influence on mosquitoes, the Mexican fruit fly, the Callitroga fly, and many other insects [6]. Possibly this compound will prove to be the first of a series of specific sexual sterilants which will be synthesised in the future for other insect species as well.

Phosphoramide Derivatives

Among these compounds, mention should be made in the first place of hexamethylphosphoramide [HMPA, hempa, tris(dimethylamino)phosphine oxide] (XXVIII), which may be regarded as a structural analogue of tepa:



(XXVIII)



(XXIX)

Hexamethylphosphoramide is the first highly effective chemosterilant in the series of numerous similar compounds which have been tested [13,40,63,66,88,89,154,155]. The majority of its derivatives are inactive and only some of them showed moderate sterilising activity.

Phosphorothioic hexamethyltriamide [thiohempa, tris-(dimethylamino)phosphine sulphide] (XXIX) may be regarded as a structural analogue of thiotepa. In its sterilising activity on certain insect species, it approaches hexamethylphosphoramide [6,155,156].

The substitution of larger alkyl or aryl groups or hetercyclic groups for hydrogen at a carbon atom leads to a lowering or loss of sterilising activity by compounds of this series.

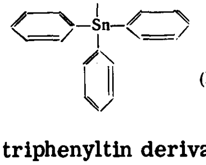
The activity of hexamethylphosphoramide in relation to certain insect species is very variable. The initial success is sometimes not repeated in subsequent tests (or in the experiments of some investigators hexamethylphosphoramide proved to be inactive in relation to insect species for which it had been claimed to be highly active in other experiments). The reason for this conflicting nature of the results is not as yet clear.

Although hexamethylphosphoramide and phosphorothioic hexamethyltriamide do not exhibit alkylating properties, their well defined physiological and cytotoxic properties give rise to changes in the cell, which resemble the phenomena occurring under the influence of alkylating agents [157]. This is consistent with the hypothesis that, like hemel, hexamethylphosphoramide is demethylated in the insect organism (in particular in the house fly) with formation of an effective alkylating agent—formaldehyde [66]. However, the latest studies [158] do not confirm these data.

The structural similarity of these compounds to aziridine derivatives and the relative simplicity of their molecules make them extremely valuable for the elucidation of the mechanism of sexual sterilisation.

Triphenyltin Derivatives

Preliminary tests on several trialkyl- and triphenyl-tin derivatives (previously employed as fungicides and insecticides) in 1960–1962 showed that they are either highly toxic or exhibit a moderate sterilising activity. After 1964 a series of studies were made on compounds of this type [74,113,159,160] exhibiting sterilising activity in very low doses. High activity is shown only by triphenyltin derivatives (XXX, R = halogen, hydroxyl, alkyl, ether group, etc.) but certain other derivatives can also show a limited activity:



(XXX)

The properties of triphenyltin derivatives indicate an activity of the antimetabolite type. They are active exclusively on insect females and the sterility which they cause is as a rule temporary. Moreover, they are effective only when administered via the intestine. Triphenyltin derivatives are highly toxic, which may be an obstacle to the sterilisation of many insect species.

Other Agents of the Mixed Type

The rapid growth of the range of substances tested as insect chemosterilants led to the discovery of sterilising activity in many compounds. Some of these deserve at least a brief mention.

In the last few years more than 100 derivatives of urea and thiourea were tested. Urea and thiourea show variable results[84,141,142,148], which can be accounted for by their toxicity for insects. The most active are cyclic derivatives of urea and thiourea[139], but they too act only on the females of certain species. Urea derivatives containing alkylating groups and known as cytostatic agents in the chemotherapy of cancer and also as effective chemosterilants were discussed above (see the 1-aziridinyl derivatives of urea).

To so called "natural products" constitute another category of compounds[6]. In the first place mention should be made of pyrrolizidine alkaloids[161,162]. However, their effectiveness is extremely limited: among the species tested, only the males of the house fly proved to be susceptible to monocrotaline. The products of the hydrolytic decomposition of monocrotaline did not exhibit a sterilising activity.

Hydroquinone derivatives were discussed above as antagonists of progesterone derivatives and will not be considered further here. Certain antibiotics should also be mentioned (streptomycin, biotin, and others)[163,164].

Colchicine was described as one of the first chemosterilants of Drosophila females as early as 1947.[165] Unfortunately its toxicity for many species and its specific effect of females alone greatly reduces the scope of its applications[85,94,166].

Compounds capable of acting selectively on the hormonal control of reproductive functions are of considerable interest. Here undesirable effect on other functions of the organism can be greatly limited. Only the first step has been taken on these lines[38,39,167-170], but they open up vast prospects for this method of influencing the populations of harmful species.

Many organic and inorganic insecticides[37,38,41,43,171-173] in sublethal doses suppress to a greater or less extent the reproduction of insects. These compounds are probably not of great interest as sterilising agents because the sterility in such cases may be a consequence of the general debilitating effect of the sublethal doses. On the other hand, cases of an increase in the fertility of insects under the influence of insecticides are well known. However, any effect of insecticides, inhibiting or stimulating reproduction, may be important in the assessment of the long term consequences of their application.

Recent studies led to the discovery of sterilising activity in certain groups of compounds which were neither mutagenic agents, nor antimetabolities, nor insecticides. For example, various organic and inorganic boron compounds proved to be chemosterilants for *Cochliomyia hominivorax* Coq. Here the sterilising activity is directly proportional to the amount of boric acid produced in the hydrolysis of the test compound[174].

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In conclusion it is necessary to consider certain requirements which must be met by compounds tested as chemosterilants. High sterilising activity depends to a considerable degree on the chemical nature of the compounds, on the steric positions of its atoms, and also on the physical properties (solubility, capacity for migration, and others). A low solubility of the preparation gives rise to difficulties not only in the technique of its application, but also to a considerable degree determines its capacity for migration within the organism.

The toxicity of the compound for insects, warm-blooded animals, and man is also an important criterion of its usefulness as a chemosterilant. Preparations which are highly toxic for insects can appreciably lower their viability apart from sterilisation (reduction of the life-span of the treated individuals, lowering of the competitive capacity of males or the competitive capacity of spermatozoa, etc.). This can appreciably reduce the effectiveness of the method of sexual sterilisation. It should be noted that all compounds with sterilising activity are more or less toxic for insects. A criterion of the effectiveness of the preparation may be the ratio LD_{50}/ED_{50} or LD_{100}/ED_{100}, which has come to be called the "safety factor", where LD_{50} and LD_{100} are lethal doses for 50% and 100% of the individuals and ED_{50} and ED_{100} are the corresponding doses causing sterility; the chemosterilant may be regarded as more effective the higher is the ratio. A "safety factor" (SF_1) of 5 and above is regarded as satisfactory for the majority of chemosterilants[26]. However, it is not constant for all values of LD and ED and therefore, for a complete characterisation of the sterilant, it is necessary to determine a further two safety factors (SF_2 and SF_3).[65,66,140] The "safety factor" SF_2 may be defined by the formula

$$SF_2 = \frac{LD_{0.01} - ED_{99.99}}{ED_{99.99}} .$$

The third "safety factor" SF_3 is similar to SF_2:

$$SF_3 = \frac{LD_{0.01}}{ED_{99.99}},$$

where $LD_{0.01}$ is the maximum dose tolerated (or the dose resulting in the death of 0.01% of the individuals) and $ED_{9.99}$ is the minimum dose, sterilising 99.99% of the individuals. Compounds for which SF_2 is equal to or greater than zero and SF_3 is equal to or greater than unity can sterilise all insects without killing them. Preparations with negative SF_2 and SF_3 greater than -1 may be used to sterilise insects but then some of the treated individuals are destroyed. The degree of risk for man and warm-blooded animals is various for different groups of chemosterilants. The most dangerous and toxic are the derivatives of chloroethylamine and aziridine, which prevents their large scale practical application.

The phytotoxicity of sexual sterilants has been less investigated. Only apholate is an exception in this respect. Plants tolerate spraying with 1–2.5% solutions of the preparation without harm and only spraying six times in succession moderately retards the growth of plants, causes the dying off of leaves etc.[22] Naturally, even moderate phytotoxicity can limit the application of the chemosterilant in the treatment of populations under natural conditions.

The stability of the compounds can also be of great importance. Aziridine derivatives readily polymerise, are unstable in an acid medium, but are usually stable in an alkaline medium. The instability of the preparations makes their application difficult. The volatility of the compounds is also undesirable since it increases the danger from the preparation and can give rise to additional technical difficulties. On the other hand, it eliminates the problem of stable residues of chemosterilants. The high rate of metabolism of chemosterilants in warm-blooded animals and man, which, however, depends on the reactivity of the compound, somewhat reduces the potential danger of these substances.

The universality of the action of chemosterilants has a marked influence also on their effectiveness. The most effective preparations are active when administered both via the intestine and on contact. When the preparation administered in a particular way is inactive, it gives rise in the first place to technical difficulties in its application, but its effectiveness is only indirectly influenced. However, some chemosterilants are capable of sterilising only members of one sex. This property is directly reflected in their effectiveness. A preparation having a 95% activity and sterilising both males and females is twenty times more effective than a preparation capable of sterilising only members of one sex[12]. Moreover, the separations of the released insects in accordance with their sex is not always technically feasible.

Another requirement which must be met by chemosterilants is specificity of their action. The majority of the existing sterilants act not only on insect species but also on other invertebrate and warm-blooded animals. When sterilisation procedures based on the treatment of the pest population under natural conditions are employed, the specificity of the method is ultimately determined by the specificity of the action of the chemosterilant employed. Naturally, compounds exhibiting not only group specificity (i.e. acting on representatives of the same order, family, and genus) but also species specificity are necessary. However, difficulties then arise in the determination of the sterilising activity of the preparation, since tests are carried out a limited number of objects (the house fly, meat flies, etc.). When sexual sterilisation involving the release of sterile insects is employed, the problem of the specificity of the action of the preparations is not quite so acute, but this procedure is more laborious and expensive, since it necessitates the preliminary mass breeding of an enormous number of insects.

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Improvement of Resistance of Glass-reinforced Plastics to Water by Means of Hydrophobic Adhesive Compounds

A.I.Mikhal'skii

Hydrophobic adhesives have been widely used to improve the resistance of glass-reinforced plastics to water. They are either applied to the surface of the glass filler, or introduced into the plasticiser or the polymeric binder.
Various mechanisms are discussed and compared, by means of which hydrophobic adhesives influence the properties of glass-filled polymers. The enhancement of the water resistance of the glass-reinforced plastics could result from improved mechanical adhesion between the polymer matrix and the glass, from a more uniform distribution of internal stresses in the boundary layer, from greater cohesive strength of the polymer film on the filler surface, and from increased adhesion between polymer and filler, which is due to the formation of stronger adsorption bonds between them. Special attention is paid to the possible formation of a chemical bond between the hydrophobic adhesive and the glass and silica surface.
A list of 114 references is included.

CONTENTS

I. Introduction

The main method for producing high-strength materials in modern technology is the reinforcement of polymers with fillers. The working characteristics of the material are determined by the combination of properties of the components and their interaction. Hence the improvement in the physical and mechanical properties of the reinforced polymer is not a consequence solely of the introduction of a high-strength filler into the system. The strengthening effect of the filler depends on a series of mechanical, physical, and chemical phenomena related to the structure of the polymer and the surface properties of the filler. The complex of phenomena occurring in the polymer–filler boundary layer is especially important. Rebinder[1] suggested that the reinforcing action of the filler is due to the transition of the polymer at its interface into a strengthened oriented state. Burov and Andreevskaya[2] discussing the mechanism of the strengthening action of glass fibre in glass-reinforced plastics, considered that the binder, while of low strength in the mass, became considerably stronger in thin films on the filler surface. The founding of Kargin's school of the theory of polymer structure was followed by considerable development of these views. Papers in recent years have extended these concepts to take into account the influence of the filler on the supermolecular structure of the polymer.

Lipatov, who observed the elevation of the glass point of a series of polymers as a function of the filler content[3] and the nature of the solvent for the polymer[4], suggested that reinforcement could be discussed in terms of adsorption. The nature of the solvent, the surface geometry of the filler, and adsorption interaction between the polymer and this surface affect primarily the number of possible conformations of the polymer molecule in the vicinity of the surface. Since this number is considerably diminished under the influence of adsorption forces, polymer molecules in adjacent layers are more loosely packed, while their flexibility is restricted. The glass point is determined by the mobility not only of the chain segments but also of the supermolecular structures. Thus the effect noticed by Lipatov is associated with a sharp limitation on the mobility not of single polymer chains on the filler surface but of the supermolecular structures which they form. Investigation of the dielectric relaxation of filled polymers[5] also shows that interaction with the surface restricts principally the mobility of supermolecular structures, whereas that of the chain segments changes little.

With polyhexanoamide as example Solomoko et al.[6] showed that the presence of a filler improves the mechanical properties of polymer films by changing the size of the spherulites. It is interesting that this process can be controlled in the required direction by surface modification of the filler. For example, two types of Aerosil—the original and an aminated sample—were used in this work[6]. In the former case the polyhexanoamide spherulites decreased in size from 30 to 26 μm on the introduction of 0.1% of the filler, and to 14 μm with 5%. In the latter case a greater decrease in size of the spherulites—to 19 μm—was found at a filler concentration of 0.1%; further increase in concentration did not affect their size. The aminated Aerosil surface shows a greater tendency to interact with the polymer, which leads to a substantial change in the mobility of the macromolecules, and hence in the conditions of formation of the spherulites. It is noteworthy that the mechanical properties of the films are improved only at low filler concentrations (0.1%), i.e. when the strength is influenced only by the morphology of the polymer. At high filler concentrations the mechanical properties of the polymer film deteriorate owing to the appearance of defects in the system.

The strength of a filled polymer is determined in considerable measure by the internal stresses. Lipatov[5,7,8] emphasises in particular that, with increase in the rigidity and the interaction energy of the polymer chain with the filler surface, the system departs further from equilibrium during hardening of the polymeric binder. This decreases the number of points of contact between the polymer chain and the filler surface, which lowers their adhesive interaction and also causes the appearance of internal stresses, these being especially large in systems having a large surface, e.g. glass-reinforced plastics. Under certain conditions of mechanical constraint the stresses produced in the material during its forming later supplement those caused by its use. For example, the action on a filled polymer of various agents, among which moisture is the most typical under the working conditions of glass-reinforced plastics, will lead to an appreciable deterioration in properties†. This is the more important in that water, because of its high polarity, possesses great competitive power for interactions at the polymer – filler boundary.

Thus a paramount requirement in the production of high-strength polymeric materials which are reliable during operation is to create conditions at the polymer – filler interface which will ensure maximum adaptability of the macromolecular chains to the geometry of the filler surface, an adequate number of points of contact with the latter, and strengthening of adhesion bonds.

II. Principles of Matching Hydrophobic Adhesives to Polymer Systems

A procedure which has proved its value during recent years has been to use hydrophobic adhesives in glass-reinforced plastics filled with thermoplastics and elastomers. Alkylalkoxysilanes containing various functional groups in the organic radical have been most widely used in this connection.

A fairly wide range of such compounds have now been prepared and tested. Many workers[9-21], on examining their efficiency as a function of composition, have shown that the choice of hydrophobic adhesives as modifiers for polymeric materials reinforced with glass fibre must be based on the potentiality for chemical interaction between functional groups of modifier and polymer. General recommendations, supported by practical results, are in effect to use derivatives of vinyl- or methacryloyl-alkoxysilanes for polyester resins and derivatives of amino- or epoxy-alkoxysilanes for epoxide and phenolic resins.

Jellinek and Hanson showed[22] that the primary amino-group in 3-aminopropyltriethoxysilane (A-1100) is involved in cross-linking the epoxy-resin into a network structure. Vanderbilt and Clayton[23] noted the efficiency of unsaturated silanes with elastomers vulcanised in the presence of peroxides, the degree of cross-linking having been raised by the additional use of dienes containing conjugated double bonds. According to these workers the latter were able to bond the organosilicon product on the surface of the glass fibre and the elastomer.

Somewhat different criteria are used to select modifiers for thermoplastic materials reinforced with glass fibre. In the opinion of Plueddemann the decisive factor for the efficiency of a modifier is its compatibility with the polymer[24]. Since chemical interaction of the components is improbable, compatibility is ensured by similarity in polarity. More strongly polar properties of the modifier should have improved the adhesion of polymer to glass. However, Plueddemann showed[24] the presence of a maximum, the strength of the material reaching a limit and then falling with increased polarity of the modifier. An important part is obviously played by the orientation of the organic radicals in the modifier on the surface of the glass, which diminishes the effective polarity of the modifier when deposited on glass.

Plueddemann's hypothesis is supported by the work of Lee[25], who studied the wetting of polysiloxane finishing films on a glass surface, for which he determined the critical surface tension γ_{cr}. The latter was a measure of the polarity of glass surfaces which had been treated with various compounds. It was highest for 3-glycidyloxypropyltrimethoxysilane, and lowest for vinyltrimethoxysilane (42.5 and 25 dyn cm^{-1} respectively). From an examination of a fairly wide range of finishes Lee concluded that the functional groups of the finish are arranged horizontally on the surface. Hence the conformation of the molecules of the finish in the boundary layer are such that its polarity is not determined solely by the type of functional group, since the latter may occupy different positions relative to the surface of the glass.

Sterman and Marsden[26], however, do not exclude chemical interaction between hydrophobic adhesives and thermoplastic materials at the end-groups of the polymer or at free radicals formed by degradation of individual polymer chains during forming. On this hypothesis it is obviously difficult to make a practical recommendation for the choice of modifier. These workers therefore combined the components empirically, after examining a fairly wide range of compounds and assessing them from the change in mechanical and electrical properties of the filled thermoplastic materials produced by the action of water.

III. Procedures for Modifying Glass-filled Polymers with Hydrophobic Adhesives

In the present-day manufacture of glass-reinforced plastics hydrophobic adhesives are applied in three ways— deposition of the modifier from dilute solution on the filler (finishing), incorporation in the lubricant for the glass fibre, and finally direct incorporation in the polymeric binder. Since hydrophobic adhesives were first used as finished, many papers have been published on this technique. They cover optimum recipes for the finishes, temperature schedules for fixing them on the glass surface[27], and the effect of various physicochemical factors on the properties of the resulting materials.

It has been noted above that the choice of modifier is specific to each kind of binder. This has been illustrated[9-15] by actual examples of the use of finishes in glass-reinforced plastics, the properties of the latter being assessed after subjection to moisture. Losev, Aslanova, et al.[13] have examined the effect of ten aminoethoxysilane finishes, with various substituents attached to the nitrogen atom, on the mechanical properties of a glass-reinforced epoxy-resin, and shown that the water resistance is lowered by replacing an amino-hydrogen atom by e.g. a butyl radical. However, introduction of a second amino-group into an aminoalkylethoxysilane (AGM-3), although it improves the properties of phenol – formaldehyde plastics, has an adverse effect on the properties of the epoxy-resins. This is explained by the greater reactivity of the latter. It probably affects formation of the polymeric structure on the filler surface, which is too active towards the given polymer and hence intensifies the disequilibrium of the system during setting[7].

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† The above is not the only reason for the adverse effect of moisture.

The properties of glass-reinforced plastics can be improved, not only by a specific choice of finish, but also by using a mixture of finishes of the same class. Voitsekhovich et al.[14] note that more monolithic glass-reinforced plastics are obtained by using a mixture of di- and tri-ethoxyaminosilanes (ADE-2 and ADE-3). Grinevich[15] showed that a mixture of methyl and vinyl siliconates (GKZh-11 and GKZh-12) is an effective finish for an unsaturated polyester resin, whereas a mixture of vinyl and allyl siliconates (GKZh-12 and GKZh-18) is required for a polyester–polyacrylate resin. The latter improves the mechanical properties of a thermosetting glass-reinforced plastic in the initial state, and reduces the loss in strength after treatment with boiling water to 11%, whereas when vinyltriethoxysilane is used the loss in strength is 32%. After air hardening of the same resin a smaller change in strength is observed on finishing with vinyltriethoxysilane, although the efficiency of a mixture of GKZh-12 and GKZh-18 is maintained because the initial strength is increased. Thus the action of a finish is governed not only by the class of compound to which it belongs but also by peculiarities in its molecular structure and by the composition of the polymeric binder.

Nevertheless, a correct choice of finish based on the above principles still does not ensure that it will be efficiently used. Finishing is a technical process, for which conditions must be determined and maintained. Thus the properties of a glass-reinforced plastic will depend on the quantity of finish applied, the conditions of hydrolysis, the pH of the working solution, the temperature at which the finish is fixed on the glass fibre, the duration of this process, and several other factors. Biefeld and Phillips[27] give the temperatures at which finishes are fixed on glass depending on their functionality and the nature of the groups which are likely to interact with the surface. However, technical schedules developed for one finish can by no means always be used for treatment with other finishes[28] even belonging to the same class.

The second method of modification—the use of active lubricants—eliminates several adverse technical factors in the thermochemical treatment of fillers[39-42]. A finish incorporated into the lubricant comes into contact with a clean glass surface, which is freshly formed and therefore more active. The treatment of individual glass fibres avoids the effect of capillary flow of the finish and enables a more uniform film of the alkylalkoxysilane to be obtained on the filler. Furthermore, the introduction into the lubricant of an elastomer or a plasticiser, e.g. dibutyl sebacate, lowers the internal stresses in the surface layer of the binder during setting[23]. The above peculiarities were probably a consequence of the less sharply defined dependence of the strength of the glass-reinforced epoxy–phenolic plastic on the period of immersion in water when an active lubricant containing AGM-3 was used than in the case of thermochemical treatment with AGM-3 finish[29]. It is noteworthy that neither short-period nor long-term tests in air reveal differences in the method of applying AGM-3.

It was shown[29] that the third method of modification—the incorporation of an epoxyalkylalkoxysilane (ES) into the resin—did not have the proper effect: the strength of the glass-reinforced plastic depended quite markedly on the time it was immersed in water. Obviously, no analogy can be drawn here between the first two and the last method of modification with the aim of comparing their efficiency, since the last case involved a finish of a quite different class, containing epoxy-groups instead of amino-groups.

A systematic study of methods for modifying glass-reinforced plastics with hydrophobic adhesives was made by Kiselev and Bodrova[16]. They used a series of binders—phenol–furaldehyde–formaldehyde (FN), resol (BSL), phenol–formaldehyde (VFT), this third resin modified with viniflex, and butyral–phenol (BF-2)—to examine the effect of aminoethoxysilanes (A-1100, AM-2) and an ethoxysilane containing hydroxyl in the organic radical (MR-1), incorporated into the resin, on the stability of glass-reinforced plastics after treatment with water and a highly humid environment. With the optimum content of active additive in the binder glass-reinforced textolites retain 65–90% of their strength after subjection to boiling water for 2 h, whereas the usual value for an unmodified plastic is ~30%. The dielectric characteristics of the glass-reinforced textolites were used to assess the method of modification with aminoethoxysilanes; they showed that the stabilisation effect is most completely developed when the additive is introduced into the resin.

Other papers[17-21] also indicate an improvement in the properties of glass-reinforced plastics when ethoxysilanes are used as modifiers for the binder. The advantages of this method over finishing are firstly that the binder comes into contact with a more uniform surface, which possesses better wetting properties than a surface treated with a finish[34]. The tendency of the molecules of the finish to aggregate[34], especially when applied from aqueous solutions, aggravates the impairment of wetting.

Zisman[35] considers that, even with a small contact angle, individual cavities on the rough surface of a finished glass fibre remain unfilled with resin because of its high viscosity and rapid polymerisation. On the application of a load or of water to the plastic, stress concentrations will arise around each of the cavities, which will impair its properties. Bascom and Romans[36] examined the influence of such microdefects on the strength of a glass-reinforced epoxide plastic and found that, in order to reduce their number, it was necessary to make the wetting angle smaller and improve the technique of impregnation, e.g. by using a variable tension in the filament passing through the impregnating solution.

Further, the distribution of hydrophobic adhesive in the resin–filler system probably has a certain effect on the properties of the glass-reinforced plastic. Thus Kenyon[37] has shown that, in spite of the greater adhesion interaction of an epoxy-resin with glass finished with the product A-1100, the use as finish of 3-glycidyloxypropyltrimethoxysilane (A-187) produces a greater improvement in the mechanical strength of the plastic (Table 1 and diagram). He ascribes this inconsistency to the differing abilities of the finishes to diffuse inside the resin adjacent to the filler surface. This changes the depth of the modified binder near the surface of the filler, which in the present case probably determines the strength of the glass-reinforced plastic.

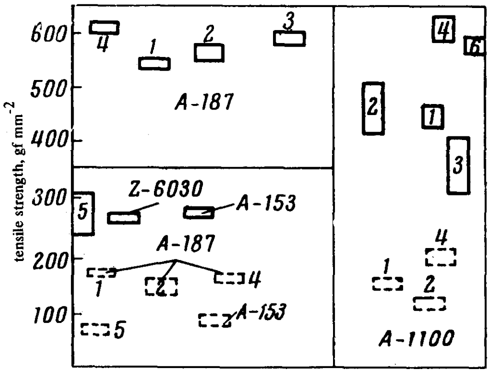
We shall attempt to compare the processes undergone by the binder in a glass-reinforced plastic modified by a hydrophobic adhesive, using Lipatov's views[5,7,8] on the mechanism of the reinforcing effect of fillers in polymers. Application of a finish to the filler surface increases its tendency to interact with the polymer, since the finish contains groups capable of interacting with the binder. Hence the rate of setting of the resin will be far higher on the finished surface than in bulk. The polymer molecules, having combined with it through the appropriate functional groups, lose their mobility, and are unable to pass into the equilibrium state. The formation of chemical bonds on the surface is then a favourable factor, whereas the strain in the polymer molecules is undoubtedly an adverse factor. Incorporation of a hydrophobic adhesive into the binder does not influence to such an extent formation of the polymer structure near the filler, so that the system will be closer to equilibrium.

Table 1. Strength of adhesion between Epon 815 resin and glass[37] (in conformity with ASTM D 1344-57).

Surface modifier		Breaking load, kg
brand	chemical name	
—		110
A-153	phenyltriethoxysilane	160
Z-6030	3-methacryloylpropyltrimethoxysilane	200
A-187	3-glycidyloxypropyltrimethoxysilane	297
A-1100	3-aminopropyltriethoxysilane	414
"Inner-layer" modifier + A-1100	—	502

New problems inevitably arise in the modification of binders with active additives[16-20]. Sterman and Marsden[19] studied the effect of several additives on the properties of polyester, epoxide, and phenolic resins containing various powdered fillers (glass, quartz, kaolin, calcium carbonate, etc.). From a comparison of the effect of hydrophobic adhesives when used as finishes and when introduced into the binders (0.5–2%) these workers concluded that the active additive migrates from the bulk of the resin to the surface of the filler, thereby enhancing the stability of the glass-reinforced plastic to the same extent as does the finish. Migration is confirmed by the improved stabilising effect of the additive on the properties of the material when the filled composition is kept until it sets. Immediate setting, for example, will not give the effect observed for some time (19 h). These workers show further that the action of the additive is connected with the presence of the filler (the strength of pure resin mouldings is unaffected by silanes) and depends on its nature. Addition of an active product has no effect on the strength of a composition filled with calcium carbonate, but considerably improves the properties of systems filled with glass, quartz, etc. A necessary condition for an alkoxysilane to be effective is that it should be hydrolysed on the filler surface. Preheating kaolin at 120°C removes most of the water from its surface, so that the mechanical properties of a filled resin become worse. This does not apply to fillers to whose surface water is more firmly bound (glass, quartz). Finally, assessing the influence of the technique of hardening on the properties of plastics modified by addition of a silane, these workers note that the condensation of a finish and its adhesion to the surface are not complete without further heating, continued for a definite time until gelling occurs.

Vanderbilt and Jaruzelsky[18] studied the mechanical properties of butadiene–styrene, polyester, and epoxide resins containing similar fillers, and paid special attention to the choice of optimum quantities of the additives A-1100 and A-172 (vinyltris-2-methoxyethoxysilane) introduced into the resin. The content of these did not exceed 2% on that of the filler, 4.6% based on the binder. These workers showed that, when quartz was used as filler, the optimum content of the silane was 0.5–1% on the filler. The additive has different effects on the properties of different resins: the strength of butadiene–styrene mouldings, which are weak in the original state, is increased several times; whereas the increase for epoxy-mouldings, which possess greater strength, is small. It is considered[18],[38] that the epoxy-resin contains functional groups which tend to interact with the original surface of the filler to form stable bonds, and these ensure quite good mechanical properties for the plastic independently of the presence of a silane. The butadiene–styrene resin is unable to form such bonds, and therefore the action of an added hydrophobic adhesive, which promotes interaction of the resin with the filler surface, is shown in a sharp increase in strength.



Strength of Epon 815 resin filled with finished glass microspheres: —) in the dry state; --) after immersion in boiling water for 24 h. Finishing process: 1) finish dissolved in hexane; 2) finish dissolved in acetone; 3) finish dissolved in CCl_4; 4) "inner-layer" modifier applied before finishing[37]; 5) finish absent; 6) filler absent.

A different situation is found after filled mouldings have been subjected to boiling water for 7 days: the strength indices of the unmodified butadiene–styrene resin remain at the same level, whereas those of the epoxy-resin are substantially diminished. The presence of a hydrophobic adhesive then produces an increase in strength: as a result of modification the strength of a specimen after the treatment with water has increased several times. This was explained by the different amounts of water absorbed by the resins—3% for the expoxy-resin, 0.3% for the butadiene–styrene resin.

The above workers[18] confirm for calcium carbonate other data[19] showing that a filler containing on the surface neither water nor groups capable of hydrolysing an ethoxysilane produces no change in strength of mouldings as a result of their modification. No effect is produced by adding to the resin–calcium carbonate system the product A-172 which has previously been hydrolysed with water. Noting the necessity for at least partial hydrolysis of the additive introduced into the binder for a glass-reinforced plastic, Vanderbilt and Jaruzelsky consider that the amount of water needed is present in actual resins: even the "driest" butadiene–styrene resin contains 0.04% of water.

The interaction of moisture in the binder FN with the added aminoethoxysilane AM-2 was studied by Kiselev and Bodrova[16] using the Karl Fischer method. With not more than 2% of additive the moisture content decreases, after which it increases somewhat owing to the accumulation of water formed presumably by the condensation of silanols, which are products of the hydrolysis of AM-2. The additive content corresponding to the minimum on the curve is the optimum content for the given resin, but it will vary somewhat on passing to other batches. Apart from correct choice of the concentration of the hydrophobic adhesive in the resin, the possibility that it may affect the setting of the binder must be taken into account; this aspect is ignored in most papers.

In conclusion it must be noted that there are several practical reasons, in addition to the above considerations, for the greater efficiency of the use of additives rather than finishes. Elimination of a finishing stage, requiring special equipment, from the industrial production of glass-reinforced plastics simplifies the process and makes it far more economic. Furthermore, glass cloth containing a finish or an active lubricant on the surface is unsuitable for prolonged storage after impregnation with the binder, since premature setting of the resin takes place as a consequence of the high surface concentration of modifier on the cloth. Impregnation of glass cloth with a modified binder does not have such a great effect on its viability.

In view of the above facts the incorporation of hydrophobic adhesives in the polymeric binder is the most economical prodedure for modifying glass-reinforced plastics to improve their resistance to water.

IV. Mechanisms by which Alkylalkoxysilanes Influence the Properties of Glass-reinforced Plastics

It has been noted above that the incorporation of hydrophobic adhesives into the binder involves their migration on the filler surface, just as finishing involves diffusion of the finish into the bulk of the resin. Thus some common phenomena are observed in glass – resin – alkyloxysilane systems, independently of the method of introducing this last component. We have noted individual differences above. Now let us examine possible mechanisms by which the finish influences the properties of glass-reinforced plastics, assuming to a first approximation that they are applicable to any of the modification procedures.

The properties of filled systems are not determined solely by those of their separate components—polymer and filler. Processes occurring at the interface between the two phases acquire great importance[1-8], especially with systems having a large surface (glass-reinforced plastics). It is here that the greatest effect of modification by a hydrophobic adhesive must be expected. Several authors discuss the role of the finish in terms of mechanical "swaging" of the fibre by the binder and the friction arising between them. In fact, the coefficient of linear expansion α_t of polymeric binders is more than ten times that of glass fibre‡, so that after the material has set and cooled the glass fibres are firmly held in the polymer matrix. In this case physical contact—pressure and friction—governs interaction of the components. Landsman and Klunder[39] consider that water, penetrating into a glass-reinforced polyester plastic, has a lubricating effect on the contact surface between resin and glass, and diminishes the friction between the components. They support their conclusion by the fact that the strength of the plastic, although dropping greatly under the influence of water, is almost completely restored after drying. Vašta and Zvonař[40] and also Skupin[41], while sharing this view, consider that the role of the finish is to restrict access of water to the surface of the fibres, so that the friction between the components varies to a less extent.

In effect these workers[40,41] consider only one of the properties of the finish, which is rendering the glass surface hydrophobic. However, as shown above, the choice of finish is not entirely determined by this property. In particular, Clark and Plueddemann[21], by treating glass cloth initially with chlorosilane and then with Z-6030 finish (3-trimethoxysilylpropyl methacrylate), obtained from a polyester resin a plastic possessing high water-repellency but low strength in both dry and wet states. Application of the finish Z-6030 to the surface of the original glass cloth considerably improved the mechanical properties of the glass-reinforced plastic. Replacement of the active additives AM-2 and MR-1 in the binder FN by methyltriethoxysilane[16] resulted in a deterioration in the properties of the glass-reinforced plastic, although methyltriethoxysilane tends to make the glass more water-repellent.

There is no doubt about the mechanical adhesion between filler and binder in a glass-reinforced plastic[40-42]. However, the behaviour of the system is determined probably not so much by its magnitude as by the uniformity of distribution of the stresses which arise. The part played by the finish must evidently be appraised on these lines, with the effect of the mechanical "swaging" of the fibres on the properties of the glass-reinforced plastics taken into account. It is obviously for this reason that some authors regard the finish as an interlayer, which diminishes the internal stresses in the plastic. This opinion is held in particular by Hooper[43], who considers that the presence of the finish lowers the interfacial tension during forming of the system. Erickson et al.[44] assume that the finish changes the adsorptive power of the glass surface, leading e.g. to preferential adsorption of the hardener in the surface layer. As a result of this, thin polymer films adjacent to the glass surface acquire a different structure and different properties. These workers[44] consider that their elasticity increases, so that the stresses in the boundary layer become smaller.

The above views[43,44], however, have not found practical confirmation by other investigators, and to some extent even contradict the latter. Hooper[43], when discussing the decrease in internal stresses in a filled plastic due to the deformability of the layer of finish, does not consider the effect of modifying the surface on the formation of adjacent polymeric structures, which according to Lipatov[7] will be less in equilibrium and more strained on interaction with the filler surface. The views of Erickson et al.[44] also contradict the position of Lipatov, who, considering the effect of the interface on the structure of three-dimensional polymers[45], has shown that a filler increases the effective density of the polymer network as a result of the appearance of additional branch points on interaction with the surface.

Thus great caution must be exercised in speaking of an increase in the elasticity of a hardened polymer in the

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‡ For example, glass E has $\alpha_t = 4.8 \times 10^{-6}$ deg^{-1}, while the corresponding value for polyester resins is $(80-150) \times 10^{-6}$ deg^{-1}.

boundary layer. It is not in vain that Kenyon[37] has used, together with finishes, the so called "inner-layer modifier"§, which was applied to finished glass particles. This artefact on the surface of the filler in a polymer film possesses enhanced elasticity and improves the strength characteristics of the glass-reinforced plastic in dry and wet states (Table 1). Furthermore, the presence of the "inner-layer modifier" led to an increase in the strength of the plastic with increase in the bulk content of filler, which was not observed in its absence. These facts indicate efficient plasticisation of the binder directly adjacent to the filler surface, and show that the layer of finish on the glass most probably does not produce a relaxation of internal stresses which are due to the effect of the filler surface on the formation of polymeric structures. For the same reason plasticising additives have an appreciable effect in active lubricants[33].

Trostyanskaya and Poimanov[46-48] take a different view of the decrease in internal stresses under the influence of a finish in a glass-reinforced plastic. They consider that the hydrate sheath of the glass, while inhibiting hardening (e.g. in the case of phenol–formaldehyde resins), changes the density of the hardenable resin as the distance from the interface increases, which intensifies the internal stresses in the plastic. Treatment of the glass fibre with finishes (MR-1, AM-2, etc.) eliminates the action of the hydrate sheath of the glass and results in a more uniform setting of the binder, which improves the properties of the glass-reinforced plastic.

The possibility has been discussed above that adhesion between glass fibre and binder may be accomplished by mechanical "swaging". This is only one of the factors determining the strength of a reinforced plastic. Another factor, which in the opinion of most investigators is more important, is the formation of strong adhesive bonds between polymer and filler. The action of finishes has been discussed in detail from this point of view by Andreevskaya and her coworkers[49-51], and also by several other authors[52-55]. The presence of a finish on the surface of the glass fibre was shown to strengthen adhesion between the hardened resin and the glass. The investigations were made[49-55] on models representing the interaction of the components in actual glass-reinforced plastics, and in several cases the laws deduced were confirmed by the results of mechanical tests on such a plastic[49]. The increase in adhesion interaction between binder and finished glass surface was explained[49-56] by formation of a chemical bond between finish and resin during hardening of the latter.

Spectroscopic analysis has in fact shown changes in the structural constitution of the compositions studied. Thus Nikonova[52,53] has observed a decrease in intensity of the 1600 cm^{-1} band, corresponding to vibrations of the vinyl group in the finish, during the setting of a polyester resin in the presence of vinylalkoxysilane (GVS-9). Wende and Gähde[57,58] examined the infrared spectra of glass cloth treated with vinyltrichlorosilane, followed by methyl methacrylate in the presence of benzoyl peroxide. From the variation in intensity of the 3060-cm^{-1} band, which is also associated with vibrations of the vinyl group, they showed that ~67% of surface vinyl groups are involved in copolymerisation with methyl methacrylate. Other methods of investigation also indicate reaction between the polymer resin and the finish. Consideration of the thermal deformation and the elastic properties of phenol–formaldehyde and urea–formaldehyde resins reveals[17,55,56] that the introduction of alkylalkoxysilanes—AM-2 and MR-1 [17,56], AGM-9 and ES [55] —leads to the formation of a denser network in the hardened polymer. This was regarded as due to chemical interaction between resin and finish.

Thus it can be accepted on the basis of a number of investigations[53-59] that the increase in strength of adhesion between polymeric resins and a finished glass surface is due to the formation of a chemical bond between the binder and the layer of finish. Hence it is not fortuitous that different finishes have different effects on the adhesion of the binder to a glass fibre. For example, AGM-9 and ES increase the strength of adhesion between a glass fibre and a urea resin[54] to about 130 kgf cm^{-2}, whereas AGM-3 increases it to 56 kgf cm^{-2} (compared with 29 kgf cm^{-2} for the original glass fibre). In tests on aluminium borosilicate and basalt fibres[50] finish AM-2 increases the strength of adhesion by 30% in the case of an epoxy–phenol binder (480 instead of 366 kgf cm^{-2}), and by 20% with a butyral–phenolic binder (e.g. 260 instead of 216 kgf cm^{-2}).

Besides the chemical composition of the binder and the character of the glass surface, internal stresses at the polymer–filler interface influence the adhesive strength, these arising from defects in the glass surface and from the shrinkage of the binder when it sets. The contribution made by these stresses to the adhesive strength is especially great with large shrinkages of the binder, and can be diminished with a uniform distribution of stress over the interface. The lubricant (a paraffin emulsion) has a characteristic effect on the adhesion of glass fibre to various resins[50]. The presence of a lubricant lowers the surface energy of the glass and also avoids the formation of any specific bonds with the binder. Thus application of a lubricant would be expected to be accompanied by a decrease in adhesive strength, as has been observed[50] for an epoxy-resin (258 instead of 303 kgf cm^{-2}), the shrinkage of which does not exceed 3%. With modifications of a polyester resin having larger shrinkages (5.8–8.5%) the presence of a lubricant on the glass increased the adhesive strength from 110 to 134 kgf cm^{-2}. The ability of a plastic paraffin layer to "resorb" surface tensions makes a larger contribution to the change in adhesive strength than does change in the nature of the glass surface. This suggests that surface tensions in the polymer–filler system influence its properties. The action of a finish was not assessed from this point of view[50]. However, the results obtained have something in common wtth data[33,37] showing that a plasticiser in an active lubricant has a favourable effect on the properties of glass-reinforced plastics.

The properties of reinforced materials depend not only on the forces of adhesion between binder and glass fibre—mechanical or physicochemical in character—but also on the cohesive strength of the components. Tikhomirov[60], in particular, regards this as the decisive factor. He employed in his discussions the concept of a critical contact surface, at which the "aggregate" strength of the adhesive bonds between each individual fibre and the polymer matrix is equivalent to the tensile strength of the fibre. The ratio of the breaking load of the glass fibre to its strength of adhesion to the polyester resin gives a value of 0.025 mm^2 for the critical contact surface, which corresponds to a fibre length of ~0.5 mm. Thus accord-

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§ The "inner-layer modifier" was the same epoxy-resin from which the glass-reinforced plastic had been obtained, but it contained a polyester plasticiser. As a result the modulus of elasticity of the resin on the surface of the finished glass could be lowered by a factor of 8.

ing to Tikhomirov it is sufficient to ensure in a glass-reinforced plastic complete contact between binder and fibre for a length of 0.5 mm in order that fracture of the material will be determined by the strength of the fibres. Further increase in adhesive strength will bring no advantage. Since the fibres normally used are longer than 30 mm, efforts to increase adhesion are not justified in all cases[60]. Discussing problems of the surface modification of the filler, this worker considers it incorrect to explain the strengthening of materials[49-55] by increase in the adhesion interaction with the polymer, which is not the cause of the improvement in strength but merely accompanies it. He refers[60] to Rebinder's work[1], and explains reinforcement as an increase in the cohesive strength of the binder in thin films on the modified glass surface. In fact the finish, by reacting chemically with the resin[52,53,55-58] and also raising the interaction energy of the latter with the filler, changes the properties of the binder in the glass-reinforced plastic in conformity with the views of Lipatov[7]. However, the question posed by Tikhomirov of the unjustified increase in adhesion interaction in glass-reinforced plastics must be regarded as debatable.

In connection with Tikhomirov's concept[60] of increasing the cohesive strength of the filler to strengthen the polymeric material we must consider several papers[61-64] which report an increase in the strength of glass produced by applying an organosilicon film to its surface. Removal of adsorbed water from the surface will obviously be of no little importance here, since it affects the surface tension, and the strength will increase in conformity with Griffiths' equation

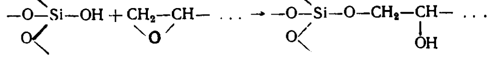
$$\sigma^2 = \frac{2\gamma E}{\pi a}$$

where σ is the tensile strength of the glass, γ its surface tension, E the Young's modulus, and a the depth of the cracks.

Outwater and Ozaltin[61] showed that treatment with the finishes A-1100 and A-172 increases the initial strength of glass by about 18%, and boiling diminishes it by a smaller amount. Thus a finish can have a favourable effect on the cohesive strength of both polymer and filler. For the present it is difficult to say whether this is decisive.

V. Reasons for Improvement of Water Resistance of Glass-reinforced Plastics

Hydrophobic adhesives have found application in glass-reinforced plastics not so much because they improve the properties of the latter in the initial state as because of the high stability conferred to the action of moisture. The question arises as to how finishes, by increasing the strength of adhesion between resin and glass, are able to maintain it at a high level after the plastic has been kept in water. Being highly polar, water is able to destroy adsorption bonds at the resin–glass interface—both weak dispersion bonds (of energy not exceeding 1–2 kcal mole^{-1}) and polarisation bonds—and then the still stronger hydrogen bonds (5–10 kcal mole^{-1}). Furthermore, water is able to break down chemical bonds which are unstable to hydrolysis. For example, an epoxy-resin is capable of forming a chemical bond with a glass surface[38]:



(I)

However, the resulting C–O–Si bond is hydrolytically unstable.

Zisman[35] examined the specific effects of finishes on the susceptibility of glass-reinforced plastics to the action of water, and discussed two possible causes—change in the ability of water to penetrate the plastic when a finish was used, and the formation of hydrolytically stable chemical bonds at the resin–glass boundary.

Three molecular diffusion processes—through the mass of polymer, along the glass–polymer interface, and finally through any protective film on the glass at sites not covered by the resin—underlie the mechanism of the penetration of water into a glass-reinforced plastic. The permeability of the glass-reinforced plastic to water changes with modification of the properties of the polymer and the glass surface. Intermolecular (cohesive) interaction of the polymer plays some part in this: increase in such interaction impedes diffusion of water between the macromolecules. Thus the cohesive strength of various films on glass, including those formed by the polymer or the finish, determines the rate of the diffusion process, which will also depend on the hydrophilic character of the surface. In this respect the action of the finish is in effect to produce on the glass a highly cohesive layer which is not readily wetted by water. Zisman remarks, however, that on this basis finishing will have a large effect when the whole surface of the glass fibres is made water-repellent and the angle of wetting is ~90°, since only then does the ability of water to penetrate the system by capillarity become insignificant.

With regard to the role of chemical bonds Zisman notes that intermolecular physical forces are sufficient to obtain a high-strength glass-reinforced plastic; these develop with good wetting and filling of the cracks in the glass by the binder, i.e. with a sufficient area of contact. This is consistent with Tikhomirov's views[60]. However, Zisman[35] and Dean[38] consider that formation of a chemical bond between resin and glass is desirable in cases in which the stability of the plastic to the action of a corrosive medium must be raised. Dean[38] states that, among all the forces acting between an ionic solid (glass) and a resin, only covalent bonds (50–100 kcal mole^{-1}) are not weakened by the action of water. A large number of chemical bonds is not required to strengthen the material; moreover, it is undesirable, since according to Dean their purpose at the interface is to ensure the simultaneous operation of the far weaker van der Waals forces. For steric reasons chemical bonds possess low mobility, and the presence a large number of them lead to strain in the surface layer of polymer.

Furthermore, the decrease in strength of glass-reinforced plastics after being kept in water is in some measure due to plasticisation of the binder. Whereas Zisman and Dean completely ignore this aspect, Pohl[65] assigns paramount importance to it. He determined the dynamic bending modulus of elasticity of a glass-reinforced plastic and the torsional modulus of rigidity, and attributed[65] variation in the former to destruction of adhesion bonds between resin and filler and change in the latter to plasticisation of the binder.

The investigation was made on a glass-reinforced polyester plastic with vinyltrichlorosilane and the product A-172 as finishes. Pohl showed that keeping the plastic in boiling water produced a more marked change in the dynamic modulus of rigidity than in the modulus of elasticity. The stabilising effect of the finish shows far more clearly in shear tests. Thus he assumes that the action of water on a glass-reinforced plastic is determined primarily by its plasticising ability, and he draws an analogy between water and acetone, towards the action of the latter of which the finish was also useful. This investigation[65] was made essentially on a single material (a glass-reinforced polyester plastic), and it is therefore difficult to transfer the author's confidently expressed point of view to other systems, the action of water on which may develop differently, e.g. as a consequence of a change in the chemical composition of the resins and of their specific properties in general.

Clark and Plueddemann[21] and also Vanderbilt[66] assume that a layer of finish, chemically combined with the resin, reacts with the glass by means of bonds which readily tend to recombine, as a result of which the finish moves, as it were, along the surface of the glass, relieving local stresses. Hydrogen bonds and single siloxane bonds are considered[21] as possibilities, the latter formed by interaction of surface hydroxysilyl groups of the glass with alkoxyl or hydroxysilyl groups of the finish. The authors assume that single –Si–O–Si– bonds are capable of recombination, while hydrogen bonds prevent removal of the finish by water. Although the latter statement cannot be accepted[35,38], the contribution of hydrogen bonds to strengthening at the resin–finish–glass boundary is not open to doubt. The view[21] that local stresses are "relieved" by a layer of finish has much in common with Hooper's ideas[43], which we have already discussed.

Thus the question arises of the nature of the bonds between glass and finish. Arguments are given[53,57,58] in support of a chemical (siloxane) bond formed by interaction of alkoxy- and hydroxy-groups of the finish with surface hydroxyls of the glass or silica. If this mechanism is accepted, it is easy to explain the improved resistance to water of glass-reinforced plastics modified with hydrophobic adhesives, since the –Si–O–Si– bond is stable to hydrolysis.

VI. Interaction of Silicate Surfaces with Simple Analogues of Alkylalkoxysilanes

Before analysing this work let us consider, as the closest model to glass, the chemistry of a silica surface and its interaction with certain silanes. The hydroxyl coating on silica includes[67,68] various types of hydroxy-groups—isolated or free, 5.2–5.4 Å or at least 3.1 Å apart; paired hydroxyls linked by a hydrogen bond, the distance between them being 2.52–2.60 Å; and groups of three or four hydrogen-bonded hydroxyls—and is accompanied by a polymolecular film of water the main adsorption centres of which are either bound hydroxyls and coordinatively unsaturated silicon atoms (sites with groups of three or four bound hydroxyls)[68–71] or free hydroxy-groups[72,73]. It has been estimated[67] that on an Aerosil surface containing no adsorbed water the concentration of free hydroxyls per 100 $Å^2$ is 2.6, and that of bound hydroxyls 2.2.

Formation of a hydrogen bond between hydroxy-groups on a silica surface affects their properties. Firstly, they show far less tendency to any kind of interaction—specific adsorption or chemisorption—with organic compounds[67,72]; secondly, they are more liable to removal from the silica surface on heat-treatment[71,74], as a result of which some of the bound hydroxyls become free hydroxyls.

In the infrared absorption spectra of SiO_2 (silica, Aerosil, porous glass) vibrations of the O–H bond in free hydroxyls are represented by a narrow band at 3750–3745 cm^{-1} [67,69,71], and those in bound hydroxyls by a broad band in the range 3750–3000 cm^{-1} [67], after which O–H vibrations of adsorbed water molecules occupy the range 3750–2800 cm^{-1} in the case of silica[72]. In glasses undergoing crystallisation all the above bands are displaced to lower frequencies[75,76]: e.g. a band at 3500–3640 cm^{-1} corresponds to vibrations of free hydroxyls. Furthermore, new bands may appear[75] owing to formation of the strongest hydrogen bonds between hydroxyls in glasses having a low silica content (e.g. below 62%).

The mechanism of the interaction between certain substances and a silica surface can be assessed from the change in intensity of the vibrational bands corresponding to the different types of hydroxy-groups. In particular Kiselev and his coworkers[67,72,77] have shown that the adsorption of aromatic compounds (benzene, toluene, etc.) and of alcohols (methanol, ethanol) produces a sharp drop in intensity of the absorption band due to free hydroxyls. Furthermore, removal of the latter from the surface diminishes its ability to adsorb such compounds. The intensity of the 3750-cm^{-1} band decreases even at low surface coverage with alcohol molecules, whereas the intensity of the band due to bound hydroxyls does not change at all[72]. Hence only free surface hydroxyls are involved in the specific adsorption of alcohols. Sidorov[71] considers that bound hydroxyls are involved in this process at or above 550°C. However, this temperature is so high that in practice all bound hydroxy-groups are removed, the surface being enriched with free hydroxyls[67,74,78].

The weakening and complete disappearance of the band due to free hydroxyls when the Aerosil is treated with alcohols indicates[72] the occurrence of alkoxylation on the silica surface, i.e. the formation of surface Si–O–C bonds. Ease of alkoxylation of silica with alcohols was probably one of the reasons for the concept of chemical reaction between a silica surface and complicated hydroxy- and alkoxy-derivatives, including finishes.

A number of papers have been published on the interaction of Aerosil[67,79–83], silica gel[78,84], glass fibre[57,58,85], and microporous glass[86] with alkylchlorosilanes. Davydov et al.[67] showed that treatment of Aerosil with trimethylchlorosilane results in disappearance of the band due to free hydroxyls (3750 cm^{-1}) but leaves that due to bound hydroxyls unchanged. This phenomenon was explained by two causes—firstly energetic (a certain amount of energy is required to rupture the hydrogen bond of surface hydroxyls, but the heat of reaction with trimethylchlorosilane is only 11 kcal $mole^{-1}$), and secondly steric hindrance (the areas occupied by one trimethylsilyl group and one free hydroxyl together with one bound hydroxyl are roughly equal: i.e. the remaining chlorosilane molecules are unable to approach the bound hydroxyls after the more active free hydroxyls have reacted).

From the appearance, in the infrared spectra of silica modifications treated with trimethylchlorosilane[85,86], of bands in the region of C–H-stretching vibrations (2970 cm^{-1}) and their preservation after the solvent has been washed off and the sample subjected to prolonged vacuum treatment, it was concluded that the chemical reaction

$$-O-Si(O-)_2-OH + ClSi(CH_3)_3 \xrightarrow{-HCl} -O-Si(O-)_2-O-Si(CH_3)_3 . \qquad (II)$$

took place on the silica surface. This is the only possible reaction involving an alkylated monochlorosilane on the silica surface which will yield an alkylated silyl coating. A side-reaction is hydrolysis of the trimethylchlorosilane followed by condensation to a dimer, but the resulting hexamethyldisiloxane is easily removed by vacuum treatment. An equally unambiguous interpretation can be given to the treatment of Aerosil with dimethyl chlorosilane[83], which contains only one functional group (chloro) capable of chemical reaction.

The properties of a trimethylsilyl coating on silica have been studied by adsorption[79-81,84], chromatographic[78,84], and mass-spectrometric[87] methods. Borisenko, Kiselev, et al.[84] showed that the most uniform trimethylsilyl surface coating is formed by treating silica gel with trimethylchlorosilane in the absence of traces of water (dry silica gel and the silane were sealed in an ampoule) at a high temperature. The defects in the coating permit only the small molecules of acetone to penetrate to the residual surface hydroxyls. These defects are inaccessible to the larger benzene molecules, which tend to interact specifically with a silica surface[77]. The decrease in the retention volumes of benzene on the surface by a factor of 50 and the lowering of the heat of adsorption from 11 to 6 kcal mole^{-1} as a result of its trimethylsilylation[84] suggest that the actual nature of the adsorption process has changed: whereas specific adsorption of benzene is observed on hydroxylated silica, the adsorption on a trimethylsilylated surface is non-specific. The results indicate not only a fundamental change in the surface properties of the silica but also complete shielding of the residual hydroxyls by the trimethylsilyl coating (under the given conditions of treatment), which excludes any interaction whatever with substances whose molecules are not smaller than those of benzene. This is confirmed by comparing the areas occupied by a trimethylsilyl group, a free hydroxyl, and a bound hydroxy-group[67].

Different results were obtained[84] when silica gel was treated with dimethyldichlorosilane: the retention volume of benzene changed roughly tenfold in comparison with the original surface. However, this ratio was poorly reproducible because the dimethyldichlorosilane formed a polymer, polydimethylsiloxane. This was considered[84] to impair the uniformity of the alkylsilyl coating. The great influence of secondary processes on the character and degree of modification of the silica surface becomes still more evident when it is remembered that dimethyldichlorosilane interacts with two types of surface hydroxyls: besides the free hydroxy-groups some of the bound hydroxyls react with the chlorine atoms[67], so that the silica surface should have undergone more profound changes than on treatment with trimethylchlorosilane. However, this does not occur[84], for the reaction analogous to (II) is not the sole reaction.

Burushkina, Chuiko, et al.[82] have used methylvinyldichlorosilane to make a detailed study of the interaction of a dichlorosilane with an Aerosil surface. Treatment of the Aerosil with the vapour at various temperatures (20–400°C) was assessed from the change in intensity of a series of bands in the infrared spectrum of the modified Aerosil. The effects of temperature, duration of treatment, and preliminary dehydration of the Aerosil were noted. Thus evacuating the Aerosil at 200°C before treatment increased the number of silyl groups grafted to the surface. Their number successively decreased on passing to the higher temperatures of 400° and 500°C. The increase was attributed to the freeing of hydroxysilyl groups perturbed by a hydrogen bond. This obviously implies the rupture of hydrogen bonds between surface hydroxyls and adsorbed water molecules. The decrease was caused by loss of a proportion of the surface hydroxysilyl groups and hence a decrease in the active centres. Since only bound hydroxyls are removed at 400–500°C [67,71,74], not only free but also bound hydroxyls are involved in the reaction of methylvinyldichlorosilane with the silica surface. The rate curves[82] enable this process to be interpreted as chemisorption, with hydroxysilyl groups regarded as reactive centres. The experimental conditions excluded formation of the polysiloxane polymer, so that systematic examination of chemical interaction on the surface was possible.

VII. Interaction of Glass and Silica Surface with Actual Finishes

Methods of studying the reactions of simple organic silanes have been used to investigate the interaction of actual finishes with a silica surface[53,57,58,88-91]. The infrared spectrum of a finished glass fibre contains new bands[53,57,58] belonging to the finish—stretching vibrations of C–H in the range 3000–2800 cm^{-1} [53] and vibrations of the vinyl group at 3070–3055 cm^{-1} [57,58]—which are not appreciably affected by prolonged (at least 30 h) rinsing of the glass fibre with the solvent, subsequent vacuum treatment (0.001 mmHg at 200°C for 2 h), and boiling in a weak alkali (0.5% ammonia solution for 2 h) [53]. The stability of the grafted groups is regarded[53,57,58] as proof of the formation of a chemical bond between finish and glass, since no other bonds are able to retain the layer of finish on the surface under such severe conditions. The most probable reaction in these systems will occur between halogeno-, hydroxy-, and alkoxy-groups in the finish and hydroxysilyl groups in the glass. On the basis of this scheme the authors conclude that a siloxane bond may be formed at the finish–glass boundary.

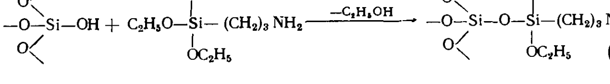
This conclusion was fully substantiated by a study of the interaction between trimethylchlorosilane and a silica surface[86]. The compounds used in the above researches[53,57,58]—finish GVS-9, vinyltrichlorosilane, vinyltriethoxysilane in its original state and partly hydrolysed—are multifunctiona: GVS-9 contains three ethoxyethoxy-groups attached to the silicon atom, and the others contain three halogeno-, ethoxy-, or hydroxy-groups. The experimental method, which ultimately simulated the behaviour of a finish on the surface of an actual filler, in no way excluded any additional reactions due to hydrolysis and condensation of the compounds used. Since all the finishes[53,57,58] were terfunctional, they might give rise to network polysiloxanes.

Wende and Gähde[57,58] showed that treating glass cloth with a chlorinated vinylsilane results in the formation of a grafted compound which is stable in a vacuum at 300°C (for 1 h). Treatment with an ethoxy-derivative gives no band at 3060 cm^{-1} in the infrared spectrum of the glass cloth which had been subsequently heated at 100°C. However, partial hydrolysis of the vinyltriethoxysilane results in the appearance of a band due to vinyl groups, although it is far weaker than for treatment with vinyltrichlorosilane. The authors interpret their observations in terms of the different abilities of chloro-, hydroxy-, and ethoxy-groups to form a chemical bond with the glass surface. They do not dwell on the complete consistency of this pattern with the ability of the compounds to polymerise: chloro-substituents are easily hydrolysed even in the air, whereas particular conditions are needed with alkoxy-groups, so that hydrolysis of the ethoxysilane was necessary before application to the glass surface. This process is accelerated in alkaline medium, and it is probably for this reason that Nikonova[53] finds that finishes graft to an alkaline glass fibre to a greater extent than to an alkali-free glass fibre. Conversion of even the small proportion of finish molecules into a network polysiloxane and adsorption of the latter on the glass fibre will result in the formation on the glass surface of a polymer which firstly is insoluble, since it has a network structure, and secondly is thermostable, like all polysiloxanes. The structural groups which the authors observed in the infrared spectra are present both in the initial finish and in the polymer formed from it. Thus their results[53,57,58] leave no doubt as to the formation on the glass surface of grafted compounds which are stable to various agencies, but these results in no way determine the nature of the compounds or the character of the interaction with the surface. In our view the unequivocal conclusion that an Si−O−Si bond is formed between finish and glass is unjustified with the given experimental method.

More thorough spectroscopic investigations have been made[88-91] at the Pisarzhevskii Institute of Physical Chemistry of the Ukrainian SSR Academy of Sciences. The experimental conditions simulated less closely the finishing of a glass filler, but permitted a deeper insight into its mechanism. The test materials were 3-aminopropyltriethoxysilane and Aerosil, the former is widely employed as a finish, and the latter is a convenient form of silica for spectroscopic investigations. Conditions of treatment were varied widely: Aerosil was modified with the 3-aminopropyltriethoxysilane both as the vapour (at 20−150°C) and as dilute solutions in benzene (at 20−80°C). Determinations were made of the statistical exchange capacity (SEC) to characterise the concentration of groups grafted to the surface. Besides the C−H-stretching vibrations (3000−2800 cm^{-1}), the antisymmetric (3367 cm^{-1}) and symmetric (3288 cm^{-1}) N−H vibrations of the primary amino-group[88,89] and the O−H vibrations of the surface hydroxyls were examined in the infrared spectra of the modified Aerosils.

The main conclusions on the mechanism by which a finish adds to a silica surface were based on the insolubility and great thermal stability of the grafted compound in a vacuum (300°C at 10^{-4} mmHg), the weakening and complete disappearance of the band due to free surface hydroxyls (3750 cm^{-1}) with increase in the statistical exchange capacity of the specimens[88,89], and finally the decrease in the concentration of ethoxy-groups in the surface compound[90]. In the last case the calculation was made from determinations of carbon in the specimens: the concentration of ethoxy-groups was found by subtracting the carbon in propyl groups from the total carbon content, the number of propyl groups having been calculated from the concentration of amino-groups.

Results are presented[90] showing that increase in the statistical exchange capacity of the specimens is accompanied by a change in the ratio of amino-groups to ethoxyl from 1 : 2 to 1 : 1. Since the theoretical ratio for the initial substance in 1 : 3, it is obvious that the molecules of the finish lose some of their ethoxy-groups during transformation on the surface. On the basis of the observations[88,89] the surface reaction is given as



(III)

Thus, although additional information has been obtained on the nature of structural groups on the Aerosil surface, the same conclusion is reached as before[53,57,58] on the formation of a siloxane bond. The fundamental possibility of the formation of a cross-linked polysiloxane from 3-aminopropyltriethoxysilane is not considered, nor is its tendency to hydrolysis under the treatment conditions discussed.

Nevertheless, this process is of interest if only because it leads to a decrease in the ethoxyl content of the grafted layer, and hence should be considered in interpreting the results[90]. Furthermore, the absence of the 3750-cm^{-1} band in the spectra of the modified Aerosil is not unequivocal evidence that free surface hydroxyls are involved in reaction (III), since other O−H vibrational bands were observed, e.g. at 3690 cm^{-1} [89]. This band is due to bound hydroxyls[67], and its presence may imply conversion of free into bound hydroxyls as a consequence of specific adsorption of the compound on the surface. It was obviously in this connection that the hydroxyl concentration of the Aerosil was determined[90] by deuterium exchange and mass spectrometry, and compared with the content of amino-groups on the Aerosil surface. This revealed that increase in the statistical exchange capacity to a particular value was accompanied by a decrease in the content of hydroxy-groups. Further increase in the concentration of amino-groups by a factor of 2.5 produces almost no change in the hydroxyl content of the surface (Table 2). Thus the question arises of incomplete realisation of the proposed reaction mechanism (III).

Table 2. Mass-spectrometric analysis of aminoalkylated Aerosils after deuterium exchange[90].

Conditioning temp., °C	SEC after conditioning (15 h), mmole g^{-1}	Duration of exchange, h	Total exchangeable centres on surface, mmoles g^{-1}	Quantity of centres, mmoles g^{-1} for the groups	
				NH_2	OH
200	0.14	2	1.49	0.28	1.21
200	0.39	2	1.51	0.78	0.73
200	0.57	2	1.52	1.14	0.38
200	0.93	3	2.20	1.86	0.34
200	1.41	3	3.18	2.82	0.36

How is it possible to graft 2.82 millimoles of amino-group per gramme to the silica surface if, after a concentration of 1.14 mole NH_2 g^{-1} has been reached, surface hydroxyls are not involved in the process? An obvious answer is to postulate that molecules of the finish can undergo independent transformation with the formation of polymeric derivatives on the Aerosil surface, but it is difficult to assess the relative proportions of these processes. It is hardly possible to check them from the variation in the ethoxyl content, since transformation of the finish—whether etherification on the surface (scheme III) or the cocondensation of molecules—involves the liberation of ethanol, which interacts readily with a silica surface[79-81]. After treatment of Aerosil with 3-aminopropyltriethoxysilane vapour at 150°C a band appeared in the infrared spectrum[90] at 2985 cm^{-1}, which corresponds to antisymmetric vibrations of the methyl group in the presence of a C_2H_5-O bond. Thus, an additional possibility is ethoxylation of the surface, which probably accompanies[90] the main processes, and under favourable conditions will become increasingly dominant. The absence of the 2985-cm^{-1} band with the other Aerosil modifications may not be complete proof of the absence of ethoxylation, since the concentration of grafted ethoxy-groups is probably small, and a strong band due to C–H-stretching vibrations (2935 cm^{-1}) is superimposed on their characteristic band (2985 cm^{-1}).

Consequently interaction between the silica surface and ethanol, which is a product of the hydrolysis and the condensation of the ethoxysilane, should lead both to a decrease in the concentration of surface hydroxyls and to a change (decrease) in the ratio of amino- to ethoxy-groups in the grafted compound. The experimental results, including those in Table 2, are interpreted[90] solely as a consequence of condensation of the ethoxy-groups of the silane with hydroxysilyl groups of the silica. In our view, however, all the observed phenomena may be due also to other processes—firstly hydrolysis and condensation of the terfunctional finish into a cross-linked polymer adsorbed on the silica surface, and secondly ethoxylation of the Aerosil surface by ethanol liberated in the first process. The unequivocal conclusion that a chemical bond is formed between finish and silica surface is open to doubt, since the phenomena observed by these workers can be explained by other processes.

An interesting investigation was made by Tertykh, Chuiko, et al.[91] on the part played by amino-groups in the reaction between 3-aminopropyltriethoxysilane and an Aerosil surface. This group was characterised by two absorption bands—at 3380 and 3305 cm^{-1}—which were displaced to shorter wavelengths by vacuum treatment at 450°C, their frequencies becoming respectively 3500 and 3425 cm^{-1}. This substantial shift in the bands was explained by breakdown of the hydrogen bond between the primary amino-groups in the finish and the free hydroxyls on the silica. This bond is quite stable, since it is destroyed only after vacuum treatment at 450°C, when the hydroxyls hydrogen-bonded to amino-groups were split off, i.e. when "removal of one of the components of the hydrogen-bonded complex" takes place. As long as the complex does not break down, the aminoalkylated Aerosil is not involved in specific adsorption interaction with methanol and acetone. After destruction of the complex these compounds are adsorbed on the surface, which results in broadening of the 3425-cm^{-1} band.

The results[91] show that the amino-group of the finish is able to interact with the silica surface with formation of a fairly stable bond. At present, of course, this conclusion applies only to 3-aminopropyltriethoxysilane, for other amino-alkoxysilanes have not been studied from this point of view. An analogous investigation would enable us not only to establish the possibility of interaction between finishes and a silica surface through the amino-groups but also to ascertain the effect of substituents attached to the nitrogen atom on its tendency to surface reaction.

It has been shown[92] that analogues of real finishes—aminoalkylethoxysilanes containing one ethoxy-group—do in fact react chemically with a silica surface. This is proved by the preservation of bands due to CH-stretching vibrations in the spectrum of the Aerosil after extraction and high-temperature vacuum treatment. Formation of any thermostable derivatives of the aminoalkylsilane not grafted to the surface was excluded by the monofunctionality of the agent. The use of model compounds led to the conclusion[92] that chemical reaction is possible between an ethoxy-group in the aminoalkylsilane and the surface hydroxyls of Aerosil.

It is difficult to say to what extent this process occurs with finishes containing two or three ethoxy-groups and showing a tendency to more complicated reactions. Since these compounds have proved effective for practical application, it would be of great interest to examine their tendency to polymerisation in contact with a glass surface and determine the contribution of this process to the general pattern of transformation of the finish on the surface.

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The above review was written at the beginning of 1969. While it was being prepared for publication a considerable number of papers appeared on improvements to the application of hydrophobic adhesives in polymeric materials and on extensions to their field of use[93-97]. It has been proposed[93,94] that finishes and active additives should be employed not only in glass-reinforced plastics but also in glues, sizes, coatings, and moulding compositions. New modifiers have appeared which improve adhesion in filled polymers, e.g. finishes based on modified epoxy-resins[98] and novel organosilicon compounds containing nitrogen[99].

Hydrophobic adhesives find application in the most recent and promising types of composite materials, e.g. in a glass-reinforced plastic based on a thermostable polyimide resin[100] and in carbon-reinforced plastics[101]. The properties have been described[100] of glass-reinforced plastics based on a polyimide binder obtained from the dianhydride of benzophenone-3,3′,4,4′-tetracarboxylic acid and *m*-phenylenediamine. Glass cloth S-994 was used as filler, with its surface modified three ways: it was subjected to heat-treatment; it was finished with product A-1100 after heat-treatment; and it was treated with product HTS during stretching of the glass fibres. The presence of the modifier on the glass cloth produced a sharp increase in the water resistance of the material: 90–99% of its bending strength was maintained after immersion in boiling water for 2 h, whereas a glass-reinforced plastic based on the heat-treated glass cloth retained only 45% of the initial strength. A second, no less important point is the sharp increase in the initial strength of the glass-reinforced polyimide plastic resulting from modification of the filler with products A-1100 and HTS: the bending strength of the material in the dry state was changed from 2140 to 3060–3670 kg cm^{-2}. Thus there is no doubt about the prospects for modifying glass-reinforced polyimide plastics with a finish to raise their initial strength and their resistance to water. However, the problem arises of preserving the strength of the material at high temperatures, since thermal stability remains a primary requirement of such plastics. Finishing a glass cloth with product A-1100 has an adverse effect on the strength of the material during its thermal aging at 316°C, while the use of product HTS leads to a sharp deterioration in the strength indices after aging at this temperature for 300 h. Research workers will probably direct their efforts towards developing methods for stabilising glass-reinforced polyimide plastics which will enable the heat resistance of the material to be maintained while its water resistance is improved.

Alkylalkoxysilanes have hitherto been used in polymeric materials filled with glass, silica, quartz, etc. However, Harris et al.[101] have found an effective method of applying hydrophobic adhesives in carbon-reinforced plastics. They have been able to strengthen a carbon-reinforced polyester plastic considerably by applying alkoxysilanes containing epoxy-groups in the organic radical (A-186 and

A-187) to the surface of carbon fibre previously immersed in boiling 70% nitric acid for 2 h. The strength of the plastic is already increased by the use of oxidised fibres, but their finishing leads to further increases in tensile strength (from 56.6 to 63.7 kgf mm^{-2}), bending strength (47.5 to 53.0 kgf mm^{-2}), and shearing strength (2.52 to 2.77 kgf mm^{-2}). The shear tests indicate that the strengthening of the material due to oxidation and finishing of the carbon fibres is 35% (2.77 compared with 2.06 kgf mm^{-2}). In order to achieve the same improvement solely by oxidising the carbon fibres in boiling nitric acid, the time of immersion would have to be increased from 2 to 24 h. Preliminary oxidation of carbon fibres in aqueous medium is regarded as yielding surface hydroxyls, and the interaction with the silane finish occurs by a mechanism analogous to that observed with glass-reinforced plastics. On studying the fracture of specimens by scanning electronic stereoscopy, however, peculiarities were noted[101] in the detachment of the finished carbon-fibre surface from the mass of the binder. A layer of finish or binder usually remains on the finished glass surface[37]. The surface of a carbon fibre torn from a polymer matrix, however, contained no trace of finish and was entirely similar to an unfinished surface. The explanation given[101] is that the finish bonds more strongly to the binder than to the carbon fibre.

Thus hydrophobic adhesives are beginning to be used, not only in new types of resins, but also in combination with new forms of filler. Hence the interest of research workers in the chemistry of the interaction between these modifiers and various kinds of surfaces is not accidental. Broun, Korolev, et al.[102] used the infrared spectra to estimate the content of grafted groups on the surface of titanium dioxide (anatase, rutile), and showed[103] that, unlike silica, the same number of trimethylsilyl groups are grafted on independently of whether the surface is treated with trimethylchlorosilane or trimethylethoxysilane. Furthermore, these workers observed the formation of carboxylates on a titanium dioxide surface treated with trimethylchloro- and trimethylacetoxysilanes.

Information on the interaction of simple alkylalkoxysilanes with a silica surface has been extended. The relative activities of trimethyl-ethoxy-, -acetoxy-, and -chloro-silanes and their firmness of retention on silica have been characterised[103] by the surface concentrations of grafted trimethylsilyl groups. In the spectrum of Aerosil treated with dimethoxydimethylsilane vapour[104] the band due to C–H vibrations in the trimethylsilyl group (at 2965 cm^{-1}) was accompanied by a band at 2953 cm^{-1}, both of which remained after vacuum treatment of the specimen at 450°C. The appearance of a band at 2853 cm^{-1} is explained[104] by the grafting of methoxy-groups to the silica surface. In fact the spectrum of Aerosil which has been treated with methanol contains a band at 2857 cm^{-1}. Thus this work[104] has shown that the main reaction between dimethoxydimethylsilane and silica—analogous to scheme (III)—is accompanied by a secondary reaction, in which the methanol liberated reacts with surface hydroxyls. The possibility of such interaction has been discussed above (Section VII), and this paper[104] supplies experimental confirmation.

Johanson et al.[105],[106] labelled organosilanes with carbon-14 to examine their interaction with silica and alkali free glass surfaces. They found that trimethylchlorosilane was adsorbed on the glass than on silica, On immersion of the glass in boiling water or on exchange with unlabelled trimethylchlorosilane molecules, however, the number of primarily adsorbed molecules greatly diminished. This suggested that the interaction of trimethylchlorosilane with glass is not confined to chemical reaction with surface hydroxyls, but includes adsorption interaction of additional molecules of the substance with surface metal ions. In contrast to trimethylchlorosilane, trimethylsilanol is easily removed from a silica surface. From this it is assumed that trimethylsilanol adds to a silica surface by means of hydrogen bonds between its own hydroxyl and those of the silica. By using ammonia as catalyst for the silanol condensation, however, these workers were able to prevent the adsorbed trimethylsilanol molecules from exchanging with those in the solution. After desorption the silica retained 90% of the grafted molecules, instead of the 20% observed in the absence of ammonia. Thus a transition from a hydrogen bond to a chemical bond between the compound and the silica surface was accomplished.

It has been shown[105], with hexamethyldisilazane as example, that adsorbed water has a vigorous effect on the transformation of organosiloxanes in contact with a glass surface. For this purpose the water adsorbed on glass was replaced by ^3H_2O, and the variation in its amount during reaction with hexamethyldisilazane was followed. It was established that water causes conversion into trimethylsilanol, which in the presence of the ammonia liberated forms a chemical bond with the glass.

Daley and Rodriguez[107] pay great attention to the hydrolysis of finishes on a glass surface. In their opinion this process precedes interaction of actual finishes with the surface, and its extent affects the properties of glass-reinforced plastics. They checked the hydrolysis of vinyltriethoxysilane (A-151), hydroxypropyltrimethoxysilane (A-174), and pentyltrimethoxysilane (Y-2815) from the variation in intensity of the chromatographic peak of the unhydrolysed finish on contact with glass. Hydrolysis of the finishes was catalysed by alkali-metal ions in the glass, which had an especially marked effect on A-151, whose relatively small molecules most easily approached the surface ions[107]. Glass was finished with the product A-151 under various conditions: (i) particles of glass were merely introduced into a solution of the finish; (ii) acetic acid was added initially, and then the glass; and (iii) the glass was added, and only then was the solution acidified. Hydrolysis of the finish occurred to the greatest extent in case (ii), its completeness being shown in the mechanical properties of polystyrene filled with the finished glass. The polymer had its highest bending strength (510 kgf cm^{-2}) when it contained glass particles finished in the absence of acid, i.e. when hydrolysis of the finish was insufficiently advanced. When hydrolysis was most complete, the strength of the filled polymer had its minimum value (440 kgf cm^{-2}). The explanation given[107] is that the finish, hydrolysed by acetic acid, is deposited on the glass surface only after some delay. This probably involves formation on the glass of a layer of finish, which results in less effective interaction between polymer and filler.

Recent papers[108–110] have examined the adsorption of water on silica, and its effect on the wetting and adhesion of silicate surfaces[111]; others have assessed the destructive effect of water on glass-reinforced plastics and the possibility of diminishing it by means of hydrophobic adhesives[112–114]. The opinion is expressed[112] that water breaks the bonds at the boundary between polyester resin and glass by leaching substances of low molecular weight out of the resin, so that the binder shrinks. Eakins assumes[113] that in general the action of water on glass-reinforced plastics consists in penetrating the material and increasing the rigidity of the layer of resin on the surface of the glass. This diminishes the ability of the surface layer of polymer to relieve the stresses arising on the formation of cracks and their extension to the filler surface. Furthermore water, by rupturing hydrolytically unstable bonds between glass and resin, disturbs the closeness of packing of binder macromolecules in the surface layer, which permits access of water to the rest of the material. It is considered[112,113] that the use of finishes diminishes the destructive action of water on glass-filled polymers.

Garanina, Semenova, et al.[114] have shown that the properties of a glass-reinforced plastic, in both dry and wet states, can be improved by slightly drying the glass cloth at 80°C for 1.5 h before production of the material. Such removal of water from the filler surface lowers the number and size of microdefects (pores) in the material. These observations are especially significant when it is remembered that the application to glass cloth of most finishes, e.g. aminoalkylethoxysilanes[114], considerably increases the amount of water adsorbed on the glass surface.

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Ionisation Potentials of Aromatic and Heterocyclic Compounds

V.K.Potapov

The relation between the ionisation potentials of aromatic and heterocyclic compounds and their electronic structures is considered. The nature of the orbitals in the ground states of molecules of different structures is examined on the basis of an analysis of the ionisation potentials. It has been shown how substituents affect the positions of the electronic levels of aromatic compounds.
The bibliography includes 57 references.

CONTENTS

I. INTRODUCTION

During recent years, there has been an increase in the number of studies on the photoionisation of organic compounds in the gas phase, dealing with the investigation of the electronic structure of molecules and the mechanism of their decomposition on ionisation. The advances achieved in this field are due to the successful development of the technique of the accurate determination of adiabatic ionisation potentials (i.p.) by the photoionisation method.

At the present time this method has been developed and used to determine ionisation potentials by Soviet and non-Soviet investigators[1-9]. Valuable information about the upper ionisation potentials of aromatic compounds was obtained by photoelectronic spectroscopy[10-12].

The ionisation potentials of a large number of aromatic and heterocyclic compounds containing $>$N–, $>$C=O, –O–, and –S– groups in different positions are now known. However, this information has not been arranged systematically, which makes it difficult to discover the characteristic properties of the structures of organic compounds.

From the standpoint of electronic structures and the influence of chromophoric groups and substituents on the π-electron system, aromatic compounds can be usefully divided in three main groups.

1. Aromatic-hydrocarbons with an upper π-electron level in the ground state.
2. Aromatic compounds in which the heteroatoms supply a lone pair of p electrons to the π-electron system: (a) compounds with a chromophoric group outside the ring (aniline, phenol, and others); (b) heterocyclic compounds containing the –N$<$, –O–, and –S– groups (pyrrole, furan, and others).
3. Aromatic compounds in which each heteroatom supplies one p electron to the π-electron system: (a) nitrogen-containing heterocyclic compounds (pyridine and others); (b) aromatic compounds with a carbonyl group (quinones).

This classification of aromatic and heterocyclic compounds, based on an analysis of their ionisation potentials, provides information about the energies and the nature of their molecular and atomic orbitals.

This review deals with studies on the electronic structure of aromatic compounds of the above type on the basis of ionisation potentials, corresponding to the removal of electrons from different orbitals in the ground state, and the influence of substituents and heteroatoms on the nature and positions of π-orbitals.

II. IONISATION POTENTIALS OF AROMATIC HYDROCARBONS

The electronic structure of polycyclic aromatic hydrocarbons is characterised by a stable π-electron system ensuring a high energy stability of molecules of this type in photochemical and radiation-chemical reactions. Thus the mass spectra of benzene and naphthalene show a relatively low yield of fragment ions formed as a result of the disruption of the ring. The reactivity of aromatic polycyclic compounds in photochemical reactions is determined by the nature of their excited electronic states ($\pi\pi^*$). As a result of the delocalisation of electrons in the π orbitals of both the ground and excited electronic states, the valencies produced are common to the molecule as a whole, which determines the relative passivity of the ($\pi\pi^*$) states with respect to intermolecular interactions and the low photochemical activity of polycyclic hydrocarbons[13].

Accurate values of the first ionisation potentials for hydrocarbons were obtained by the photoionisation method mainly during the last few years (Table 1). The upper ionisation potentials corresponding to the energies of removal of electrons from various filled inner orbitals have been determined from the photoelectronic spectra of the molecules (Table 2).

The first ionisation potentials of polycyclic hydrocarbons (benzene, naphthalene, anthracene) decrease with the number of π electrons in the molecule, which is due to the decrease of the energy of the upper filled π orbital in consequence of the increase of the conjugation energy. It follows from the molecular orbital theory that the energy of the upper filled π orbital is linearly related to the first ionisation potential of the given molecule[1,14]. Accordingly, the first ionisation potential may be represented as follows:

$$I_p = -(\alpha + m_i\beta),$$

where α is the Coulombic integral, β the resonance integral, and m_i the coefficient of the energy of the ith molecular orbital. This equation has the specific form $I_p = 5.78 + 3.75\, m_i$ and holds satisfactorily for polycyclic hydrocarbons.

It has been shown[15] that the upper ionisation potentials of aromatic hydrocarbons and the energies of the filled π orbitals in the ground state are also correlated in the zeroth Hückel approximation.

Table 1. First ionisation potentials of aromatic hydrocarbons.

Compound	Ionisation potential, eV									
	photoionisation	Refs.	spectroscopy	Refs.	photoelectronic spectroscopy	Refs.	electron impact	Refs.	calc.	Refs.
Benzene	9.246±0.005	9	9.247	16	9.24	11				
o-Xylene	8.56±0.01	7	—	—	—	—	—	—	—	—
m-Xylene	8.57±0.01	7	—	—	—	—	—	—	—	—
p-Xylene	8.44±0.01	7								
Naphthalene	8.12±0.01 8.14±0.02	7 18	8.13	19.20	8.12	15	—	—	8.12	21
α-Methylnaphthalene	7.96±0.01	7	—	—	—	—	—	—	8.28	22
β-Methylnaphthalene	7.96±0.01	7	—	—	—	—	—	—	—	—
Anthracene	7.38±0.03	28								
	7.41	18	7.41	18	—	—	—	—	7.38	22
	7.3	23	—	—	—	—	—	—	7.3	24
Phenanthrene	7.75	18	7.69	18					7.96	25
									8.02	21
Azulene	7.41±0.01	18,26	7.41	18	7.42	15				
Indene			—	—	8.13	15	—	—	—	
Biphenylene			—	—	—	—	7.95±0.3	15	—	—
Biphenyl	8.27±0.01	7	—	—	—	—	—		—	—
p-Terphenyl			7.7	18						
Toluene	8.82±0.01	6	—	—	—	—	9.10	27	—	—
Diphenylmethane	—	—	—	—	—	—	8.95	27	—	—
Triphenylmethane	—	—	—	—	—	—	8.80	27	—	—
Naphthacene	6.88±0.03	28	—	—	—	—	—	—	—	—

Thus the following relation holds for the ionisation potentials and the π-orbital energies of benzene, indene, azulene, and biphenylene:

$$I_p^j = 6.22 + (2.77 \pm 0.15)\,m_j,\ \text{eV},$$

where m_j is the coefficient of the energy of the jth π orbital in the ground state of the given molecule.

Table 2. The first and upper ionisation potentials of aromatic compounds.

Compound	Ionisation potential, eV				References
Benzene	9.24	11.48	14.0	16.83	11
Naphthalene	8.12	8.90	10.0	10.85	15
Indene	8.13	8.95	10.29	11.58	15
Azulene	7.42	8.49	9.91	10.85	15
Anthracene	7.41	9.25			18
Phenanthrene	7.75	9.35			18
Biphenyl	8.20	9.08	9.70	11.02	15

The resonance integral $\beta = 2.77 \pm 0.15$ eV is consistent with the estimate obtained from the ionisation potentials. This equation was used to estimate the ionisation potentials of the compounds investigated and showed good agreement with the experimental data in Table 2. Naturally, such an examination is important for the determination of the sequence and nature of the upper and lower π orbitals in the ground state of the given molecule.

The ionisation potentials of benzene were determined by El Sayed et al. from the ultraviolet absorption spectra on the basis of the convergence limits of the Rydberg series[16]. The first and second ionisation potentials, which are 9.247 and 11.489 eV, were attributed to the removal of electrons from π orbitals. The Rydberg series converging to 16.84 eV and representing a vibrational progression with a frequency of 900 cm^{-1} was attributed to the removal of an electron from the σ_{CC} orbital. The ionisation potentials of benzene determined from high-resolution photoelectronic spectra[11] agreed to a high degree of accuracy with the corresponding spectroscopic values (Fig. 1 and Table 2).

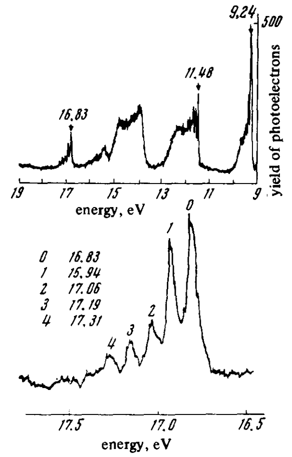

Figure 1. High-resolution photoelectronic spectrum of benzene.

The structure of the vibrational levels converging to the third ionisation potential also consists of a progression: 17.31, 17.19, 17.06, 16.94, and 16.83 eV. The results of these two investigations and also new studies on the photoionisation of benzene[4,5] (Fig. 2) established that the first and second ionisation potentials of benzene, 9.246 and 11.489 eV respectively, correspond to the energies of the removal of an electron from the π orbitals of the ground state and the ionisation potential of 16.83 eV corresponds to the removal of an electron from the σ_{CC} orbital. The photoionisation threshold at 14 eV (see the photoelectronic spectrum in Fig. 1) is probably also associated with the removal of an electron from the σ orbital, since according to the photoionisation data for benzene $C_6H_5^+$ fragment ions are formed at an energy of 13.8 eV.[5]

It should be noted that the calculation by the self-consistent field molecular orbital (SCF-MO) method for the benzene molecule[29] yielded unduly high energies for the upper σ_{1g} orbital. This is the reason for the incorrect assignment of the ionisation threshold associated with the removal of electrons from this σ orbital in a series of experimental studies on the ionisation potentials of benzene before the studies on the photoionisation[4,5] and photoelectronic spectra[11].

In the vicinity of the first ionisation potential the photoionisation curve for benzene shows breaks at energies of 9.33 ± 0.01 and 9.42 ± 0.01 eV, associated with the vibrational excitation of the second overtone of the ν_{18} symmetrical vibrations (670–690 cm^{-1}) of the molecular ion in the

Rydberg series converging to the first ionisation potential[5,30].

The ionisation potentials of anthracene and phenanthrene were determined from the electronic absorption spectra[18] on the basis of the convergence limits of the Rydberg series. The same workers determined by the photoionisation method the first ionisation potentials of naphthalene, anthracene, phenanthrene, and azulene, which agreed with the spectroscopic values. The photoionisation curves for anthracene and phenanthrene in Fig. 3 show that the vibrational excitation levels of the molecular ions observed in the vicinity of the first ionisation potentials are diffuse, which makes their assignment difficult.

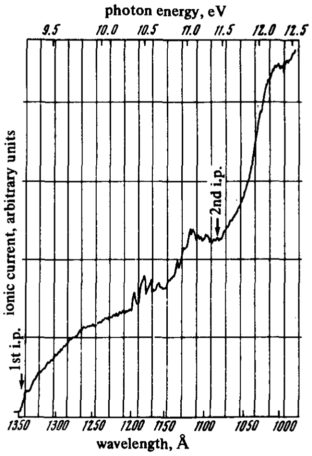

Figure 2. Photoionisation curve for benzene recorded on an MKh-1311 mass-spectrometer.

Absorption bands converging to the second ionisation potential have been observed on photoionisation curves between the first and second ionisation potentials of polycyclic hydrocarbons. The structure of the maxima is shown most distinctly for benzene in the energy range 10.4–11.2 eV (Fig. 2) (the first four maxima constitute a vibrational progression with a frequency of 0.09 eV), which can be accounted for by pre-ionisation from Rydberg molecular states, converging to the second ionisation potential of benzene corresponding to the removal of an electron from the π orbital $1b_1$ (a_{2u} level)[5]. The vibrational structure of the pre-ionisation bands of toluene is not resolved. The position of the first toluene band agrees with that of the first absorption band of toluene vapour due to the excitation of electrons from the lower π_1 orbital.

Pre-ionisation bands at energies of 9.1 and 9.0 eV converging to the second ionisation potentials of 9.25 and 9.35 eV have been observed for anthracene and phenanthrene[18]. It is noteworthy that the pre-ionisation levels of phenanthrene and azulene are of a pre-dissociation type.

The ionisation potentials of benzene, biphenyl, and *p*-terphenyl, corresponding to the removal of an electron from the upper π orbitals of these molecules, decrease with the number of phenyl rings in the chain, which is probably associated with the decrease of the energy of the upper filled π orbitals of this series of compounds in consequence of the conjugation between the π electrons of the phenyl groups. This conclusion is confirmed by the fact that the ($\pi\pi^*$) electronic transition band is displaced towards long wavelengths by 2200 cm^{-1} on addition of the phenyl group[32].

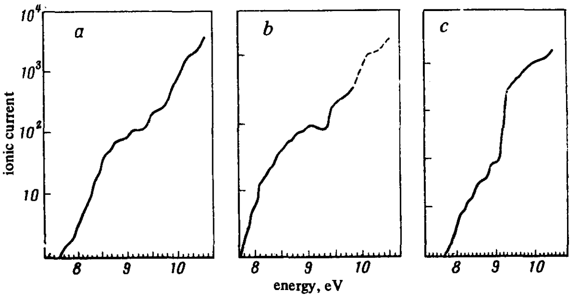

Figure 3. Photoionisation curves: *a*) anthracene; *b*) phenanthrene; *c*) phenothiazine.

A characteristic feature of the electronic structures of the phenyl derivatives of methane (toluene, diphenylmethane, and triphenylmethane) is that the ionisation potentials of these molecules differ little[27]. The insignificant decrease in this series of the energy of removal of electrons from upper filled π orbitals is evidence of only a weak interaction between the π electrons in the phenyl rings in consequence of their non-coplanarity. This feature of the electronic structure is shown also in the decomposition of the phenyl derivatives of methane. For example, the decomposition of triphenylmethane on ionisation takes place with a change in the initial tetrahedral configuration of the molecule and the formation of the stable $(C_6H_5)_3C^+$ ion having a planar configuration.

III. IONISATION POTENTIALS OF AROMATIC COMPOUNDS WITH HETEROATOMS

1. Benzene Derivatives

The substitution of a hydrogen atom in benzene by chromophoric groups may lead to a change in the nature and positions of the upper electronic levels of the ground state of the molecule. The incorporation of the unshared electron pair of the heteroatom in an electron-donating substituent into the π electron system in benzene leads to the removal of the degeneracy of the upper e_{1g} level and the splitting of the energies of the π_3 and π_2 orbitals. The π_3 orbital (B_1 symmetry) corresponds to the maximum electron density at the carbon atom and the π_2 orbital (A_2 symmetry) corresponds to a node. Analysis of the photoelectronic spectra of mono- and *p*-substituted benzene derivatives quoted by Baker et al.[11] shows that the band at 9.40 eV, corresponding to the first vertical ionisation potential of benzene, broadens or splits when the hydrogen atom is substituted (Table 3).

For toluene, diffuse bands corresponding to the first ionisation potential are observed. The splitting of the energies of the π_3 and π_2 levels is probably fairly small and cannot be determined from the photoelectronic spectrum. The same conclusion follows also from the analysis of the initial section of the photoionisation curve for toluene[5].

Table 3. Vertical ionisation potentials of benzene derivatives according to Turner[11].

Compound	Ionisation potential, eV			$I_{\pi_2}-I_{\pi_3}$	Ionisation potential, eV
	π_3		π_2		π_1
Benzene	—	9.40	—	—	11.5
Toluene	8.9	—	9.13	0.2	—
Phenol	8.75	—	9.45	0.70	—
Anisole	8.54	—	9.37	0.83	11.2
t-Butoxybenzene	8.75	—	9.33	0.58	—
αα*α*-Trifluoroanisole	—	10.00	—	—	—
ααβββ-Pentafluorophenetole	—	9.97	—	—	—
Chlorophenol	8.69	—	9.75	1.07	—
t-Butoxy-*p*-chlorobenzene	8.72	—	9.76	1.04	—
p-Bromobenzene	8.52	—	9.60	1.08	—
p-Bromoanisole	8.49	—	9.65	1.16	—
p-Dimethoxybenzene	7.90	—	9.19	1.29	—
p-Methoxybenzaldehyde	8.87	—	9.77	0.90	—
Aniline	8.04	—	9.11	1.07	11.5
N-Methylaniline	7.73	—	9.03	1.30	—
NN-Dimethylaniline	7.51	—	9.03	1.52	—
NN-Diethylaniline	7.51	—	9.11	1.60	—
Trifluoro-*N*-dimethylaniline	—	10.00	—	—	—
p-Chloroaniline	8.18	—	9.51	1.33	—
p-Toluidine	7.78	—	9.02	1.24	—
p-*NN*-Dimethyltoluidine	7.48	—	9.06	1.58	—
Fluorobenzene	9.5	—	9.86	—	11.8
Chlorobenzene	9.31	—	9.71	—	12.2
Bromobenzene	9.25	—	9.78	—	11.8
Iodobenzene	8.78	—	9.75	—	—
ααα-Trifluorotoluene	—	9.90	—	—	11.9
Nitrosobenzene	—	9.97	—	—	—
Nitrobenzene	—	10.26	—	—	—
Benzonitrile	—	10.02	—	0.2	11.8
Benzaldehyde	—	9.80	—	—	—
p-Difluorobenzene	9.50	—	10.24	0.74	12.1
p-Chlorofluorobenzene	9.26	—	10.07	0.81	12.3
p-Dichlorobenzene	9.17	—	9.57	0.67	12.7
p-Chloromethylbenzene	8.90	—	9.57	0.67	11.7
p-Chloro-ααα-trifluorotoluene	9.80	—	10.19	0.39	12.5
p-Chloronitrobenzene	9.99	—	10.46	0.45	—
p-Chloronitrosobenzene	9.74	—	10.27	0.53	—
p-Chlorobenzaldehyde	9.59	—	9.88	0.29	12.4
p-Bromochlorobenzene	9.04	—	9.96	0.92	—
p-Dichlorobenzene	8.97	—	9.95	0.98	11.9
p-Bromotoluene	8.71	—	9.45	0.74	—
p-Bromo-ααα-trifluorotoluene	9.55	—	10.02	0.47	—
p-Bromobenzonitrile	9.54	—	10.41	0.87	—
p-Xylene	8.71	—	9.21	0.50	—

In aromatic ethers C_6H_5OR, where the unshared electron pair of oxygen is conjugated with the π electrons of the phenyl group, the π_3 and π_2 orbitals of phenol are split—to the extent of 0.70 and 0.83 eV in the case of anisole. In *p*-butoxybenzene $C_6H_5OC(CH_3)_3$ the splitting is less. It follows from the photoelectronic spectra of alkyl phenyl ethers (Fig. 4 and Table 3) that the second ionisation potential hardly changes but the first decreases on substitution. This finding leads to the conclusion that the substitution of hydrogen by alkyl groups leads to a decrease of the energy of the π_3 orbital with B_1 symmetry, while the energy of the π_2 orbital with A_2 symmetry hardly changes under these conditions. For this reason, the first ionisation potentials of alkyl phenyl ethers (Table 4) correspond to the removal of electrons from the upper π_3 orbitals of type B_1 and decrease in the series phenol, anisole, and phenetole, and the second ionisation potentials correspond to the removal of an electron from the π_2 orbital of type A_2. On passing to benzyl methyl ether, where the conjugation between the unshared pair of the oxygen *p* electrons and the π electrons of the phenyl group is weakened, the first ionisation potential is higher compared with those of alkyl phenyl ethers.

The photoelectronic spectra of trifluoromethyl phenyl ether and pentafluoroethyl phenyl ether do not show a splitting of the first ionisation band due to the breakdown of conjugation between the unshared electron pair of oxygen and the π electrons of the phenyl group. This may be attributed to the powerful inductive effect of the fluorine atoms, which leads to a change in the nature of the unshared electron pair of oxygen and an increase of the energy of the upper π level.

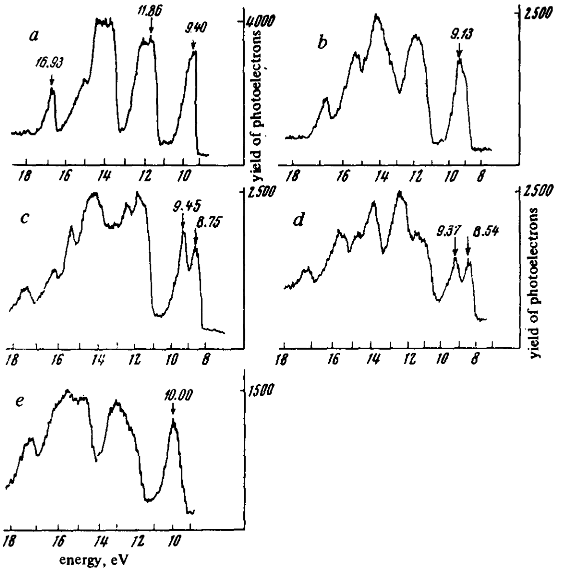

Figure 4. Photoelectronic spectra: *a*) benzene; *b*) toluene; *c*) phenol; *d*) anisole; *e*) $C_6H_5OCF_3$.

Table 4. First adiabatic photoionisation potentials of aromatic compounds containing the $-\mathrm{N}<$, –O–, and –S– groups outside the ring.

Compound	Ionisation potential, eV	Refs.	Compound	Ionisation potential, eV	Refs.
Aniline	7.70±0.02	7	α-Naphthylamine	7.30±0.03	28
N-Methylaniline	7.34±0.03	17	β-Naphthylamine	7.25±0.03	28
NN-Dimethylaniline	7.14±0.03	17	Diphenylamine	7.25±0.03	35
Benzylamine	8.64±0.03	17	Triphenylamine	6.86±0.03	35
m-Toluidine	7.50±0.03	17	Phenol	8.50±0.01	7
NNN'N'-Tetra-methylphenylene-diamine	6.18±0.05	33	Anisole	8.22±0.02	7
			Phenetole	8.13±0.02	7
			Benzyl methyl ether	8.85±0.03	36
o-Fluoroaniline	7.95±0.02	34			
m-Fluoroaniline	7.90±0.02	34	*o*-Fluorophenol	8.66±0.01	7
p-Fluoroaniline	7.82±0.02	34	Benzenethiol	8.33±0.01	7

The above characteristics of the electronic structures of alkyl phenyl ethers are well illustrated by the position of the upper π-electron levels in the ground state shown in Fig. 5.

For *p*-substituted benzenes containing –OR groups, the splitting of the energies of the π_3 and π_2 orbitals is fairly large (1.0–1.2 eV), but their investigation requires a more detailed examination of the photoelectronic spectra and the photoionisation potentials of the molecules.

The ionisation potentials of aniline and its derivatives in Table 4 were first determined by Viletov and coworkers[17,37,38] and assigned to the removal of electrons from π orbitals. These investigations also showed that in the vicinity of the threshold the photoionisation curves are diffuse and the probability of the formation of molecular ions in the vibrational ground state is low.

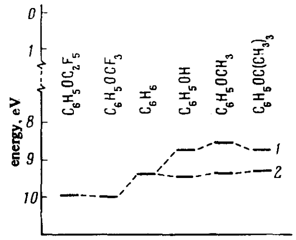

Figure 5. Positions of the upper π-electron levels in the ground state of alkyl phenyl ethers: *1*) π_3 (symmetry B_1); *2*) π_2 (symmetry A_2).

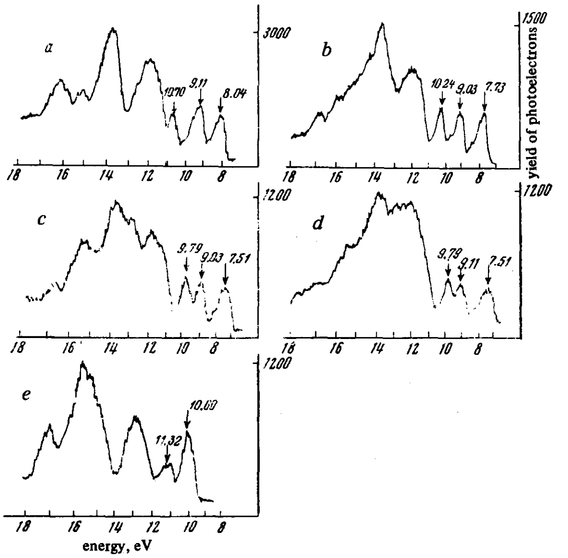

Figure 6. Photoelectronic spectra: *a*) aniline; *b*) *N*-methylaniline; *c*) *NN*-dimethylaniline; *d*) *NN*-diethylaniline; *e*) $C_6H_5N(CF_3)_2$.

The substitution of a hydrogen atom by an amino-group leads to an appreciable separation of the π_3 and π_2 orbitals, mainly due to the decrease of π_3 orbitals of type B_2 which correspond to maximum electron density at the point of substitution. For aniline, this splitting is 1.07 eV and, on consecutive substitution of hydrogen atoms in the amino-group by CH_3 groups, amounts to 1.3 eV for *N*-methylaniline and 1.52 eV for *NN*-dimethylaniline (Table 3 and Fig. 6).

The second ionisation potentials of aniline and its derivatives, associated with the removal of electrons from π_2 orbitals of type A_2 with an electron density node at the point of substitution, remain virtually constant.

The substitution of hydrogen atoms in the alkyl groups by fluorine atoms [$C_6H_5N(CF_3)_2$] leads to the breakdown of conjugation between the unshared electron pair of nitrogen and the π electrons of the phenyl group and the displacement of the first ionisation band towards higher energies. The absence of conjugation between the unshared electron pair of nitrogen and the π electrons of the phenyl group in benzylamine also leads to an increase of the first ionisation potential compared with aniline and its derivatives. It is interesting to note that decomposition processes with abstraction of a hydrogen atom from the methylene group, associated with ionisation as a result of the removal of an electron from the orbital of the unshared pair in the amino-group, are observed for benzylamine at a photon energy exceeding 9.5 eV.[37]

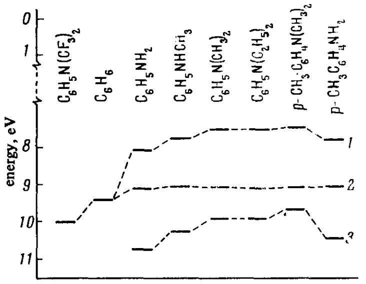

Figure 7. Positions of the upper π-electron levels of aniline and its derivatives: *1*) π_3 (B_1 symmetry); *2*) π_2 (A_2 symmetry); *3*) $\pi 2p_z$ ($-N\langle$).

The photoelectronic spectrum of aniline in Fig. 6 also shows that the third ionisation potential (vertical) of 10.70 eV corresponds to the removal of an electron from the π orbitals with maximum electron density at the nitrogen atom. The third adiabatic ionisation potential of aniline determined from the photoionisation curve is 10.2 eV.[37] It is interesting to compare the change in the third vertical ionisation potential of aniline, as hydrogen atoms in the amino-group are substituted, with the first ionisation potentials of aliphatic amines:

NH_3	CH_3NH_2	$(CH_3)_2NH$	$C_6H_5NH_2$	$C_6H_5NHCH_3$	$C_6H_5N(CH_3)_2$
10.16 eV	9.18 eV	8.36 eV	10.70 eV	10.24 eV	9.79 eV

Fig. 7 shows the positions of the upper filled electronic levels of aniline and its derivatives showing that the separation between the π_3 and π_2 orbitals decreases as the hydrogen atoms in the amino-group are substituted by alkyl groups, owing to the decrease of the energy of the π_3 orbital with B_1 symmetry. Under these conditions, the energy of the π_2 orbital with A_2 symmetry remains virtually unchanged for all aniline derivatives. The nature of the change in the energy of the $\pi(2p_z)$ orbital associated with the unshared $2p_z$ electron pair of nitrogen is the same as for the π_3 orbital.

Analysis of the photoelectronic spectra of $C_6H_5CF_3$, C_5H_5CN, C_6H_5NO, and $C_6H_5NO_2$ shows that the first ionisation band is not split but is displaced towards higher energies (the ionisation potentials of these molecules exceed that of benzene). This may be attributed to the transfer of charge from the benzene ring to the substituents owing to the inductive effect (CF_3) and the negative mesomeric effect ($-CN$, $-NO_2$).

The ionisation potentials of mono- and *p*-substituted benzenes corresponding to the removal of an electron from the lower π_1 orbital, analogous to the $\pi_1(a_{2u})$ orbital of benzene, as a rule exceed the second ionisation potential of benzene (11.49 eV).[11] This is shown more clearly by halogeno-derivatives of benzene and the rule of addivity holds most satisfactorily when substituents are introduced into the 1- and 4-positions (Table 3).

The change in ionisation potentials associated with the removal of an electron from the σ_{CC} orbitals can also be followed in halogeno-derivatives of benzene. Thus the ionisation potential corresponding to the removal of an electron from the σ_{CC} orbital changes on substitution of hydrogen by fluorine from 16.83 to 17.4 eV and on substitution by chlorine and bromine the changes are to 16.7 and 17.0 eV respectively.

The above analysis of the electronic structure of benzene derivatives based on the photoionisation potentials is confirmed also by theoretical calculations. The calculation by the Pariser–Parr–Pople method showed[39] that in aniline the non-bonding electrons of nitrogen are conjugated with the π-electrons of the phenyl ring. The upper filled $3b_1$ and $1a_2$ aniline π orbitals have electronic configurations similar to those of the corresponding upper $2b_1$ and $1a_2$ benzene π orbitals and the lower $1b_1$ aniline π orbital corresponds to the lower $1b_1$ benzene π orbital. The $2b_1$ aniline π orbital, which is located between the $1a_2$ and $1b_1$ orbitals, has the maximum electron density at the nitrogen atom.

The substitution of hydrogen atoms in the amino-group of aniline by phenyl groups leads to a lowering of the first ionisation potential to 7.25 eV (diphenylamine) and 6.68 eV (triphenylamine)[35]. This finding may be attributed to a decrease of the energies of the upper π orbitals in consequence of the conjugation between the phenyl rings via the unshared pair of nitrogen. Calculations by the LCAO-MO method showed that compounds such as diphenylamine have a single π-electron system[40]. The conjugation between the unshared pair of nitrogen and the π-electron system of the aromatic group in α-naphthylamine and β-naphthylamine also leads to a decrease of the energies of the upper π orbitals and hence the ionisation potentials.

2. Nitrogen-containing Heterocyclic Compounds

The ionisation potentials of azines were investigated in studies on photoionisation[7,41] and photoelectronic spectroscopy[9,15,42,43] (Tables 5 and 6).

Information about the nature and energies of the π and *n* orbitals from which electrons are abstracted on ionisation may be obtained by comparing the experimental ionisation potentials with the calculations of the wave functions and the energies of azabenzenes and azanaphthalenes[42,44,45].

It has been shown[42] that the energies of the upper π orbitals in the ground states of benzene, pyridine, and pyrazine are the same, while those for pyrimidine and pyridazine are higher by 0.4 eV. The energy of the *n* orbital of the unshared pair of nitrogen does not change in the series pyridine, pyrazine, and pyrimidine, but decreases for pyridazine in consequence of the powerful Coulombic interaction between the electrons of the two unshared pairs of nitrogen. On this basis, the first adiabatic ionisation potentials of pyridine and pyrazine, 9.31 and 9.36 eV respectively (Table 5), were assigned to the removal of an electron from the π orbital and the first ionisation potentials of pyrimidine and pyridazine were attributed to the removal of an electron from the *n* orbital of the unshared pair of nitrogen.

Table 5. First adiabatic ionisation potentials of nitrogen-containing heterocyclic compounds.

Compound	Ionisation potential, eV	Refs.	Compound	Ionisation potential, eV	Refs.
Benzene	9.246±0.005	9	Phthalazine	8.68	42*
Pyridine	9.32±0.03	7	Anthracene	7.41	18
Pyrazine	9.29±0.01	41	Acridine	7.78±0.03	28
Pyrimidine	9.35±0.01	41	Phenazine	8.4	23
Pyridazine	8.90	42*	2-Methylpyridine	9.02±0.03	7
Naphthalene	8.14±0.02	43	3-Methylpyridine	9 04±0.03	7
Quinoline	8.62±0.01	41	4-Methylpyridine	9.04±0.03	7
Isoquinoline	8.55±0.02	41	2,3-Dimethylpyridine	8.85±0.02	7
Quinoxaline	9.02±0.01	41	2,4-Dimethylpyridine	8.85±0.02	7
Quinazoline	9.02	42*	2,6-Dimethylpyridine	8.85±0.02	7
Cinnoline	8.51	42*			

* The ionisation potentials were determined by photoelectronic spectroscopy.

Table 6. First and upper ionisation potentials of heterocyclic compounds[42].

Compound	Ionisation potential, eV							
Pyridine	9.31	(9.51)	10.45	12.30	—	13.83	—	—
Pyrazine	9.36	(9.51)	10.15	11.14	11.73	13.13	(13.38) 16.0	14.78 16.60
Pyrimidine	9.42	(9.64)	10.39	11.06	13.62	(13.82)	15.56	16.75
Pyridazine	8.90	(9.22)	10.53	11.16	13.63	(13.83)	15.70	16.64
Quinoline	8.62	9.07	10.64	11.42	13.07	(13.65)	15.05	16.20
Isoquinoline	8.54	9.24	10.50	11.60	(12.54)	(13.26)	15.98	16.69
Quinoxaline	8.99	10.72	11.58	(12.32)	(13.98)	15.30	16.21	17.07
Quinazoline	9.05	9.74	10.72	11.26	12.02	(13.78)	16.28	17.23
Cinnoline	8.51	9.03	9.75	10.83	12.04	12.46	13.85	16.16
Phthalazine	8.68	9.17	9.68	10.77	12.07	(12.58)	14.09	15.23
Pyrrole (Ref.10)	8.22	—	9.03	12.38	14.23	17.08	—	—
Furan (Ref.10)	8.77	—	10.21	12.62	—	—	—	—

Calculation of the energies of the filled orbitals of pyridine, pyrazine, and pyrimidine by the more accurate SCF MO method[42] confirmed the assignment of the first ionisation potentials of the azabenzenes and also showed that the energies of the *n* orbitals of nitrogen in pyridine and pyrazine slightly exceed (by 0.01–0.1 eV) the energies of the upper π orbitals. This permits the assignment of the second ionisation potentials of pyridine and pyrazine, each of which is 9.51 eV, to the removal of an electron from the orbital of the unshared pair of nitrogen. Analysis of the ionisation potentials of azabenzenes also permits an interpretation of the upper ionisation potentials of pyridine on the basis of the calculation of the orbital energies by the SCF MO method. Thus the ionisation threshold at 10.45 eV may be attributed to the removal of an electron from the $2b_1$ π orbital or the upper σ orbital. Such assignment of the ionisation potentials of pyridine was not made in earlier studies on photoelectronic spectroscopy[10] and Rydberg absorption spectra[16], because the second ionisation potential at 9.51 eV had not been observed.

Information about the nature of the π and *n* orbitals in the ground state of pyridine and pyrazine was obtained by calculating all the wave functions for the molecules by the SCF MO method[44,45], based on the derivation of special Gauss functions.

It was shown that the upper $1a_2$ pyridine π orbital has a node at the nitrogen atom and an equal charge distribution at the carbon atoms. This property of the upper $1a_2$ π orbital is clearly reflected in the similarity of the first adiabatic ionisation potentials of pyridine and benzene and also in the fact that the substitution of hydrogen atoms by methyl groups in pyridine in different positions leads to a decrease of the first ionisation potential by virtually the same amount. For example, the ionisation potentials of methylpyridines are in the range 9.02–9.04 eV. Finally, it should be noted that there is a linear relation between the first ionisation potentials of pyridine derivatives and those of the corresponding benzene derivatives[10]. This correlation constitutes yet another proof that the first ionisation potential of pyridine corresponds to the removal of an electron from the upper π orbital with A_2 symmetry. The substitution of hydrogen atoms by alkyl groups leads to a decrease of the π-orbital energies owing to the inductive effect.

Data have also been obtained[44,45] on the nature of the orbitals of the unshared pairs of the nitrogen atoms in pyridine and pyrazine. The $11a_1$ orbital of the unshared pair of the nitrogen atom in pyridine is partially delocalised (to the extent of 0.6 charge units) over the carbon and hydrogen atoms. The unshared pairs of the nitrogen atoms in pyrazine are non-equivalent both in type and as regards energy. The upper $11a$ pyrazine n orbital is delocalised, as in pyridine, while the lower $10a_1$ orbital is only slightly delocalised. The determination of the relative energy of this orbital requires a further detailed examination of the photoelectronic spectrum and the photoionisation curve of pyrazine.

The interpretation of the ionisation potentials of azanaphthalenes was achieved on the basis of the first-order perturbation theory by an empirical selection of corrections to the orbital energies derived from the first ionisation potentials of naphthalene, quinoline, and isoquinoline, obtained from the photoelectronic structures of these compounds[42]. It was shown that the first ionisation potentials of quinoline, isoquinoline, quinoxaline, and quinazine correspond to the removal of an electron from the upper π orbital and the first ionisation potentials of phthalazine and cinnoline correspond to the removal of an electron from the upper n orbital of the unshared pair of the nitrogen atom. This conclusion is consistent with data on the photoionisation of quinoline, isoquinoline, quinoxaline, phthalazine, and cinnoline[41].

Gencha and El-Sayed[41] observed on the photoionisation curves of pyrazine and pyridine a vibrational level structure in the vicinity of the first ionisation potential and attributed it to the planar vibrations of the molecular ion (by analogy with the corresponding vibrations of these molecules in the ground state)[46,47]. However, these data require revision, since the first and second ionisation potentials of azabenzenes corresponding to the removal of an electron from the π and n orbitals are similar.

The ionisation potentials of acridine and phenazine, associated with the removal of an electron from the π and n orbitals, were obtained from the electronic absorption spectra of their complexes with iodine and chloranil[23,24,48]. Acridine and phenazine are n donors in relation to iodine and π donors in relation to chloranil. The ionisation potentials calculated from the absorption spectra and corresponding to the removal of an electron from the upper filled π orbital are 7.9 and 8.4 eV respectively.

It is interesting to note that the ionisation potentials of pyridine, quinoline, and acridine on the one hand and the energies of the π,π^* and n,π^* triplet levels are correlated. For example the energy of the excited n,π^* triplet level of pyridine exceeds by 0.3 eV the energy of the lower π,π^* triplet level[49,50] and the second ionisation potential of pyridine, corresponding to the removal of an electron from the n orbital of nitrogen, exceeds by 0.2 eV the first ionisation potential corresponding to the removal of an electron from the upper $1a_2$ π orbital. However, there is no such correlation between the ionisation potentials and the excitation energies of the singlet levels of azines of this type, because the energy of the n,π^* level is even lower than the energy of the π,π^* level. This discrepancy between the ionisation and excitation energies is due to the fact that the energy of the π,π^* level exceeds that of the n,π^* level by only 0.45 eV, while the singlet–triplet splitting of the π,π^* level of pyridine is 1.1 eV, exceeding the singlet–triplet splitting of the n,π^* level by 0.75 eV.

3. Compounds with a Carbonyl Group

The first ionisation potentials of aromatic compounds containing a carbonyl group were determined in a number of studies[7,12,28,51] (Table 7).

Table 7. First photoionisation potentials of aromatic compounds containing the groups $>N-$, $-O-$, $-S-$, and $>C=O$.

Compound	Ionisation potential, eV	Refs.	Compound	Ionisation potential, eV	Refs.
p-Benzoquinone	9.95	12	Pyrrole	8.20±0.01	7.56
9,10-Anthraquinone	9.34±0.03	28		8.22	10**
	9.55	51***	*N*-Methylpyrrole	8.09±0.01	56
Fluorenone	9.42	51***	*N*-n-Butylpyrrole	7.87±0.02	56
Benzaldehyde	9.55±0.03	28	2-Methylpyrrole	7.78±0.1	56
	9.53±0.03	7	3-Methylpyrrole	7.90±0.02	56
Acetophenone	9.27±0.03	7	2,4-Dimethylpyrrole	7.54±0.02	56
Acridone	7.60±0.03	6	Furan	8.89±0.01	7
N-Methylacridone	7.53±0.03	6	2-Methylfuran	8.39±0.01	7
N-Ethylacridone	7.49±0.03	6	Furfural	9.21±0.01	7
N-Phenylacridone	7.46±0.03	6	Thiophen	8.86±0.01	7
Phenothiazine	7.7	21	2-Chlorothiophen	8.86±0.01	7
	7.62	18*	2-Bromothiophen	8.63±0.01	7
9,10-Dihydroacridine	7.24±0.03	6			

* Spectroscopy.
** Photoelectronic spectroscopy.
*** Electron impact.

It has been shown[51] that the first ionisation potential of 9,10-anthraquinone (9.55 eV) corresponds to the removal of an electron from the orbital of the unshared pair of oxygen and the second ionisation potential (10.24 eV) corresponds to the removal of an electron from the π orbital. The energy of the singlet π,π^* level of anthraquinone is higher than the energy of the n,π^* level by an amount close to the difference between the second and first ionisation potentials. There is a similar correlation also between the ionisation potentials of 9,10-anthraquinone and the energies of the triplet n,π^* and π,π^* levels[52]. This assignment of the ionisation potentials is consistent with the calculation for the 9,10-anthraquinone molecules by the Pariser–Parr–Pople method[53]. It has also been shown[53] that the first ionisation potentials of *p*-benzoquinone (9.95 eV) and benzaldehyde (9.55 eV) corresponds to the removal of an electron from the orbital of the unshared electron pair of the oxygen atom in the carbonyl group. This interpretation of the ionisation potentials agrees with the positions of the lower electronic singlet and triplet levels of *p*-benzoquinone and benzaldehyde[54].

4. Heterocyclic Compounds containing the Groups $>$N–, –O, and –S–

The unshared electron pair of the heteroatom (nitrogen, oxygen, and sulphur) in compounds of this type may be incorporated in the π-electron system of the molecule, and leads to a change of the nature of the π orbitals in the ground state and an appreciable splitting of the upper π levels of the molecules.

The question of the nature and relative positions of the electronic levels of pyrrole, furan, and thiophen remained unresolved for a long time until the studies on photoionisation and photoelectronic spectroscopy[10].

The first ionisation potentials of pyrrole, furan, and thiophen (Table 7) were determined by the photoionisation method and attributed to the removal of electrons from the π orbitals[7]. The upper ionisation potentials of pyrrole and furan have also been investigated by Turner[10] (Table 6).

The interaction of the unshared electron pair of the nitrogen atom with π electrons in the pyrrole molecule is fairly pronounced, which leads to the removal of the degeneracy of the π_3 and π_2 orbitals and the separation of their energies by 0.8 eV (Table 2). On this basis, one may assume that the π-electron system of pyrrole consists of three filled $1a_2$, $2b_1$, and $1b_1$ π orbitals. The first and second ionisation potentials of pyrrole (8.22 and 9.03 eV) correspond to the removal of electrons from the $1a_2$ and $2b_1$ orbitals.

Information on the nature of the π orbitals of pyrrole from which electrons are removed on ionisation and about the distribution of electron density at the carbon, hydrogen, and nitrogen atoms was obtained from the calculation of all the wave functions of pyrrole by the SCF MO method[55]:

Distribution of π electron density in pyrrole.

Atom in five-membered ring	$1a_2\pi$ orbital	$2b_1\pi$ orbital	$1b_1\pi$ orbital
N $(2p_z)$	—	0.76	0.9
$C_2(2p_z) \pm C_5(2p_z)$	1.40	0.03	0.72
$C_3(2p_z) \pm C_4(2p_z)$	0.60	1.21	0.38

The upper $1a_2$ π orbital, the energy of which corresponds to the first ionisation potential, has an electron density node at the nitrogen atom and a maximum at the adjacent carbon atoms (1.40). The second, $1b_1$ π orbital has an electron density node between the nitrogen atom and the centre of the molecule, a maximum at the carbon atoms not linked to the nitrogen atom, and a minimum at the nitrogen atom. The lower $1b_1$ π orbital of pyrrole embraces the entire molecular skeleton and has an electron density maximum at the nitrogen atom. Analysis of the wave functions also shows that the nitrogen atom in pyrrole "loses" 0.34 charge units to the π orbital and "acquires" 0.75 charge units from the σ orbital. Trigonal hybridisation in pyrrole is appreciably modified for nitrogen ($s^{1.37}p^{2.38}$) but for carbon remains virtually unchanged ($s^{1.06}p^{2.10}$).

It is interesting to compare data on the distribution of electron density in pyrrole with the changes in the first ionisation potential corresponding to the removal of an electron from the $1a_2$ orbital on substitution of a hydrogen atom by a methyl group in various positions, determined by the present author and Yuzhakova[56]. Table 7 shows that the maximum decrease of the first ionisation potential (by 0.42 eV compared with the first ionisation potential of pyrrole) is observed for 2-methylpyrrole, i.e. on substitution of the hydrogen atom by a methyl group at the carbon atom adjoining the nitrogen atom; at this carbon atom the $1a_2$ π orbital has a maximum electron density. The minimum change of the first ionisation potential is observed on substitution of the hydrogen atom by a methyl group at the nitrogen atom, where the $1a_2$ π orbital has an electron density node (*N*-methylpyrrole). Naturally, the replacement of a hydrogen atom by an n-butyl group does not lead to an appreciable decrease of the first ionisation potential (*N*-n-butylpyrrole).

In furan the separation of the energies of the π_3 and π_2 orbitals is even greater than in pyrrole (1.44 eV) (Table 6). The energy of the unshared pair of oxygen, which does not participate in the conjugation with the π electron system, exceeds the energies of the upper π orbitals[10].

Earlier it was noted that a characteristic feature of the electronic structure of anthraquinone is that the upper level of the ground state is populated by the unshared electron pair of the oxygen atom in the carbonyl group[51]. However, the nature and relative positions of the *n* and π electronic levels in the ground state change significantly on introduction of an amino-group into the conjugated system, which happens in acridone and its derivatives. The electronic spectra of acridone and its derivatives show that the first long-wavelength absorption band in their spectra corresponds to the ($\pi\pi^*$) electron transition and that the unshared electron pair of the amino-group participates in the exchange interaction with the electrons in the π orbitals[57].

The first ionisation potentials of acridone, *N*-methylacridone, *N*-ethylacridone, and *N*-phenylacridone (Table 7) are in the range of energies 7.6–7.46 eV and correspond to the energies of the removal of electrons from the upper π orbitals. Indeed the exchange interaction of the unshared electron pair of nitrogen with the π electrons of the molecule leads to an appreciable (compared with anthraquinone) rise of the upper π level of acridone and its derivatives, i.e. a decrease of the ionisation potential. It is necessary to remember that the energy of the nonbonding orbital of the oxygen atom in the carbonyl group changes little when the dimensions and the nature of the π-electron system are altered.

The insignificant change in the first ionisation potentials in this series is evidence that the position of the upper π level alters little under these conditions. The fact that the ionisation potential of *N*-phenylacridone is close to those of [other] acridone derivatives suggests in turn that the phenyl group is located outside the plane of the molecule.

The removal of an electron from the upper π orbital of 9,10-dihydroacridine, where there is no carbonyl group, requires a somewhat lower energy (0.2–0.3 eV) compared with *N*-alkyl derivatives of acridone. The closeness of the ionisation potentials of 9,10-dihydroacridine and diphenylamine[35] is evidence that the π-electron systems of these molecules are isoelectronic.

Phenothiazine, the first ionisation potential of which is also associated with the removal of an electron from the upper π orbital[11], should be included in this type of heterocyclic compounds, where the heteroatom supplies two nonbonding electrons to the π-electron system. A characteristic feature of the photoionisation curve of phenothiazine at higher energies is a steep rise in the region of 9.15 eV, corresponding to the second ionisation potential of the molecule.

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Thus the above analysis of the ionisation potentials of aromatic compounds permits definite conclusions concerning the nature and positions of the electronic levels of the molecules from which electrons are removed on ionisation.

The electronic structure of aromatic compounds containing heteroatoms outside the ring, the unshared electron pair of which is incorporated in the π-electron system (aniline and its derivatives, alkyl phenyl ethers), is characterised by the presence of four π orbitals. The energies of the upper π_3 and π_2 orbitals of compounds of this type are separated (compared with benzene), mainly due to the decrease of the energy of the π_3 orbital with B_1 symmetry (Figs. 6 and 7). The mass spectra of these compounds reveal their relative stability on ionisation. However, in those cases where the conjugation between the unshared electron pair of the heteroatom and the π electrons of the phenyl group is weak (for example in benzylamine), the stability of the molecules decreases owing to their decomposition into ions and radicals.

A characteristic of the structure of heterocyclic compounds, the π-electron system of which includes an unshared electron pair (pyrrole, furan) is that the upper electronic level in the ground state of molecules of this type corresponds to the π orbital with A_2 symmetry, which has an electron density node at the heteroatom. This type of upper π orbitals is clearly revealed by the different first ionisation potentials of pyrrole and its derivatives.

The ionisation potentials of nitrogen-containing heterocyclic compounds (azines), in which each heteroatom supplies one p-electron to the π-electron system, correspond to the removal of an electron from the upper π orbitals. Pyrimidine, pyridazine, phthalazine, and cinnoline, the first ionisation potentials of which correspond to the removal of an electron from the orbitals of the unshared electron pair of the nitrogen atom, are an exception.

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Metal† Hydrogen Fluorides

A.A.Opalovskii and T.D.Fedotova

The review deals with the available information on metal hydrogen fluorides. The methods of synthesis of hydrogen fluorides and their physical and chemical properties are examined and studies on the hydrogen bonds in hydrogen fluorides and their structures are discussed. The principal trends in the research in this field have been outlined on the basis of these data.

The bibliography includes 190 references.

CONTENTS

I. INTRODUCTION

Fluorine is a very reactive element and forms compounds with all other elements. Its high electronegativity and small ionic radius are largely responsible for the wide variety of the properties of fluorine-containing compounds and their large number. Among fluorine compounds one may mention interesting classes of substances such as halogen compounds of fluorine[1-4] and noble gas fluorides[5-7], the development of the studies of which is related to the general advances in the chemistry of inorganic fluorides achieved in the last decades.

Since fluorine is known to form numerous complex compounds in which it behaves as the ligand[8,9], it is interesting to examine the interaction of inorganic fluorides with fluorine-containing solvents. Among these mention should be made in the first place of hydrogen fluoride, the specific properties of which are the reason for the increasing interest in it as a solvent[9].

The high dielectric constant and low viscosity of hydrogen fluoride make it a good ionising solvent. It is an associated liquid and its self-ionisation takes place via the mechanism[10]

$$(HF_m)\xrightarrow[+]{F^-}(HF)_n\rightleftarrows H_mF^+_{m-1}+H_nF^-_{n+1}\,.$$

The equilibrium constant for this process at 0°C [9] is 2.07×10^{-11}.

Reactions in anhydrous hydrogen fluoride normally involve the participation of the solvent itself. The unusual properties of hydrogen fluoride are responsible for the wide variety of compounds formed when fluorides react with hydrogen fluoride and its solutions[11].

A characteristic feature of the reaction of many fluorides with anhydrous hydrogen fluoride is their solvation by HF molecules. This process is not characteristic solely of hydrogen fluoride but occurs also with halogen compounds of fluorine, for example. Thus it is known

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† Including ammonium hydrogen fluorides (Ed. of Translation).

that these compounds undergo self-ionisation in the liquid state[12-15]:

$$2XF_n \rightleftarrows XF^+_{n-1} + XF^-_{n+1}$$

and numerous studies in recent years have shown that their interaction with many inorganic fluorides is due to the presence of the above ions in solution and the formation of the fluorohalogenates MXF_{n+1} ($MF.XF_n$) can itself be regarded as the solvation of fluorides by the halogen fluoride[16,17].

The solvating capacity of hydrogen fluoride is well illustrated by the data of Jache and Cady[18], who established that highly soluble fluorides exhibit a greater capacity for combining with hydrogen fluoride. However, they quote only the approximate composition of the solid phase in the saturated solutions of fluorides in hydrogen fluoride after centrifugation and therefore their results cannot be regarded as final proof of the existence of definite solvates as individual compounds.

The most complete information about processes involving the solvation of inorganic fluorides by hydrogen fluoride was obtained by the physicochemical analysis of binary and ternary systems containing hydrogen fluoride and metal fluorides. The results of studies on fusion diagrams for $HF-MF_m$ systems and on isothermal solubility in $HF-MF_m-H_2O$ systems indicate the formation in such systems of individual compounds with the composition $MF_m.nHF$, which are called the acid fluorides or hydrogen fluorides of the corresponding elements.

The formation of metal hydrogen fluorides in anhydrous hydrogen fluoride may be explained as follows. Hydrogen fluoride is an extremely active acidic solvent and ionic fluorides are strong bases in relation to HF, since they dissociate in it with formation of fluoride ions[19]. This leads to a displacement of the self-ionisation equilibrium of hydrogen fluoride towards the formation of the polymeric anions $H_nF^-_{n+1}$, which combine with metal cations to form metal hydrogen fluorides. It is noteworthy that the high tendency of hydrogen fluoride to solvate the F^- anion is due to the fact that the fluorides of many metals are dissociated in hydrogen fluoride to a greater extent than their hydroxides in water, although the dielectric constants of the two solvents are similar[20]. From this point of view, it becomes understandable why metal hydrogen fluorides are formed primarily by univalent and divalent metals, the dissociation of the fluorides of which in hydrogen fluoride differs from that of the fluorides of polyvalent elements, which exhibit molecular solubility in hydrogen fluoride[21,22] or have acidic properties in this solvent, i.e. behave as acceptors of fluoride ions[23,24].

The formation of metal hydrogen fluorides is also possible in aqueous solutions of hydrogen fluoride since here there is a possibility of an autocomplex-formation process:

$$H_2O + (n+1)\ HF \rightleftarrows H_3O^+ + H_nF^-_{n+1}\ .$$

The number of HF molecules added to the metal hydrogen fluorides formed increases as the concentration of water in the solution falls.

It is interesting to note that solvation by hydrogen fluoride is observed not only for simple fluorides but is also characteristic of certain complex fluorides, provided that they are stable in anhydrous hydrogen fluoride and its highly complicated solutions. Thus in a study of ternary systems of the type $HF-H_2MF_6-H_2O$ (M = Ge or Sn) it was established that rubidium, caesium, and ammonium hexafluorogermanates and rubidium and caesium hexafluorostannates form the solid solvates $H_2MF_6.nHF$. [25-27]

The first studies on metal hydrogen fluorides were undertaken primarily in connection with their practical applications. The most important application of these compounds is in the preparation of fluorine by electrolysis. This method, used in 1886 by Moissan[28]. was subsequently developed and improved and is now the main industrial procedure for the manufacture of elemental fluorine, since it yields this important chemical industrial product in a fairly pure form and in a high yield[29-31]. Among other examples of the application of metal hydrogen fluorides, mention should be made of the use of potassium hydrogen difluoride for the preparation of pure anhydrous hydrogen fluoride[32-34]. Sodium hydrogen difluoride has found extensive application for the synthesis of anhydrous hydrogen fluoride from aqueous solutions[35] and for the elimination of hydrogen fluoride from fluorine in the industrial process[29,30].

The studies on metal hydrogen fluorides are of interest from the standpoint of the development of our knowledge of fluorine chemistry, since they are associated with important theoretical problems concerning the mechanism of the solvation of fluorides by fluorine-containing solvents, the structure of metal hydrogen fluorides, and the nature of their chemical bonds.

However, so far the only reviews of studies on metal hydrogen fluorides are restricted to chapters in monographs by Simons[36] and Ryss[8]. The publications which have appeared in the last 10–15 years on this problem and also the general progress in the development of the chemistry of inorganic fluorides make it possible in many cases to reassess the value of the earlier investigations and to draw new conclusions and generalisations. This review deals with the data available at present on the methods for the synthesis of metal hydrogen fluorides and their physical and chemical properties, structure, and the nature of their chemical bonds and the prospects of further research in this field of chemistry are discussed. The problems of the industrial utilisation of metal hydrogen fluorides are not considered, since they are dealt with in the specialist literature.

II. SYNTHESIS OF METAL HYDROGEN FLUORIDES

The first communication on the synthesis of alkali metal hydrogen fluorides was by Berzelius[37], who obtained lithium, sodium, and potassium hydrogen difluorides by dissolving the corresponding fluorides in hydrofluoric acid, and ammonium hydrogen difluoride by heating an aqueous solution of the fluoride. Later potassium hydrogen difluoride was synthesised by Fremy[38] from potassium carbonate and a hydrofluoric acid solution and became known as the Fremy salt. Borodin obtained NaF.HF and KF.HF by evaporating solutions of the fluorides in organic acids[39].

Moissan[40] synthesised compounds with the composition KF.2HF and KF.3HF from a solution of potassium hydrogen difluoride in anhydrous hydrogen fluoride. An attempt was made to obtain potassium hydrogen fluoride with the formula $KF.nHF$ by evaporating KF.HF solutions in hydrofluoric acid, but this yielded only KF.2HF contaminated with K_2SiF_6. [41]

The synthesis of the rubidium hydrogen fluorides RbF.HF and RbF.2HF mixed with RbF.3HF was first reported by Eggeling and Meyer[42]. However, subsequent investigations[43,44] showed that the compounds obtained by

Eggeling and Meyer[42] are in fact rubidium hexafluorosilicates; Eggeling and Meyer[42] described the synthesis of RbF.2HF containing a small admixture of Rb_2SiF_6 from a solution of rubidium carbonate in 40% hydrofluoric acid. Webb and Prideaux[41] described the synthesis of the hydrogen fluorides RbF.HF and RbF.2HF from a solution of rubidium fluoride in hydrofluoric acid and of RbF.3HF from anhydrous hydrogen fluoride.

The following acid salts have been reported for caesium fluoride: CsF.HF,[45] CsF.1.5HF, and CsF.2HF (approximate composition)[46], which were synthesised from anhydrous hydrogen fluoride.

According to a number of communications, silver(I) fluoride also forms acid salts. Thus Guntz[47] described the preparation of AgF.HF from a solution of AgF in hydrofluoric acid. A silver hydrogen fluoride with the composition AgF.3HF is formed in hydrofluoric acid solution and also when gaseous hydrogen fluoride acts upon dry silver fluoride at 13°C. [21,48]

In addition to the hydrogen difluoride[49], the acid fluorides with the composition TlF.2HF [50] and $TlF.2HF.0.5H_2O$ [51] were obtained for thallium(I), but subsequently it was shown that the latter compound is a hexafluorosilicate[52].

All the investigations enumerated above were concerned with the synthesis of the hydrogen fluorides of univalant metals, the fluorides of which are readily soluble in hydrogen fluoride and its solutions.

Until recently the acid salts of the fluorides of other metals, much less soluble in hydrogen fluoride, were almost unknown. Only barium hydrogen fluoride $BaF_2.HF$ was obtained[53] and the existence of the compound $PbF_2.2.5HF$ on the basis of vapour pressure data[54] for the $HF-PbF_2$ system was suggested. The reports of the existence of the acid fluorides $CaF_2.2HF.6H_2O$ [55] and $MF_2.5HF.6H_2O$ (M = Cu, Ni, Co, or Mn) [56] proved to be erroneous; the substances obtained were in fact hexafluorosilicates[57,58]. The earlier report of the synthesis of zinc hydrogen fluoride from a solution of the fluoride in hydrofluoric acid is also doubtful[59].

Although the existence of compounds with the composition $MF_m.n HF$ has been known for a long time and the publications quoted above include reports of their synthesis, it should be noted that a considerable proportion of these data are doubtful. This is mainly due to the fact that the experimental technique available at the time did not allow the early investigators to obtain the hydrogen fluorides in a pure state. As admitted by the authors themselves, the majority of the compounds synthesised contained an admixture of hexafluorosilicates or metal hydrogen fluorides of another composition. Moreover, the individuality of the hydrogen fluorides obtained was established in most cases only on the basis of chemical analysis, which gives rise to particular doubts concerning the composition of the compounds quoted, since most metal hydrogen fluorides are unstable even at room temperature and lose the combined HF molecules. This may also be reflected by the finding that certain physical constants of metal hydrogen fluorides of the same composition differ in various investigations.

The application of the methods of physicochemical analysis to the study of the interaction of metal fluorides with hydrogen fluoride and its solutions yielded accurate information about the composition and conditions of synthesis of metal hydrogen fluorides.

The first studies in this field were those of the fusion diagrams by Ruff and Staub[60] for the system $HF-NH_3$ and by Cady[61] for the system HF–KF. Later the corresponding binary systems with rubidium and caesium fluorides were investigated[62,63]. The results obtained indicate the formation in the HF–MF system of the following individual hydrogen fluorides: KF.nHF (n = 1, 2, 2.5, 3, or 4), RbF.nHF (n = 2, 3, 3.5, or 4.5), CsF.nHF (n = 1, 2, 3, or 6), and $NH_4F.n HF$ (n = 1, 2, 3, or 5). Subsequently the data on the $HF-NH_3$ system were significantly revised by Euler and Westrum[64], who reject the existence of the compound $NH_4F.2HF$.

Tananaev's studies[65–67] by isothermal solubility of the ternary systems $HF-MF-H_2O$ (M = Li, Na, or K) were an important stage in the investigation of methods for the synthesis of metal hydrogen fluorides. The value of his results consists in the fact that the possibility of synthesising a whole series of sodium and potassium hydrogen fluorides, NaF.nHF (n = 1, 2, 3, or 4) and KF.nHF (n = 1, 2, 2.5, 3, or 4) from aqueous hydrogen fluoride solutions was demonstrated, which has undoubted advantages compared with the use of anhydrous hydrogen fluoride. The formation of the hydrogen difluoride LiF.HF in the $HF-LiF-H_2O$ system (investigated up to 75% HF) was established, but, because of the slowness of the reaction LiF → LiF.HF in the solid phase, it was recommended that lithium hydrogen difluoride be obtained by crystallisation from a saturated solution of LiF in hydrofluoric acid[65].

In a subsequent reinvestigation of the $HF-NaF-H_2O$ system[68] and part of the HF–NaF system[69], metal hydrogen fluorides were obtained whose composition was similar to that established previously[66].

Further investigations of systems of the type $HF-MF-H_2O$ were undertaken by the authors of this review. In a study of the highly concentrated region of the $HF-LiF-H_2O$ system, including anhydrous hydrogen fluoride, we did not observe any phase transformations of lithium hydrogen difluoride, although its solubility increased appreciably[70]. The results of the study of the $HF-RbF-H_2O$ and $HF-CsF-H_2O$ systems over the entire range of HF concentrations showed that the interaction in these systems leads to the formation of metal hydrogen fluorides with the composition RbF.nHF (n = 1, 2, 3, or 3.5) and CsF.nHF (n = 1, 2, or 3) [71]. In the $HF-CsF-H_2O$ system we did not observe compounds with compositions intermediate between CsF.HF and CsF.2HF, as in the HF–CsF system[63]. Evidently the report of the synthesis of the caesium hydrogen fluoride with the composition CsF.1.5HF is erroneous and Mathers and Stroup[46] must have obtained a mixture.

In a study of the $HF-NH_4F-H_2O$ system, hydrogen fluorides with the compositions $NH_4F.HF$ and $NH_4F.3HF$ were found as the solid phases[72]. The acid salts 3AgF.2HF, AgF.HF, AgF.2HF, AgF.3HF, and AgF.5HF as well as a compound with the somewhat unexpected composition $6AgF.7HF.2H_2O$ were obtained for silver fluoride in the ternary system[23].

The results of studies on binary and ternary systems containing alkali fluorides and hydrogen fluoride reveal certain general features of the solvation of these fluorides by HF molecules and the formation of metal hydrogen fluorides. The solubility of alkali metal fluorides and their capacity for solvation in hydrogen fluoride increase with the ionic radius of the cation, which is evidently due to the decrease of their crystal lattice energy on passing from LiF to CsF. The maximum number of HF molecules added to caesium fluoride is six, while for lithium only the hydrogen difluoride LiF.HF is known. The solubility of ammonium fluoride in hydrogen fluoride also obeys the above relation. The formation by NH_4F of hydrogen fluorides with a larger number of combined HF molecules than in the case of rubidium fluoride can probably be accounted for by its capacity to form hydrogen bonds of two types: F–H... F and N–H... F.

Bearing in mind the ionic radius of Ag^+, silver(I) fluoride should occupy in the above series a position intermediate between the fluorides of sodium and potassium, but this is not observed, which may be due to different electronic structures of alkali metal and silver cations.

A marked tendency towards solvation would be expected for thallium fluoride, which has the highest solubility in hydrogen fluoride among univalent fluorides. However, the corresponding systems with thallium fluoride have not been investigated and therefore the problem remains unelucidated; at the present time hydrogen fluorides other than TlF.HF and TlF.2HF are unknown.

The possibility of synthesising alkaline earth metal hydrogen fluorides from aqueous hydrofluoric acid solutions was previously considered unlikely[8], although the data of Jache and Cady[18] indicated a tendency by these fluorides to combine with HF. In a study of the $HF-MF_2-H_2O$ systems (M = Ca, Sr, or Ba), Nikolaev and Ikrami[11] obtained metal hydrogen fluorides with the following compositions: $CaF_2.2HF$, $SrF_2.nHF$ (n = 1, 2, or 2.5), and $BaF_2.nHF$ (n = 1, 3, or 4.5). Lead(II) fluoride behaves in hydrogen fluoride and its solutions similarly to alkaline earth metal fluorides, the formation of $PbF_2.2.5HF$ having been established in the $HF-PbF_2-H_2O$ system[74].

The interaction of alkaline earth metal and lead fluorides with hydrogen fluoride obeys the same relation as a function of the ionic radius of the cations as for alkali metal fluorides, the only exception being the anomalously high solubility of strontium fluoride in anhydrous hydrogen fluoride. Comparison of the results of the studies on the $HF-MF_2-H_2O$ (M = Ca, Sr, Ba, or Pb) systems shows that the formation in them of the metal hydrogen fluoride begins as a rule at a higher HF concentration in solution than for univalent metal fluorides, evidently because of the greater stability of the MF_2 crystal lattice.

Recent studies on the $HF-MF_2-H_2O$ (M = Cu, Zn, Cd) systems[75,76] showed that, despite their very low solubility in anhydrous hydrogen fluoride and its concentrated solutions, the fluorides of copper, zinc, and cadmium also form the hydrogen fluorides $CuF_2.3HF$, $ZnF_2.2HF$, and $CdF_2.HF$. This suggests that the hydrogen fluorides of other divalent metals whose fluorides are sparingly soluble in hydrogen fluoride, such as HgF_2, MnF_2, etc., may also be obtained.

We may note that the studies on the systems $HF-UF_4-H_2O$ [77] and $HF-ThF_4-H_2O$ [78], where the fluorides are sparingly soluble over the entire range of concentrations of hydrogen fluoride, established the formation in the solid phase of compounds with the composition $UF_4.4HF$, $ThF_4.HF.H_2O$, and $ThF_4.4HF$, but the properties of these compounds were not investigated and their nature has not been elucidated.

In conclusion of the discussion of the methods for the synthesis of metal hydrogen fluorides, we may note that they reduce to the reaction between the fluorides and a solution of hydrofluoric acid (the conditions of synthesis are determined by the $HF-MF_m-H_2O$ solubility isotherm) or anhydrous hydrogen fluoride (the conditions are determined by the $HF-MF_m$ fusion diagram). One may also point out the possibility of the synthesis of these compounds by the thermal decomposition of metal hydrogen fluorides with a higher HF content. The principal data at present available on the solvation of fluorides by hydrogen fluoride are compiled in Table 1.

Table 1. Solvation of uni- and divalent-metal fluorides by hydrogen fluoride.

Fluoride	Radius of cation according to Belov and Bokii Å	Solubility in anhydrous HF at 0°C wt.%	No. of moles of HF in $MF_m.nHF$	Fluoride	Radius of cation according to Belov and Bokii Å	Solubility in anhydrous HF at 0°C wt.%	No. of moles of HF in $MF_m.nHF$
LiF	0.68	9.36	1	CaF_2	1.04	1.05***	2
NaF	0.98	21.79	1; 2; 3; 4	SrF_2	1.20	12.76***	1; 2; 2.5
KF	1.33	27.68	1; 2; 2.5; 3; 4	BaF_2	1.28	4.52***	1; 3; 4.5
RbF	1.49	56.50	1; 2; 3; 3.5; 4.5	PbF_2	1.26	3.40	2.5
CsF	1.65	66.60	1; 2; 3; 6	CuF_2	0.80	0.008	3
NH_4F	1.43*	29.04	1; 3; 5	ZnF_2	0.83	0.02	2
AgF	1.13	38.20	0.66; 1; 2; 3; 5	CdF_2	0.99	0.20	1
TlF	1.36	81.80**	1; 2				

* According to Goldschmidt.

** –7.8°C.

*** –3.3°C.

Hitherto it has not proved possible to obtain hydrogen fluorides containing two different metals as the cations. In principle their existence might be established by studying the corresponding binary or ternary systems.

The study of isothermal solubility in systems of the type HF–MF–M′F (M and M′ are alkali metals)[70] showed that they contain as solid phases the hydrogen fluorides of the same composition as in the HF–M(M′)F systems, the compound less soluble in hydrogen fluoride occupying a wide crystallisation field. Solid solutions and binary compounds are not formed in the systems. The type of interaction in them is determined primarily by the difference between the solubilities of the fluorides in HF and their different capacities for solvation.

III. PROPERTIES OF METAL HYDROGEN FLUORIDES

Metal hydrogen fluorides are white crystalline substances. The pyknometric densities of alkali metal hydrogen difluorides[79] and alkaline earth metal hydrogen fluorides[80] have been determined (Table 2).

The solutions of all metal hydrogen fluorides in water are acidic. The hydrogen difluorides of all alkali metals (except LiF.HF) and ammonium and also KF.2HF (at 40°C), RbF.2HF, CsF.2HF, and RbF.3HF are congruently soluble in water, which follows from the results of an investigation of the isothermal solubilities in the systems[65-67,68,71]. The solubilities of sodium, potassium, and ammonium hydrogen difluorides in water increase with temperature[66,67,81-83]. Hydrogen difluorides are insoluble in ethanol[84]. The isotherms for the ternary systems $H_2O-KCl-KHF_2$,[85] $H_2O-NH_4Cl-NH_4HF_2$,[86] and $H_2O-NH_4F-NH_4HF_2$ [87] are of a eutonic type.

The enthalpies of solution of alkali metal and ammonium hydrogen fluorides in water were determined for the first time by Peterson[88], Guntz[89], and de Forcrand[90], the data being revised subsequently[91,92] (Table 3). The standard entropy of the HF_2^- ion (16 cal mole^{-1} deg^{-1}) found by Cox and Harrop[91] differs from the value calculated previously (26 cal mole^{-1} deg^{-1}) [93]. The enthalpies of solution of the hydrogen fluorides $NH_4F.HF$ and $NH_4F.3HF$ in anhydrous hydrogen fluoride have also been determined (−5.76 and −3.35 kcal mole^{-1} respectively[94]).

The thermal properties of hydrogen fluorides are of interest primarily in connection with their practical applications; they have been most thoroughly investigated for alkali metal and ammonium hydrogen fluorides.

Table 2. Pyknometric densities of metal hydrogen fluorides.

Compound	d_{25}, g cm^{-3}	Compound	d_{25}, g cm^{-3}
LiF·HF	2.05±0.01	BaF_2·HF	4.603±0.004
RbF·HF	3.1±0.2	CaF_2·2HF	2.613±0.004
CsF·HF	3.7±0.2	SrF_2·2.5HF	3.068±0.004
TlF·HF	6.3±0.3	BaF_2·3HF	3.56±0.01
SrF_2·HF	3.999±0.004	BaF_2·4.5HF	2.947±0.004

The melting points of alkali metal fluorides determined in the early studies are in most cases erroneous, owing to the presence of impurities in the test compounds and the deviation of their compositions from stoichiometry. Thus the following melting points were found initially: 227°C [95], 215−225°C [96], and 217°C [97] for potassium hydrogen difluoride, 142°C [46] for caesium hydrogen difluoride, and 105°C [40] and 70°C [98] for KF.2HF. Later the melting points of the hydrogen fluorides were determined with greater accuracy from a study of the fusion diagrams[61−64]. Comparison of these values (Table 4) shows that the melting points of alkali metal hydrogen fluorides decrease from sodium to caesium and with increase in the number of HF molecules combined.

Table 3. Enthalpies of solution of hydrogen fluorides in water (298.16°K).

Compound	LiF·HF	NaF·HF	KF·HF	RbF·HF	CsF·HF	NH_4F·HF	AgF·HF	KF·2HF	KF·3HF
$-\Delta H°$, kcal mole^{-1}	18.60	6.2	6.0	5.31	3.73	4.85	2.0	8.0	8.6

The sodium hydrogen fluoride NaF.3HF melts incongruently[69]. According to Cady's data[61], all the potassium hydrogen fluorides melt congruently. However, in a recent paper[99] it is claimed, on the basis of a thermodynamic calculation for the decomposition reactions of the hydrogen fluorides formed as individual compounds in the HF−KF system[61], that compounds with the composition KF . 2.5HF and KF.3HF exist only in the solid state and on fusion decompose according to the mechanisms

$$2K_2H_5E_7 \rightarrow 3KH_2F_3 + KH_4F_5; \quad 2KH_3F_4 \rightarrow KH_4F_5 + KH_2F_3 .$$

The enthalpies and entropies of fusion of potassium hydrogen difluoride have been determined as 1.582 ± 0.003 kcal mole^{-1} and 3.09 ± 0.01 cal mole^{-1} deg^{-1} respectively[100,101]. The properties of potassium hydrogen fluoride melts have been investigated by a number of workers in connection with their use in the manufacture of elemental fluorine. It has been established that the addition to the hydrogen fluorides KF.HF and KF.2HF of lithium and sodium fluorides appreciably lowers the melting points despite their low solubility in the melts[61,102,103]. The viscosities and densities of KF−HF melts and the effect of the addition of lithium fluorides on them have been investigated[104].

Table 4. Melting points of hydrogen fluorides.

Compound	M.p., °C	Compound	M.p., °C
NaF·3HF	60,5	RbF·3.5HF	34—40
NaF·4HF	39.8	RbF·4.5HF	23.0
KF·HF	238.7	NH_4F·HF	126.3
KF·2HF	71.7	NH_4F·3HF	23.4
KF·2,5HF	64,3	NH_4F·5HF	−8.2
KF·3HF	65,8	CsF·HF	176.0
KF·4HF	72.0	CsF·2HF	50.2
RbF·HF	204—205	CsF·3HF	32.6
RbF·2HF	51.7	CsF·6HF	−42.3
RbF·3HF	45.0		

On the basis of a study of the densities and viscosities of HF−NH_4F melts, Semerikova and Alabyshev[104] suggested that the electrolytic dissociation of ammonium hydrogen fluorides takes place differently from metal hydrogen fluorides: ammonium hydrogen fluorides are dissociated to only a slight extent, they merely promote the dissociation of hydrogen fluoride. Sudarikov et al.[105], who investigated the $NH_4F-NH_4HF_2$ and $NH_4HF_2-KHF_2$ systems and determined the enthalpies of fusion of NH_4HF_2, disagree with this view on the mechanism of the dissociation of $NH_4F.nHF$. They believe that ammonium hydrogen difluoride dissociates in the melt according to the mechanism $NH_4HF_2 \rightleftharpoons HF_2^- + NH_4^+$, i.e. in the same way as metal hydrogen difluorides, and that the mechanism put forward by Semerikova and Alabyshev[104] is incorrect. The enthalpy of fusion of ammonium hydrogen difluoride is 15.68 kcal mole^{-1} [106]. The entropy of fusion of the hydrogen fluoride $NH_4F.3HF$ has been determined as 16 cal mole^{-1} deg^{-1}.[64]

The studies on the thermal stability of metal hydrogen fluorides are concerned mainly with alkali metal hydrogen difluorides. Wartenberg and Bosse[107] quote the following temperatures of the rapid decomposition of hydrogen difluorides:

LiF · HF	NaF · HF	KF · HF	RbF · HF	CsF · HF
210°	270°	310—440°	500—600°	550—670° .

The following decomposition temperatures have been indicated for lithium hydrogen difluoride: 105°C [108] and 27°C [65]. A more accurate value of the decomposition temperature of LiF.HF (129.5°C) was determined by measuring the temperature variation of the vapour pressure of HF over LiF.HF (36−118°C) [79]. According to Cox and Harrop[91], at 25°C the vapour pressure of HF over LiF.HF is 1.89 mmHg. The thermodynamic functions for the dissociation of LiF.HF were determined also in the last two studies (Table 5).

The vapour pressure of HF over sodium hydrogen difluoride has been investigated by numerous workers by various methods in connection with the use of sodium fluoride as an absorber of hydrogen fluoride in many technological processes. Equations have been obtained for the temperature variation of the vapour pressure of HF and the enthalpy of decomposition of sodium hydrogen difluoride has been determined[109-113]. ΔH_{decomp} for NaF.HF was also calculated from the results of calorimetric measurements[113,114] (Table 6). The decomposition temperature of sodium hydrogen difluoride is 278°C [111]. The entropy change in the decomposition of NaF.HF is 26.35 cal mole^{-1} deg^{-1}.[110] Fisher[113] obtained the following equation for the free energy of dissociation of NaF.HF:

$$\Delta F^0 = 16.11 \cdot 10^3 - 30.17T \; (157\text{—}269°) .$$

The enthalpy of decomposition of the hydrogen fluoride NaF.2HF has been found to be 10.3 kcal mole^{-1} [115] and 9.0 kcal mole^{-1}.[64]

Table 5. Thermodynamic functions of the dissociation of lithium and potassium hydrogen difluorides (298.16°K).

Thermodynamic function	LiF·HF	References	KF·HF	References
ΔC_p°, cal mole^{-1} deg^{-1}	0.35	79	0.32	100
ΔS°, cal mole^{-1} deg^{-1}	16.97	91	32.52	100
$\Delta(F^\circ - H_0^\circ)/T$, cal mole^{-1} deg^{-1}	—	—	29.86	100
$\Delta(H^\circ - H_0^\circ)$, kcal mole^{-1}	—	—	0.791	100
ΔF°, kcal mole^{-1}	3.50	79	11.63	100
ΔH°, kcal mole^{-1}	13.7±0.3	79	21.32	79
	13.41±0.05	91	21.1	99

The vapour pressure of HF over potassium hydrogen difluoride was investigated in connection with the problem of the preparation of fluorine with a minimal HF impurity and the use of KF.HF for the preparation of anhydrous hydrogen fluoride. This problem was investigated by Morgen and Hildebrand[116] in the temperature range 230.5–347.5°C. Fredenhagen and Cadenbach[96] found that KF.HF begins to decompose at 400°C and the final elimination of HF terminates at 504°C. They also noted the effect of traces of water in KF.HF on its thermal decomposition. The non-equilibrium nature of the thermal decomposition of potassium hydrogen difluoride has also been pointed out by Yatlov et al.[117], who established that the temperature of the rapid decomposition of potassium hydrogen difluoride is 600–620°C. When sodium fluoride is added to a melt of KF.HF, the vapour pressure of HF initially decreases somewhat and, when the NaF content is in excess of 5%, it increases[118].

Westrum and Pitzer[100] obtained the following relation for the dissociation pressure of KF.HF in the temperature range 196–238.8°C:

$$\lg p\,(\text{mmHg}) = 8.57 - 4000/T$$

and determined the thermodynamic functions for the dissociation process (Table 5).

The vapour pressure of hydrogen fluoride over HF–KF melts of various compositions was studied by Cady[61], who showed that the values of p_{HF} over KF.HF and KF.3HF found previously at 100° and 150°C [119] were erroneous. Cady's data were used subsequently by Sudarikov et al.[99] to establish a relation between the equilibrium hydrogen fluoride vapour pressure and the composition of the HF–KF melt. The enthalpies of decomposition of the hydrogen fluorides were determined:

$$KHF_2 \rightarrow KF + HF \qquad \Delta H = 21.1 \text{ kcal mole}^{-1} ,$$
$$KH_2F_3 \rightarrow KHF_2 + HF \qquad \Delta H = 14.3 \text{ kcal mole}^{-1} ,$$
$$KH_4F_5 \rightarrow KH_2F_3 + 2HF \qquad \Delta H = 19.3 \text{ kcal mole}^{-1} ,$$

The dissociation pressures of rubidium and caesium hydrogen difluorides have not been investigated. The standard enthalpies of decomposition of RbF.HF and CsF.HF were obtained from calorimetric measurements as 21.8 and 25.0 kcal mole^{-1} [114].

Table 6. Thermal stabilities of sodium hydrogen difluorides.

Temperature range, °C	Temperature variation of HF vapour pressure	ΔH_{decomp}, kcal mole^{-1}	References
37—100	$\lg p(\text{atm}) = 6.677 - 3940/T$	18.0	109
40—120	$\lg p(\text{mm}) = 11.19 - 4292/T$	19.6	110
100—250		14.8	111
126—205	$\lg p(\text{mm}) = 9.97 - 3830/T$	17.5	112
157—269	$\lg p(\text{mm}) = 9.475 - 3521/T$	16.1	113
		17.9	114

The vapour pressure of ammonium hydrogen difluoride was measured in the temperature ranges 70–110°C [94] and 130–237°C [106]. The enthalpy of the reaction NH_4HF_2(solid) → NH_4F(solid) + HF(gas) is 51.9 kcal mole^{-1} (thermochemical data[115]) or 51.1 kcal mole^{-1} (vapour pressure data[94]). The enthalpies of sublimation (17.05 kcal mole^{-1}) and evaporation (1.2 kcal mole^{-1}) of ammonium hydrogen difluoride have been calculated and its enthalpy of decomposition in the vapour phase has been found to be 33.85 kcal mole^{-1}.[106]

Measurements of the vapour pressure of NH_4F.3HF yielded the relation[64]

$$P\,(\text{mmHg}) = -5288/T + 20.97 \; (-10 \text{ to} + 23.4°) .$$

The enthalpy of the decomposition reaction NH_4F.3HF(solid) → NH_4HF_2(solid) + 2HF(gas) was found to be 17.6 kcal mole^{-1} [115] and 17.1 kcal mole^{-1} [94].

There exist only isolated purely qualitative data on the thermal stabilities of other alkali metal hydrogen fluorides. Thus the hydrogen fluorides NaF.3HF and NaF.4HF are known to be converted at room temperature in air into the hydrogen difluoride[66]. Under these conditions, potassium hydrogen fluorides decompose to KF.2HF, which is converted into potassium hydrogen difluoride at 150°C [67]. RbF.2HF, which is stable at room temperature, begins to split off hydrogen fluoride at 100–110°C [42] and is converted into RbF.HF after prolonged heating at 150–190°C [44].

The thermal stability of the entire series of alkaline earth metal hydrogen fluorides was investigated thermogravimetrically by the authors of this review[120]. The mechanisms of the decomposition reactions of the hydrogen fluorides were established and the intermediates in the reactions, which proceed stepwise, were determined. The existence of the previously unknown compound BaF_2.2HF was discovered in the decomposition of barium hydrogen fluoride. The kinetics of the decomposition of the hydrogen fluorides were investigated and the kinetic parameters for individual reaction stages were determined (Table 7).

According to the HF vapour pressure data for the HF–PbF_2 system, p_{HF} = 0.016 atm and ΔH_{decomp} = 4.5 kcal $mole^{-1}$ for $PbF_2.2.5HF$ at 0°C [54].

Table 7. Kinetic parameters of the decomposition reactions of alkaline earth metal hydrogen fluorides.

Decomposition mechanism	Temp. of maximum extent of reaction, °C	Reaction order *n*	Activation energy, kcal $mole^{-1}$	Frequency factor, $mole^{1-n} \times min^{-1}$
$BaF_2 \cdot 4.5HF \xrightarrow{-2.5HF} BaF_2 \cdot 2HF$	95	0.50	32.1±0.6	$9 \cdot 10^{18}$
$BaF_2 \cdot 2HF \xrightarrow{-HF} BaF_2 \cdot HF$	100	0.30	12.0±0.5	$3 \cdot 10^{6}$
$BaF_2 \cdot HF \xrightarrow{-HF} BaF_2$	224	0.35	16.7±0.6	$7 \cdot 10^{6}$
$SrF_2 \cdot 2.5HF \xrightarrow{-0.5HF} SrF_2 \cdot 2HF$	82	0.18	12.1±0.4	$8 \cdot 10^{6}$
$SrF_2 \cdot 2HF \xrightarrow{-2HF} SrF_2$	145	0,35	24.7±0.5	$4 \cdot 10^{12}$
$CaF_2 \cdot 2HF \xrightarrow{-2HF} CaF_2$	130	0.34	27.3±0.5	$3 \cdot 10^{14}$

Analysis of the available data on the thermal stabilities of alkali and alkaline earth metal hydrogen fluorides shows that their stability decreases with increase in the number of combined HF molecules and also with decrease of the ionic radius of the cation and increase of its polarising capacity.

Table 8. Thermodynamic functions of hydrogen fluorides (at 298.16°K).

Thermodynamic function	LiF·HF	NaF·HF	KF·HF	RbF·HF	CsF·HF	$NH_4F \cdot HF$	TlF·HF	NaF·2HF	$NH_4F \cdot 3HF$
C_p°, cal $mole^{-1}$ deg^{-1}	16.77	17.93	18.37	18.97	20.86	25.50	21.25	—	—
S°, cal $mole^{-1}$ deg^{-1}	16.97	21.73	24.93	29.70	32.31	27.61	34.92	27.3	79.9
$-(F^\circ - H_0^\circ)/T$, cal $mole^{-1}$ deg^{-1}	7.49	10.54	12.66	15.51	18.22	—	20.47	—	—
$H^\circ - H_0^\circ$, kcal $mole^{-1}$	2.826	3.334	3.655	3.933	4.201	4.243	4.308	—	—
$-\Delta H^\circ_{form}$, kcal $mole^{-1}$	224.2	216.6	220.0	217.3	216.1	191.4	—	292.5	337.4
$-\Delta F^\circ_{form}$, kcal $mole^{-1}$	—	207.2	—	—	—	154.9	—	—	—

Westrum and coworkers [79,98,100,114] carried out a series of studies on the thermodynamic properties of univalent metal and ammonium hydrogen fluorides. Measurements were made of the heat capacities of LiF.HF and NaF.HF (10–298.16°K), KF.HF (20–500°K), RbF.HF, CsF.HF, and TlF.HF (7–305°K), and $NH_4F.3HF$ (200–320°K). Anomalies were discovered in the temperature variation of the heat capacities of NaF.HF and $NH_4F.3HF$. The heat capacity of liquid potassium hydrogen difluoride was determined as 25 cal $mole^{-1}$ deg^{-1}. The thermodynamic functions of the hydrogen difluorides, the standard values of which are listed in Table 8, were calculated from the results of these investigations.

The following equations relating the thermodynamic functions to temperature were obtained for potassium hydrogen difluoride (the α- and β-phases):

at 330–469.2°K:

$$H_T^\circ - H^\circ = 11.353T + 11.56 \cdot 10^{-3} T^2 758 \text{ cal mole}^{-1},$$

$$C_p^\circ = 11{,}353 + 23.12 \cdot 10^{-3} T \text{ cal mole}^{-1} \text{ deg}^{-1},$$

$$S^\circ = 26.141 \lg T + 23.12 \cdot 10^{-3} T - 46.65 \text{ cal mole}^{-1} \text{ deg}^{-1};$$

at 469.2–500°K:

$$H_T^\circ - H^\circ = 23.96T - 1469 \text{ cal mole}^{-1},$$

$$C_p^\circ = 23.96 \text{ cal mole}^{-1} \text{ deg}^{-1},$$

$$S_0^\circ = 55.17 \lg T - 107.68 \text{ cal mole}^{-1} \text{ deg}^{-1},$$

$$S_{500}^\circ = 41.22 \pm 0{,}1 \text{ cal mole}^{-1} \text{ deg}^{-1}.$$

There is an appreciable regularity in the temperature variation of the heat capacities and entropies of the hydrogen difluorides MF.HF. Davis and Westrum [101] attempted to correlate the entropies and, using the relation thus obtained between the entropy and the logarithm of the atomic weight of the cation, determined $S^\circ_{298.16}$ for silver hydrogen difluoride as 30.5 cal $mole^{-1}$ deg^{-1}.

IV. THE STRUCTURE OF METAL HYDROGEN FLUORIDES AND THEIR HYDROGEN BONDS

A detailed study has been made of the structures of alkali metal, ammonium, and thallium hydrogen difluorides, which consist of M^+ cations and the linear anion $[F-H-F]^-$ formed by hydrogen bonding (Table 9).

Table 9. Structural data for alkaline earth metal, ammonium, and thallium hydrogen difluorides.

		LiF·HF	NaF·HF	KF·HF	RbF·HF	CsF·HF	$NH_4F \cdot HF$	TlF·HF
Unit cell parameters of α-phase, Å	*a*	4.72	3.47	5.67	5.90	6.14	8.40	8.58
	b	—	—	—	—	—	8.16	—
	c	13.19	13.76	6.81	7.26	7.84	3.67	—
Density of α-phase, g cm^{-3}		2.22	2.14	2.36	3.27	3.86	1.50	5.08
Conditions of phase transition		—	*p*=8.5 килобар	*T*=196°	*T*=176°	*T*=61°	—	—
Unit cell parameters of β-phase, Å	*a*	—	7.240	6.36	6.71	4.21	—	—
	b	—	6.105	—	—	—	—	—
	c	—	3.631	—	—	—	—	—
Density of β-phase, g cm^{-3}		—	—	2.02	2.73	3.81	—	—
F-F distance, Å		2.27	2.264± ±0.003	2.277± ±0.006	2.26	2.26	2.275± ±0.004, 2.269± ±0.004	~2.4

Lithium [121] and sodium [122–124] hydrogen difluorides crystallise in the rhombohedral system. NaF.HF was found to undergo a polymorphic transformation into a phase with rhombohedral symmetry at a pressure of 8.5 kbar [125]. Potassium, rubidium, and caesium hydrogen difluorides have the same structures and have two polymorphic modifications [61,63,126]. The low-temperature modification crystallises in the tetragonal system[126-128] and the high-temperature modification in the cubic system[126]. The structure of ammonium hydrogen difluoride includes additional N–H... F hydrogen bonds and the substance crystallises in the rhombohedral system[129,130]. At room temperature the crystal structure of thallium hydrogen difluoride has the highest symmetry among the hydrogen difluorides: TlF.HF crystallises in the cubic system and does not undergo a phase transformation even on cooling to the temperature of liquid helium[131].

The phase transition from the tetragonal to the cubic modification of potassium hydrogen difluoride is accompanied by appreciable heat (2.671 kcal mole^{-1}) and entropy (5.69 cal mole^{-1} deg^{-1}) change, the latter exceeding by a factor of almost two the entropy of fusion[99-101]. The study of the structure of the β-phase of potassium, rubidium, and caesium hydrogen difluorides showed an appreciable entropy of phase transition associated with the fact that the HF_2^- ions can occupy with equal probability each of the four sites on the diagonal of the cubic unit cell[126]. The volume of the β-phase also increases appreciably. The coefficients of thermal expansion of α- and β-KHF_2 and the volume change in the $\alpha \rightarrow \beta$ transition have been determined dilatometrically[132].

$$(\partial V/\partial T)_p^0 = 0.0047 \pm 0,0005 \text{ cm}^3 \text{ deg}^{-1} \text{ mole}^{-1} \, (20\text{—}135°) \ ,$$

$$(\partial V/\partial T)_p^0 = 0.015 \pm 0,004 \text{ cm}^3 \text{ deg}^{-1} \text{ mole}^{-1} \, (196\text{—}259°) \ ,$$

$$\Delta V^0_{\alpha \rightarrow \beta} = 4.2 \pm 0.1 \text{ cm}^2 \text{ mole}^{-1} .$$

The phase transition of potassium hydrogen difluoride also leads to a sharp change in its electrical conductivity[101,133]. Davis and Westrum[101] obtained the following equation for the electrical conductivity of β-KHF_2:

$$\lambda = 1.15 \cdot 10^5 \exp(-1.05 \cdot 10^4/T), \ E_{\text{act}} = 20.9 \text{ kcal mole}^{-1} .$$

Later studies on the electrical conductivity of KF.HF and KF.DF suggested that the mechanism of conduction in the crystals is associated with the migration of interstitial protons or proton defects, the formation of which involves the following activation energies[133]:

	KF · HF	KF · DF	
E_{act}, kcal mole^{-1}	21.7	23.5	α-phase
	19.8	20.9	β-phase .

The F – F interatomic distances in the HF_2^- ion in the structure of the hydrogen difluorides MF.HF provide information about the strength of the hydrogen bonds in these compounds, but the values found for them initially were determined with a large error and had to be corrected in subsequent studies.

The initial values of r_{F-F} found for sodium hydrogen difluoride (2.50 Å [122] and 2.38 Å [123]) were clearly too high. This interatomic distance was found more accurately in a neutron diffraction study of NaF.HF (Table 9) [124].

Initially the F – F distance in potassium hydrogen difluoride was found to be 2.25 Å [131] and was then corrected to 2.26 Å [128]. The latter value was adopted in all subsequent studies on KHF_2. However, in a neutron diffraction study a somewhat higher value was obtained[134] (Table 9). The studies of the crystal structures of rubidium and caesium hydrogen difluorides[126] led to the conclusion that the F – F interatomic distances in these compounds are the same as in KHF_2 (according to the data of Helmholz and Rogers[128]).

In the ammonium hydrogen difluoride structure the F – F distance was initially found to be 2.37 Å [129]. The theoretical F – F distance for the symmetrical linear HF_2 ion in NH_4HF_2 is 2.32 Å according to Pauling's data[135]. Later it was established that these values are too high and the structure of ammonium hydrogen difluoride contains hydrogen difluoride ions with two different F – F distances[130] (Table 9).

Isotope substitution of the proton in sodium and potassium hydrogen difluorides increases slightly the F – F distance in the crystal[124,136].

Using the available structural data for potassium, rubidium, and caesium hydrogen difluorides (Table 9), Waddington[137] calculated the energies of their crystal lattices as –33.0, –29.6, and –24.7 kcal mole^{-1} respectively. The enthalpy of the process $HF_2^-(\text{gas}) \rightarrow HF(\text{gas}) + F^-(\text{gas})$ which he calculated (58 kcal mole^{-1}) and also the F – F distances in the HF_2^- ion in alkali metal hydrogen difluorides obtained from structural studies (Table 9), which are much smaller than in solid hydrogen fluoride (r_{F-F} = 2.49 Å) [138], indicate the presence of a strong hydrogen bond in the hydrogen difluoride ion.

The nature of the hydrogen bond in the hydrogen difluoride ion and in the first place the position of the proton between the fluorine atoms are of interest. The latter may be assymetric as in the O–H... O bond or symmetrical, and for the symmetrical model there are two possibilities: (a) the proton is located at equal distances from the two fluorine atoms; (b) the F–H distances are unequal but the proton oscillates between two positions[139]. To solve the problem of the position of the proton in the HF_2^- ion, many different research techniques were resorted to and in most cases potassium hydrogen difluoride was investigated.

Ketelaar[140] observed in the KHF_2 infrared spectrum absorption frequencies at 1222 and 1450 cm^{-1}, which he assigned to the HF_2^- assymmetric stretching vibration doublet and explained the doublet splitting by the presence of a double potential energy minimum in this ion. However, the results of subsequent studies on KHF_2 were not consistent with this model of the hydrogen difluoride ion.

Polder[141] measured the dielectric constant of KHF_2 and observed a weak temperature variation: $d\epsilon/dT = 2 \times 10^{-4}$ (80–300°K), whereas in the case of a double minimum in the HF_2^- ion the presence of free electric dipoles should give rise to a large temperature coefficient of the dielectric constant. Analogous results were obtained by Pitzer and Westrum[142] in the measurements of ϵ for KHF_2. On the basis of the heat capacity data for potassium hydrogen difluoride at low temperatures, they also calculated its entropy in the vicinity of the absolute zero, the value obtained (26.17 cal mole^{-1} deg^{-1}) agreeing well with 26.05 cal mole^{-1} deg^{-1} found from direct calorimetric measurements. This indicates the absence of residual entropy, which should be present in the case of a double minimum, as, for example, for the hydrogen bond in ice. Moreover, the experimental dissociation pressures of potassium hydrogen difluoride fall on the line calculated theoretically without taking into account the double minimum[98].

All the above data required a new interpretation of the infrared spectrum of potassium hydrogen difluoride. Halverson[143] explained the presence in the spectrum of the 1222 and 1450 cm^{-1} absorption bands by the splitting of the 1300 cm^{-1} band owing to perturbations of the crystal lattice, but this was not confirmed by subsequent experiments. A more correct explanation was suggested by Westrum and Pitzer[100], who assigned the 1222 cm^{-1} frequency to the deformation vibrations of the HF_2^- ion (ν_2) and the 1450 cm^{-1} frequency to the asymmetric stretching vibration (ν_3), but agreed with Ketelaar[140] that the

5090 cm^{-1} band is due to the $3\nu_3$ overtone, having postulated that there is a marked negative anharmonicity of the levels associated with the ν_3 vibration in the symmetrical hydrogen difluoride ion.

Later investigations of Ketelaar and Vedder[144] of the infrared absorption and reflection spectra of KHF_2 in polarised light and of the low-temperature infrared spectra obtained by Cote and Thompson[145] agree with this frequency assignment. There is a difference in the assignment of the frequencies associated with the overtones in the work of Newman and Badger[146], who suggested a slight positive anharmonicity of the levels in the hydrogen difluoride ion.

Ibers[147] studied the potential function in the region of the stretching vibrations of potassium hydrogen difluoride. Neglecting the interaction between the HF_2^- ions and the lattice vibrations and the interaction between deformation and stretching vibrations, he calculated the force constants and absorption frequencies $[\nu_1, \nu_3(H, D), 3\nu_3(H, D)]$ and the isotope effects on bond lengths. The satisfactory agreement of these quantities with experiment is evidence of a symmetrical linear configuration of HF_2^-.

The Raman spectrum of potassium hydrogen difluoride revealed absorption bands at 595 and 604 cm^{-1}, the positions of which virtually coincided with those predicted by Ketelaar[140] for the symmetrical stretching vibrations of HF_2^-. Initially the appearance of the doublet was accounted for by resonance between two configurations of the HF_2^- ion with a double minimum[148]. However, analysis of the band intensities led the investigators to the conclusion that the splitting is caused by the interaction of individual HF_2^- ions in the crystal[149]. The infrared spectrum of KHF_2 does not show an absorption in the region of 600 cm^{-1}, which can be explained by the selection rules for the linear symmetrical configuration $[F-H-F]^-$ [145]. Thus the results of the infrared spectroscopic studies on potassium hydrogen difluoride support a symmetrical model of the HF_2^- ion.

Peterson and Levy[150] investigated the hydrogen bond in potassium hydrogen difluoride by neutron diffraction and concluded that the proton in the HF_2^- ion occupies a symmetrical position between the fluorine atoms. Later these results were subjected to critical analysis and it was shown that the use of the neutron diffraction method alone does not allow an unambiguous choice between the two models, although the difference between the mean square vibration amplitudes of the hydrogen and fluorine atoms calculated from the spectroscopic data and obtained by the neutron diffraction method is the same, which probably confirms the symmetry and linearity of the hydrogen difluoride ion[134].

An NMR study of potassium hydrogen difluoride yielded best agreement between the experimental resonance absorption line and the line calculated theoretically[151] on the assumption of the symmetrical model for HF_2^-.

However, having analysed numerous investigations of the hydrogen bond in potassium hydrogen difluoride, Blinc[152] believes that some of them are not inconsistent with the model of the HF_2^- ion having a structure intermediate between those of symmetrical and asymmetric ions, i.e. one may suppose that there is a potential barrier between two minima, but it is small.

As mentioned earlier, the energy of the hydrogen bond in the HF_2^- ion is large but the separate contributions to it of the electrostatic interaction and covalent energies are unknown. The energy 47.3 kcal mole^{-1} obtained by Davies[153] for a purely electrostatic interaction is evidently too high. The necessity to take into account the covalent component of the hydrogen bond, which is probably associated with the participation of the excited orbitals of the hydrogen atom, has been emphasised by a number of investigators[154,155]. In an NMR study of deuterated potassium hydrogen difluoride[156] the chemical shift and the screening constant for the ^{19}F NMR signal were determined: the filling coefficient for the *p*-shells of the fluorine atoms and the effective atomic charges were determined on the basis of the theory of Carplus and Das[157]. The estimates obtained agree with the assertion that, in the case of powerful interactions such as those in the HF_2^- ion, all three atoms should make significant contributions to the molecular orbital and the two electron pairs should be delocalised among the three atoms[158].

Apart from the experimental studies on the hydrogen bond in the hydrogen difluoride ion, a number of theoretical calculations of the electronic structure of the HF_2^- ion have been made by quantum-mechanical methods[159-164].

As stated above, the hydrogen bond in potassium hydrogen difluoride was investigated in greatest detail. The studies of the hydrogen bond in the entire series of univalent metal hydrogen difluorides by various physical methods (NMR, infrared spectroscopy, refractometry) were a further development of these investigations.

The NMR spectra of the hydrogen difluorides of alkali metals (except LiF.HF) [151,156,165] and ammonium[165,166] are similar in form with the spectra calculated theoretically for the hydrogen difluoride ion with a linear symmetrical configuration[151] and the absorption lines have similar second moments. This is due to the similarity of the structure of the HF_2^- ion in these compounds. The symmetrical position of the proton in sodium hydrogen difluoride has also been demonstrated by neutron diffraction studies[167]. The NMR data for lithium[156,164] and silver[167] hydrogen difluorides show that the structures of these compounds contain HF_2^- ions with a weaker hydrogen bond than in other hydrogen difluorides. This weakening of the hydrogen bond is also accompanied by a shift of the equilibrium position of the proton from the mid-point between the fluorine atoms.

Table 10. Principal absorption bands in the infrared spectra of hydrogen fluorides.

Compound	ν_1, cm^{-1}	ν_2, cm^{-1}	ν_3, cm^{-1}	Compound	ν_1, cm^{-1}	ν_2, cm^{-1}	ν_3, cm^{-1}
$CsF\cdot HF$	—	1230	1480	$BaF_2\cdot HF$	—	1158—1183	1630—1780
$RbF\cdot HF$	—	1235	1480	$SrF_2\cdot HF$	—	1152—1185	1700—1820
$KF\cdot HF$	600*	1235	1460	$CaF_2\cdot 2HF$	—	1152—1175	1520
$NaF\cdot HF$	—	1215	1600	$SrF_2\cdot 2.5HF$	—	1165—1190	1500
$LiF\cdot HF$	400—500	1160	1750	$PbF_2\cdot 2.5HF$	—	1020—1150	1800
$NH_4F\cdot HF$	—	1208	1600	$BaF_2\cdot 3HF$	—	980, 1150—1170	1650—1850
$AgF\cdot HF$	—	1160—1190	1600—1800	$CdF_2\cdot HF$	—	1165—1235	1700
$RbF\cdot 2HF$	480	1025—1070	1780	$ZnF_2\cdot 2HF$	—	1160—1215	1800
$KF\cdot 2HF$	480	1030—1100	1780	HF_{TB}	366	—	3100—3400

* Raman spectrum.

The first data on the infrared spectra of $NaHF_2$ and NH_4HF_2 were quoted in Refs. 168–171. Ketelaar et al.[170] were the first to point out the differences in the positions of the absorption bands in the infrared spectra of sodium, potassium, and ammonium hydrogen difluorides as a function of the method of preparation of the specimens for the recording of the spectra.

In a systematic infrared spectroscopic study of the entire series of alkali metal hydrogen difluorides

MF.HF (M = Cs, Rb, K, Na, and Li) and their deuterated derivatives, we investigated[172,173] the effect of various methods of preparation of the specimens on the quality of the spectrum and established optimum conditions for the recording of the spectra. The absorption frequencies associated with the deformation (ν_2) and asymmetric stretching (ν_3) vibrations of HF_2^- in the spectra of alkali metal hydrogen difluorides (Table 10) show the presence in these compounds of a strong hydrogen bond, which becomes weaker on passing along the series from caesium to lithium. In silver hydrogen difluoride the hydrogen bond is approximately as strong as in $LiHF_2$, in agreement with the NMR data[155,165,168].

In a study of the infrared spectra of sodium and potassium hydrogen difluorides at low frequencies, it was established that the absorption frequencies corresponding to the translational vibrations of the crystal lattice are not altered when the hydrogen difluorides are deuterated[174,175].

Table 11. Refractometric data for hydrogen fluorides.

Compound	Refractive indices				R_D, cm^3	$R_{H\text{-bond}}$, cm^3
	n_g	n_m	n_p	n_{av}		
$CsF \cdot HF$	—	1.414	1.410	1.413	11.06	0.73
$RbF \cdot HF$	—	1.373	1.357	1.368	8.57	0.98
$KF \cdot HF$	—	1.352	1.327	1.344	7.01	0.96
$NaF \cdot HF$	1.331	1.260	—	1.281	5.08	0.81
$LiF \cdot HF$	1.408	1.319	—	1.348	4.43	0.55
$NH_4F \cdot HF$	1.394	1.390	1.385	1.390	8.93	0.83
$KF \cdot 2HF$	1.315	1.311	1.305	1.310	9.18	0.61
$BaF_2 \cdot HF$	1.498	1.467	1.466	1.470	11.8	0.41
$SrF_2 \cdot HF$	1.472	1.473	1.418	1.442	9.6	0.47
$CaF_2 \cdot 2HF$	1.415	1.387	1.355	1.388	10.6	0.49
$SrF_2 \cdot 2.5HF$	1.400	1.380	1.344	1.374	13.0	0.42
$BaF_2 \cdot 3HF$	1.425	1.411	1.394	1.410	16.3	0.38
$BaF_2 \cdot 4.5HF$	—	1.360	—	1.360	19.8	0.40

The strength of the hydrogen bond in alkali metal and ammonium hydrogen difluorides can be estimated quantitatively with the aid of the refractometric method[176]. The first data were obtained for potassium and ammonium hydrogen difluorides[177]. Later this method was employed to study the hydrogen bonds in the entire series of hydrogen difluorides[178]. Comparison of the refraction of the hydrogen bonds (Table 11) shows that the strongest hydrogen bonds are characteristic of rubidium and potassium hydrogen difluorides, while in sodium and lithium hydrogen difluorides they are much weaker. An anomalously low refraction of the hydrogen bond was obtained for $CsHF_2$ compared with $RbHF_2$ and KHF_2, while according to the data derived by other methods the hydrogen bonds in these compounds are approximately of equal strength. This can be accounted for by the steric effect of the Cs^+ ion, which has a large ionic radius, or by its deformation[178]. The weakening of the hydrogen bond in the HF_2^- ion in ammonium hydrogen difluoride is caused by the presence in its structure of hydrogen bonds of the type N–H... F.[177]

The problems concerning the structures of alkali metal hydrogen fluorides with the composition MF.*n*HF ($n > 1$) have been investigated much less completely than for hydrogen difluorides.

There has been only one X-ray diffraction study of these compounds, in which the structure of KF.2HF was considered[179]. This hydrogen difluoride crystallises in the orthorhombic system with the unit cell constants $a = 8.52$ Å, $b = 4.09$ Å, and $c = 6.69$ Å and its density is 2.06 g cm^{-3}. The KF.2HF lattice consists of K^+ ions and the polymeric $H_2F_3^-$ anions formed by hydrogen bonding in which the F–F distance is 2.33 Å and the angles formed by the fluorine atoms are 133° and 139°. It proved possible to determine the F–H distances in $H_2F_3^-$ ions by the NMR method as 1.065 and 1.265 Å [180]. The NMR data for RbF.2HF [156,165] suggest that this compound also contains the polymeric $H_2F_3^-$ anions with the same structure. We may note that potassium and rubidium hydrogen difluorides have similar structures too.

NMR studies of RbF.3HF and CsF.3HF led to the hypothesis that their structures include the polymeric $H_3F_4^-$ anions with an asymmetric hydrogen bond[160,165]. The existence of two modifications has been established for the hydrogen fluoride NaF.3HF (transition temperature 43.1 °C), but their structures are unknown[69].

Further increase of the number of combined HF molecules in the hydrogen fluorides MF.*n*HF probably also leads to the formation of the polymeric ions $H_nF^-_{n+1}$ by hydrogen bonding, the structure of which approaches the infinite zig zag chains with asymmetric hydrogen bonds in the structure of solid hydrogen fluoride[138]. The presence of such anions has also been suggested for silver hydrogen fluorides with the composition AgF.*n*HF ($n > 1$) [168].

The low-frequency molecular vibrations in the hydrogen fluorides NaF.2HF and KF.2HF were investigated by a method based on the non-elastic scattering of slow neutrons[181]. An infrared spectroscopic study of the hydrogen fluorides MF.2HF (M = Rb or K) was undertaken for the first time by the present authors[172,173] and it was found that there is a significant difference between the infrared spectra of the MF.HF and MF.2HF compounds, owing to the presence in the structure of the latter of $H_2F_3^-$ ions.

The asymmetric stretching vibrations of the $H_2F_3^-$ ion are shown in the region of 1780 cm^{-1}, while deformation vibrations give rise to a broad band with a maximum at 1025–1100 cm^{-1}. The appearance in the MF.2HF spectrum of an absorption band with a frequency of 480 cm^{-1}, which was assigned to the symmetrical stretching vibration of $H_2F_3^-$, can be explained by the fact that for the $H_2F_3^-$ ion with an asymmetric hydrogen bond this vibration is not forbidden in the infrared spectrum.

Later data[182] on the infrared spectra of KF.2HF and KF.2DF agreed fully with the above absorption frequencies of the $H_2F_3^-$ ion and their assignment. The force constants of $H_2F_3^-$ were also estimated in the above investigation, the results indicating an asymmetric position of the proton in this ion.

Comparison of the infrared spectra of the hydrogen fluorides MF.HF and MF.2HF reveals a weakening of the hydrogen bond with increase in the number of combined HF molecules (Table 10). Comparison of the vibration frequencies in the infrared spectra of KF.HF, KF.2HF, and solid hydrogen fluoride[183] with the F–F and F–H distances in these compounds shows that they vary in parallel.

In a refractometric study of the hydrogen fluoride KF.2HF, the refractions of the $H_2F_3^-$ ion (6.93 cm^3) and its hydrogen bond (0.61 cm^3) were calculated[178]. These values agree well with the regular change in the strength of the hydrogen bond in the hydrogen fluorides with increase in the number of combined HF molecules (Table 11).

Thus the study of the structure of alkali metal hydrogen fluorides by physical methods established the presence in them of complex anions with the composition $H_nF^-_{n+1}$, in which the strength of the hydrogen bond increases with increase in the ionic radius of the cation and with decrease of the number of combined HF molecules.

Ikrami, Ruchkin, and Nikolaev[80,184] and the present authors[156,185] investigated the structure of alkaline earth metal hydrogen fluorides. Using the NMR method, it proved possible to deduce the structures of these compounds. Analysis of the adsorption line form and the second moments of the NMR spectra of the hydrogen fluorides $MF_2.HF$ established that they contain the anions HF_2^- and F^-. An increase in the number of combined HF molecules leads to the formation of two hydrogen difluoride ions in compounds with the composition $MF_2.2HF$. In the hydrogen fluorides $MF_2.3HF$ the additional HF molecule adds to the HF_2^- ion, forming $H_2F_3^-$. Thus the addition of HF to alkaline earth metal fluorides is somewhat different from the addition to the fluorides of univalent elements, since here there is an equal possibility of the formation of a hydrogen bond with each fluoride ion in MF_2. Evidently, solvation takes place with formation of the most symmetrical structures, identical anions being formed when the number of combined hydrogen fluoride molecules is even[156,185]. The structures of the hydrogen fluorides of other divalent metals (lead, copper, zinc, and cadmium[74-76]) may be represented similarly.

The ^{19}F NMR and ^1H NMR spectra of alkaline earth metal hydrogen fluorides indicate some asymmetry in the position of the proton in the hydrogen difluoride ion in their structure, which is quite reasonable, since, although accurate values of the interatomic distances in the $MF_2.nHF$ lattices are unknown, an estimate of r_{F-H} in the HF_2^- ion based on NMR data indicates the presence in them of a much weaker hydrogen bond than in potassium and sodium hydrogen difluorides[156,185].

The first results of studies on alkaline earth metal hydrogen fluorides by infrared spectroscopic[184] and refractometric[80] methods led the investigators to the conclusion that the hydrogen bond in these compounds is much stronger than in hydrogen fluoride but weaker than in potassium hydrogen difluoride and also to the hypothesis that the polymeric ions $H_nF_{n+1}^-$ are formed in metal hydrogen fluorides with the composition $MF_2.nHF$ ($n > 1$). In a reinvestigation of the infrared spectra of calcium, strontium, and barium hydrogen fluorides, we concluded[173] that the spectra of hydrogen fluorides with the compositions $CaF_2.2HF$ and $SrF_2.2.5HF$ may be interpreted in terms of a structure with two hydrogen difluoride ions. On the other hand, the absorption bands in the region 740–750 cm^{-1}, which were assigned[184] to the polymeric ions $H_nF_{n+1}^-$, were found to be due to the decomposition products of the hydrogen fluorides. The characteristic absorption frequencies of the HF_2^- ions in the infrared spectra of $MF_2.nHF$ indicate a steady weakening of the hydrogen bond in alkaline earth metal hydrogen fluorides with decrease of the ionic radius of the cation, as in the case of alkali metal hydrogen fluorides (Table 10).

Thus alkali and alkaline earth metal hydrogen fluorides are formed via hydrogen bonds of the type $F-H...F$, which lead to the formation of the ions $H_nF_{n+1}^-$. However, in alkaline earth metal hydrogen fluorides the hydrogen bond is on the whole weaker and their structures may include several types of anions.

The hydrogen bond in hydrogen fluoride solutions has not so far been investigated. Studies have been made on aqueous solutions of alkali metal hydrogen difluorides by the NMR method[186-188] in which the concentration dependence of the ^{19}F signal and the chemical shift of the HF_2^- ion were determined. Infrared spectroscopic studies on potassium hydrogen difluoride solutions in water established that the hydrogen bond in the hydrogen difluoride ion is somewhat stronger in solution than in the crystalline state[189]. It was not possible to obtain the Raman spectrum and a KHF_2 solution, which has been explained[190] by the markedly ionic character of the bond in the hydrogen difluoride ion.

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The above data show that until recently the study of metal hydrogen fluorides was restricted to those of alkali metals and among them only the hydrogen difluorides were largely investigated in greater detail. The advances in the chemistry of inorganic fluorides in the last decades, the development of synthetic chemistry, and the advances in experimental techniques greatly expanded our knowledge in this field of fluorine chemistry, which is of theoretical and practical importance. The difficulties in experiments with metal hydrogen fluorides—substances which are frequently extremely unstable and hygroscopic, liberating on decomposition the corrosive hydrogen fluoride—have now been overcome in the majority of cases, ensuring that the experiments are carried out with fairly pure substances of the required composition. In addition, the present level of development of physical research methods undoubtedly promotes a further expansion of comprehensive studies on metal hydrogen fluorides. A characteristic feature of the investigations in recent years is an increasing interest in higher alkali metal hydrogen fluorides $MF.nHF$ ($n > 1$) and divalent metal hydrogen fluorides.

Analysis of the data at present available on metal hydrogen fluorides permits an outline of the principal trends in the development of investigations in this field.

1. Physicochemical study of systems containing hydrogen fluoride and metal fluorides with the aim of synthesising new metal hydrogen fluorides.
2. The study of the physical and chemical properties of metal hydrogen fluorides and their solutions.
3. The study of the thermal stability of metal hydrogen fluorides and the determination of its quantitative characteristics.
4. Thermodynamic study of metal hydrogen fluorides.
5. The study of the crystal structures of metal hydrogen fluorides and their hydrogen bonds by various physical methods.

The development of investigations in the field of metal hydrogen fluorides along the lines indicated above will lead to the preparation of many new compounds of this class and will expand our knowledge of the properties of metal hydrogen fluorides. Moreover, further study of metal hydrogen fluorides will evidently lead to new types of their applications in science and engineering.

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Institute of Inorganic Chemistry,
Siberian Division of the USSR
Academy of Sciences, Novosibirsk

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Stereochemistry of Certain Catalytic Reactions of Cyclic Hydrocarbons in the Presence of Group VIII Noble Metals

O.V.Bragin and A.L.Liberman

The mechanisms of certain catalytic reactions in the presence of solid catalysts—mainly Group VIII noble metals—are discussed in the review. Attention has been concentrated on the stereochemistry of the reactions. It has been shown that the modern conformational hypotheses may be successfully employed to investigate the detailed mechanisms of a number of heterogeneous-catalytic reactions, in particular certain stereochemical reactions of cyclic hydrocarbons. The most widely adopted mechanisms of the hydrogenation of dialkylcyclo-olefins and also di- and poly-alkylbenzenes have been examined and discussed. Both types of reactions are genetically related and the proportions of the stereoisomers obtained serve in many cases as a definite criterion for the selection of a particular reaction mechanism. The configurational isomerisation of di- and poly-cycloalkanes—a reaction involving direct interconversion of the isomers—has been examined in detail. The direct involvement of hydrogen in this reaction, which at first sight appears to be unimolecular but is in fact bimolecular, has been demonstrated.
The bibliography includes 125 references.

CONTENTS

I. INTRODUCTION

This review is devoted to the mechanisms of certain catalytic reactions where stereochemical-factors play a very significant role. By combining and mutually supplementing the usual catalytic and stereochemical concepts, in particular those of conformational analysis, hypotheses of great promise for the understanding of the detailed mechanisms of heterogeneous catalytic reactions are obtained. This view is confirmed by certain studies quoted in a number of reviews[1-8], where the above approach is employed in some form.

The general concept of reaction mechanism is nowadays understood to involve collisions of reacting species, redistribution of electron density in the species, and other elementary stages, taking into account in each individual step in as great detail as possible the stereochemistry of the conversion of the reactants into products. This presupposes the knowledge of the so called activated complex or transition state, which entails not only the enumeration of the molecules or species involved in it but also geometrical factors (interatomic distances and angles). Therefore the problem of determining the mechanism of a particular reaction has become unusually complex. Bond and Wells[4] believe that the mechanism has been elucidated when sufficient information has been obtained on the following three questions: (a) the nature of all the species participating in the reaction; (b) the qualitative types of their interactions making a major contribution to the overall reaction; (c) the quantitative aspects of these interactions—relative rather than absolute. This view is probably correct.

Whereas in homogeneous reactions this problem is frequently simplified by the fact that the mechanisms of many such reactions are identical and their transition states are very similar, in heterogeneous catalytic reactions there arises a new specific factor, which is very difficult to take into account—the compound adsorbed on the surface. Indeed, the principal difficulty in the interpretation of the mechanism of a heterogeneous catalytic reaction consists in the fact that the surface itself is actively involved in the reaction and is essentially one of the reactants. The problem is complicated by the fact that it is virtually impossible to determine the concentration of the active surface at the instant of the reaction step. Nevertheless the information about the geometry of the distribution of the surface catalyst atoms, i.e. about the type of crystal lattice and its defects and also about the steric distribution of the reactants and products, is all the more important. The sum total of such knowledge may promote the understanding of the stereochemistry of the complex adsorbed on the surface, i.e. may provide certain more detailed hypotheses concerning the mechanism of heterogeneous catalytic reaction.

In the light of the considerations set out above, certain stereochemical reactions of cyclic hydrocarbons are discussed in this review. The first part reviews the studies on the hydrogenation of di- and poly-alkylcyclo-olefins, and the second deals with the stereochemistry of the hydrogenation of the benzene ring with two or three alkyl groups. The hydrogenation of dialkylcyclo-olefins and also di- and poly-alkylbenzenes results in the formation of stereoisomeric (in relation to the plane of the ring) cycloalkanes. The proportions of the steric isomers depend on the structures of the starting materials and on the hydrogenation conditions (pressure, temperature, catalyst, medium, etc.) and may serve as a definite criterion for the validity of a particular hypothetical reaction mechanism. Finally the last section is devoted to the direct interconversion of stereoisomeric di- and poly-alkylcycloalkanes. This reaction, which we have called configurational isomerisation, is, by virtue of its relative simplicity, a good model for the elucidation of the details of the structure of the activated complex adsorbed on the catalyst surface.

In this review, particular attention has been devoted to configurational isomerism also because there is virtually no review in the literature where it is discussed in any detail, although we believe that, because of a number of important characteristics discussed below, it merits special consideration.

II. HYDROGENATION OF CYCLO-OLEFINS

There is a fairly large literature on the hydrogenation of cyclo-olefins in the presence of Group VIII metals. The fundamental finding is that the hydrogenation of dialkylcyclo-olefins in the presence of heterogeneous catalysts leads not only to *cis*- but also to *trans*-isomers. Probably *cis*- addition of hydrogen is accompanied by *trans*-hydrogenation over various catalysts under different conditions.

The relative amounts of the *cis*- and *trans*-isomers depend on the structure and positions (relative to one another and the double bond) of the alkyl groups, on the nature of the catalyst, on hydrogen pressure, and, if the hydrogenation is carried out in a liquid phase, on the solvent and the pH. The formation of *trans*-products under these conditions is very important for the understanding of the hydrogenation mechanism. This reaction is one of the most typical examples of the use of stereochemistry for a more detailed investigation of the mechanism of heterogeneous catalytic reactions.

Before considering specific studies on the hydrogenation of substituted cyclo-olefins and the conclusions which follow from them, it is necessary to consider briefly various types of steric forms of substituted five- or six-membered cycloalkanes in order to comprehend better the possibilities in their interconversions and the nature of the energy barriers overcome in these processes.

Classical stereochemistry, which deals with the positions of atoms in space, takes into account only interatomic distances and valence angles. This already made it possible to understand many characteristics of the behaviour of cyclic molecules. However, a new enormous advance in this respect was made in modern stereochemistry after the introduction of conformational concepts.

The modern conformational concepts are based on the fact that the steric relations between neutral atoms not linked directly to one another are not determined by volumes depending on atomic radii but on effective or van der Waal's volumes. These volumes, which in recent years have come to be called conformational volumes, are much larger than the atomic volumes (for example the atomic radius of the hydrogen atom is 0.30 Å and its conformational radius is 1.2 Å) and these in fact determine the relative positions in space of the individual components of molecules, provided that their interrelations are not influenced by some other more powerful interactions. In particular, the steric distribution of atoms in alkane and cycloalkane molecules is largely determined by the conformational volumes of neighbouring, but not linked directly, hydrogen atoms. When these atoms approach one another to distances slightly exceeding the sum of their van der Waals radii, repulsion forces arise between them. When the distance between non-bonded atoms are equal to this sum, the repulsion forces increase sharply. Further mutual approach or overlapping of the van der Waals radii may lead to the instability or even the breakdown of the molecule. Under the influence of these forces, all the hydrogen atoms in the molecule tend to take up positions as far away from one another as possible.

In any organic molecule, except the simplest, there is a possibility of a multiplicity of relative positions of all its components (atoms or groups) with different distances between non-bonded atoms. If there is a possibility of interconversion of such distributions merely as a result of rotation about particular bonds without their dissociation, the states corresponding to each distribution are called conformations (conformations of molecules or groups).

Each conformation is characterised by its own set of distances between non-bonded atoms and consequently by its own sum of non-bonding interactions (repulsion of non-bonded atoms). Thus different conformations of any organic molecule are usually energetically non-equivalent even if none of the bond lengths and valence angles deviate from the normal values.

The molecule can pass from one conformation to another by internal rotation (for reasons which will become clear subsequently, this rotation can no longer be referred to as free). Certain conformations have an energy minimum in the sense that, whatever the direction of the internal rotation, the sum of the energies of non-bonding interactions increases, i.e. the potential energy of the molecule as a whole also increases. All conformations of this type have a certain stability, but the energy minima in different conformations of a single molecule may have unequal depths; for this reason, their stabilities also differ. The most favourable of these conformations of a molecule is frequently referred to as the usual conformation or simply as the conformation of the given molecule. On the other hand, other conformations are distinguished by energy maxima, i.e. internal rotation can only decrease their energy. Naturally, such conformations are unstable. Since the transitions from one favourable conformation to another by internal rotation necessarily proceed via conformations with maximum energies, such unfavourable conformations are frequently called rotational barriers. Thus one may say that the ease of transition from one favourable conformation to another is determined by the height of the barrier separating them. On rotation of one part of the molecule relative to another about a bond, a series of rotational barriers are overcome in succession. Therefore it would be incorrect to call such rotations free.

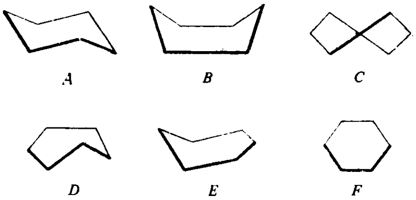


Figure 1. Conformations of cyclohexane: *A*) chair form; *B*) boat form; *C*) twist form; *D*) half-chair form; *E*) envelope form; *F*) planar form.

All that has been said above must be taken into account in one way or another in an experimental study and discussion of the stereochemistry of catalytic reactions. In particular, according to the concepts of classical stereochemistry, cyclohexane can exist in two states free from angular strain—the chair and boat forms (Figs. 1*A* and 1*B*). However, Raman[9] and infrared[10] spectra, electron diffraction[11], and other physical methods have shown that in fact it exists in virtually only one state. This finding was explained by conformational concepts.

It was found that cyclohexane can exist in six conformations (Figs. 1*A*–1*F*), which are energetically non-equivalent. In form *F* the conformational strain is greatest owing to the particular proximity of all six adjacent hydrogen atoms on either side of the ring. In addition there is in this case also a considerable Baeyer strain. Hydrogen atoms assume the most favourable positions in form *A* and it is least strained. It is followed, as regards the amount of strain, by form *C* and then form *B*. All these factors can be traced on special Stuart–Briegleb models taking into account the conformational volumes of the atoms. The difference between the energies of forms *A* and *C* is 5–6 kcal mole^{-1} which is sufficiently large for the concentration of form *C* in real cyclohexane to be much less than 1%. Therefore cyclohexane normally consists of molecules in the chair form. The energy relations of the most interesting transitions between the three conformations of cyclohexane are presented in Fig. 2.

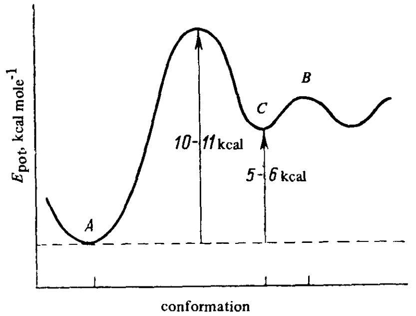


Figure 2. Potential curves for the interconversions of cyclohexane conformers (*A*, *B*, and *C*)—see Fig. 1.

When one of the hydrogen atoms in the cyclohexane molecule is replaced by a CH_3 group, the latter can be either in an equatorial (*e*) or an axial (*a*) position. However, in the *a*-form the non-bonding interactions between the methyl group and the hydrogen atoms in the 3- and 5-positions (the so called 1,3-interactions) prove to be fairly appreciable. On the other hand, in the *e*-form the CH_3 group is relatively remote from the ring and such interactions do not occur. The difference is 1.6–1.8 kcal mole^{-1}.[12] Thus methylcyclohexane is predominantly in the *e*-form. Thermodynamic calculations[12] and also electron diffraction data[11] confirm this conclusion. It has been shown experimentally[13] that at 25°C equilibrium is rapidly established between the *e*- and *a*-forms in which about 95% of the molecules are in the *e*-form and only 5% in the *a*-form. This does not of course mean that methylcyclohexane must react only in the *e*-form, since the energy barrier between the two conformations is lower than the activation energy for the majority of reactions.

When two hydrogen atoms in the cyclohexane molecule are replaced by substituents, for example in dimethylcyclohexane, a new type of stereoisomerism arises—the *cis–trans* isomerism of di- and poly-substituted cycloalkanes. According to conformational analysis, *cis*-1,2-, *trans*-1,3-, and *cis*-1,4-dimethyl-cyclohexanes each have one axial and one equatorial group. Only one conformation is possible for them, since ring inversion yields an identical structure, i.e. $ea \rightleftharpoons ae$. On the other hand, *trans*-1,2-, *cis*-1,3-, and *trans*-1,4-dimethylcyclohexanes might each consist of two forms—*ee* and *aa*. However, the powerful non-bonding 1,3-interaction of two axial CH_3 groups in dimethylcyclohexane and hydrogen atoms gives rise to an additional strain in the molecule. It is so great that the concentration of the diaxial form in the equilibrium mixture proved to be negligible.

It must be specially emphasised that conformational isomers, for example the diequatorial and diaxial forms of *trans*-1,2-dimethylcyclohexane, can be converted into one another as a result of rotation about single C–C bonds. This is a usual case of rotational isomerism and therefore on conversion of one chair-form into another the configuration of dialkylcyclohexane does not change. On the other hand, *cis*- and *trans*-dialkylcycloalkanes are configurational isomers, i.e. they differ by the steric distribution of groups about one of the asymmetric carbon atoms. Consequently the interconversion of the *cis*- and *trans*-isomers requires a rearrangement, i.e. a "jump" by the substituents at this asymmetric carbon atom from one position to another, which necessarily involves the dissociation of the old and the formation of a new bond and consequently a considerable energy expenditure.

Many of the points discussed above refer to a greater or lesser degree also to cyclopentane hydrocarbons. The stereochemistry of this class of hydrocarbons has now been investigated in fair detail.

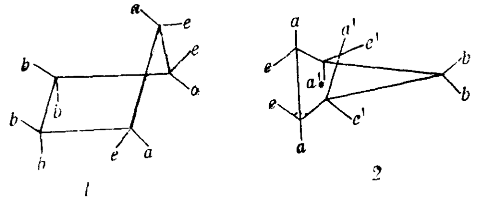


Figure 3. Conformations of cyclopentane: *1*) envelope form; *2*) half-chair form; (*a* and *a'*—axial and quasiaxial bonds respectively; *e* and *e'*—equatorial and quasiequatorial bonds; *b*—bisectional bonds).

Experimental measurements of the entropy of gaseous cyclopentane[14,15] and calculated data[12] show that the cyclopentane ring is not coplanar. According to conformational considerations analogous to those for cyclohexane, the planar conformation of cyclopentane is highly strained. Therefore the ring bends in space owing to the internal strain and some distortion of the valence angles. In this process two conformations are produced: the envelope and half-chair forms (Fig. 3), similar to the corresponding conformations of cyclohexane. Their Baeyer strain is greater than in the planar form but this is compensated by an energy gain owing to the decrease of the conformational strain. The envelope form is slightly more favourable than the half-chair form. As in cyclohexane, the side bonds in cyclopentane are not identical. In the envelope form there are equatorial (*e*) and axial (*a*) bonds (Fig. 3), fully analogous to the corresponding positions in cyclohexane. In the half-chair form there exist also quasiequatorial (*e'*) and quasiaxial (*a'*) bonds with slightly different directions relative to the "plane of the ring" compared with the *e* and *a* bonds. In addition in both forms there exists also a special bisectional (*b*) bond position which is energetically intermediate between the *e*- and *a*-bonds. The energy differences between the *e*- and *a*-positions in cyclopentane are smaller than in cyclohexane: for the methyl group, the energy difference is 0.75–0.9 kcal mole^{-1}.[16–18]

In cyclopentane the site where the ring atom is displaced from the plane is not fixed; the system undergoes simultaneously vibrations about the most stable position and pseudohomogeneous rotation in which the site of the bend rotates about the ring.

Like cyclohexane hydrocarbons, di- and poly-alkylcyclopentanes exist in the form of *cis*- and *trans*-isomers. *Trans*-1,2-dimethylcyclopentane is thermodynamically more stable, like *trans*-1,2-dimethylcyclohexane. For the same reason, *cis*-1,3-dimethylcyclopentane is more stable than the *trans*-isomer.

Proceeding now to the discussion of specific studies on catalytic hydrogenation, account must be taken of the characteristics of the steric structures of the starting materials and the final products. In many cases this approach leads to new possibilities for the elucidation of reaction mechanisms.

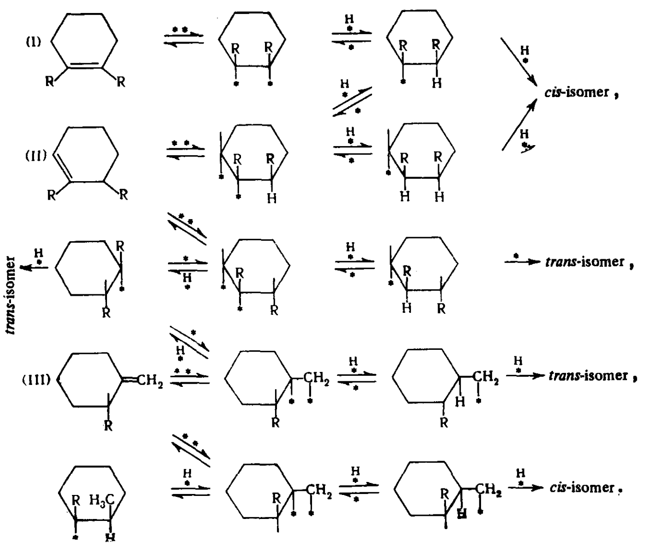


Figure 4. Mechanism of the hydrogenation of dialkylcyclo-olefins according to Siegel and Smith[20] (*—adsorption centre).

In a series of studies of Siegel and coworkers[2,7,19-22] and also in those of Burwell[1,23,24] and Sauvage and coworkers[25,26] certain definite generalisations have been made and certain considerations have been put forward concerning the mechanism of the hydrogenation of disubstituted cyclo-olefins in the presence of metal catalysts. However, one must not overestimate the information obtained in these studies, as there exist processes (for example the migration of the double bond in the ring) which must be taken into account for the concepts about the reaction mechanism to be adequately rigorous. For example, it is known that on a platinum catalyst there are differences in the rates and stereoselectivity of the hydrogenation of 1,2-dimethylcyclohexene and its 2,3-isomer. The structure of the first gives rise to its adsorption in the form of a π-complex or a σ-1,2-diadsorbed state, in which both CH_3 groups assume the *cis*-configuration on hydrogenation. On the other hand, in 2,3-dimethylcyclohexene the two sides of the ring are not identical. Therefore, when a substituent in the 3-position is directed away from the surface of the catalyst in the adsorption process, σ-1,2-diadsorbed *cis*-2,3-dimethylcyclohexane is formed as an intermediate, which is then desorbed as the *cis*-form. On the other hand, when the CH_3 group in the 3-position is directed towards the surface in the adsorption process, *trans*-1,2-dimethylcyclohexane is formed. To account for the observations made in the hydrogenation of cyclo-olefins, Siegel and Smith[20] proposed the mechanism shown schematically in Fig. 4.

The mechanism takes into account two important factors: (a) the simultaneous hydrogenation and migration of the double bond in the ring and (b) the effect of hydrogen on the hydrogenation and the relative rates of formation of the *cis*- and *trans*-isomers of 1,2-dimethylcyclohexanes.

Indeed it has been shown experimentally[20] that an increase of hydrogen pressure at 25°C over the initial 1,2-dimethylcyclohexene in acetic acid results in an increase of the amount of the *cis*-isomers of 1,2-dimethylcyclohexane in the catalytic reaction mixture (82% at atmospheric pressure and 93.5% at 150 atm H_2; see also Fig. 5).

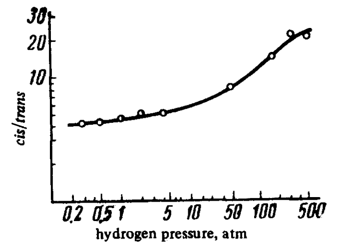
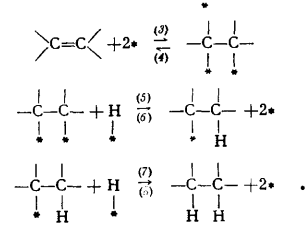


Figure 5. Variation of the stereoselectivity of the hydrogenation of 1,2-dimethylcyclohexene with hydrogen pressure[20].

According to Siegel and coworkers[7,20,21], the above mechanism of the hydrogenation of cyclo-olefins is consistent with the Horiuti–Polanyi mechanism[27] of the hydrogenation of unsaturated hydrocarbons:



$$H_2 + 2* \underset{(2)}{\overset{(1)}{\rightleftarrows}} 2\underset{\substack{|\\ *}}{H}$$

$$>C=C< + 2* \underset{(4)}{\overset{(3)}{\rightleftarrows}} -\underset{\substack{|\\ *}}{\overset{|}{C}}-\underset{\substack{|\\ *}}{\overset{|}{C}}-$$

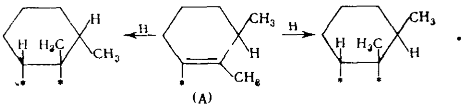
$$-\underset{\substack{|\\ *}}{\overset{|}{C}}-\underset{\substack{|\\ *}}{\overset{|}{C}}- + \underset{\substack{|\\ *}}{H} \underset{(6)}{\overset{(5)}{\rightleftarrows}} -\underset{\substack{|\\ *}}{\overset{|}{C}}-\underset{\substack{|\\ H}}{\overset{|}{C}}- + 2*$$

$$-\underset{\substack{|\\ *}}{\overset{|}{C}}-\underset{\substack{|\\ H}}{\overset{|}{C}}- + \underset{\substack{|\\ *}}{H} \underset{(8)}{\overset{(7)}{\rightleftarrows}} -\underset{\substack{|\\ H}}{\overset{|}{C}}-\underset{\substack{|\\ H}}{\overset{|}{C}}- + 2* \quad .$$

In their explanation of the increase of the concentration of *cis*-1,2-dimethylcyclohexane with increasing hydrogen pressure, the authors suggest that at sufficiently high hydrogen pressures the overall course of the reaction is determined by the formation of an αβ-diadsorbed state [reaction (3)]. On the other hand, at low hydrogen pressures the rate-limiting stage is the formation of the semihydrogenated state [reaction (5)]. According to Siegel[7], examination of the individual stages shows that the rate of reaction (3) is independent of hydrogen pressure†, while the rates of reactions (5) and (7) are functions of the surface concentration of hydrogen and consequently its pressure. Then the rate of stage (7) depends in the first place on the concentration of the semihydrogenated state, which is itself a function of hydrogen pressure, and in the second place it depends directly on the concentration of adsorbed hydrogen. Therefore stage (7) should be accelerated by increasing hydrogen pressure to a greater extent than all others. The increase of the yield of *cis*-1,2-dimethylcyclohexane with increasing hydrogen pressure is probably associated with this factor (Fig. 5). It is specially noted that the structures of the species adsorbed on the catalyst and produced by reactions (3) and (5) are significantly different: the diadsorbed species largely retains the geometry of the olefin, while the semihydrogenated state has essentially a saturated structure.

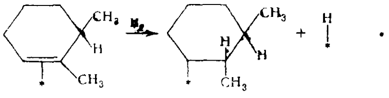
It is noteworthy that, although the mechanism proposed by Siegel and coworkers[20] (Fig. 4) is in fact consistent with the experimental data, it is by no means unique and has been criticised. Thus Bond and Wells[4] note that the reaction with such a mechanism should proceed towards the thermodynamically less stable cyclo-olefin—2,3-dimethylcyclohexene. Moreover, it appears unlikely that the latter would be desorbed to a sufficient extent.

Smith and Burwell[28] and also Sauvage and coworkers[25,26] proposed a different pathway for the formation of stereoisomeric cycloalkanes. These workers suggest that the intermediate stage in the hydrogenation may be the radical A disadsorbed by a dissociative mechanism, which then reacts with formation of both the *cis*- and *trans*-isomers:



(A)

Yet another interpretation of the appearance of *trans*-isomers in the hydrogenation of cyclo-olefins is that of Gault et al.,[29] who suggest the possibility of a direct addition of hydrogen from the bulk phase to the π-complex adsorbed on the catalyst surface:



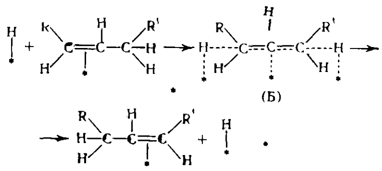
In this mechanism of hydrogenation the stage involving isomerisation to the corresponding 2,3-cyclo-olefins becomes obligatory for the formation of the *trans*-isomers from 1,2-dimethylcyclopentene and 1,2-dimethylcyclohexene. However, this as well as the preceding mechanism (in contrast to Siegel's work[7,20]) do not explain the experimental results obtained when the hydrogen pressure is altered (Fig. 5).

It is also necessary to note that in recent years the concept of intermediate adsorbed compounds of the π-allyl type has been successfully employed to explain the mechanism of hydrogenation, deuterium exchange, and other reactions of hydrocarbons[30-40]. A π-allyl complex of one metal atom and three carbon atoms with a common electron cloud, produced as a result of the loss of one hydrogen atom by the initial olefin, is then considered as the intermediate surface compound:

$$RCH{=}CHCH_2R' \xrightarrow[-H]{*} RCH{-}CH{-}CHR .$$

It is postulated that the adsorbed π-allyl compound has a structure similar to those of the known π-allyl complexes of palladium[41]. In this connection the finding[20] that the migration of the double bond in the hydrogenation of substituted cyclo-olefins takes place only in the presence of hydrogen is of undoubted interest. This phenomenon has features in common with the analogous relation in the case of open-chain olefinic hydrocarbons[42-44] and also the relations which we discovered[45] in a study of the configurational isomerisation of di-alkylcycloalkanes, described in Section IV.

In a discussion of the stereochemistry of the hydrogenation of disubstituted cyclopentanes in the presence of many Group VIII noble metals, we proposed an associative version of double bond migration in olefins, in particular in cyclo-olefins, with participation of activated hydrogen. The double bond migrates via a transition state of the π-allyl type (B), which subsequently decomposes into the isomeric cyclo-olefin and adsorbed hydrogen:



Within certain limits, this transition state (B) resembles the π-allyl complex described above, although in principle it differs from it by the fact that it is not a kinetically independent species and does not exist for any appreciable time on the catalyst surface. This last mechanism has the advantage, compared with the dissociative mechanism, in that it does not require the assumption of a complete dissociation of the C–H bond in the first reaction stage, which is known to require a considerable energy expenditure. Different versions of the adsorption of cyclo-olefins on the surface of various catalysts have been examined[46] and it has been concluded that the rate of migration of the double bond depends significantly on the geometry of the transition complex, determined by the nature of the catalyst.

Tables 1–3 present data on the stereoselectivity of the hydrogenation of various cyclo-olefinic hydrocarbons over platinum, palladium, and other Group VIII metal catalysts.

Examination of Table 1 reveals a considerable scope for the analysis and comparison of the data for the hydrogenation of cyclo-olefins of a very wide variety of structures and permits additional conclusions concerning the mechanism of this reaction. Table 1 shows that a definite relation obtains between the structures of the initial cyclo-olefins and the stereoselectivity of their hydrogenation on the same catalyst. For example, on PtO_2 the amount of the *cis*-isomer formed in the hydrogenation of the cyclo-olefins under consideration decreases in the sequence shown in Fig. 6.

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† Strictly speaking, the rate of reaction (3) depends on hydrogen pressure, since the number of free active centres on the catalyst surface on which the olefin may be adsorbed with formation of αβ-diadsorbed species depends on the amount of hydrogen in the system. When this factor is taken into account, Siegel's conclusion[7] becomes even more convincing, since at high pressures of H_2 an increase in its amount in the system lowers the rate of formation of αβ-diadsorbed species even more [reactions (3) and (6)].

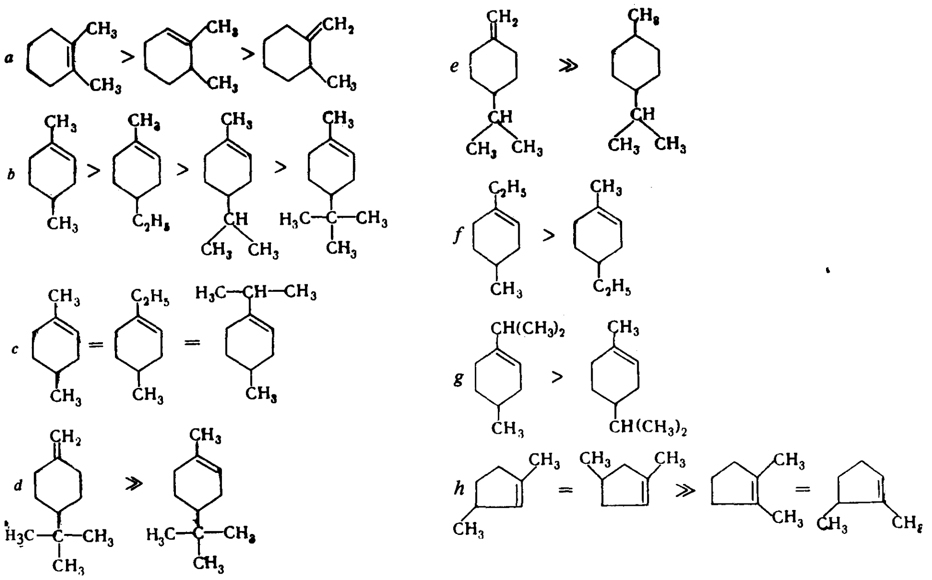

Figure 6. Relative decrease of the formation of the *cis*-isomer in hydrogenation over PtO_2.

Table 1. Stereoselectivity of the hydrogenation of certain dialkylcyclohexanes and alkylalkylenecyclohexanes in the presence of PtO_2 [19,25], Pd/C,[26] and Rh/C [47] at 25°C in acetic acid.

Initial hydrocarbon	*cis*-Isomer in hydrogenation products, %					
	1 atm. H_2, PtO_2		2.5 atm. H_2, PtO_2	1 atm. H_2, Pd/C		1 atm. H_2, Rh/C
	complete hydrogenation	partial hydrogenation		complete hydrogenation	partial hydrogenation	
1,2-Dimethylcyclohexene	$82^a.83^b$	81^c	78	—	25^d	—
2,3-Dimethylcyclohexene	$77^a.72^b$, 77^c	75^a	70	—	23^d	—
2-Methyl-1-methylenecyclohexane	$70^a.70^c$	69^a	64	—	28^d	—
1,3-Dimethylcyclohexene	74	74	77	—	—	—
2,4-Dimethylcyclohexene	—	—	70	—	—	—
3-Methyl-1-methylenecyclohexane	—	—	68	—	—	—
1,4-Dimethylcyclohexene	57	57	55	28	31	61
4-Methyl-1-methylenecyclohexane	75	74	56	29	29	—
1-Ethyl-4-methylcyclohexene	58	58	—	27^e	—	55
4-Ethyl-1-methylcyclohexene	48	47	—	24^e	—	55
1,4-Diethylcyclohexene	—	49^e	—	25^e	—	54
4-Isopropyl-1-methylcyclohexene	43	43	—	26	21	52
1-Isopropyl-4-methylcyclohexene	58	50	—	21	—	54
4-Isopropyl-1-methylenecyclohexane	81	83	—	24	20	—
1-Isopropylidene-4-methylcyclohexane	36	—	—	18	—	—
4-t-Butyl-1-methylcyclohexene	37	36^f	—	—	34^h	—
4-t-Butyl-1-methylenecyclohexane	83	$83^f.70^g$	—	—	33^h	—

a) 1 atm H_2 (Ref. 20); b) 2 atm H_2 (Ref. 20); c) 0.5 atm H_2 (Ref. 20); d) Pd/Al_2O_3 (Ref. 20); e) Ref. 47; f) Ref. 21; g) Pt/Al_2O_3 (Ref. 21); h) Pd/Al_2O_3 (Ref. 21).

Table 2. Stereoselectivity of the hydrogenation of dialkylcyclopentenes and 2-methyl-1-methylenecyclopentanes on various Group VIII metals at 25°C and 1 atm of H_2 in n-hexane[46].

Initial cyclo-olefin	Catalyst	*cis*-Isomer in hydrogenation product, %	Initial cyclo-olefin	Catalyst	*cis*-Isomer in hydrogenation product, %
1,2-Dimethylcyclopentene	Pt/C	35^a	1,2-Dimethylcyclopentene	Ir/C	90^a
ditto	Pd/C	35^a	2-Methyl-1-methylenecyclopentane	Pd/C	$\sim25^b$
»	Rh/C	65^a	2-Ethyl-1-methylcyclopentene	Rh/C	60^a

a) The initial hydrocarbon contained 20% of the corresponding 2,3-dialkylcyclopentene.
b) In acetic acid solution[21].

For example row *a* shows the most favourable positions of the double bond in the six-membered cyclo-olefin for the *cis*-addition of hydrogen. On the other hand, the identical proportions of the *cis*- and *trans*-isomers obtained in the hydrogenation of 1,2- and 2,3-dimethylcyclopentenes (row *g*) suggest that, under the chosen conditions, the interconversion of these isomers is significantly faster than their hydrogenation. Row *c* shows that the length and bulk of the group located directly at the double bond do not in fact affect the stereoselectivity of the hydrogenation of cyclohexenes. This conclusion should probably still be regarded as preliminary, since the hydrocarbons investigated do not include 1-t-butyl-4-methylcyclohexene. The bulky substituent at the double bond can screen it to a certain extent, altering the stereoselectivity of the hydrogenation. At the same time examination of row *b* indicates a definite influence of the bulk of the substituent in the 4-position relative to the double bond: in the hydrogenation of 4-t-butyl-1-methylcyclohexene the amount of the *cis*-isomer formed is much less than in the case of 1,4-dimethylcyclohexene. Naturally, the above relations may be modified by altering the experimental conditions, in particular the catalyst, pressure, etc.

It follows from Table 1 that platinum and palladium catalysts exhibit different stereoselectivities in the hydrogenation of cyclohexenes. On a platinum catalyst in acetic acid solutions, the hydrogenation products are mainly the *cis*-isomers, while on a palladium catalyst the products are the *trans*-isomers. According to the view of Gault et al.,[29] these facts can be accounted for by the different capacities of these metals for the formation of intermediate π-allyl complexes. While on palladium π-allyl complexes predominate, on platinum the reaction proceeds to a considerable degree also with participation of a σ-bonded intermediate compound.

Table 3. Stereoselectivity of the hydrogenation of certain dialkylcyclopentenes in the presence of PtO_2 at 25°C in acetic acid[21] and under other conditions[48-50] (unless otherwise stated the figures refer to Ref. 21).

Initial hydrocarbon	*cis*-Isomer in hydrogenation product, %		Initial hydrocarbon	*cis*-Isomer in hydrogenation product, %	
	at 1 atm H_2	at 3 atm H_2		at 1 atm H_2	at 3 atm H_2
1,2-Dimethylcyclopentene	43;49[a]	45	2-n-Butyl-1-methylcyclopentene	28[b,c]	—
2,3-Dimethylcyclopentene	44	41	1-Ethyl-2-n-propylcyclopentene	13[c,d]	—
2-Methyl-1-methylene-cyclopentane	81	71	2-n-Butyl-1-ethylcyclopentene	14[c,d]	—
1,3-Dimethylcyclopentene	92	91	1,2-Dibutylcyclopentene	16[c,d]	—
2,4-Dimethylcyclopentene	91	91			

a) Pt black[48]. b) Pt/C (without solvent)[49]. c) The initial hydrocarbon contained 15–40% of the corresponding 2,3-dialkylcyclopentene. d) Pt/C (in alcohol)[50].

Table 1 shows that the stereospecificity of rhodium in the hydrogenation of cyclohexenes is very similar to that of platinum. The different stereoselectivities of various Group VIII noble metals in hydrogenation have been demonstrated by Bragin et al.,[46] for 1,2-dialkylcyclopentenes (Table 2). It was found (Fig. 7) that in a neutral n-hexane medium rhodium and particularly iridium catalysts form preferentially *cis*-dialkylcyclopentanes, while platinum and palladium catalysts give rise mainly to the *trans*-isomers.

Table 3 presents data on the hydrogenation of a number of dialkylcyclopentenes in the presence of various platinum catalysts. The specific effect of various catalysts (platinum, palladium, and rhodium) is also shown in the hydrogenation of octalins:

9,10-octalin

1,9-octalin

It might have been expected that 9,10-octalin would tend to undergo only *cis*-addition under the conditions of heterogeneous hydrogenation. However, as for 1,2-dimethylcyclopentene and 1,2-dimethylcyclohexene, the hydrogenation of 9,10-octalin on various catalysts results in the formation of both *cis*- and *trans*-decalins. The results are presented in Table 4.

It would appear that the relations obtained might be accounted for by the above considerations concerning the mechanism of the hydrogenation of 1,2-dimethylcyclohexene. However, it has been observed that the hydrogenation of 1,9-octalin catalysed by palladium yields more *cis*-decalin than the hydrogenation of 9,10-octalin. Therefore in this case the formation of *trans*-decalin from 9,10-octalin cannot be a result of the isomerisation of the latter to 1,9-octalin. The data in Table 4 as well as the results given previously show that, among the three metals discussed, the rhodium catalyst favours most the *cis*-addition of hydrogen.

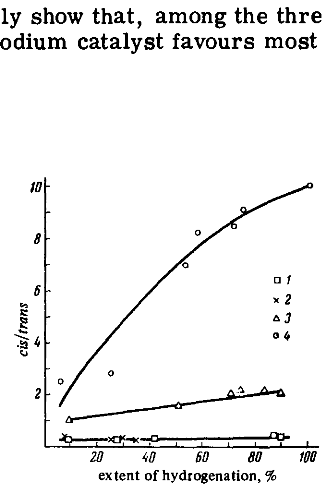

Figure 7. Stereoselectivity of the hydrogenation of 1,2-dimethylcyclopentene on Group VIII metals[46]: *1*) Pt/C; *2*) Pd/C; *3*) Rh/C; *4*) Ir/C.

The solvent and in particular the pH have a great influence on the stereoselectivity of liquid-phase hydrogenation. Thus Skita[53] and Auwers[54] showed that the hydrogenation of cyclo-olefins in an acid medium takes place mainly with formation of *cis*-isomers and in a neutral medium with formation of *trans*-isomers. Later this was also noted by Kazanskii and coworkers[55,56].

Table 4. Stereoselectivity of the hydrogenation of octalins in the presence of a number of Group VIII metals at 20°C at atmospheric pressure in acetic acid.

Octalin hydrogenated	Catalyst	*cis*-Isomer in hydrogenation products, %	References
9,10-Octalin	Pd/C	10; 7[a]	26
ditto	$Pd/BaSO_4$	12	26
»	PtO_2	51; 50	25; 51
»	Pt black	66; 50[b]	52
»	Rh/C	74; 67[a]	24
1,9-Octalin	Pd/C	21	26
ditto	$Pd/BaSO_4$	23	26

a) In ethyl alcohol. b) In ether.

The stereoselectivity of the hydrogenation of a triple bond in a cyclic hydrocarbon is also of definite interest. Partial hydrogenation of a cyclononyne, cyclodecyne, and cycloundecyne over various palladium catalysts results as a rule in the formation of a *cis*-olefin, i.e. *cis*-addition of hydrogen takes place[57-62]. Table 5 presents the conditions and results of the hydrogenation of the above cyclic acetylenic hydrocarbons in the presence of various palladium catalysts.

Turner and Meador[63] obtained data on the heat of hydrogenation of the *cis*- and *trans*-isomers of cyclo-octene, cyclononene, and cyclodecene and found that in acetic acid solution in the presence of PtO_2 the heat of hydrogenation of the *trans*-isomers is greater than that of the corresponding *cis*-isomers.

Examination of the above versions of the hydrogenation mechanism leads to the conclusion that none of them can account for all the experimental data available. Probably there is as yet no general mechanism for the hydrogenation of cyclo-olefins. It may be that, as the system (initial hydrocarbon, catalyst, and solvent) and the hydrogenation conditions are altered, there is also an appreciable change also in the reaction mechanism. Whereas under conditions of liquid-phase hydrogenation at room temperature and atmospheric pressure π-complexes and compounds of the π-allyl type may predominate as intermediates, under more severe conditions the reaction may proceed also via some other mechanism. Then in many cases factors such as the nature of the catalyst, the geometry of the active surface, the polarity of the medium, the structure of the initial cyclo-olefin, etc., play a decisive role. A significant role must be attributed in this case also to intramolecular isomerisation—the migration of the double bond in the ring. This process is undoubtedly fairly significant in all the reactions examined above and itself depends greatly on the nature of the primary adsorption of the initial compounds on the surface of the catalyst.

Table 5. Stereoselectivity of the hydrogenation at 25°C of cyclic C_9–C_{11} hydrocarbons containing a triple bond.

Initial hydrocarbon	Catalyst	Solvent	Reaction product	References
Cyclononyne	$Pd/BaCO_3$	ethyl acetate	*cis*-cyclononene	57
ditto	Pd/norite	methanol with admixture of pyridine	ditto	58
Cyclodecyne	$Pd/CaCO_3$	methanol	*cis*-cyclodecene	59
ditto	$Pd/BaCO_3$	ethyl acetate	ditto	60
	$Pd/CaCO_3$	petroleum ether (b.p.60-70°) with admixture of quinoline	»	61
	Pd/norite	methanol with admixture of pyridine	»	58
Cycloundecyne	$Pd/CaCO_3$	methanol	*cis*-cycloundecene	62
ditto	Pd/norite	methanol with admixture of pyridine	93% *cis*- and 7% *trans*-cycloundecene	58

According to the literature[34-36], the hydrogenation of cyclohexenes may be regarded to some extent as one of the stages of the hydrogenation of aromatic hydrocarbons. Therefore the data in the present section constitute to an appreciable degree an introduction to the next. Both sections are related and supplement one another.

III. HYDROGENATION OF AROMATIC HYDROCARBONS

The study of the stereoselectivity of the hydrogenation of di- and poly-substituted aromatic hydrocarbons can greatly expand the existing concepts concerning the mechanism of the hydrogenation of benzene and its derivatives. The conclusions arrived at in many studies are largely the same as those obtained in the hydrogenation of di- and poly-substituted cyclohexenes, although in many cases the specific characteristics of the initial substances hydrogenated are shown to some extent.

The hydrogenation of aromatic hydrocarbons has been investigated by many workers on different catalysts under different conditions (solvent, temperature, pressure). However, the stereochemical aspect of this reaction has as yet been inadequately examined, since the majority of studies have been of a purely preparative type. In the main the hydrogenation of di- and poly-alkyl benzenes has been studied on platinum and nickel catalysts. It was found that on both catalysts a certain amount of *trans*-isomers was formed as well as the *cis*-isomers. Nevertheless it would appear that simple addition of six hydrogen atoms to the aromatic ring when the latter undergoes planar adsorption should lead exclusively to the *cis*-form. Therefore here the following questions are mainly of interest: in what way are the *trans*-isomers of the cyclohexane series formed and via what intermediate stages, and whether these intermediate compounds are desorbed (at least partially) with subsequent readsorption on the catalysts or do all stages take place directly in the adsorption layer? The amount of *trans*-isomer formed depends on the nature of the catalyst and the hydrogenation conditions. Table 6 demonstrates the most typical results for

Table 6. Stereoselectivity of the hydrogenation of certain aromatic hydrocarbons on Group VIII metals[a].

Initial hydrocarbon	Catalyst	Hydrogenation temp., °C	*cis*-Isomer in hydrogenation products, %	References
1	2	3	4	5
o-Xylene	PtO_2	25[b]	95	19
ditto	PtO_2	25	92	64
»	PtO_2	25[c]	93	64
»	Pt black	25	~91	65
»	PtO_2	85	87.3	66
»	Os/asbestos	50—70	*cis*[d]	67
»	Rh/C	100[e]	89.2	68
»	Ru/C	100[e]	92.6	68
»	(2.5%Rh + 2.5%Pt)/C	100[e]	91.4	68
»	Ni	175	*trans*[d]	67
»	Ni	180	~50	65
m-Xylene	PtO_2	25	86	19
ditto	PtO_2	25	77	64
»	PtO_2	25[c]	85	64
»	PtO_2	25[f]	77	69
»	PtO_2	84	81	66
»	Rh/C	100[e]	73.7	68
»	Ru/C	100[e]	84.5	68
»	(2.5%Rh + 2.5Pt)/C	100[e]	77.4	68
p-Xylene	PtO_2	25[b]	74	19
ditto	PtO_2	25	73	64
»	PtO_2	25[c]	82	64
»	Os/asbestos	50—70	*cis*[d]	67
»	PtO_2	85	66.6	66
»	Rh/C	100[e]	63.6	68
»	Ru/C	100[e]	69.7	68
»	Pd/C	160[e]	47.3	68
»	(2.5%Rh + 2.5%Ru)/C	100[e]	55.4	68
»	(2.5%Rh + 2.5%Pt)/C	100[e]	64.5	68
»	(2.5%Rh + 2.5%Pd)/C	100[e]	65.0	68
»	Pt black	200	20	65
»	Ni	175	*trans*[d]	67
»	Ni	180	20	65
o-Ethyltoluene	PtO_2	25[b]	77	70
p-t-Butyltoluene	»	25	61	64
ditto	»	25[c]	71	64
p-Di-isopropylbenzene	Raney Ni (dehydrated)	190[d]	~50	71
Tetralin	PtO_2	25[f]	91	69
Naphthalene	PtO_2	25[f]	77	69
1,3,5-Trimethylbenzene	Pt, Ni	175	90	72
1,3,5-Triethylbenzene	»	175	97	72

a) Unless otherwise stated, the dehydrogenation was carried out at atmospheric pressure.
b) Hydrogenation at 2.5 atm H_2.
c) Hydrogenation at 300 atm H_2.
d) Predominantly the isomer specified.
e) Hydrogenation at 70 atm H_2.
f) Hydrogenation at 120 atm H_2.

the stereoselectivity of the hydrogenation of *o*-, *m*-, and *p*-xylenes and also certain other di- and tri-alkylbenzenes over various heterogeneous catalysts.

Analysis of Table 6 leads to the isolation of a number of relations.

1. Under mild hydrogenation conditions, a mixture of the *cis*- and *trans*-isomers is obtained, but the former as a rule predominates.

2. In the hydrogenation of 1,2- and 1,4-dialkylbenzenes, the relative amount of the *trans*-isomer increases and becomes dominant as the temperature is raised from 25° to 180°C. In the hydrogenation of *m*-xylene in the same temperature range, constant preferential formation of the *cis*-isomer is observed. One should remember that in the 1,2- and 1,4-series the *trans*-isomers are energetically more favoured (*ee*-substituents) than the *cis*-isomers (*ae*-substituents), while in the 1,3-series the *cis*-isomers are diequatorial and therefore energetically more favoured.

3. The relative amounts of the *cis*- and *trans*-isomers obtained in the hydrogenation of each of the three xylenes are related to the relative positions of the substituents. In the hydrogenation of xylenes under similar conditions the content of the *cis*-isomer in the reaction product diminishes in the sequence *ortho* > *meta* > *para* (for example in the hydrogenation over PtO_2 at 25°C in acetic acid or over Rh/C and Ru/C at 100°C).

4. Tetralin and naphthalene‡ behave under similar hydrogenation conditions like 1,2-dialkylbenzenes and 1,3,5-trialkylbenzenes behave like 1,3-dialkylbenzenes. Not only the nature of the metal employed but also its relative content in the catalyst has a considerable influence on the stereoselectivity of the hydrogenation. It has been found that in the hydrogenation of *o*- and *p*-xylenes on Rh/C the content of the *trans*-form of the corresponding dimethylcyclohexane increases with the concentration of the metal in the catalyst; on the other hand, in the hydrogenation of *m*-xylene the content of the *trans*-form of 1,3-dimethylcyclohexane diminishes somewhat. The relevant data are presented in Table 7.

The study of the effect of the carrier is very important in an examination of the stereoselectivity of the hydrogenation of the aromatic ring. Table 8 presents the results of the hydrogenation of all three xylenes on 5% rhodium, and ruthenium catalysts deposited on different carriers. It has been shown that, among the six carriers investigated, activated charcoal leads to preferential *cis*-addition of hydrogen; moreover, it has been discovered that as a rule more *cis*-isomers are formed on the ruthenium catalyst than on rhodium.

The mechanism of the hydrogenation of aromatic hydrocarbons has been discussed by many investigators, but the problem is very complex and there is as yet no generally accepted view on this subject. According to the multiplet theory, the hydrogenation of aromatic compounds on the surface of metal catalysts takes place with planar adsorption of the aromatic ring on the metal surface (platinum, nickel, cobalt, copper, ruthenium, iridium, palladium, rhodium, osmium, and rhenium). This mechanism has been discussed in a number of papers by Balandin[73] and many Soviet and non-Soviet investigators have shown that the above metals, which have a face-centred cubic or hexagonal lattice with interatomic distances in the range up to 2.49 Å for nickel and 2.77 Å for platinum, are indeed hydrogenation–dehydrogenation catalysts. According to the multiplet theory, when an aromatic ring undergoes planar adsorption, it does not leave the active centre until six hydrogen atoms have added either in succession or all at once. The problem of the formation of *trans*-substituted cyclohexanes remains open.

Table 7. Stereoselectivity of the hydrogenation of xylenes on various Rh/C* catalysts[68].

Catalyst (wt.g)	Initial xylene	*trans*-Dimethylcyclohexane in hydrogenation products, %	Catalyst (wt.g)	Initial xylene	*trans*-Dimethylcyclohexane in hydrogenation products, %
5%Rh/C (0.3)	*ortho-*	10.8	5%Rh/C (0.3)	*para-*	36.4
30%Rh/C (0.3)	*ortho-*	18.7	30%Rh/C (0.3)	*para-*	48.9
5%Rh/C (0.3)	*meta-*	26.3	30%Rh/C (0.05)	*para-*	47.0
30%Rh/C (0.3)	*meta-*	23.0			

* All the experiments were carried out at 100°C and an initial pressure of 70 atm H_2.

In their discussion of the mechanism of the hydrogenation of benzene, Farkas and Farkas[74] suggested that the rate-limiting stage of this reaction is the interaction of the adsorbed benzene with two adsorbed hydrogen atoms:

$$C_6H_6(\text{ads.}) + 2H(\text{ads.}) \xrightarrow[\text{slow}]{} C_6H_8(\text{ads.}) \xrightarrow[\text{fast}]{2H_2} C_6H_{12} + \text{catalyst (Ct)}\,.$$

Table 8. Effect of the carrier on the stereoselectivity of the hydrogenation of three individual xylenes on rhodium and ruthenium catalysts[68]*.

Catalyst	*trans*-Forms of dimethylcyclohexanes in hydrogenation products, %		
	1.2-	1.3-	1.4-
Rh/C	6.5	15.6	22.7
Ru/C	3.0	9.3	23.8
Rh/kieselguhr	7.1	19.7	31.9
Ru/kieselguhr	6.0	—	27.0
$Rh/SrCO_3$	8.0	23.8	25.0
$Ru/SrCO_3$	4.3	11.8	31.8
$Rh/BaCO_3$	15.8	30.3	30.3
$Ru/BaCO_3$	3.6	15.7	27.6
$Rh/BaSO_4$	14.2	18.2	34.5
$Ru/BaSO_4$	5.2	14.4	—
Rh/Al_2O_3	8.0	27.8	29.5
Ru/Al_2O_3	9.7	14.7	29.4

* All the experiments were carried out at 20°C and an initial pressure of 3.5 atm H_2; all the catalysts contained 5 wt.% of the metal.

At the same time according to these authors, deuterium exchange involving benzene takes place via a dissociative mechanism:

$$C_6H_6 + \text{Ct} \rightarrow C_6H_5(\text{ads.}) + H(\text{ads.})$$

and further

$$C_6H_5(\text{ads.}) + D(\text{ads.}) \rightarrow C_6H_5D + \text{Ct}\,.$$

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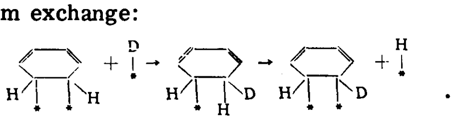
‡ The stereochemistry of the hydrogenation of these hydrocarbons and their homologues in the presence of metal catalysts has been described in detail in a recently published review by Weitkamp[8].

According to Horiuti and Polanyi[27], both reactions (hydrogenation and deuterium exchange) involve an associative mechanism and in the first case the two hydrogen atoms are added consecutively:

Hydrogenation:

$$C_6H_6(ads.) + 2H(ads.) \rightarrow C_6H_7(ads.) + H(ads.) \xrightarrow[slow]{} C_6H_8(ads.) \xrightarrow[fast]{2H_2} C_6H_{12} + Ct.$$

Deuterium exchange:



Later Greenhalgh and Polanyi[75] showed that, if in deuterium exchange via the dissociative mechanisms the rate-determining stage is the interaction of the adsorbed phenyl radicals with a deuterium atom, then both mechanisms (dissociative and associative) are described by the same kinetic equation.

In a number of studies[76-78] of the hydrogenation of benzene on a nickel catalyst and of xylenes on ruthenium, rhodium, nickel, and PtO_2 catalysts, the formation of a small amount of the corresponding cyclo-olefins was observed. Thus in the hydrogenation of *p*-xylene[77] the formation of 1,4-dimethylcyclohexene was discovered and in the hydrogenation of *m*-xylene that of 1,3- and 2,4-dimethylcyclohexenes, although the rates of hydrogenation of cyclo-olefins are significantly higher than those of the corresponding aromatic hydrocarbons[79]. On this basis, Siegel and coworkers[78] suggest that the hydrogenation of aromatic hydrocarbons in the presence of heterogeneous catalysts proceeds via the intermediate formation of cyclo-olefins, which are then very rapidly hydrogenated further in accordance with the mechanism described previously (Fig. 4).

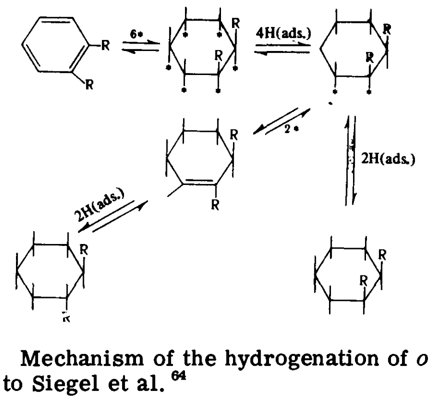
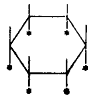


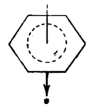
Figure 8. Mechanism of the hydrogenation of *o*-xylene according to Siegel et al.[64]

The mechanism proposed by Siegel and coworkers[64] is presented below in Figs. 8, which shows the possible pathways in the formation of the *cis*- and *trans*-isomers of 1,2-dimethylcyclohexane from *o*-xylene. In the same study the authors investigated the relative amounts of the *cis*- and *trans*-isomers as a function of hydrogen pressure. It was found that for aromatic hydrocarbons, as for cyclo-olefins, this ratio increases with hydrogen pressure. However, it follows from the work of Siegel and coworkers[19,20,64] that the hydrogenation of xylenes gives an appreciably greater amount of the *cis*-isomers than the hydrogenation of the corresponding cyclo-olefins. Therefore the considerations adduced above concerning the hydrogenation mechanism do not appear very convincing.

The most widely held view, which has been reflected in a number of investigations[34,35,64] in recent years, is that the hydrogenation reactions of aromatic hydrocarbons and cyclo-olefins have a number of stages in common. Therefore both can involve common partially hydrogenated intermediates adsorbed on the surface of the catalyst. One can easily imagine two versions of the adsorption of the aromatic ring on the catalyst: (I) the formation of six new σ bonds[64] and (II) the formation of a π complex of benzene with the catalyst[35]:



(I)



(II)

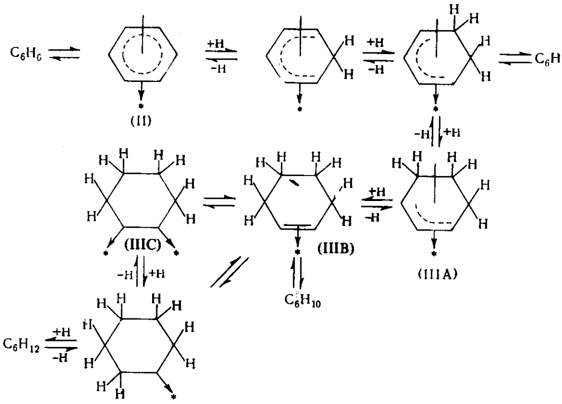


Figure 9. Mechanism of the hydrogenation of benzene according to Rooney[35].

We believe that model (II) is energetically more favoured and hence more probable. Rooney[35] represents the hydrogenation of benzene as a process involving the transformation of (II) via a series of intermediates into cyclohexene and further into cyclohexane. Then the cyclohexene adsorbed on the catalyst surface is represented either as a π-allyl adsorbed structure (IIIA) or as a π-complex (IIIB) (see the mechanism in Fig. 9). Probably the stereoselectivity of the hydrogenation of dialkylbenzenes depends primarily on the last step in the transformation of structure (IIIA) or (IIIB) [or their σ-diadsorbed analogue (IIIC)] into the corresponding dialkylcyclohexane. In turn, the similarity (or the difference) in the stereoselectivity of the hydrogenation of disubstituted aromatic compounds and the corresponding cyclohexenes can serve as a criterion of the similarity of the mechanisms of the hydrogenation of the hydrocarbons in these classes. It is noteworthy that, according to Rooney, the structures (IIIA) and (IIIB) represented in the above mechanism may be hydrogenated not only by adsorbed hydrogen but also by the hydrogen in the bulk phase. Thus, these concepts may account for the formation of *cis*- and *trans*-cyclohexanes in the hydrogenation of aromatic compounds.

In conclusion of this section it must be emphasised that, under mild hydrogenation conditions (Table 6), *cis*-addition of hydrogen with the formation of the *cis*-isomer predominates. Under more severe conditions, the situation changes: as mentioned above, with increase of temperature, the amount of the *trans*-isomer rises appreciably. We believe that this phenomenon is largely caused by the configurational isomerisation of the *cis*-isomer formed in the hydrogenation process. Indeed, it has now been shown that in the presence of many Group VIII metals the *cis*- and *trans*-isomers of di- and poly-alkylcycloalkanes are interconverted at a high rate (see Section IV). However, in none of the studies quoted above is the possibility of such direct interconversions of stereoisomers under severe hydrogenation conditions of aromatic hydrocarbons in any way discussed. Nevertheless, as shown in the next section, such possibility must be taken into account. At the same time, it should be specially noted that under mild conditions (particularly at room temperature), configurational isomerisation does not take place. Therefore, it cannot be used to explain the formation of *trans*-isomers under these conditions. Indeed, at room temperature the mixture of the stereoisomeric 1,3-dimethylcyclohexanes in thermodynamic equilibrium should contain, according to calculation, only about 5% of the *trans*-isomers, but in the hydrogenation of *m*-xylene under these conditions 14–23% of *trans*-1,3-dimethylcyclohexane is formed (Table 6). Thus, in order to explain the formation of the *trans*-isomers in the hydrogenation of aromatic compounds, it is necessary to resort to a special mechanism. In this sense, Rooney's mechanism[35] is supported by insufficient evidence.

IV. CONFIGURATIONAL ISOMERISATION OF STEREOISOMERIC DI- AND POLY-ALKYLCYCLOALKANES

As already mentioned in the preceding section, until recently the mechanism and characteristics of the direct interconversion of the stereoisomeric di- and poly-alkylcycloalkanes were hardly discussed in the literature. However, these reactions have a direct bearing on the composition of the reaction products formed as a result of the hydrogenation of both cyclo-olefins and aromatic hydrocarbons. The mechanism below (Fig. 10) represents the reversible interconversion of the *cis*- and *trans*-forms of di-alkylcycloalkanes, which takes place readily in the presence of many Group VIII metals. In this process there is at least formally no addition of atoms to or their abstraction from the initial molecule, the molecular skeleton remaining unchanged, and only one of the alkyl groups migrates from one side of the ring to the other, i.e. the configuration of one of the ring carbon atoms changes. In this connection the reaction discussed received a special name—configurational isomerisation[80]. Below it will be shown why the term *cis–trans* isomerisation encountered in the literature should not be employed in this case. These interesting and at first sight simple reactions constitute a convenient model which may yield important information about the detailed mechanism of heterogeneous catalysis and about the intermediate activated complex, the formation and decomposition of which govern the course of this reaction.

Configurational isomerism was described for the first time by Zelinskii and Margolis[67] in 1932 for the stereoisomeric 1,2- and 1,4-dimethylcyclohexanes. These workers observed that the *cis*-forms of the above hydrocarbons are converted into the corresponding *trans*-forms under the influence of a nickel catalyst. Subsequent investigation showed that these reactions do not result in the formation of the individual stereoisomers but their mixtures, the composition of which approaches to some extent the composition of mixtures at thermodynamic equilibrium.

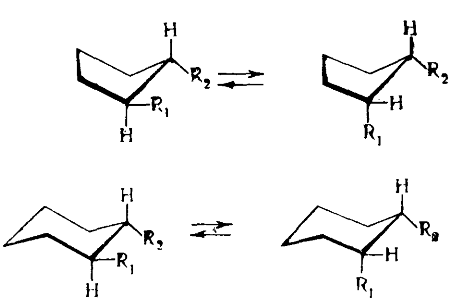
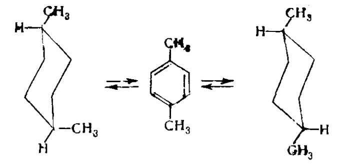


Figure 10. Configurational isomerisation of stereoisomeric 1,2-dialkylcycloalkanes.

Whereas in the series of cyclohexane homologues the mechanism of the interconversion of the stereoisomeric forms could be readily represented in terms of the intermediate formation of aromatic hydrocarbons,



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for other ring compounds (in particular cyclopentane homologues) such possibility is excluded. Therefore the work of Kazanskii et al.,[81] in which they observed for the first time configurational isomerism in the cyclopentane series, is extremely unexpected and interesting. It was shown that the hydrogenolysis of stereoisomeric 1,2,3-trimethylcyclopentane on a platinum catalyst is accompanied by configurational isomerisation. For any initial stereoisomer, the thermodynamically most stable $1^c,2^t,3^c$-form predominates in the catalytic reaction mixture, the amount of the $1^c,2^c,3^t$-isomer is significantly less, and the $1^c,2^c,3^c$-stereoisomer is present in an altogether negligible amount.

After this first publication on the configurational isomerisation of stereoisomeric trimethylcyclopentanes, this reaction was not discussed in the literature for about 15 years. Only at the beginning of the 1960's, after the work of Gault et al.[29] and the first publications by the present authors[82,83], configurational isomerisation of cyclopentane homologues became the subject of discussion by a number of Soviet and non-Soviet investigators. We showed[82] that in the presence of platinised charcoal stereoisomeric 1,2-dimethylcyclopentanes are readily interconverted over a wide temperature range (150–280°C). The configurational isomerisation takes place at a significantly higher rate than the accompanying hydrogenolysis of the five-numbered ring. Later we showed[83] that, together with platinum, rhodium, osmium, iridium, and palladium are also active catalysts promoting configurational isomerisation. Subsequently this range of catalysts was extended to include ruthenium[80] and cobalt[84].

Deuterium exchange in polymethylcyclopentanes on the surface of metallic films (platinum, palladium, nickel, and rhodium) was investigated[29]. Together with D–H exchange, a study was made of the configurational isomerisation of the *cis*- and *trans*-forms of 1,1,3,4-tetramethylcyclopentane and also *cis*-1,2-dimethylcyclopentane. Having investigated the kinetics of deuterium exchange and configurational isomerisation, Gault and coworkers concluded that the rates of both reactions are described by an equation for a first-order process and can be expressed as follows:

deuterium exchange:

$$-d(d_0)/dt = k_H[(d_0) - (d_0)_\infty]/[100 - (d_0)_\infty]\ ; \qquad (I)$$

configurational isomerisation:

$$-dx/dt = k_I(x - x_\infty)/(100 - x_\infty)\ , \qquad (II)$$

where k_H and k_I are the rate constants for reactions (I) and (II) respectively, d_0 is the concentration of the initial hydrocarbon not containing deuterium at time t, $(d_0)_\infty$ the equilibrium concentration of the initial hydrocarbon not containing deuterium, x the concentration of the initial *cis*- or *trans*-isomer at time t, and x_∞ the equilibrium concentration of the initial *cis*- or *trans*-isomer.

After simple rearrangement, these equations can be put in the form

$$\lg\frac{x - x_\infty}{x_0 - x_\infty} = \frac{k_I}{k_H}\,\frac{100}{100 - x_\infty}\,\lg\frac{(d_0)}{100} \qquad (III)$$

where x_0 is the concentration of the initial *cis*- or *trans*-isomer at time $t = 0$.

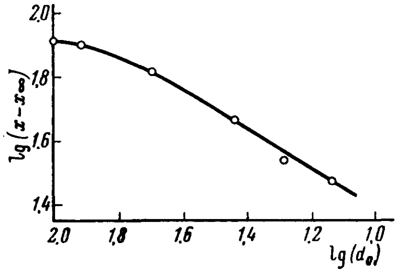
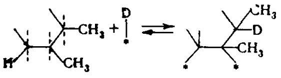


Figure 11. Relation between the configurational isomerisation and deuterium exchange of *cis*-1,1,3,4-tetramethylcyclopentane on a palladium catalyst[29].

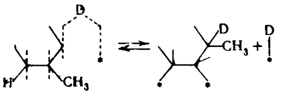
It follows from Eqn. (III) that the relation between $\lg(x - x_\infty)$ and $\lg(d_0)$ should be linear, which the authors indeed observed (Fig. 11) for the configurational isomerisation and deuterium exchange of *cis*-1,1,3,4-tetramethylcyclopentane on a palladium catalyst at 65°C in the above range of values of $\lg(d_0)$.

These data show that both reactions are definitely related: the greater the extent of deuterium exchange the more far-reaching is the configurational isomerisation. The authors explain certain deviations of the experimental points from the straight line by the fact that the reactions investigated do not obey the equation for a first-order process altogether rigorously over the entire range of concentrations of the initial hydrocarbon.

The slope of the straight line (0.51) shows that the rate of deuterium exchange is approximately twice as high as that of configurational isomerisation. Probably the ratio of the rates of these two reactions depends primarily on the nature of the catalyst and not on the experimental temperature, since the results obtained in the presence of the same palladium catalyst at 87° and 146°C are very close to those at 65°C described above. In the presence of other catalysts investigated the rate of deuterium exchange predominates over that of configurational isomerisation to an even greater extent. On the basis of the data obtained, the authors conclude that these two reactions have a common mechanism and that they both take place with formation on the surface of the catalyst of transition complexes of the π-allyl type. They believe that the first reaction stage consists in the formation of this type of adsorption complex, located in a single plane which also contains all the methyl groups of the initial molecule. The second stage is the interaction of the adsorbed π-complex with the atom or molecule of hydrogen (deuterium) adsorbed on the catalyst surface. For 1,2-dimethylcyclopentane, the addition of hydrogen or deuterium to this type of adsorbed π-complex can be represented by the following two reversible processes:



, (A)



. (B)

They show that the adsorbed π-complex arises in the reaction of the catalyst with the p orbital of the carbon atom, which is shown by dashed lines. In mechanism (A) the adsorbed deuterium atom attacks the ring from below, adding to the p orbital of the carbon atom bound to the methyl group. In mechanism (B) deuterium adds to the p orbital of the carbon atom after attacking the ring from above. After the addition of deuterium or hydrogen to the adsorbed π-complex and after the desorption of 1,2-dimethylcyclopentane, the sp^3 hybridisation of carbon atoms in the latter is restored with formation of *cis*-1,2-dimethylcyclopentane [mechanism (A)] or the *trans*-form [mechanism (B)] respectively. The authors of this mechanism suggest that the first stage—the step involving the dissociative chemisorption of the initial hydrocarbon with formation of an adsorbed π-complex of the allyl type—is rate-determining. Thus in their analysis of studies on the configurational isomerisation of dialkylcycloalkanes, Bragin et al. noted that in previous investigations this reaction was always accompanied by other processes (hydrogenolysis, deuterium exchange, dehydrogenation). After a large-scale study of the conditions under which configurational isomerisation takes place, we demonstrated[84] the possibility of a smoother course of this reaction, without any side and secondary processes. It was found that the configurational isomerisation of 1,2-dimethylcyclopentane on platinum and palladium catalysts below 200°C at space velocities of 1.4–21.6 h^{-1} takes place quite successfully without being complicated by side processes. At the same time on other Group VIII noble metals (osmium, ruthenium, rhodium, and iridium) at 200°C hydrogenolysis products were formed (particularly vigorously on the Ru/C catalyst). However, at 150°C and below there were virtually no side reactions on these metals either and the rate of configurational isomerisation remained appreciable. Comparison of the relative activities of the metals enumerated above, deposited on activated charcoal, showed that their catalytic activities are extremely varied. In all cases Pt/C and Rh/C showed the greatest activity and the remaining four catalysts were significantly less active. Comparative data on the configurational isomerisation of *trans*-1,2-dimethyl- and *trans*-2-ethyl-1-methyl-cyclopentanes, obtained on six of the above catalysts, are presented in Fig. 12. The results for the corresponding *cis*-isomers of the cyclopentane and the stereoisomeric cyclohexane hydrocarbons were similar.

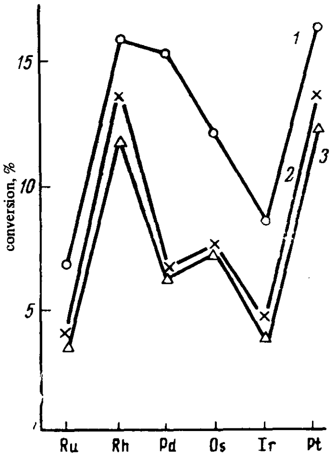


Figure 12. Relative activities of Group VIII metals in configurational isomerisation[84]: *1*) and *2*) *trans*-1,2-dimethylcyclopentane at 300° and 200° respectively; *3*) *trans*-2-ethyl-1-methylcyclopentane at 200°C.

In a study of the kinetics of the configurational isomerisation of stereoisomeric 1,2-dialkylcyclopentanes we showed[80,85] that, under the conditions investigated, this reaction is of zero (or nearly zero) order with respect to the hydrocarbons. The conversion of the energetically more stable *trans*-forms of 1,2-dimethyl-, 2-ethyl-1-methyl-, and 1-methyl-2-n-propyl-cyclopentanes into the *cis*-isomers requires a somewhat greater activation energy than the reverse process. The activation energies found on platinum, rhodium, and cobalt catalysts are similar and are listed in Table 9.

Kalechits and coworkers[86] carried out the configurational isomerisation of 1,3-dialkylcyclopentanes. The conversion of *cis*-1,3-dimethylcyclopentane into the *trans*-form over an iron–platinum catalyst takes place up to concentrations close to equilibrium; the reverse transformation occurs to a relatively low extent.

In the studies of Petrov and coworkers[87] the configurational isomerisation of stereoisomeric di- and poly-alkylcyclopentanes was employed to establish thermodynamic equilibrium between them and to calculate a number of thermodynamic functions.

In all the studies on configurational isomerisation quoted above hydrogen or deuterium was always present to some extent in the reaction zone. In one of our early investigations[83] we suggested that hydrogen chemisorbed on the surface of the catalyst may enter into the composition of the transition complex and thereby may play a significant role in the reaction. Subsequently this hypothesis was tested and confirmed experimentally. Thus in one of our investigations[45] we considered a number of possible mechanisms of configurational isomerisation, the essential feature of which consists in the application to this reaction of various modifications of the dissociative and associative modes of adsorption of the initial hydrocarbon. The adsorption of the latter by a dissociative mechanism can lead to the formation of either ions or radicals. In this case the formation of carbonium ions can probably be excluded, since it would have to be accompanied by a more profound skeletal isomerisation (the formation of a six-membered ring), which was not observed either in experiments in a flow system or under pulse conditions. The second possibility is the intermediate formation of radicals adsorbed on the surface of the catalyst. This process should take place in at least two stages: (a) chemisorption of the hydrocarbon with formation of radicals (monomolecular reaction) and (b) addition of hydrogen to these radicals from the side opposite to that from which it had been abstracted (bimolecular reaction). In the second stage the attack of hydrogen on the mono- or di-adsorbed (chemisorbed) complex, results in the formation of the hydrocarbon stereoisomeric with the initial compound and the free catalyst. For instance, the two stages can be represented schematically in the following way:

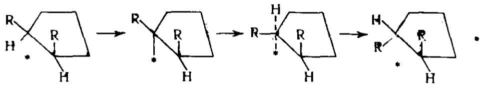


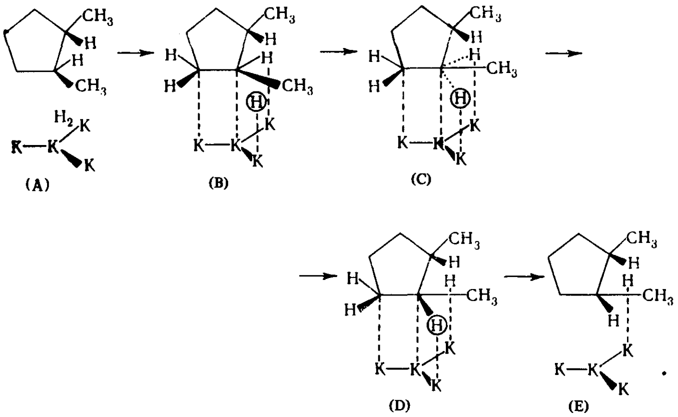
Table 9. Activation energies for the configurational isomerisation of stereoisomeric 1,2-dialkylcyclopentanes[80,85].

Initial hydrocarbon	Activation energy Q, kcal mole^{-1}		Initial hydrocarbon	Activation energy Q, kcal mole^{-1}	
	Pt/C	Rh/C		Pt/C	Rh/C
trans-1,2-Dimethylcyclopentane	12	14.5	*trans*-1-Methyl-2-n-propylcyclopentane	9	—
cis-1,2-Dimethylcyclopentane	10	9.5	*cis*-1-Methyl-2-n-propylcyclopentane*	5	—
trans-2-Ethyl-1-methylcyclopentane	16.5	—			
cis-2-Ethyl-1-methylcyclopentane	7.5	—			

* In the presence of 18% Co/C, the activation energy for the conversion of *cis*-1-methyl-2-n-propylcyclopentane into the *trans*-form was 7.5 kcal mole^{-1}.

In this version the rate of reaction is determined by either the first or the second stage. Further studies excluded the first stage—the formation of the adsorbed complex—from the rate-limiting steps.

Nevertheless, we believe it likely that the intermediate transition complex is formed by an associative mechanism. The data quoted below on the participation of hydrogen as a second reactant in configurational isomerisation, the absence of dehydrogenation and skeletal isomerisation products under mild reaction conditions, and also kinetic results are consistent with this view. The kinetic results demonstrate a comparatively low activation energy for configurational isomerisation, whereas the dissociation of the C–H bond (the first stage in the formation of the transition complex by the dissociative mechanism) requires a significantly greater energy expenditure. The transition complex formed by the associative mechanism probably includes the reacting hydrocarbon molecule, the active catalyst surface, and a hydrogen species. The formation and breakdown of this activated complex proceed by a mechanism identical or formally similar to the S_N2 Walden inversion:



The mechanism presents the stages in the conversion of *trans*-1,2-dimethylcyclopentane into the *cis*-form. The initial *trans*-1,2-dimethylcyclopentane (A) is adsorbed via two carbon atoms and one hydrogen atom on three adsorption centres of the catalyst with formation of (B). The hydrogen atom adsorbed in an adjacent position attacks the hydrocarbon molecule and the transition complex (C) is formed. The latter then breaks down with incorporation of the attacking hydrogen atoms in the hydrocarbon molecule and with simultaneous loss by the molecule of another hydrogen atom [stage (D)]. This results in the formation of *cis*-1,2-dimethylcyclopentane adsorbed on the catalyst surface, which is then desorbed [stage (E)].

It should be noted that the available data do not as yet provide sufficient grounds to decide whether the mechanism proposed is truly of S_N2 type or only bears a formal resemblance to it. A reaction involving an S_N2 mechanism requires attack by either an anion or a negatively polarised group. In the case discussed this could be a negatively polarised hydrogen atom, the hydride ion, or an H_2^- ion. The existence of the last two species on films of a number of Group VIII metals was demonstrated by Krasil'shchikov and Antonova[88]. However, there is as yet no direct evidence for the presence of such species under the conditions of configurational isomerisation. Nevertheless, it is noteworthy that a number of studies have shown[88,94] that hydrogen may be chemisorbed on the surface of certain metals (including platinum) in the form of species other than neutral atoms. In the adsorption layer hydrogen atoms may be polarised by the conductivity electrons of the metal, forming with the atoms of the latter dipoles, the properties of which resemble those of hydride ions.

The above considerations demonstrate the important role which hydrogen plays in configurational isomerisation. For this reason, special series of experiments were performed in which the effects of the concentration and the space velocity of hydrogen on the rate of configurational isomerisation were elucidated.

In experiments where stereoisomeric 1,2-dimethylcyclopentanes mixed with inert gases (helium, argon, and nitrogen) and also with methane were passed over a platinum catalyst, we discovered that under these conditions the reaction does not take place at all. However, when the carrier gas contains quite a low concentration of hydrogen (about 3%), the reaction begins at an appreciable rate; on further increase of the hydrogen concentration in the gas, the rate of reaction rises and, beyond a certain hydrogen concentration, reaches a constant value and no longer alters (Fig. 13).

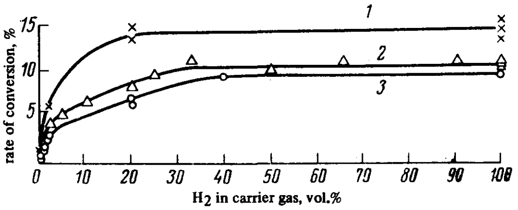


Figure 13. Variation of the rate of the configurational isomerisation of *cis*- and *trans*-1-2-dimethylcyclopentanes on Pt/C with the ratio of H_2 and N_2 (or He) in the carrier gas[45]: *1*) *cis*-isomer at 110°C (H_2 + N_2); *2*) and *3*) *trans*-isomer at 220°C (H_2 + He) and 150°C (H_2 + N_2) respectively.

The study of the effect of the space velocity of hydrogen on the rate of configurational isomerisation led to similar results. This is shown in Fig. 14, where the ascending sections of the curves are indeed similar to the corresponding sections in Fig. 13. They show that at low hydrogen flow rates, i.e. at low hydrogen concentrations in the mixtures of hydrocarbons, the rate of reaction depends significantly on the hydrogen concentration and tends to zero when the latter is reduced. The subsequent decrease of the rate of reaction (the descending sections in Fig. 14) can be explained by the fact that, at a certain instant, the increase of the rate of supply of hydrogen leads to an appreciable decrease of the duration of contact of the mixture as a whole. In the experiments presented in Fig. 13 this phenomenon was not observed, since, whatever the mixture composition, the duration of contact was kept constant from the beginning to the end of the experiment.

The above relations are very similar to those observed for bimolecular reactions and suggest that in the presence of platinum hydrogen does not behave as a simple carrier gas but as a second reactant in configurational isomerisation. The principal relations remain the same on other Group VIII metals[45]. In an atmosphere of hydrogen these metals activate configurational isomerisation, while in the absence of hydrogen the isomerisation does not occur. However, a more detailed study revealed certain specific features of particular metals, but the decisive role of hydrogen, demonstrated previously on platinum, was found to apply also to palladium, rhodium, ruthenium, osmium, and iridium.

Thus we believe that the associative mechanism of configurational isomerisation[45], of the S_N2 Walden inversion type, may be extended also to the other Group VIII metals investigated.

The mechanisms discussed above emphasise the fundamental role of hydrogen in configurational isomerisation. The relations obtained are not exceptional and have a number of analogies in other reactions. Thus it was noted earlier that the *cis–trans* isomerisation of olefins on Group VIII metals also takes only in the presence of hydrogen or deuterium[42–44]. In this connection, the work of Siegel and coworkers[20,21] quoted above, in which it was noted that the hydrogenation of cyclo-olefins on platinum and palladium catalysts is accompanied by isomerisation with migration of the double bond in the ring while in the absence of hydrogen the isomerisation does not occur, is of definite interest. Probably the mode of action of these catalysts has certain features in common in the above reactions, although their specific mechanisms may in fact be different.

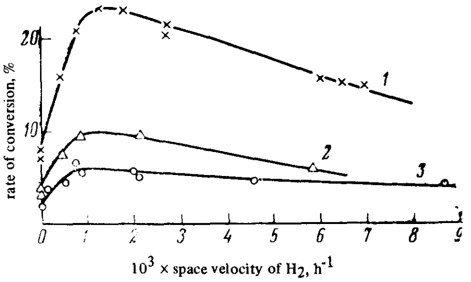


Figure 14. Variation of the rate of the configurational isomerisation of *cis*- and *trans*-1,2-dimethylcyclopentanes on Pt/C with the space velocity of hydrogen[45]: *1*) *cis*-isomer at 110°C; *2*) and *3*) *trans*-isomer at 150° and 130°C respectively.

Almost all the papers quoted above, in which the configurational isomerisation is discussed, refer to hydrocarbons of the cyclopentane series. However, there are indications in the literature that configurational isomerisation takes place also in other cyclic systems. Thus Gault, Maire, and coworkers[39,95,96] investigated the simultaneous hydrogenolysis, deuterium exchange, and configurational isomerisation of stereoisomeric 1,2-dimethylcyclobutanes on platinum, palladium, rhodium, and nickel catalysts. According to these authors, the above reactions of cyclobutane homologues have identical or similar mechanisms with formation of intermediate complexes of the π-allyl type.

Allinger and coworkers widely employed configurational isomerisation for the attainment of thermodynamic equilibrium between stereoisomers and for the calculation of the thermodynamic functions of stereoisomeric 1,3-dimethylcyclo-octanes[97], decalins[98], bicyclo[5,2,0]nonanes[99] and bicyclo[5,3,0]decanes[100].

The reaction has been widely investigated in the cyclohexane series, but not in quite such detail as for cyclopentane hydrocarbons. This is probably due to the complications which arise due to the accompanying dehydrogenation reaction and possibly also the somewhat lower rate of the configurational isomerisation of cyclohexane homologues compared with cyclopentanes[84]. The rate of attainment of thermodynamic equilibrium in the series of cyclohexane homologues depends on the nature and activity of the catalyst employed, the experimental conditions, and the properties of the initial isomers. Thus Waterman and coworkers[101] showed that, in the presence of a nickel/kieselguhr catalyst at 170–180°C and a hydrogen pressure of 7–8 atm, *cis*- and *trans*-1,3- and 1,4-dimethylcyclohexanes reached thermodynamic equilibrium more rapidly than 1,2-dimethylcyclohexanes. Under the influence of Raney nickel, *trans*-1,2-dimethylcyclohexane attains equilibrium faster than the corresponding *cis*-isomer. Allinger and coworkers[102–107] carried out a series of studies on the conformational analysis of the stereoisomeric cyclohexane homologues, which in the presence of a palladium catalyst can be reversibly interconverted by configurational isomerisation. The composition of the thermodynamic equilibrium mixtures formed in this process enabled the authors to calculate the equilibrium constants, a number of thermodynamic functions, and also the energies of the interconversion of a number of conformers.

Petrov, Zakharenko, and coworkers[108,109] also determined the equilibrium ratios of stereoisomeric di- and poly-alkylcyclohexanes with the aid of configurational isomerisation. The work of Eliel[110–112], who investigated the configurational isomerisation of stereoisomeric mono- and di-alkylcyclohexanols, is of interest too. These studies yielded information about the relative rates of interconversion, esterification, and oxidation of stereoisomeric alkylcyclohexanols and also yielded the conformational energies of various axial alkyl groups in stereoisomeric 1,3- and 1,4-dialkylcyclohexanols.

In these and certain other studies the term epimerisation (and correspondingly the terms epimerisation conditions and rate of epimerisation) is applied to configurational isomerisation but, from our point of view, it is non-rigorous and may lead to an incorrect understanding of the essential features of the reaction. Indeed, the term epimerisation is usually applied to a racemisation process involving one asymmetric centre (of the several present) in the molecule of an optically active substance. For example, the conversion of D-*trans*-1,2-dimethylcyclopentane, which has two asymmetric centres, into the L-*trans*-stereoisomer can be legitimately called epimerisation, but the conversion of the *trans*-form into the *cis*-form is a completely different reaction. In configurational isomerisation stereoisomeric dialkylcycloalkanes are not as a rule optically active and, for example, the interconversion of *cis*-1,2-dimethylcyclohexane and its *trans*-form is the interconversion of two racemates. We believe that the mechanism of the interconversions of stereoisomeric dialkylcycloalkanes is fundamentally different also from the mechanism of the *cis–trans* isomerisation of olefins and this is why we propose a special name for the former reaction, i.e. configurational isomerisation.

Shopov and Andreev[113] showed that the rate of dehydrogenation of stereoisomeric dialkylcyclohexanes depends on the nature of the catalyst. Thus on a platinum catalyst the *cis*- and *trans*-forms of 1,2-dimethylcyclohexane are dehydrogenated to xylene at the same rate, while on palladium and nickel the *trans*-form is dehydrogenated at an appreciably lower rate. This is probably associated in some way with the different relative rates of the configurational isomerisation of the *cis*- and *trans*-isomers of dimethylcyclohexane in the presence of various catalysts. Indeed, in the configurational isomerisation of the *cis*- and *trans*-isomers of 1,3-dimethylcyclohexane we found that[84] platinum and rhodium catalysts are more active than other Group VIII noble metals.

Our finding[45] that on all Group VIII noble metals the configurational isomerisation of cyclohexane homologues takes place only in the presence of hydrogen§, as in the cyclopentane series, is extremely important. The study of the kinetics of the configurational isomerisation of *cis*-1,2- and *trans*-1,3-dimethylcyclohexane showed[115] that the activation energies for the conversion of these hydrocarbons into the corresponding stereoisomers are 7.5 and 6 kcal mole^{-1}. These and other facts obtained in the study of the configurational isomerisation of cyclohexane hydrocarbons indicate a number of similar features of these reactions in the cyclopentane and cyclohexane series. In the first place these include the direct participation of hydrogen in the reaction, the absence of cyclo-olefins and aromatic hydrocarbons under mild conditions of configurational isomerisation, fairly close activation energies, etc. All these findings suggest that the configurational isomerisation of cyclohexane homologues takes place by an S_N2 mechanism identical with or similar to the mechanism described above for stereoisomeric dialkylcyclopentanes.

It may be supposed that such an S_N2 mechanism plays a role not only in the reactions of the classes of compounds discussed above, but also in many others. This hypothesis is based on the exo ⇌ endo isomerisation of alkyl substituents in the series of bridged bicyclic hydrocarbons described by Plate and coworkers[116,117].

In conclusion, it should be noted that at the present time the stereochemical approach to certain catalytic reactions, in particular hydrogenation or hydrogenolysis, is comparatively widely employed. The studies of the hydrogenolysis of optically active compounds began by Bonner[118] and continued by Japanese investigators[119-122] are very promising in this connection. The structure of the initial compounds, the nature of the metal, its concentration in the catalyst, and sometimes the carrier employed influence the mechanism of hydrogenolysis, which, depending on these factors, can proceed via S_N1, S_N2, or S_i mechanisms. These studies have been analysed in Klabunovskii's review[5]. In this connection, the series of investigations by Balandin, Klabunovskii, and coworkers[123-125] of the structure of the active catalyst surface by the hydrogenation of molecules with a rigid steric configuration are also of undoubted interest.

The study of model reactions in which the starting materials undergo minimal changes (ortho–para conversion of hydrogen, configurational isomerisation, etc.) and the use for investigation of optically active and labelled compounds in combination with the latest physical techniques for the study of the catalyst itself constitutes new and promising approaches to the elucidation of the fine details of reactions on the surface of the catalyst.

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§ The special role of hydrogen as a non-stoichiometric reactant in a number of processes (configurational isomerisation, double bond migration in olefins, and others) has been discussed by Eidus and Ershov[114].

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Zelinskii Institute of Organic
Chemistry, USSR Academy
of Sciences, Moscow

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Advances in Asymmetric Hydrogenation. Catalytic Synthesis of Optically Active Hydroxy- and Amino-acids

E.I.Klabunovskii and E.S.Levitina

In the present review an attempt is made to follow the general relations in the formation of optical isomers and to elucidate the optimum conditions for the reactions on the basis of an analysis of the available literature data on the catalytic synthesis of aminoacids with reference to data on the hydrogenation of C=C and C=O bonds in optically active compounds. The extremely interesting and promising field of asymmetric hydrogenation using dissymmetrical heterogeneous catalysts, which requires special treatment, has been dealt with in the review only in connection with the synthesis of aminoacids.
The bibliography includes 87 references.

CONTENTS

I. INTRODUCTION

Asymmetric hydrogenation has always attracted the attention of investigators as one of the methods for the preparation of optically active compounds by the addition of hydrogen to the multiple bonds C=C, C=O, and C=N, in the presence of an asymmetrising agent (an optically active group in the molecule, a dissymmetric catalyst). Recently there has been a particular growth of interest in asymmetric hydrogenation in connection with the application of new methods for the synthesis of optically active α-aminoacids.

The advances in asymmetric hydrogenation have not yet been reflected in an adequate compilation of the relevant studies. There are only a few obsolete reviews [1,2] in Japanese.

Asymmetric catalysis is based on the concept of the *cis*-addition of hydrogen from the catalyst surface, which has been expressed quantitatively in Balandin's multiplet theory of catalysis and theory of hydrogenation. According to the multiplet theory, the addition of hydrogen to the molecule of an unsaturated compound takes place in a reaction sphere of minimum volume without the desorption of the intermediate semihydrogenated species from the catalyst surface. The presence of the heterogeneous catalyst surface gives rise to additional steric hindrance in this process and promotes its stereospecificity.

The formation of optically active compounds in asymmetric heterogeneous catalytic hydrogenation confirms the mechanism of *cis*-addition, since otherwise, in *trans*-addition or for desorption of the semihydrogenated species, the racemate would be formed in the bulk phase. At the same time these data show that, under the conditions investigated, the impact hydrogenation mechanism is unlikely and it must be assumed, in accordance with the multiplet theory, that the reaction takes place in direct contact with the catalyst. According to Balandin's hydrogenation theory [3], the activation of the compound hydrogenated B and hydrogen H takes place at different centres K' and K respectively, and the centre K may be subdivided further into centres A which are responsible for the separate adsorption of hydrogen atoms. Then the stages in the attainment of adsorption equilibrium at the two types of centre are represented by mechanisms (1) and (2) and the rate-limiting stage of the process is represented by mechanism (3):

$$B + K' \rightarrow BK';\ H_2 + K' \rightarrow H_2K';\ C + K' \rightarrow CK', \qquad (1)$$

$$B + K \rightarrow BK;\ H_2 + K \rightarrow H_2K \rightarrow 2\,(H \cdot A);\ C + K \rightarrow CK, \qquad (2)$$

$$BK' + HA \rightarrow XK'A;\ XK'A + HA \rightarrow CK' + K, \qquad (3)$$

where C is the reaction product and X the semihydrogenated species, which is not released into the bulk phase from the catalyst surface and which undergoes all transformations on the surface. The adsorption of compound B (to be hydrogenated) at centres K' [mechanism (1)] and the rate-limiting stage [mechanism (3)] must take place on the sterically least hindered side of the molecule, which determines the stereochemistry of the product.

The occurrence of asymmetric synthesis is due to the difference between the rates of formation of the optical isomers of the product C from the initial compound B:

$$\begin{tikzcd} B \arrow[r, "k_d"] \arrow[dr, "k_l"'] & (+)\,C \\ & (-)\,C \end{tikzcd},$$

which is determined by the difference between the free energies of activation $\Delta F^{\neq}$ for the diastereoisomeric transition states. According to the transition state theory, the specific rate of formation of one of the optical isomers, for example, the (+)-isomer, is defined as follows:

$$k_d = \frac{kT}{h} e^{-\frac{\Delta F_d^{\neq}}{RT}} .$$

For two competing reactions involving the formation of the (+)- or (−)-isomers, we have, $k_d/k_l = C_d/C_l$ and for a transmission coefficient close to unity the ratio of the rate constants for the formation of the (+)- and (−)-isomers is

$$\ln\frac{k_d}{k_l} = \ln\frac{C_d}{C_l} = \left(\frac{\Delta S_d^{\neq}}{R} - \frac{\Delta H_d^{\neq}}{RT}\right) - \left(\frac{\Delta S_l^{\neq}}{R} - \frac{\Delta H_l^{\neq}}{RT}\right) =$$
$$= \left(\frac{\Delta S_d^{\neq}}{R} - \frac{\Delta S_l^{\neq}}{R}\right) - \left(\frac{\Delta H_d^{\neq}}{RT} - \frac{\Delta H_l^{\neq}}{RT}\right) = \frac{\Delta\Delta S_{d-l}^{\neq}}{R} - \frac{\Delta\Delta H_{d-l}^{\neq}}{RT} ,$$

where the enthalpy of activation $\Delta H^{\neq}$ is related to the experimentally determined activation energy E by the equation

$$\Delta H^{\neq} = E - RT .$$

Low values of $\Delta\Delta S^{\neq}$ indicate a similarity of the structures of the diastereoisomeric transition states.

The specific rotation of the product is determined from the expression

$$\alpha_{D}^{t} = \alpha_{obs} \times 100/lC,$$

where α_{obs} is the observed optical rotation in a layer of length l (in decimeters) at a concentration C (1 g per 100 ml solution). The molecular rotation $[M]_{\lambda}^{t}$ is defined thus:

$$[M]_{\lambda}^{t} = [\alpha]_{\lambda}^{t} \frac{M}{100} .$$

The optical purity (P, %), also called the optical yield or the asymmetric yield, is defined by the ratio of $[\alpha]_{D\,found}$ for the product to the maximum specific rotation quoted in the literature $[\alpha]_{D(lit.)}$ for the optically pure compound:

$$p = \frac{[\alpha]_{D(found)}}{[\alpha]_{D(lit)}} \cdot 100 = \frac{[M]_{D(found)}}{[M]_{D(lit)}} \cdot 100 .$$

The specificity Sp_{+}, or the ratio of the fraction of one optical isomer to the other in a given compound, determined from the expression

$$Sp_{+} = \frac{[(+)\text{-isomer}]}{[(-)\text{-isomer}]} = \frac{100+p}{100-p} ,$$

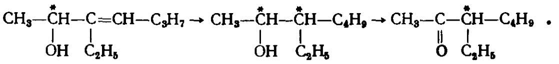
varies in the range $\infty \geqslant Sp \geqslant 1$.

Two methods are employed at present for the determination of the optical purity of the compound. The first requires the separation of the optical isomers in a pure form or in the form of their diastereoisomers. This procedure includes, apart from the classical method of the isolation of usually one optical isomer by the recrystallisation of the diastereoisomers, the method of isotope dilution[4], a kinetic method[5], and an enzymatic method. In the second procedure it is sufficient to determine analytically the ratio of the diastereoisomers, for example by gas-liquid chromatography (Weygand[6], Belikov and coworkers[7]) or by NMR (Raban and Mislow[8,9]).

The stereochemistry of the asymmetric hydrogenation of C=C and C=O bonds, on which extensive data have accumulated recently, provides valuable information for the understanding of the catalytic synthesis of optically active aminoacids.

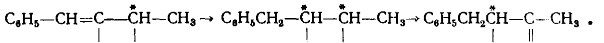
II. HYDROGENATION OF OPTICALLY ACTIVE UNSATURATED AND CARBONYL COMPOUNDS

Arcus and coworkers[10-12] made a detailed study of the stereochemistry of the hydrogenation of optically active compounds on nickel using as an example optically active 3-ethylhept-3-en-2-ol[10] and 3-methyl-4-phenylbut-3-en-2-ol[11]. The initial asymmetric centre in the molecules is destroyed by oxidising the hydrogenation product to the corresponding ketone by the mechanism



$$\mathrm{CH_3-\underset{OH}{\overset{*}{C}H}-\underset{C_2H_5}{C}=CH-C_3H_7 \rightarrow CH_3-\underset{OH}{\overset{*}{C}H}-\underset{C_2H_5}{\overset{*}{C}H}-C_4H_9 \rightarrow CH_3-\underset{O}{\overset{}{C}}-\underset{C_2H_5}{\overset{*}{C}H}-C_4H_9} .$$

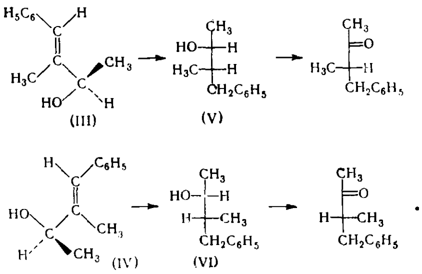
The experimental results showed that in the hydrogenation of (–)- and (+)-3-ethylhept-3-en-2-ol there is partial asymmetric synthesis with an optical yield of 76 and 36% of the (+)- and (–)-ketones respectively. The authors explained this finding by postulating that the substrate molecule is oriented with respect to the catalyst surface predominantly in the sterically least hindered conformation. The stereochemistry of the transition state has been examined in the hydrogenation of (–)-3-methyl-4-phenylbut-3-en-2-ol[11]. In this case the product is (+)-3-methyl-4-phenylbutan-2-ol and, after oxidation of the alcoholic group with chromium trioxide, (–)-3-methyl-4-phenylbutan-2-one:



$$\mathrm{C_6H_5-CH=\underset{CH_3}{C}-\underset{OH}{\overset{*}{C}H}-CH_3 \rightarrow C_6H_5CH_2-\underset{CH_3}{\overset{*}{C}H}-\underset{OH}{\overset{*}{C}H}-CH_3 \rightarrow C_6H_5CH_2\underset{CH_3}{\overset{*}{C}H}-\underset{O}{C}-CH_3} .$$

(I) (II)

We shall consider the structure of the transition state on the surface of the catalyst. The molecule of *trans*-3-methyl-4-phenylbut-3-en-2-ol can be adsorbed in conformations (III) or (IV) (the plane of the figure corresponds to the catalyst surface):

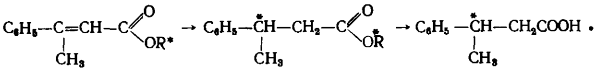


In the hydrogenation of (III) and (IV) hydrogen approaches from behind the plane of the figure with formation of the diastereoisomers (V) and (VI). It is postulated that the adsorption of the molecule in conformation (III) is the most probable, since in conformation (IV) the two bulky methyl groups are located too close to one another. Since the specific rotation of the pure diastereoisomers (I) and the ketones (II) was unknown, the degree of asymmetric synthesis (more precisely "dissymmetric synthesis") was estimated by quantitative gas-chromatographic analysis of the diastereoisomeric alcohols and, in two experiments, from the hydrogenation of (–)-3-methyl-4-phenylbut-3-en-2-ol and was found to be 22 and 17%.

The hydrogenation of racemic *trans*-4-phenylpent-3-en-2-ol[12] in conformations corresponding to (III) and (IV) gives a mixture of the four possible diastereoisomers, which consist of two pairs of optical isomers. The degree of dissymmetric synthesis in the two experiments proved to be 50 and 57% respectively. The proposed method, based on the chromatography of diastereoisomers, is extremely promising in the study of the stereochemistry of the reactions of various compounds, since there is no need to determine the optical activity of the product and it is possible to employ racemic compounds.

It was noted long ago that the stereochemistry of the activating optically active group determines to a considerable degree the effectiveness of asymmetric catalysis.

In the hydrogenation of optically active esters of β-methylcinnamic acid on platinum black, Vavon and Yakubovicz[13] obtained, after hydrolysing the hydrogenation products, optically active β-phenylbutyric acid with different degrees of optical purity:

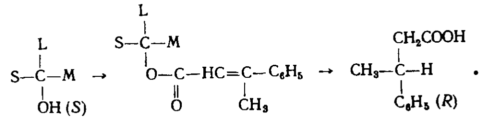


$$\mathrm{C_6H_5-\underset{CH_3}{C}=CH-C{\overset{O}{\underset{OR^*}{\lessgtr}}} \rightarrow C_6H_5-\underset{CH_3}{\overset{*}{C}H}-CH_2-C{\overset{O}{\underset{O\overset{*}{R}}{\lessgtr}}} \rightarrow C_6H_5-\underset{CH_3}{\overset{*}{C}H}-CH_2COOH} .$$

Menthol, neomenthol, *cis*- and *trans*-carvomenthols, and 3α- and 3β-cholestanols were employed as the optically active alcohols. The highest optical yield (20%) of β-phenylbutyric acid was obtained when menthol was employed.

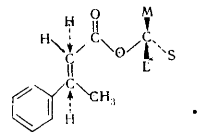
Hydrogenation of hydrocinchoninium salts of β-methyl and β-(α'-naphthyl)cinnamic acids on platinum oxide gave β-phenylbutyric acid with $[\alpha]_{546} = +4.5°$ and an optical yield of 9% and β-(α′-naphthyl)-β-phenylpropionic acid with $[\alpha]_{546} = -0.5°$. The stereochemistry of the catalytic hydrogenation of β-methylcinnamic acids was examined in detailed by Prelog[14,15].

The stereochemistry of asymmetric hydrogenation is determined by the difference between the sizes of the substituents at the asymmetric carbon atom in the activating alcohol. An increase of the difference between these sizes leads to an increase of the optical yield of the reaction. If L, M, and S are respectively large, medium, and small substituents at the asymmetric carbon atom, then the configurations of the optically active alcohol and the optical isomer of β-phenylbutyric acid obtained in excess are related as shown in the scheme below [i.e. under the conditions investigated, the (S)-configuration of the alcohol promotes the formation of the (R)-configuration of the acid]:

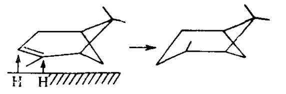


$$\text{S—C(L)(M)—OH}\ (S) \rightarrow \text{S—C(L)(M)—O—C(=O)—HC=C(CH}_3\text{)—C}_6\text{H}_5 \rightarrow \text{CH}_3\text{—C(CH}_2\text{COOH)(H)—C}_6\text{H}_5\ (R).$$

Examination of the conformation of the molecule of β-methylcinnamic acid shows that all the atoms, except the substituents L, M, and S, lie in the same plane. Hydrogen attacks the double bond from the sterically least hindered side, i.e. from the side of the small substituent S:



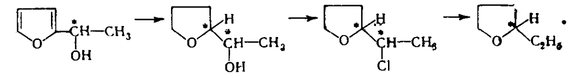
This should result in the formation of (−)-(R)-β-phenylbutyric acid. Table 1 shows that this mechanism, based on Prelog's rule, does indeed hold in the hydrogenation of the menthyl and bornyl esters of β-methylcinnamic acid. However, in the hydrogenation of neocarvomenthyl and 3α-cholestanyl esters Prelog's rule does not hold. It may be supposed that the rigid configuration of the molecule, which hinders the catalytic process, has an effect in this case. This is clearly shown, for example, in the hydrogenation of bicyclic compounds with bridged systems. Thus the hydrogenation of (+)-α-pinene on Raney nickel (W-3) in ether at 107°C and 100 atm results in the formation of almost exclusively *cis*-pinane, because α-pinene is adsorbed on the catalyst in such a way that the isopropylidene bridge is directed away from the catalyst[12]:



Prelog and coworkers[15] showed that the asymmetric yield of β-phenylbutyric acid depends also on the experimental conditions. Thus, in the hydrogenation of the ester of β-methylcinnamic acid and t-butylmethylmethanol on Raney nickel, Pd/C, and PtO_2 in acetic acid, the optical yield was greatest in the last case.

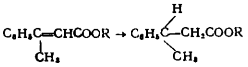
The degree of asymmetric synthesis is also influenced by the location of the dissymmetric centre in the molecule. The greatest asymmetrising effect of this centre may be expected when it is adjacent to the reacting group. Vavon[13] explained the low degree of asymmetric synthesis in the hydrogenation of optically active β-methylcinnamic esters by the remoteness of the optically active group from the group of reacting atoms.

The remoteness of the asymmetric centre in the ester precludes racemisation, whereas the racemisation at the α-asymmetric carbon atom proceeds extremely readily. This can account for the failure of the attempt at asymmetric synthesis in the preparation of a furan derivative by the hydrogenation on nickel of optically active furylmethylmethanol, which was undertaken by Duveen and Kenyon[16] on the basis of the mechanism

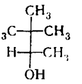
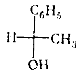
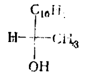
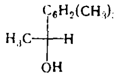
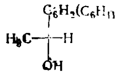


The product obtained after the removal of the initial asymmetric centre proved to be optically inactive. It is also possible that the choice of reaction conditions was inappropriate.

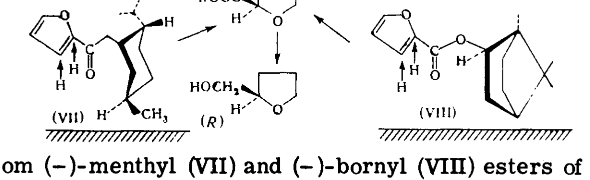
Table 1. Asymmetric hydrogenation of β-methylcinnamic acid esters.



$$C_6H_5C(CH_3)=CHCOOR \rightarrow C_6H_5C(H)(CH_3)-CH_2COOR$$

R	Optical rotation of product		Optical yield of acid, %
	established in Ref.13, deg	sign of rotation predicted by Prelog's rule	
S-(+)- 	− 4.7	(−)	8.5
S (−) 	− 2.5	(−)	4.5
S (−) 	− 4.2	(−)	7.5
R (+) 	+ 7.5	(+)	13
R (+) 	+15.5	(+)	27
(-)-(R)-mentol	+12	(+)	21
(+)-(S)-neomenthol	− 4.9	(−)	8.6
(+)-*trans*-carvomenthol	− 1.8		3.1
(-)-(R)-*cis*-carvomenthol	− 3.2	(+)	5.8
3-α-cholestanol	− 3	(+)	5.2
3-β-cholestanol	− 2.3		4.0

Asymmetric hydrogenation of the furan ring was achieved by Godunova, Klabunovskii et al.[17] by the mechanism



from (−)-menthyl (VII) and (−)-bornyl (VIII) esters of furancarboxylic acid. On the $Pd(OH)_2/C$ catalyst, the hydrogenation (150 atm, 20°C) takes place stereospecifically with formation of about 20% of an excess of the (*R*)-isomer. The ester of tetrahydrofurancarboxylic acid is reduced by $LiAlH_4$ to an alcohol, which is characterised by a positive optical rotatory dispersion curve. Examination of the stereochemistry of the transition states (VII) and (VIII) in accordance with Prelog's rule shows that (−)-(*R*)-menthol and (−)-(*R*)-borneol lead to tetrahydrofuryl alcohol with the same (*R*)-configuration as the product.

The stereochemical concepts based on Prelog's rule have been increasingly adopted in catalysis in recent times but one must consider the following important factor, which makes it necessary to employ this rule with caution. As stated above, asymmetric catalysis is due to the differences between the free energies of activation for diastereoisomeric transition states. When the difference between these quantities for the (+)- and (−)-products is large, a sharp difference may be expected between the curves relating the optical yields of the two optical isomers to reaction temperature.

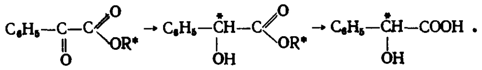
Pracejus[18] showed experimentally that the asymmetric yield of methyl β-phenylpropionate in the reaction of methylphenylketen with methanol promoted by acetylquinine as a dissymmetric catalyst increases sharply when the reaction temperature is reduced and that at −111° it reaches 74%, which corresponds to $Sp = 6.6$. The (−)-(*R*)-ester is formed almost 7 times faster than the (+)-(*S*)-isomer with $\Delta\Delta H^{\neq}_{R-S} \simeq -2.8$ kcal mole^{-1} and $\Delta\Delta S^{\neq}_{R-S} = -13$ cal mole^{-1} deg^{-1}. Hence it follows that $\Delta H^{\neq}_{S}$ of the sterically more hindered reaction leading to the formation of the (+)-(*S*)-isomer is higher by about 2.8 kcal mole^{-1} than for the reaction with formation of the (−)-(*R*)-isomer and the entropy of activation $\Delta S^{\neq}_{S}$ for the (+)-(*S*)-isomer exceeds by 13 e.u. $\Delta S^{\neq}_{R}$ for the (−)-(*R*)-isomer.

These data confirm the theoretical postulates and show that stereospecific catalysis, in which the entropy factor plays an important role, takes place above the isokinetic temperature[19] where a compensation effect [simultaneous increase (or decrease) of $\Delta H^{\neq}$ and $\Delta S^{\neq}$] is observed.

The above data show at the same time the importance of studying the temperature variation of the asymmetric reaction, since the change in the sign of the optical rotation and of the optical yield of the product at an arbitrary temperature (such as, for example, the temperature at which the Grignard reaction was carried out in Prelog's experiments) may lead to incorrect conclusions concerning the configurational relations. Therefore Prelog's method for the determination of such relations is applicable only for high differences between the free energies of activation for the diastereoisomers investigated and for fairly high optical yields. These limiting conditions still await experimental confirmation.

In the catalytic synthesis of optically active compounds and in the determination of the configuration, the stereochemical relations are complicated still more by the effect of the nature of the catalyst and of adsorption on its surface. This is seen from the hydrogenation of keto-compounds as an example.

The catalytic hydrogenation of α-ketoacids esterified by certain optically active alcohols was investigated by Mitsui and coworkers[20-25]. They chose for investigation benzoylformic acid, the asymmetric reduction of which by aluminium amalgam and other agents had been studied previously. The heterogeneous catalytic hydrogenation of optically active esters of benzoylformic acid was carried out on metallic catalysts (Raney nickel, PtO_2, Pd/C, $Pd/CaCO_3$, and $Pd/BaSO_4$). The experimental results showed (Table 2) that the hydrogenation of (−)-menthyl[20] and (+)-bornyl[21] esters with subsequent hydrolysis yield optically active mandelic acid:



$$C_6H_5-\underset{\underset{O}{\|}}{C}-C\overset{O}{\underset{OR^*}{\swarrow}} \rightarrow C_6H_5-\underset{\underset{OH}{|}}{\overset{*}{C}H}-C\overset{O}{\underset{OR^*}{\swarrow}} \rightarrow C_6H_5-\underset{\underset{OH}{|}}{\overset{*}{C}H}-COOH\ .$$

However, it was found that the sign of the rotation of the product is almost independent of the nature of the catalyst employed and is wholly determined by the presence on the catalyst surface of traces of acid or alkali, which may be inferred from the procedure employed in the preparation of the catalyst.

When catalysts containing traces of a base (B), such as PtO_2, Raney nickel, and Pd/C–B were used, (−)-menthyl (−)-mandelate and (+)-bornyl (+)-mandelate were obtained respectively; after hydrolysis they yielded (−)- and (+)-mandelic acids. On the other hand, the hydrogenation of the above esters under the same conditions on "acidic" catalysts (A) gave (+)- and (−)-mandelic acids. The reduction of cholesteryl esters of benzoyl formic acids on "acidic" and "alkaline" catalysts leads to racemic mandelic acid[21]. In the hydrogenation of (−)-α-phenylethyl ester of benzoylformic acid[22] the sign of the rotation of mandelic acid depends on the nature of the surface of the catalyst employed[22]; namely on "alkaline" and "acidic" catalysts the (+)- and (−)-mandelic acids were obtained (Table 2). However, the reduction of the (−)-α-phenylethylamide of benzoylformic acid was unaffected by the nature of the catalyst surface; the laevorotatory hydroxyacid was obtained in both cases[22].

To elucidate the influence of substituents in the ester molecule on the mechanism of the asymmetric reduction of α-ketoacids under the conditions of heterogeneous catalysis, a study was made of the hydrogenation of (−)-menthyl esters of certain other α-ketoacids: pyruvic, t-butylglyoxylic[23], and α-naphthylglyoxylic[24,25]. It was found that the ester of α-naphthylglyoxylic acid behaves in this reaction like the ester of benzoylformic acid, i.e. on "acidic" (platinum with added hydrochloric acid etc.) and "alkaline" catalysts, the (+)- and (−)-α-naphthylglyoxylic acids were obtained[24]. On the other hand, the sign of the rotation of the lactic and t-butylglyoxylic acids was independent of the nature of the catalyst surface[23]. In the reduction of (−)-menthyl esters of the corresponding α-ketoacids, the (+)-hydroxyacids were always obtained (Table 2).

The interpretation of the results from the standpoint of Prelog's rule showed that the hydrogenation of (−)-menthyl benzoylformate on "alkaline" catalysts presupposes the *trans*-conformation (IXa) of the group $-\overset{\overset{O}{\|}}{C}-\underset{\underset{O}{\|}}{C}-$, while on "acidic" catalysts it is necessary to postulate the *cis*-conformation (IXb):

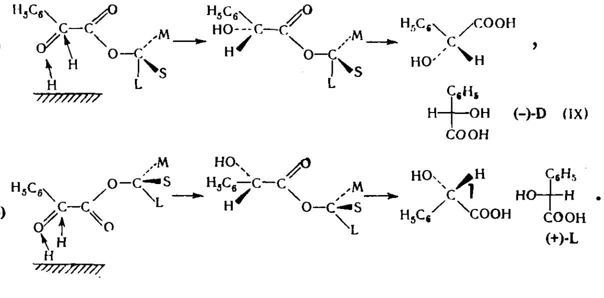
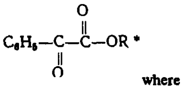
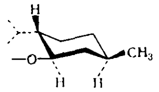
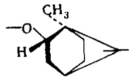
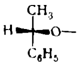
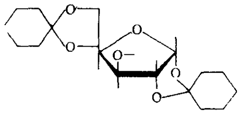
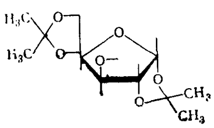
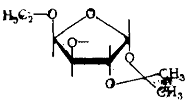
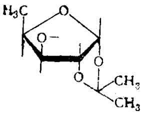
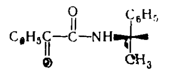
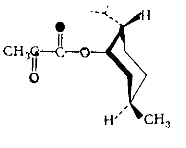
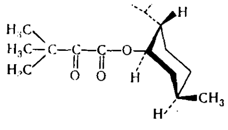
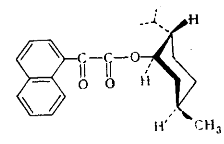
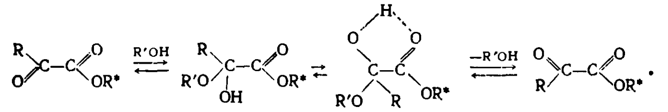
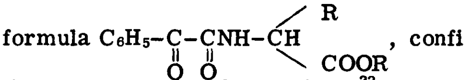


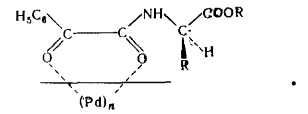
Table 2. Dependence of the configuration of the hydrogenation product on the nature of the catalyst[20–25,27].

Substrate	Reaction product: hydroxyacid formed	Reaction product: configuration, sign of rotation, optical yield (%), and most effective catalyst: "acidic"	"alkaline"
 where R*:	mandelic acid		
(a) (-)-(R)-menthyl 	ditto	(+)-L; 16.8% 5% Pd/C—B+ +HCl	(-)-D; 21.7% PtO_2
(b) (+)-(S)-bornyl 	»	(-)-D; 7.2% 5 %Pd/C+ +HCl	(+)-L; 22.9% PtO_2
(c) cholesteryl	»	0 %	0 %
(d) (-)-D-α-phenylethyl 	»	(-)-D; 2.4% Pd/C—A	(+)-L; 3.6%, Ni
(e) sugar derivatives 	»	(+)-L; 24.1 5% Pd/C—A	(-)-D; 44.6% Raney Ni
	»	(+)-L; 20.3% 5% Pd/C—A	(-)-D; 36.7% Raney Ni
	»	(+)-L; 9.4% 5% Pd/C—A	(-)-D; 19.9% Raney Ni
	»	(+)-L; 12.8% 5% Pd/C—A	(-)-D; 14.0 Raney Ni
	mandelic acid	(-)-D; 10.8% Pd black	(-)-D; 25.0 Ni
	(+)-L-lactic acid	(+)-L; 22% Pd/C—A	(-)-L; 33% PtO_2
	(+)-t-butyl glycolic acid	(+); 17% Pd/C—A	(+); 41% PtO_2
	naphthylglycolic acid	(+)-D; 16.5% Pd, $Pd(OH)_2/C$	(-)-L; 54.6% PtO_2

The formation of this energetically less favourable *cis*-conformation can be accounted for by the presence of a hydrogen bond between the carbonyl groups:



In the reduction of the (−)-α-phenylethylamide of benzoylformic acid the configuration of the reaction product is independent of the nature of the catalyst; the laevorotatory mandelic acid was always obtained. Consequently the optically active acid amide reacts preferentially in the *cis*-conformation (IXb) in the presence of both "acidic" and "alkaline" catalysts. Harada and Matsumoto[26], who investigated the hydrogenation on Pd/C of the amide derivatives of benzoylformic acid with the general formula  $C_6H_5-\underset{O}{\underset{\|}{C}}-\underset{O}{\underset{\|}{C}}NH-CH\begin{smallmatrix}R\\COOR\end{smallmatrix}$, confirmed the hypotheses of Mitsui and coworkers[22]. According to the authors' postulate, the *cis*-conformation of the molecule is stabilised by the formation of a five-membered cyclic complex with the catalyst:



On the other hand, the (−)-menthyl esters of pyruvic and t-butylglyoxylic acids probably react predominantly in the transoid conformation (IXa)

Kawana and Emoto[27] used certain monosaccharide derivatives as asymmetrising agents. The hydrogenation of the corresponding esters of benzoylformic acid on Pd/C−A, Pd/C−B and Raney nickel gave the optically active hydroxyacids after hydrolysis. Under the conditions of "alkaline" catalysts (Pd/C−B, Raney nickel), (−)-D-mandelic acid is the product, while the use of an "acidic" catalyst Pd/C−A gives (+)-L-mandelic acid. These and other results discussed above are compiled in Table 2, which shows that the configuration of the hydroxyacid formed depends on the nature of the surface of the catalyst employed and on the conformation in which the substrate is preferentially adsorbed on the catalyst surface.

The optical purity of the product is influenced by other factors, such as, for example, the chemical nature of the catalyst employed, the solvent, the duration of hydrogenation, and the time during which the solution is kept before hydrogenation. The use of a series of different catalysts showed that the most effective of the "acidic" catalysts is 5% Pd/C−A with added hydrochloric acid—the optical yield then reaches $p = 24\%$, while with "alkaline" catalysts the maximum asymmetric yield was obtained on the PtO_2 catalyst: $p = 54.6\%$, which exceeds by a factor of 8−10 the asymmetric yield found in the presence of homogeneous catalysts of this reaction. Since the addition of acid or alkali to the catalyst leads to a change of the optical purity of the isomer formed in excess, it would be extremely important to investigate the effect of the pH of the medium on the stereospecificity of the process.

An interesting variation of the asymmetric yield with the solvent employed has been noted (Table 3).

If the solution tested is kept for several hours before hydrogenation, the optically active acid obtained is more laevorotatory than the acid formed by the hydrogenation of the solution without preliminary standing. These results can be accounted by the mutarotation of the benzoylformic acid esters. Indeed Glazer and Turner[28], who investigated the mutarotation of the above esters, showed that the equilibrium optical rotation of the esters decreases with decrease of the dielectric constant of the solvent empolyed (Table 4).

Table 3. Optical rotation of mandelic acid obtained in the hydrogenation of (−)-menthyl benzoylformate in various solvents.

Catalyst	Solvent					
	methanol	ethanol	1-propanol	2-propanol	ether	benzene
Alkaline PtO_2	−18.8	−4.3	−45.4	−42.5	−37.0	−47.2
Acidic 5% Pd/C-A	+ 8.3	+4.2	+17.0	+ 8.3	+ 5.6	+ 6.0

Evidently the observed sequence (with certain exceptions) is the reverse of that presented in Table 3. This indicates a possible relation between the effectiveness of the catalytic asymmetric synthesis of mandelic acid and the degree of mutarotation of menthyl phenylglyoxylate in the corresponding solvent; the greater the degree of mutarotation, the lower the purity of the product. Consequently, an increase of the polarity of the solvent lowers in this case the effectiveness of the asymmetric synthesis.

Table 4. Variation of the specific rotation of (−)-menthyl benzoylformate with the solvent[28].

$[\alpha]_{5461}^{25}$	Solvent			
	methanol	ethanol	1-propanol	2-propanol
Initial	−54	−54	−54	−52
Equilibrium	−75	−60	−61	−52
Δ	21	8	7	0

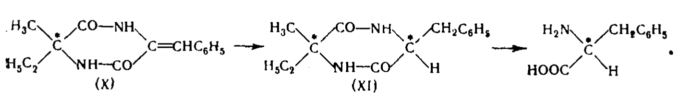
The same relation in the synthesis of aminoacids was observed by Harada and Matsumoto[29] (for a more detailed description, see p. 1044). So far the results presented in Table 2 do not allow definite conclusions concerning the correlation between the configurations of the asymmetric alcohol and the hydroxyacid formed. The results require further revision and in particular a study of the dependence of asymmetric yield on temperature, pH, and the solvent.

III. CATALYTIC ASYMMETRIC SYNTHESIS OF α-AMINOACIDS

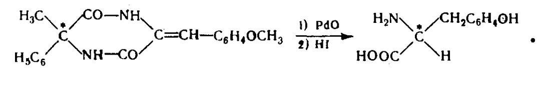
1. Hydrogenation of C=C Bonds in Optically Active Compounds

Optically active α-aminoacids may be obtained by the catalytic reduction of the C=C bond in dehydro-α-aminoacids in the presence of an asymmetrising agent. The number of examples of such asymmetric syntheses in the literature is fairly large[30-35].

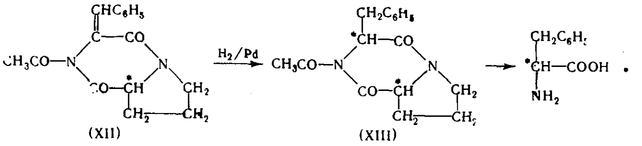
Akabori and coworkers[30,31] obtained L-phenylalanine with $[\alpha]_D^{21} = -34.0°$ by the hydrogenation over platinum oxide of the mixed anhydride of dehydrophenylalanine and L-isovaline (X). The asymmetrising agent (L-isovaline) was then eliminated in the hydrolysis of the diastereoisomer (XI) formed:



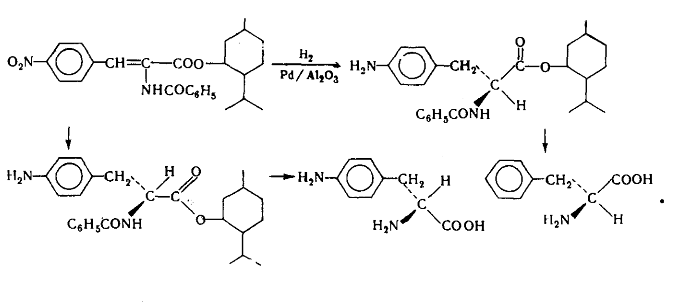
Maeda[32], who employed (+)-D-α-amino-α-phenylpropionic acid instead of isovaline, carried out a similar asymmetric synthesis and obtained L-tyrosine in 35% optical yield:



Bergman and Tietzmann[33] reduced the optically active dioxopiperazine formed by N-acetyldehydrophenylalanyl-L-proline (XII) over palladium black and obtained a 50% yield of the cyclic dimer of N-acetyl-L-phenylalanyl-L-proline (XIII) with $[\alpha]_D^{22} = +202.6°$ and after its hydrolysis L-phenylalanine with $[\alpha]_D^{27} = -33.9°$:

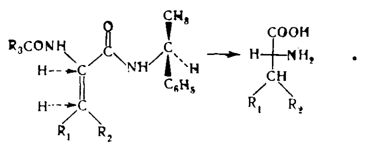


Pedrazzolli[34] achieved an asymmetric synthesis involving the catalytic dehydrogenation of the C=C bond over Pd/Al_2O_3 by reducing the (−)-menthyl ester of α-benzamido-p-nitrocinnamic acid and obtained a mixture of diastereoisomers. The separation of the latter showed that the (SR)-diastereoisomer is present in excess, with (SR) : (RR) = 68 : 32. After the hydrolysis of the hydrogenation products to p-aminophenylalanine, it was found that the degree of asymmetric synthesis is p = 34%. When the bornyl ester was employed, the final product proved to be optically inactive:



Sheehan and Chandler[35] carried out the asymmetric synthesis of valine and phenylalanine by the catalytic hydrogenation on Raney nickel of the optically active alkylamides of α-acetamido-β-methylcrotonic and α-benzamidocinnamic acids. Optically active α-phenylethylamine was employed as an asymmetrising agent. In accordance with Prelog's rule, when (−)-phenylethylamine is employed [provided one adopts for the (−)-amine the configuration indicated in the scheme], the products are

(–)-D-valine and (+)-D-phenylalanine, while the use of (+)-phenylethylamine leads to their optical isomers:

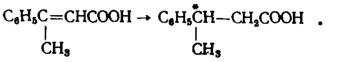


1) $R_1 = CH_3$, $R_2 = CH_3$, $R_3 = C_6H_5$; (–)-D; $p = 18\%$

2) $R_1 = CH_3$, $R_2 = CH_3$, $R_3 = CH_3$; (–)-D; $p = 39\%$

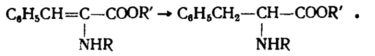
3) $R_1 = C_6H_5$, $R_2 = H$, $R_3 = C_6H_5$; (+)-D; $p = 6\%$

The first data on the asymmetric reduction of β-methylcinnamic acid by hydrogen transfer were quoted by Lipkin and Stewart[36,37]; the use of Raney nickel in the presence of D-glucose led to β-phenylbutyric acid with $\alpha_D = 0.42°$ ($p = 5\%$):



$$C_6H_5\underset{\displaystyle CH_3}{C}{=}CHCOOH \rightarrow C_6H_5\underset{\displaystyle CH_3}{\overset{*}{C}H}{-}CH_2COOH\ .$$

By reducing acetamido- and benzamido-cinnamic acids on Raney nickel in the presence of glucose, Nakazaki[38] obtained phenylalanine in a very low optical yield (Table 5):



$$C_6H_5CH{=}\underset{\displaystyle NHR}{C}{-}COOR' \rightarrow C_6H_5CH_2{-}\underset{\displaystyle NHR}{CH}{-}COOR'\ .$$

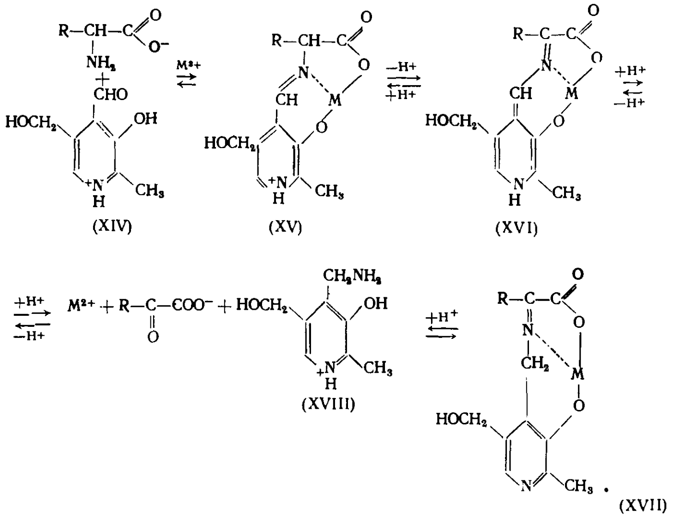
Table 5. Reduction of acylaminocinnamic acids on nickel in the presence of glucose.

R	Acid, g	Glucose, g	Ni, g	Reaction temp., °C	Phenylalanine	
					α_D, l2	$[\alpha]_D$
CH_3CO	4.1	7.9	0.8	30	–0.02	–2.22
CH_3CO	3.9	7.7	1.0	24	+0.03	+3.26
C_6H_5CO	4.0	5.9	1.0	28	+0.02	+1.96

The author interpreted the results as asymmetric reduction with hydrogen transfer, in which glucose is a hydrogen donor and the nickel catalyst an activator and hydrogen-transferring agent. However, the reliability of the data obtained is extremely doubtful, since the observed rotations are within the limits of the error of the measurement.

2. Preparation of Aminoacids by the Reduction of the C=N Bond

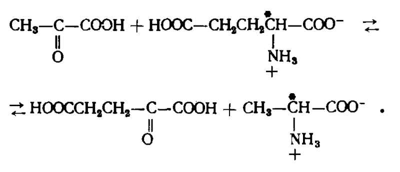
A large number of facts indicate a significant role of the C=N bond in biochemical processes. Although many details of enzymatic reactions are still not clear, certain simplest enzyme systems with a C=N group have been thoroughly investigated. Snell and coworkers[39] proposed a fairly simple mechanism for the transfer of the amino-group from an aminoacid to a ketoacid catalysed by pyridoxal in the presence of certain complex-forming metals:



The reverse transfer by the reaction of pyridoxamine (XVIII) with the ketoacid is possible via the intermediate states (XVII) → (XVI) → (XV); as a result pyridoxal (XIV) is regenerated.

The catalytic methods for the synthesis of optically active aminoacids by the hydrogenation of compounds containing the azomethine group C=N can be divided into three types: (1) enzyme-catalysed transamination of optically inactive aminoacids and ketoacids; (2) transamination of ketoacids and optically active aminoacids; (3) reductive transamination of ketoacids in the presence of optically active amines.

In reactions of the first type the enzyme plays the role of an asymmetrising agent, which probably forms intermediate complexes analogous to (XV) ⇌ (XVI) ⇌ (XVII). For example, L-alanine and α-oxoglutaric acid react in the presence of muscle tissue enzymes, forming pyruvic and L-glutamic acids[40,41]. The reaction between pyruvic and L-glutamic acid catalysed by pyridoxal phosphate and an enzyme leads to the formation of L-alanine[42]:

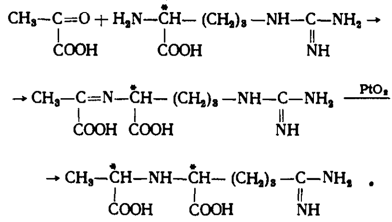


$$CH_3{-}\underset{\displaystyle O}{\overset{\|}{C}}{-}COOH + HOOC{-}CH_2CH_2\underset{\displaystyle \overset{+}{N}H_3}{\overset{*}{C}H}{-}COO^- \rightleftarrows$$
$$\rightleftarrows HOOCCH_2CH_2{-}\underset{\displaystyle O}{\overset{\|}{C}}{-}COOH + CH_3{-}\underset{\displaystyle \overset{+}{N}H_3}{\overset{*}{C}H}{-}COO^-\ .$$

An aminoacid in an optically active form can have a similar asymmetrising effect in the reaction; however, the degree of asymmetric activation is usually low. Thus the reaction of L-alanine or L-phenylalanine with α-oxoglutaric acid catalysed by copper-pyridoxal phosphate gives rise to glutamic acid[43] in which the ratio of the L- and D-isomers is 55 : 45. In this case the asymmetric synthesis takes place as a result of the formation of dissymmetric intermediate chelates, which may be protonated stereospecifically.

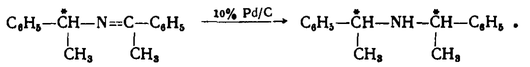
The third type of asymmetric synthesis of aminoacids is achieved when an optically active aminoacid or amine is employed as the asymmetrising agent. Thus the hydrogenation on PtO_2 of a mixture of L-arginine and pyruvic acid in aqueous solution gives octopine $\{[\alpha]_D^{20} = +22.3°\}$.[44,45]

It is suggested that the mechanism of this reaction consists in the reduction of an intermediate Schiff base[46]:



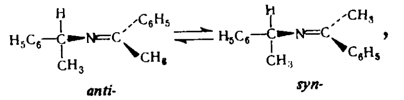
$$CH_3-\underset{COOH}{C}=O + H_2N-\underset{COOH}{\overset{*}{C}H}-(CH_2)_3-NH-\underset{NH}{\underset{\|}{C}}-NH_2 \rightarrow$$
$$\rightarrow CH_3-\underset{COOH}{C}=N-\underset{COOH}{\overset{*}{C}H}-(CH_2)_3-NH-\underset{NH}{\underset{\|}{C}}-NH_2 \xrightarrow{PtO_2}$$
$$\rightarrow CH_3-\underset{COOH}{\overset{*}{C}H}-NH-\underset{COOH}{\overset{*}{C}H}-(CH_2)_3-\underset{NH}{\underset{\|}{C}}-NH_2 .$$

The hydrogenation on Pd/C of the Schiff base obtained from acetophenone and α-phenylethylamine $\{[\alpha]^{25}_{D} = -40.5°\}$ results in the formation of an almost pure optically active product (p = 97.5%) and not a mixture of the optical isomer and the meso-form[47]:



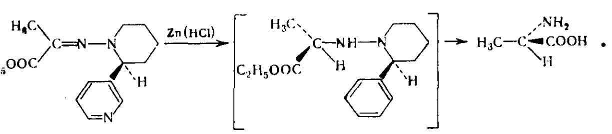
$$C_6H_5-\underset{CH_3}{\overset{*}{C}H}-N=\underset{CH_3}{C}-C_6H_5 \xrightarrow{10\%\ Pd/C} C_6H_5-\underset{CH_3}{\overset{*}{C}H}-NH-\underset{CH_3}{\overset{*}{C}H}-C_6H_5 .$$

This result can be explained by the fact that in the initial compound, which is an equilibrium mixture of two *syn*- and *anti*-isomers,

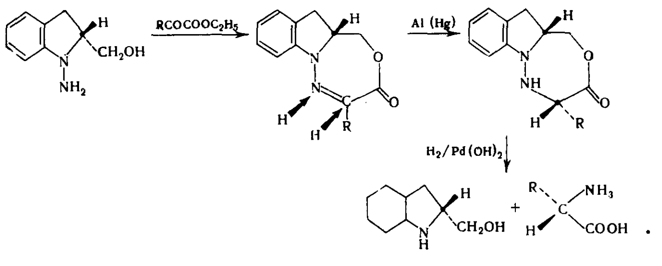


the less stable *syn*-isomer is hydrogenated at a higher rate, which leads to the optically active amine.

A method based on the reduction of the azomethine bond in the system C=N–N– with subsequent dissociation of the N–N bond was employed by Akabori[48,49] and Kost et al.[50] When α-ethoxycarbonylethylidene-N-aminoanabasine (formed from pyruvic acid and N-aminoanabasine) is reduced with zinc in alcoholic hydrochloric acid, D-alanine is formed in an optical yield of 40%:



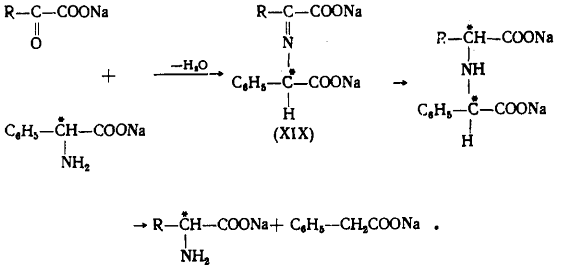
An exceptionally high optical yield was obtained by McCaully[51], who achieved a new synthesis from an optically active hydrazone-lactone (obtained from optically active 1-amino-2-hydroxymethylindoline and a ketoacid), the hydrolysis of which gives alanine (R = CH_3; p = 82%) and α-aminobutyric acid (R = C_2H_5, p = 98%), the initial 1-amino-2-hydroxymethylindoline being regenerated:



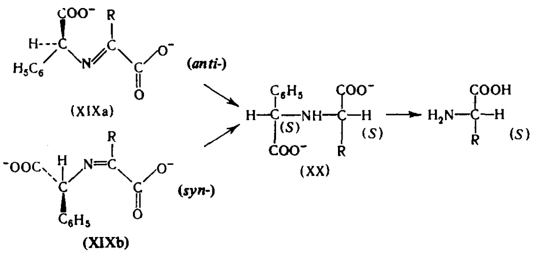
The high stereospecificity of the reaction in the stage involving the reduction by aluminium amalgam can be explained[52] by the *cis*-disposition of the five- and seven-membered rings in the molecule, which forces hydrogen to approach predominantly from one side.

Harada[53,54] employed as an asymmetrising agent optically active phenylglycine, the sodium salt of which was found to undergo readily hydrogenolysis on Pd/C at the C–N bond, giving ammonia and phenylacetic acid.

On the basis of this property, it proved possible to synthesise optically active alanine and α-aminobutyric, glutamic, and aspartic acids from the corresponding ketoacids and optically active phenylglycine according to the mechanism

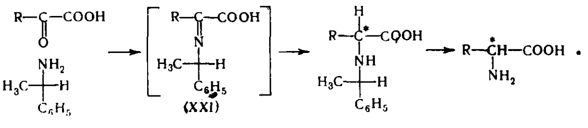


The asymmetric yield of α-aminoacids reaches 40 to 60%. To avoid an alteration of the optical yield during the isolation and purification of the product, measurements were made of the optical activities of the corresponding 2,4-dinitrophenyl derivatives of the aminoacids, which were separated chromatographically on Celite[55]. The mechanism proposed for this reaction consists in the asymmetric reduction of the intermediate Schiff base (XIX). Examination of the conformations of compound (XIX) led to the conclusion[53] that the hydrogenation of both possible isomers [the *syn*-isomer (XIXb) and the *anti*-isomer (XIXa)] leads to the same configuration of compound (XX):



According to this mechanism, the use of (S)-phenyl glycinate as the asymmetrising agent should give the aminoacid with the (S)-configuration and the use of (R)-phenylglycinate should give the corresponding (R)-amino acid. The results showed that these hypotheses are quite valid. It is interesting that the asymmetric yield changes little with increase in the size of the alkyl group at the α-carbon atom of ketoacids.

Hiskey and Northrop[56] obtained optically active aminoacids by hydrogenating the azomethine derivatives of α-ketoacids and (−)- and (+)-α-phenylethylamine on Pd/C, PtO_2, and $Pd(OH)_2/C$ catalysts according to the mechanism

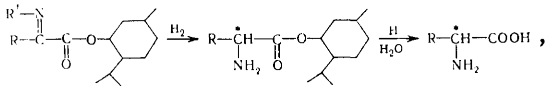


Compound (XXI) (a Schiff base) was not isolated or identified, being immediately subjected to catalytic hydrogenation and hydrogenolysis with formation of the aminoacid. The results of these experiments are presented in Table 6, which shows that the configuration of the aminoacid formed depends on that of the α-phenylethylamine employed: the (+)-amine promotes the formation of the D-aminoacid. The optical yield of the aminoacid varies with the hydrogenation catalyst employed. The maximum optical yield was observed on 10% Pd/C. The addition of acid or alkali does not influence the course and the degree of asymmetric synthesis, in contrast to the asymmetric hydrogenation of ketoacids[22-24]. The size of the alkyl group in the α-ketoacid has a powerful influence on the degree of asymmetric synthesis. Thus, whereas the optical yield of D-alanine (R = CH_3) was 85%, under the same conditions phenylalanine (R = $C_6H_5CH_2$) was obtained with an optical yield of 56% and the optical yield of leucine [R = $(CH_3)_2CHCH_2$] was zero.

Table 6. Asymmetric yield of aminoacids obtained by the transamination of α-ketoacids RCOCOOH with optically active α-phenylethylamine.

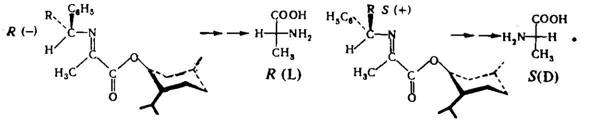
α-ketoacid, R	Catalyst	Configuration of amine	Yield of aminoacid, %	Configuration, sign of rotation, optical yield of aminoacid, %
CH_3	10% Pd/C	(+)	47.9	*D*, (—); 85.2
CH_3	10% Pd/C	(—)	43.1	*L*, (+); 90.7
CH_3CH_2	10% Pd/C	(—)	84.9	*L*, (+); 81.4
CH_3CH_2	$Pd(OH)_2/C$	(+)	71.7	*D*, (—); 71.7
CH_3CH_2	PtO_2	(+)	59.2	*D*, (—); 56.3
$(CH_3)_2CH$	10% Pd/C	(+)	15.7	*D*, (—); 64.2
$(CH_3)_3$	$Pd(OH)_2/C$	(+)	0.0	—
$C_6H_5CH_2$	10% Pd/C	(+)	53.8	*D*, (+); 56.4
$C_6H_5CH_2$	10% Pd/C	(—)	65.0	*L*, (—); 56.0

The asymmetric synthesis of aminoacids by the hydrogenation of the C=N bond was also investigated by Harada and Matsumoto[26,58]. The oximes of the (–)-menthyl esters of pyruvic, α-oxobutyric, and phenylglyoxylic acids and also the Schiff bases of these esters with benzylamine and optically active α-ethyl-α-methylbenzylamines were employed as the starting materials:

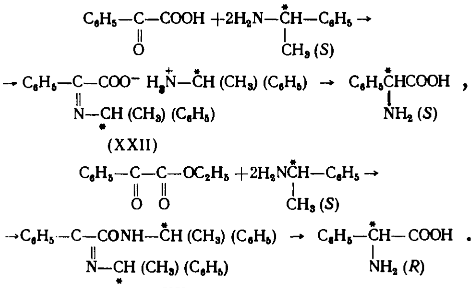


where R = CH_3, C_2H_5, or C_6H_5 and R′ = OH, $C_6H_5CH_2$, $C_6H_5CH(CH_3)$, or $C_6H_5CH(C_2H_5)$.

Table 7 shows that (–)-D-aminoacids are formed with a higher asymmetric yield in the hydrogenation of the oximes than in the hydrogenation of the corresponding Schiff bases with benzylamine. The stereochemistry of the reaction is consistent with Prelog's rule. On the other hand, the hydrogenation of Schiff bases with optically active amines showed that the asymmetric atom of the amine has a more marked influence on the stereospecific addition of hydrogen, namely when the (–)-(*R*)-amine was employed, the product was the (+)-L-aminoacid with a 19–24% optical yield. But when the steric effects of both asymmetric atoms are concerted, the yield of the aminoacid increases sharply and reaches 60%. Table 7 also shows that an increase in the size of the alkyl group at the asymmetric atom of the amine lowers the optical purity of the aminoacid formed. To account for these results, the following stereochemical reaction pathway was suggested[26,58]:



Kanai and Mitsui[59], who applied the method of Hiskey and Northrop[56,57], obtained optically active phenylglycine by the hydrogenation of benzoylformic acid and its ethyl ester in the presence of optically active (*S*)-phenylethylamine on various catalysts [PtO_2, Raney nickel, Pd/Cb, Pd/Ca, $Pd(OH)_2/C$]. It was established that the hydrogenation of ethyl benzoylformate on all the catalysts gives (*R*)-phenylglycine, while the hydrogenation of the acid itself under the same conditions leads to (*S*)-phenylglycine:



$$C_6H_5-\underset{\underset{O}{\|}}{C}-COOH+2H_2N-\underset{\underset{CH_3\,(S)}{|}}{\overset{*}{C}}H-C_6H_5\rightarrow$$

$$\rightarrow C_6H_5-\underset{\underset{N-\underset{*}{C}H\,(CH_3)\,(C_6H_5)}{\|}}{C}-COO^-\;H_3\overset{+}{N}-\overset{*}{C}H\,(CH_3)\,(C_6H_5)\rightarrow C_6H_5\underset{\underset{NH_2\,(S)}{|}}{\overset{*}{C}}HCOOH\ ,$$

(XXII)

$$C_6H_5-\underset{\underset{O}{\|}}{C}-\underset{\underset{O}{\|}}{C}-OC_2H_5+2H_2N\underset{\underset{CH_3\,(S)}{|}}{\overset{*}{C}}H-C_6H_5\rightarrow$$

$$\rightarrow C_6H_5-\underset{\underset{N-\underset{*}{C}H\,(CH_3)\,(C_6H_5)}{\|}}{C}-CONH-\overset{*}{C}H\,(CH_3)\,(C_6H_5)\rightarrow C_6H_5-\underset{\underset{NH_2\,(R)}{|}}{\overset{*}{C}}H-COOH\ .$$

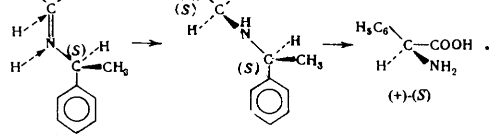
(XXIII)

Table 7. Asymmetric synthesis of aminoacids by the hydrogenation of oximes and Schiff bases of (–)-menthyl esters of ketoacids.

R′ in initial compound	Catalyst	Yield, %	Optical purity of DNP-aminoacids*, %	Aminoacid
		(–)-Menthyl pyruvate		
OH	5% Pd/C	67	*D*-(—), 24.6	alanine
OH	$Pd(OH)_2/C$	70	*D*-(—), 24.5	ditto
$C_6H_5CH_2$	5% Pd/C	79	*DL*-(±), 0	»
$C_6H_5CH_2$	$Pd(OH)_2/C$	77	*D*-(—), 16.3	»
(—) $C_6H_5CH(CH_3)$	5% Pd/C	62	*L*-(±), 24.0	»
(—) $C_6H_5CH(CH_3)$	$Pd(OH)_2/C$	57	*L*-(+), 19.1	»
(—) $C_6H_5CH(C_2H_5)$	$Pd(OH)_2/C$	56	*S*-(+), 15	»
(+) $C_6H_5CH(CH_3)$	5% Pd/C	67	*D*-(—), 65.8	»
(+) $C_6H_5CH(CH_3)$	$Pd(OH)_2/C$	61	*D*-(—), 59.6	»
(+) $C_6H_5CH(C_2H_5)$	$Pd(OH)_2/C$	55	*R*-(—), 36	»
		(–)-Menthyl α-oxobutyrate		
$C_6H_5CH_2$	5% Pd/C	74	*DL*-(±), 0	α-aminobutyric acid
$C_6H_5CH_2$	$Pd(OH)_2/C$	69	*D*-(—), 7.6	ditto
OH	5% Pd/C	64	*D*-(—), 20.5	»
OH	$Pd(OH)_2/C$	62	*D*-(—), 20.7	»
		(–)-Menthyl phenylglyoxylate		
OH	5% Pd/C	88	*D*-(—), 49.1	phenylglycine
OH	$Pd(OH)_2/C$	84	*D*-(—), 44.2	ditto

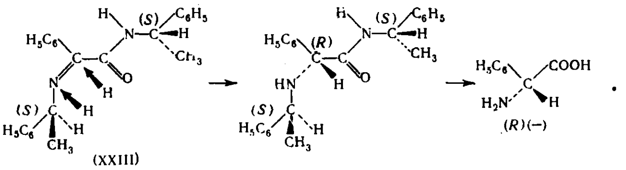
*DNP-aminoacid = dinitrophenyl derivative of aminoacid (Ed. of Translation).

The optical yield of phenylglycine did not exceed 2–3% with the exception of the hydrogenation of compound (XXII) on the highly stereospecific catalyst $Pd(OH)_2$, where the optical yield reached 73%. The authors suggested the following mechanism for the hydrogenation of compound (XXII):



(XXII)

To account for the experimental data, it is necessary to postulate that compound (XXIII) reacts preferentially in the conformation where the imino- and amido-groups are in the *trans*-positions:



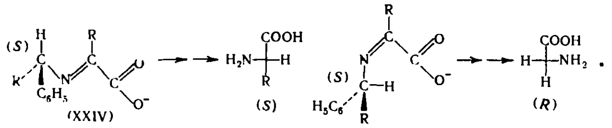
(XXIII)

An attempt was made[26] to investigate the mechanism of the asymmetric synthesis of α-aminoacids by the hydrogenation of the C=N bond. The hydrogenation was carried out on a $Pd(OH)_2/C$ catalyst at room temperature. Three types of reactions were investigated: (1) hydrogenation of the Schiff bases of α-ketoacids with (−)-(*S*)- and (+)-(*R*)-α-methylbenzylamines and (−)-(*S*)- and (+)-(*R*)-α-ethylbenzylamines; (2) hydrogenation of the oximes of (−)-(*S*)-*N*- and (+)-(*R*)-α-methylbenzylbenzoylformamide and (−)-(*S*)-*N*- and (+)-(*R*)-*N*-α-ethylbenzylbenzoylformamide; (3) hydrogenation of the Schiff bases of (−)-menthyl pyruvate with (−)-(*S*)- and (+)-(*R*)-α-methylbenzylamines and (−)-(*S*)- and (+)-(*R*)-α-ethylbenzylamines (Table 8); (4) hydrogenation of the Schiff bases of the isobutyl ester of pyruvoyl-(+)-(*S*)-alanine and the isobutyl esters of pyruvoyl-(+)-(*S*)- and -(−)-(*R*)-valines with benzylamine (Table 12).

Table 8. Hydrogenation of the Schiff bases of α-ketoacids and optically active α-methyl- and α-ethylbenzylamines.

Substrate $R-\underset{\underset{O}{\Vert}}{C}-\underset{\underset{O}{\Vert}}{C}OH$ R=	Sign of rotation of α-R-benzylamine	Yield, %	Aminoacid		DNP-amino-acid
			Configuration, sign of rotation	Optical purity, %	Optical purity, %
CH_3	CH_3 (−)	78	*S*, (+)	63	67
	C_2H_5 (−)	76	*S*, (+)	52	52
	CH_3 (+)	76	*R*, (−)	77	65
	C_2H_5 (+)	72	*R*, (−)	39	51
C_2H_5	CH_3 (−)	72	*S*, (+)	37	39
	C_2H_5 (−)	69	*S*, (+)	36	33
	CH_3 (+)	70	*R*, (−)	38	37
	C_2H_5 (+)	68	*R*, (−)	39	36
C_6H_5	CH_3 (−)	73	*S*, (+)	28	30
	C_2H_5 (−)	70	*S*, (+)	25	24
	CH_3 (+)	73	*R*, (−)	29	31
	C_2H_5 (+)	69	*R*, (−)	24	26
$C_6H_5CH_2$	CH_3 (−)	73	*S*, (−)	12	14
	C_2H_5 (−)	70	*S*, (−)	5	10
	CH_3 (+)	71	*R*, (+)	13	14
	C_2H_5 (+)	71	*R*, (+)	5	11
CH_2CH_2COOH	CH_3 (−)	74	*S*, (+)	13	12
	C_2H_5 (−)	75	*S*, (+)	2	6

The reaction of type 1 was investigated to test the mechanism proposed by Kanai and Mitsui[59]. Table 8 shows that the optical purity of the aminoacids formed depends on the bulk of the alkyl group in the α-ketoacid; namely the optical purity falls in the series $CH_3 > C_2H_5 > C_6H_5 > CH_2C_6H_5 > CH_2CH_2COOH$. The use of α-methylbenzylamine leads in all cases to a higher optical purity than is obtained with α-ethylbenzylamine. The data quoted contradict the mechanism proposed by Kanai and Mitsui[59]. If the conformations of molecules (XXII) and (XXIII) which they proposed are correct, the optical purity of the aminoacids should be independent of the size of the alkyl group and the optical yield should be higher when α-ethylbenzylamine is employed. Therefore it is necessary to put forward another mechanism for reactions of type 1:



(XXIV)

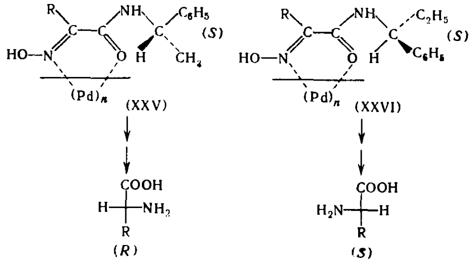
According to the experimental data, the structure (XXIV) is tentative but the increase in the size of the alkyl substituents both in the ketoacid and in the amine hinders the approach of hydrogen to the molecule, which lowers the optical purity of the product. This mechanism accounts satisfactorily for the experimental results and is consistent with the mechanism proposed by Hiskey and Northrop[56].

In reactions of type 2 optically active phenylglycine is obtained by the hydrogenation of the corresponding oxime. The results are given in Table 9.

Table 9. Hydrogenation of the oximes of optically active α-methyl- and α-ethyl-benzylbenzoylformamides.

Configuration of amine	Aminoacid			DNP-aminoacid
	yield, %	configuration, sign of rotation	Optical purity, %	Optical purity, %
CH_3, (-)-(*S*)	56	*R*, (−)	1.5	5.5
C_2H_5, (-)-(*S*)	52	*S*, (+)	1.4	8.8
CH_3, (+)-(*R*)	53	*S*, (+)	0.8	4.9
C_2H_5, (+)-(*R*)	48	*R*, (−)	2.1	10.0

When (*S*)- or (*R*)-α-methylbenzylamines were employed, the products were (*R*)- and (*S*)-phenylglycines respectively, in agreement with Prelog's rule. However, the use of (*S*)- and (*R*)-α-ethylbenzylamines yielded (*S*)- and (*R*)-phenylglycines. To account for these results, it is necessary to postulate that both structures (XXV) and (XXVI) react in the cisoid conformation, as shown in the scheme below:



However, when the methyl group of the optically active amine is replaced by the ethyl group, the molecule should probably react more readily in conformation (XXVI) and give rise to the (*S*)-aminoacid. The carbonyl and azomethine groups can interact with the catalyst (Pd/C) forming coordinate bonds and giving rise to a five-membered cyclic complex. This stabilises the *cis*-conformation of the substrate molecule. The possibility of the formation of such complexes for compounds with C=O and C=N bonds was discussed by Hartung and coworkers[60].

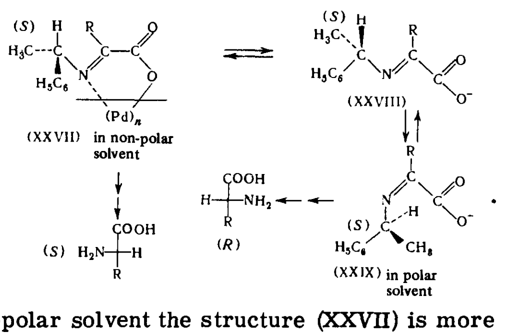
The study of the hydrogenation of optically active azomethine derivatives in various solvents showed that an increase in the polarity of the solvent leads to a decrease of the optical density of the aminoacid formed (alanine, phenylalanine, phenylglycine) and even to a change in the sign of the rotation (glutamic acid) (Table 10)[29].

Table 10. Effect of solvents on the configuration and optical yields of aminoacids.

R—CO—COOR′	Configuration of amine, R in $R-\overset{*}{C}H(NH)_2C_6H_5$	Solvent	Aminoacid $R-CHNH_2COOH$		
			yield, %	configurational	optical purity*, %
$R=CH_3$ $R'=H$	(-)-(*S*)-CH_3	THF	33	(+)-(*S*)	66
		C_2H_5OH	78	(+)-(*S*)	67
		H_2O + pyridine	78	(+)-(*S*)	40
		$NaOH + H_2O$	69	(+)-(*S*)	33
	(-)-(*S*)-C_2H_5	C_2H_5OH	76	(+)-(*S*)	52
		$C_2H_5OH + H_2O + NaOH$	65	(+)-(*S*)	37
		$CH_3OH:H_2O=1:4+NaOH$	75	(+)-(*S*)	31
	(+)-(*R*)-naphthyl	C_2H_5OH	76	(-)-(*R*)	83
		$C_2H_5OH+H_2O+NaOH$	65	(-)-(*R*)	73
$R=CH_3$ $R'=CH_2C_6H_5$	(-)-(*S*)-CH_3	hexane	75	(+)-(*S*)	72
		ethyl acetate	49	(+)-(*S*)	60
		isopropyl alcohol	56	(+)-(*S*)	46
		dimethylformamide	47	(+)-(*S*)	50
		CH_3OH	61	(+)-(*S*)	38
		dioxan: $H_2O = 45:55$	71	(+)-(*S*)	29
		$CH_3OH:H_2O=2:1$ **	75	(+)-(*S*)	35
		$CH_3OH:H_2O=1:2$ **	63	(+)-(*S*)	39
		$CH_3OH:H_2O=1:4$ **	76	(+)-(*S*)	29
		H_2O **	45	(+)-(*S*)	41
	(+)-(*R*)-CH_3	dioxan	72	(-)-(*R*)	58
	(+)-(*R*)-C_2H_5	hexane**	66	(-)-(*R*)	74
	(+)-(*R*)-naphthyl	hexane**	31	(-)-(*R*)	86
		ethyl acetate	31	(-)-(*R*)	78
$R=C_6H_5$ $R'=H$	(-)-(*S*)-CH_3	C_2H_5OH	73	(+)-(*S*)	30
		$H_2O + NaOH$	60	(+)-(*S*)	24
$R=CH_2COOH$, $R'=H$	(-)-(*S*)-CH_3	$C_2H_5OH + H_2O + NaOH$	38	(+)-(*S*)	58
			11	(-)-(*R*)	45
$R=(CH_2)_2COOH$ $R'=H$	(-)-(*S*)-CH_3	isopropyl alcohol + triethylamine	82	(+)-(*S*)	14
		C_2H_5OH	74	(+)-(*S*)	12
		CH_3OH + triethylamine	78	(+)-(*S*)	5
		dioxan: $H_2O = 2:8$ + triethylamine	60	(-)-(*R*)	19
		$CH_3OH:H_2O=1:2+NaOH$	68	(-)-(*R*)	27
		H_2O + pyridine	55	(-)-(*R*)	27
	(+)-(*R*)-C_2H_5	C_2H_5OH	75	(-)-(*R*)	6
	(-)-(*S*)-C_2H_5	$H_2O:CH_3OH=2:1+NaOH$	56	(-)-(*R*)	30

*The optical purity was calculated from the optical rotation of the dinitrophenyl derivatives of the aminoacids.
**The reaction mixture was not homogeneous.

The results suggest that the reactive conformation of the molecule changes under the influence of the solvent according to the mechanism



In a non-polar solvent the structure (XXVII) is more favourable, since the electrostatic attraction between the catalyst and the substrate is greater than under conditions where polar solvents are employed; the weak solvation of the substrate molecules in non-polar solvents promotes a more ready formation of the intermediate complex with the catalyst. In polar solvents the non-chelate structure (XXIX), which can be converted into the non-chelate structure (XXVIII) with decrease of the polarity of the medium, is more likely.

A study of the hydrogenation of oxaloacetic acid in the presence of various amines was undertaken to obtain optically active aspartic acid[61]. It was found that, depending on the amine and the solvent employed, either a mixture of alanine and aspartic acid or alanine alone are obtained (Table 11). The hydrogenation of the Schiff base with benzylamine in alcoholic solution gives racemic alanine. A similar result is also obtained with optically active α-methyl- and α-ethyl-benzylamines. On the other hand, when (+)-(*S*)- and (−)-(*R*)-phenylglycines were used, mixtures of (+)-(*S*)-alanine and (+)-(*S*)-aspartic acid and of (−)-(*R*)-alanine and (−)-(*R*)-aspartic acid were obtained:

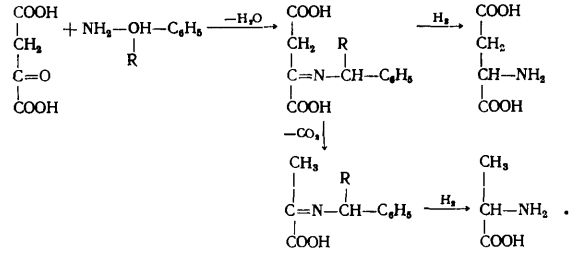


Table 11. The formation of optically active alanine and aspartic acid from oxaloacetic acid and α-alkylbenzylamines.

Configuration of amine	Solvent	Yield, %	Configuration of aminoacid	Optical yield of DNPh-aminoacid, %
(-)-(*S*)-CH_3	C_2H_5OH	78	(+)-(*S*)-alanine	69
(-)-(*S*)-CH_3	H_2O, C_2H_5OH (1:1) + NaOH	60	(+)-(*S*)-alanine (-)-(*R*)-aspartic acid	51 45
(-)-(*S*)-C_2H_5	C_2H_5OH	75	(+)-(*S*)-alanine	52
(-)-(*S*)-C_2H_5	H_2O, C_2H_5OH (1:1) + NaOH	56	(+)-(*S*)-alanine (-)-(*R*)-aspartic acid	37 25
(+)-(*R*)-naphthyl	C_2H_5OH	75	(-)-(*R*)-alanine	83
(+)-(*R*)-naphthyl	H_2O, C_2H_5OH (1:1) + NaOH	65	(-)-(*R*)-alanine	73
(+)-(*S*)-COOH	H_2O, NaOH	40	(+)-(*S*)-alanine (+)-(*S*)-aspartic acid	60 53
(-)-(*R*)-COOH	H_2O, NaOH	38	(-)-(*R*)-alanine (-)-(*R*)-aspartic acid	62 53

The above reaction mechanism presupposes that the Schiff base of oxaloacetic acid formed can be readily decarboxylated with formation of the corresponding Schiff base of pyruvic acid, the hydrogenation and subsequent hydrogenolysis of which give alanine.

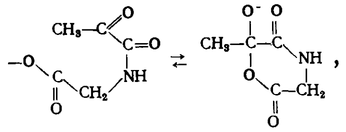
The mechanism of the asymmetric hydrogenation of azomethine derivatives of α-ketoacids proposed above[26] consists in the formation of an intermediate complex (XXV, XXVI) of the compound with the Pd catalyst and the subsequent adsorption of the substrate molecule on the catalyst surface and the addition of hydrogen to the C=N bond. This mechanism is proved by the results of an investigation of similar reactions in media of different polarity[29] and also the study of asymmetric hydrogenation of compounds with a peptide bond[57,62]. Hiskey and Northrop[57] achieved the asymmetric synthesis of peptides in the following experiments:

(a) reduction of *N*-pyruvoylglycine with optically active α-methylbenzylamine;

(b) reduction of *N*-pyruvoyl-L-alanine with optically active α-methylbenzylamine;

(c) reduction of *N*-pyruvoyl-L-alanine with benzylamine.

The experimental results showed that in the hydrogenation of the Schiff bases of pyruvoylglycine with (−)- and (+)-α-methylbenzylamines the optical yield of alanylglycine (30–60%) is lower than in the reduction of pyruvic acid under the same conditions (cf. Table 6). This can be accounted for by the unfavourable interaction between the keto- and carboxy-groups,

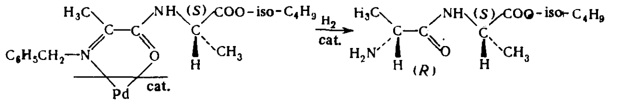


and also by an increase of steric hindrance due to the bulky substituent (glycine) at the carboxy-group of the ketoacid. Steric correlations in accordance with Prelog's rule hold in the reaction: when the (−)-amine is employed, the L-peptide is obtained and the (+)-amine gives rise to the D-peptide. The hydrogenation of *N*-pyruvoyl-L-alanine under the same conditions showed that the asymmetric atom of L-alanine does not play the main role in the formation of the new asymmetric centre: when the D-amine was employed, the product contained an excess of the D-L-isomer of the dipeptide, while in the presence of the L-amine, the L-L-isomer was obtained in excess. The hydrogenation of *N*-pyruvoyl-L-alanine in the presence of optically inactive benzylamine was carried out to elucidate the asymmetrising effect of the L-alanyl part of the molecule. Contrary to expectation, the D-L-dipeptide was found to be in an excess, although Prelog's rule predicts the formation of the L-L-dipeptide.

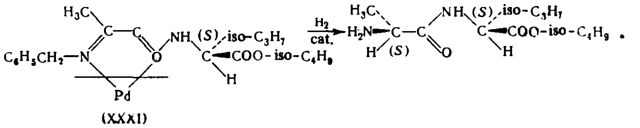
It is noteworthy that the dipeptides were obtained in these reactions in low yields (up to 30%). Possibly this is because *N*-pyruvoylalanine is reduced to lactic acid at a higher rate than that of the formation of the Schiff base; indeed lactic acid was found in the reaction mixture in a yield greater than 80%.

Harada and Matsumoto[62] achieved similarly the asymmetric synthesis of certain alanyl dipeptides and found that, in the hydrogenation of the Schiff bases of the isobutyl and methyl esters of *N*-pyruvoyl-(*S*)-alanine with benzylamine, the newly formed asymmetric atom has the (*R*)-configuration, i.e. the results are consistent with those of Hiskey and Northrop[57]. But, when the esters of optically active valine, leucine, phenylalanine, phenylglycine, and aspartic and α-aminobutyric acids were employed as the asymmetrising agents, the (*S*,*S*)-alanyl dipeptide was formed preferentially.

The authors proposed the following stereochemical mechanism for the reaction:



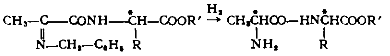
(XXX)



(XXXI)

When the alkyl substituent at the asymmetric carbon atom is R = CH_3, the substrate molecule reacts preferentially in conformation (XXX), but when the R group is larger than methyl, in all other reactions hydrogenation takes place preferentially with the substrate in conformation (XXXI). In both conformation (XXX) and (XXXI) the C=N and C=O groups are in the *cis*-positions stabilised by the formation of a complex with the catalyst. If the asymmetrising agent has the (*S*)-configuration, the hydrogenation of the molecule in conformation (XXX) leads to the formation of (*R*)-alanine, while conformation (XXXI) induces the formation of (*S*)-alanine. The hydrogenation of the Schiff bases and oximes of α-oxobutyric acid activated by various optically active aminoacids showed that in this case the reaction takes place preferentially in conformation (XXXI) (Table 13).

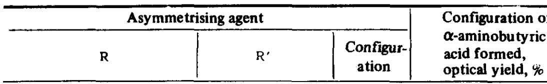
Table 12. Asymmetric synthesis of alanyl dipeptides



$$CH_3-\underset{\underset{N-CH_2-C_6H_5}{\|}}{C}-CONH-\underset{\underset{R}{|}}{\overset{*}{C}H}-COOR' \xrightarrow{H_2} CH_3\underset{\underset{NH_2}{|}}{\overset{*}{C}H}CO-HN\underset{\underset{R}{|}}{\overset{*}{C}H}COOR'$$

Asymmetrising agent			Configuration of alanine formed, optical yield, %
R	R′	Configuration	
CH_3	$CH_2CH(CH_3)_2$	*S*	*R*, 64
CH_3	CH_3	*S*	*R*, 52
C_2H_5	$CH_2CH(CH_3)_2$	*S*	*S*, 41
$(CH_3)_2CH$	$CH_2CH(CH_3)_2$	*S*	*S*, 32
$(CH_3)_2CH$	$CH_2CH(CH_3)_2$	*R*	*R*, 32
$(CH_3)_2CH$	CH_3	*S*	*S*, 17
$(CH_3)_2CHCH_2$	$CH_2CH(CH_3)_2$	*S*	*S*, 35
$(CH_3)_2CHCH_2$	CH_3	*S*	*S*, 18
$C_6H_5CH_2$	$CH_2CH(CH_3)_2$	*S′*	*S*, 25
$(CH_3)_2CHCH_2OOCCH_2$	$CH_2CH(CH_3)_2$	*S*	*S*, 25
C_6H_5	$CH_2CH(CH_3)_2$	*R*	0

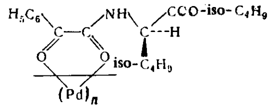
Table 13. Asymmetric synthesis of α-aminobutyric acid.



$$C_2H_5-\underset{\underset{N-R'}{\|}}{C}-CONH-\underset{\underset{R}{|}}{\overset{*}{C}H}-COOCH_2CH(CH_3)_2 \xrightarrow[\text{catalyst}]{H_2} \xrightarrow[H_2O]{H^+} \overset{*}{C}H_3CH_2\underset{\underset{NH_2}{|}}{\overset{*}{C}H}COOH$$

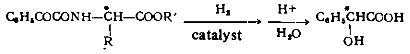
Asymmetrising agent			Configuration of α-aminobutyric acid formed, optical yield, %
R	R′	Configuration	
C_6H_5	OH	*R*	0
$C_6H_5CH_2$	$CH_2C_6H_5$	*S*	*S*, 12
$C_6H_5CH_2$	OH	*S*	*S*, 9
$(CH_3)_2CHCH_2OOCCH_2$	$CH_2C_6H_5$	*S*	*S*, 28

That the reaction proceeds via the formation of a complex of the substrate with the catalyst is proved to some extent by the study of the asymmetric synthesis of mandelic acid[62] (Table 14). Assuming that the molecule (for example in the synthesis of mandelic acid) forms with the catalyst a complex via two C=O bonds,



the authors concluded that the steric hindrance in the adsorption of keto-compounds is lower than for the azomethine derivatives (oximes and Schiff bases). The substituent at the C=N bond in the azomethines (OH or $CH_2C_6H_5$) increases the steric hindrance between the substrate and the catalyst and therefore the use of (*S*)-alanine alone (R = CH_3) leads to the (*R*)-configuration of the new asymmetric atom, i.e. the molecule reacts in conformation (XXX). In the hydrogenation of the keto-group the use of esters of (*S*)-alanine (R = CH_3) and (*S*)-leucine [R = $(CH_3)_2CHCH_2$] yields (*R*)-mandelic acid and only the use of (*S*)-valine [R = $(CH_3)_2CH$] gives rise to (*S*)-mandelic acid. Consequently in the first two reactions the substrate molecule reacts in conformation (XXX) and in the last case the preferred conformation is (XXXI).

Table 14. Asymmetric synthesis of mandelic acid



$$C_6H_5COCONH{-}\overset{*}{C}H(R){-}COOR' \xrightarrow[\text{catalyst}]{H_2} \xrightarrow[H_2O]{H^+} C_6H_5\overset{*}{C}H(OH)COOH$$

Asymmetrising agent			Configuration of mandelic acid, optical yield, %
R	R′	Configuration	
CH_3	CH_3	*S*	*R*, 3
CH_3	$CH_2CH(CH_3)_2$	*S*	*R*, 14
CH_3	$CH_2CH(CH_3)_2$	*R*	*S*, 13
$(CH_3)_2CHCH_2$	$CH_2CH(CH_3)_2$	*S*	*R*, 11
$(CH_3)_2CH$	$CH_2CH(CH_3)_2$	*S*	*S*, 2

The numerous examples quoted above demonstrate a significant effect of the substituent at the reacting bond on the effectiveness of asymmetric catalysis. Formally this phenomenon may be described by the correlation equation derived by Ugi[63] for asymmetric hydrogenation, which is of the form

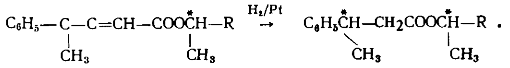
$$\lg Sp = \lg\frac{p}{100-p} = \varkappa\tau\delta_p,$$

where $\varkappa$ is the "chirality parameter" determined from $\varkappa = (\lambda_1 - \lambda_2)(\lambda_2 - \lambda_3)(\lambda_3 - \lambda_1)$ (λ_1, λ_2, and λ_3 are constants characterising the groups linked to the asymmetric atom in the ligands) and τ and δ_p are empirical constants.

Table 15. Calculation of the stereospecificities *Sp* from Ugi's equation for the hydrogenation of β-methylcinnamic acid esters.

R	$\varkappa$	δ_p	*Sp* (for τ = 0.110) calc.	*Sp* (for τ = 0.110) found	λ_R constant for group R
$(CH_3)_3C$	—0.730	—1	54.6	54.3	1.49
C_6H_5	—0.283	—1	52.0	52.3	1.23
2,4,6-$(CH_3)_3C_6H_2$	0.918	1	55.8	56.5	1.58
1-$C_{10}H_7$	—0.375	—1	52.5	53.8	1.29
2,4,6-$(C_6H_{11})_3C_6H_2$	2.303	1	64.3	63.5	2.10

For the hydrogenation of a number of optically active esters of β-methylcinnamic acid in acetic acid on platinum at 20°C, the calculated values of *Sp* agree well with experiment (Table 15).

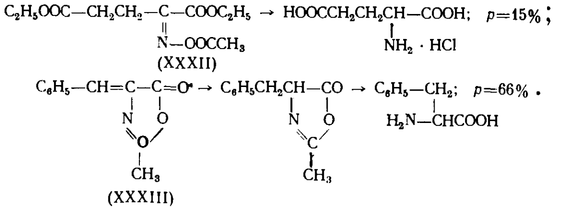


$$C_6H_5{-}C(CH_3){=}CH{-}COO\overset{*}{C}H(CH_3){-}R \xrightarrow{H_2/Pt} C_6H_5\overset{*}{C}H(CH_3){-}CH_2COO\overset{*}{C}H(CH_3){-}R\,.$$

IV. CATALYTIC SYNTHESIS OF OPTICALLY ACTIVE AMINOACIDS ON DISSYMMETRIC CATALYSTS

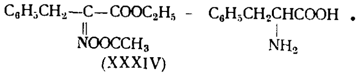
The first unsuccessful attempts at the asymmetric hydrogenation of acetophenone on nickel in the presence of cholic acid or sodium deoxychelate may be regarded as attempts at modifying the catalyst surface by adding an optically active compound to produce a dissymmetric catalyst[64]. Thus the asymmetric reduction by hydrogen transfer[36–38] could also be interpreted as involving interaction to some extent between the hydrogen donor (glucose) and the surface of the metal catalyst whereby the latter is specifically modified.

Isoda and coworkers[65] showed for the first time that the catalyst obtained by the reduction of the Pd–L-tyrosine complex is capable of promoting the asymmetric hydrogenation of compounds (XXXII) and (XXXIII) with formation of (–)-D-glutamic acid and (+)-D-phenylalanine:



Partial optical activation of the aminoacids formed is observed also in the hydrogenation of compounds (XXXII) and (XXXIII) on Raney nickel treated with (–)-tyrosine, (–)-leucine, (–)-phenylalanine, or (–)-arginine. Treatment with (–)-methionine does not lead to optically active products. At the same time modification of the Pd/C catalyst with methionine can be achieved and the hydrogenation of α-acetamidocinnamic acid (XXXIV) on such a catalyst leads to the formation of L-phenylalanine[66].

Isoda and coworkers[65] were guided by the statements of Akabori and coworkers[67–99], who obtained a dissymmetric catalyst by reducing $PdCl_2$ (33 wt. %) deposited on silk fibres at 50°C and 80 atm. In their first communications, Akabori and coworkers stated that such a catalyst is capable of promoting the asymmetric synthesis of aminoacids by the hydrogenation of (XXXII), (XXXIII), and (XXXIV) with an appreciable asymmetric yield—39, 38, and 26% respectively:



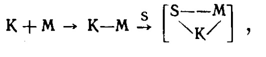
$$C_6H_5CH_2{-}C({=}NOOCCH_3){-}COOC_2H_5 \rightarrow C_6H_5CH_2CH(NH_2)COOH\,.$$

(XXXIV)

However, it is difficult to reproduce these results[70,71]. The studies of the effect of disymmetric nickel catalysts modified by optically active compounds were developed further in a number of investigations by Izumi, Akabori, and coworkers[70–73], mainly in the hydrogenation of the carbonyl group on the catalyst modified with (+)-tartaric acid[74] and aminoacids.

Klabunovskii and Petrov[75,76] extended the study of modified nickel catalysts to the hydrogenation of the C=N bond. Thus the hydrogenation of acetophenoxime takes place asymmetrically (*p* = 2.6%), which suggests that there is a possibility of the application of these catalysts in the synthesis of optically active aminoacids. This method has an undoubted advantage over others, since there is no need to introduce an asymmetrising group into the initial molecule.

There are so far few data on the mechanism of the asymmetrising effect of modified catalysts but already certain conclusions may be made[75,77]. Probably asymmetric hydrogenation takes place only with formation of a fairly stable intermediate complex via the mechanism



where S is the substrate, M the optically active modifying agent, and K the catalyst.

The formation of such a complex fixes the conformation of the reacting molecule in a particular way. The M–K, K–S, and S–M interactions in the complex may be examined in succession.

The M–K bond is responsible for the modification of the catalyst and the formation of a surface nickel complex with the modifying substance (hydroxy- or amino-compound). Such complexes are centres for asymmetric hydrogenation and the maximum asymmetric effect will be observed for the optimum stability of the complex. Approximate data on the stability of the M–K bond may be obtained from the stability constants K_S of nickel complexes of hydroxy- or amino-acids. Comparison of the literature data for the stability constants of the nickel complexes of certain aminoacids and the stereospecificities Sp shows that Sp passes through a maximum as K_S increases, i.e. an unduly high stability of the complex has an unfavourable effect on asymmetric catalysis—a situation analogous to the energy correspondence (the equality of the adsorption potential of the optimum catalyst to half the sum of the energies of the reacting bonds in the molecule) considered in the multiplet theory of catalysis. Klabunovskii showed[77] that there is an approximately linear relation between the logarithm of the stereospecificity Sp and the change in the enthalpy ΔH of the catalyst modifying agent employed in the hydrogenation of methyl acetoacetate on nickel modified with tartaric, malic, and mandelic acids, alanine, and leucine:

$$RT \ln Sp \simeq \Delta H \ .$$

The K–S bond is altered under the influence of the modification of the catalyst and therefore the bonding energy Q between the atoms in the reacting molecule and the catalyst Q_{K-S} will differ from the value $Q_{K'-S}$ for the unmodified catalyst K′.

The experimental data[70–73,78–80] show that, since fairly stable complexes are formed on chemisorption of C=O, C–OH, and C=N groups in the reacting molecule, the asymmetrising property of the catalyst is shown only in relation to C=O and C=N but not C=C bonds.

It is so far difficult to make a quantitative assessment of the S–M bond and therefore the only measure of the interaction between the molecules of the substrate and the modifying agent is the stereospecificity of the reaction.

Qualitative data may be obtained about the nature of the K–S and K–M bonds by means of the energy calculations of the multiplet theory of catalysis. The energies of the bonds of nickel with oxygen and nitrogen (57.7 and 29.3 kcal) greatly exceed the values for palladium and platinum (44.1 and 25.1 kcal; 34.3 and 24.4 kcal) and therefore nickel is readily modified by compounds containing free amino- and hydroxy-groups and forms more readily reactive complexes with substrates containing C=O and C=N bonds. At the same time the energy of the bond with hydrogen decreases in the series $Q_{Pt-H} > > Q_{Pd-H} > Q_{Ni-H}$, which facilitates the adsorption of the reacting compound on nickel and the oriented adsorption of the substrate molecule becomes rate-limiting.

However, these theoretical concepts still require a detailed experimental and quantitative development.

The validity of the hypothesis that asymmetric catalysis takes place via the formation of intermediate complexes is apparently confirmed by the known cases of the asymmetric synthesis of aminoacids[81,82] and asymmetric reactions under the influence of disymmetric catalysts[83–87].

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Zelinskii Institute of Organic
Chemistry, USSR Academy
of Sciences, Moscow

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Acyl Phosphites

E.E.Nifant'ev and I.V.Fursenko

The review deals with an interesting new field among organophosphorus compounds—the chemistry of acyl phosphites. The possible ways of synthesising and the chemical properties of these highly reactive compounds have been examined together with the likely mechanisms of the reactions considered.

The bibliography includes 111 references.

CONTENTS

I. INTRODUCTION

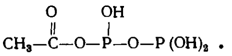
One of the results of the rapid development of the chemistry of organophosphorus compounds has been the discovery and detailed study of new classes of substances. In particular, one of such classes is acyl phosphites. Like other mixed anhydrides of phosphorus and carboxylic acids, acyl phosphites readily enter into phosphorylation and acylation reactions with nucleophilic agents. They react also with electrophilic agents owing to the presence of the unshared electron pair in the outer shell of the phosphorus atom. This property of acyl phosphites is responsible for the very wide range of reagents which react with them and makes them interesting objects for theoretical studies as well as important key substances in organophosphorus synthesis.

The majority of investigations of acyl phosphites have been carried out very recently and therefore there are no relevant reviews. This and also the appearance in the chemistry of acyl phosphites of certain new trends, characteristic also of other classes of organic derivatives of phosphorus, made it desirable to write the present article. The review is not merely a compilation. Together with a description of the advances in this field of chemistry, the authors make a critical assessment of certain experimental studies and put forward a number of general considerations concerning this subject.

II. SYNTHESIS OF ACYL PHOSPHITES

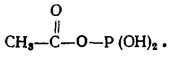
1. The Reaction of Phosphorous Acid and Dialkyl Phosphites with Carboxylic Acid Anhydrides

In order to elucidate the structure of phosphorous acid, in 1866 Menshutkin allowed it to react with acetyl chloride and obtained a substance to which he attributed the following structure:



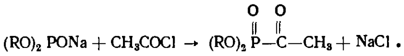
$$CH_3-\overset{\overset{O}{\|}}{C}-O-\overset{\overset{OH}{|}}{P}-O-P(OH)_2\,.$$

Somewhat later Vvedenskii achieved the reaction of phosphorous acid with acetic anhydride and isolated a crystalline product, which he believed to be monoacetyl phosphite:



$$CH_3-\overset{\overset{O}{\|}}{C}-O-P(OH)_2\,.$$

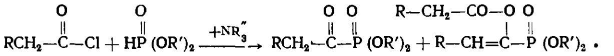
The same substance was obtained by Brooks[3] in a reaction of acetyl chloride with phosphorous acid under somewhat milder conditions than in Menshutkin's reaction. However, Cade[4] established on the basis of chemical and X-ray diffraction data that in fact the above workers did not obtain a mixed anhydride but acetylphosphonic acid: $CH_3C(O)PO(OH)_2$. Cade's conclusion concerning this reaction is consistent with the data of A. E. Arbuzov, who showed that sodium (and potassium) salts of dialkyl phosphites react with acetyl chloride to form 1-ketophosphonic acids[5]:



$$(RO)_2PONa + CH_3COCl \rightarrow (RO)_2\overset{\overset{O}{\|}}{P}-\overset{\overset{O}{\|}}{C}-CH_3 + NaCl\,.$$

Ketophosphonates are obtained similarly also in the reaction with benzoyl chloride[6].

The reaction of carboxylic acid chlorides with dialkyl phosphites in the presence of tertiary amines has also been discussed in the literature. Here the products are not acyl phosphites, α-ketophosphonates and the corresponding enol carboxylates being isolated in a high yield[7]:

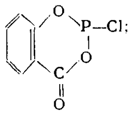


$$RCH_2-\overset{\overset{O}{\|}}{C}-Cl + H\overset{\overset{O}{\|}}{P}(OR')_2 \xrightarrow{+NR''_3} RCH_2-\overset{\overset{O}{\|}}{C}-\overset{\overset{O}{\|}}{P}(OR')_2 + R-CH=\overset{\overset{R-CH_2-CO-O}{|}}{C}-\overset{\overset{O}{\|}}{P}(OR')_2\,.$$

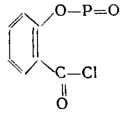
Thus so far it has not proved possible to find conditions under which phosphorous acid and salts of dialkylphosphorous acid react with carboxylic acid anhydrides to form $-\overset{\overset{O}{\|}}{C}-O-P\langle$ fragments and not $-\overset{\overset{O}{\|}}{C}-\overset{\overset{O}{\|}}{P}\langle$. However, in view of the limited number of publications on this question, one cannot state categorically that there is no possibility of developing methods for the synthesis of acyl phosphites on the basis of such reactions.

2. Reaction of Phosphorus(III) Acid Chlorides with Carboxylic Acids and Their Salts

Acyl phosphites were obtained for the first time by Anshutz and Emery[8] by the reaction of phosphorus trichloride with salicylic acid. They discussed two possible structures of the products:



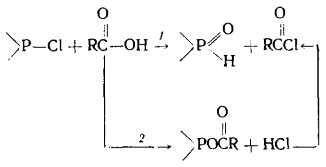
(IA)



(IB)

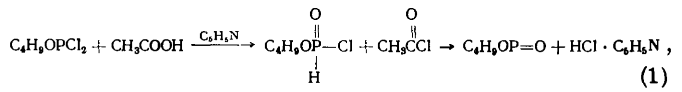
On the basis of preparative data for the reaction of carboxylic acids with phosphorous trichloride, which leads to acyl chlorides, the authors concluded that their compound has the structure (IB). This formula was attributed to compound (I) in the well known monograph of Kosolapoff[9]. Later Young[10] and Cade and Gerrard[11] established that the original conclusion was erroneous and the structure (IA) was assigned to the substance obtained by Anshutz and Emery. The data allowing this conclusion can be more usefully dealt with below in the section concerned with the reaction of amines with acyl phosphites (see p. 1059).

Further discussion of the preparation of acyl phosphites by the reaction of carboxylic acid with phosphorus(III) acid chlorides makes it necessary to consider the mechanism of this reaction. Cade and Gerrard[12] attempted to elucidate this problem. They attempted to discover whether there is a direct exchange of chlorine bound to the phosphorus atom for the hydroxy-group of the carboxylic acid (mechanism *1*) or whether chlorine is substituted by the acyloxy-group with formation of an acyl phosphite which reacts *in situ* with the hydrogen chloride liberated (mechanism *2*):

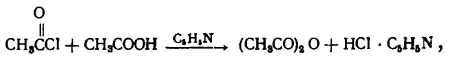


Bearing in mind that in the presence of pyridine acetyl chloride and acetic acid react to form acetic anhydride and pyridine hydrochloride[13] (this reaction takes place extremely rapidly even at −78°C), the authors carried out the reaction of dibutyl phosphorochloridite with two moles of acetic acid in the presence of one mole of pyridine. It was thought that, if the reaction proceeds via mechanism *1*, the acetyl chloride formed in the presence of pyridine should immediately react in the second stage with the residual mole of acid, forming acetic anhydride and pyridine hydrochloride. On the other hand, if the process proceeded via mechanism *2*, then the reaction products should contain acetyl dibutyl phosphite, pyridine hydrochloride, and one mole of unreacted acid.

Since Cade and Gerrard obtained a 92% yield of acetic anhydride, they considered it proved that the reaction of carboxylic acids with phosphorus(III) acid chlorides takes place via mechanism *1*. Attributing great importance to the formation of acetic anhydride in their experiments and failing to see another mechanism of its formation, these workers suggested that mechanism *1* obtains also when a carboxylic acid salt and pyridine are introduced into the reaction with phosphorochlorodites. In this connection the considerations they put forward concerning the mechanism of the reaction of butyl phosphorodichloridite with two moles of acetic acid and two moles of pyridine, which leads to the formation of diacetyl butyl phosphite[12], are noteworthy. They asserted that at the beginning there is "as usual" a direct exchange of one of the chlorine atoms of butyl phosphorodichloridite for a hydroxy-group with formation of acetyl chloride and butyl hydrogen phosphorochloridite, which decomposes into butyl metaphosphite and pyridine hydrochloride. Subsequently acetyl chloride reacts with another mole of acetic acid and forms acetic anhydride, which reacts with the metaphosphite to give diacetyl butyl phosphite:



$$C_4H_9OPCl_2 + CH_3COOH \xrightarrow{C_5H_5N} C_4H_9O\underset{H}{\overset{O}{\overset{\|}{P}}}{-}Cl + CH_3\overset{O}{\overset{\|}{C}}Cl \rightarrow C_4H_9OP{=}O + HCl\cdot C_5H_5N\,, \tag{1}$$



$$CH_3\overset{O}{\overset{\|}{C}}Cl + CH_3COOH \xrightarrow{C_5H_5N} (CH_3CO)_2O + HCl\cdot C_5H_5N\,, \tag{2}$$

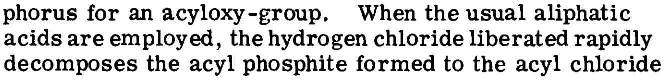
$$C_4H_9OP{=}O + (CH_3CO)_2O \rightarrow C_4H_9OP(OCOCH_3)_2\,. \tag{3}$$

Cade and Gerrard saw a confirmation of this mechanism in the fact that the metaphosphite formed by the controlled hydrolysis of butyl phosphorodichloridite indeed reacted with acetic anhydride to form diacetyl phosphites. Thus, having discovered a new way of synthesising acetyl phosphite (unfortunately they quote only one example, which precludes the consideration of this reaction in a separate section), the authors omitted from all their discussions another way in which the actual products may be formed: namely by the reaction of equimolar amounts of acyl phosphite and carboxylic acid to give dialkyl phosphite and acetic anhydride[14] (see p. 1056). Having disregarded this possibility, Cade and Gerrard could not find an alternative mechanism for the formation of acetic acid anhydride in their experiments and therefore arrived at an incorrect conclusion concerning the reaction of carboxylic acids and their salts with phosphorus(III) acid chlorides.

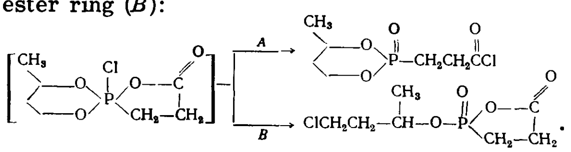
That the conclusion of Cade and Gerrard was incorrect was subsequently shown experimentally by Anderson and Young[15–17], who successfully employed dialkyl phosphorodichloridites in reactions with carboxylic acids in the presence of tertiary amines in order to obtain acyl phosphites.

The above analysis of the literature data shows that most probably the reaction of carboxylic acids and their salts with phosphorus(III) acid chlorides consist in a nucleophilic substitution of a chlorine atom bound to phosphorus for an acyloxy-group. When the usual aliphatic acids are employed, the hydrogen chloride liberated rapidly decomposes the acyl phosphite formed to the acyl chloride and acid phosphite and therefore mixed anhydrides cannot be obtained by this method. Cyclic acyl phosphites synthesised from acids having substituents with functional groups are more resistant to the action of hydrogen chloride. For example, salicylic acid reacts with phosphorus dichloride to form compound (IA) without a hydrogen chloride acceptor. Similarly mercaptoacetic acid gives a stable mixed anhydride[18,19]. Probably acyl phosphites based on other acids with specific structural factors can also be prepared in this way.

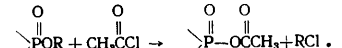
In a discussion of the general problem of the reaction of phosphorochloridites with carboxylic acids, it is necessary to consider in greater detail the studies on $\alpha\beta$-unsaturated acids carried out in recent years. A mechanism different from those analysed above has been proposed for this case. Acrylic and methacrylic acids react with cyclic glycol phosphorochloridites to form oligomeric products. The reaction proceeds readily and in some cases with liberation of heat. It is suggested that the mechanism of the process includes as the initial stage nucleophilic attack by the phosphorus atom on the β-carbon atom in the acid with subsequent cyclisation[20,21]:



The authors believe that the cyclic product can isomerise in two ways: with opening of the anhydride ring (*A*) or the ester ring (*B*):

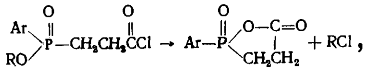


They assert[20,21] that the ester ring is opened since the infrared spectrum of the products has an intense band at 1720 cm^{-1}, which can only be due to the carbonyl group in the ester and not the acid chloride group; moreover the substance contains hardly any mobile chlorine. Thus, if the above mechanism is adopted, one may conclude that the quasiphosphonium chloride decomposes anomalously, since in such cases the chloride anion usually attacks the more electrophilic carbon of the carbonyl group (mechanism *A*). It is more likely that, if a bicyclic quasiphosphonium intermediate is in fact formed in this reaction, it decomposes via mechanism *A* with subsequent conversion into the product postulated in mechanism *B*. This hypothesis is consistent with the available data concerning the tendency of neutral phosphonates[22] and phosphates[23] to react with acetyl chloride:



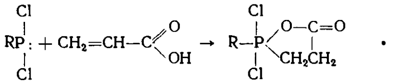
$$(RO){>}\overset{O}{\overset{\|}{P}}OR + CH_3\overset{O}{\overset{\|}{C}}Cl \rightarrow (RO){>}\overset{O}{\overset{\|}{P}}{-}O\overset{O}{\overset{\|}{C}}CH_3 + RCl\,.$$

Moreover, the above hypothesis is confirmed directly by the latest work of Pudovik and coworkers, who quote data on the reaction of ester chlorides of phosphonous acids with $\alpha\beta$-unsaturated acids. They succeeded in isolating the chlorides of phosphonocarboxylic acids and in showing that they are unstable and readily undergo cyclisation[24,25]:

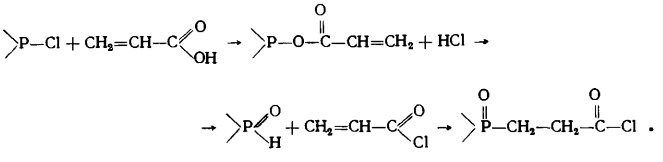


i.e. a reaction takes place, the possibility of which had not been taken into account in studies dealing with the reaction of alkylene phosphorochloridites with unsaturated acids[20,21].

In conclusion of the discussion of the reaction of phosphorus(III) acid chlorides with $\alpha\beta$-unsaturated acids, it is necessary to consider the results obtained in the investigation of the reaction of the unsaturated acids with dichlorophosphines. Here the only products isolated were the chloride anhydrides of phosphorylates carboxylic acids[26,27], the formation of which was explained by the mechanism already considered:



Thus one may say that, according to published data, the reaction of phosphorus(III) acid chlorides with $\alpha\beta$-unsaturated acids proceeds via a stage involving the formation of a cyclic compound. However, the formation of a cyclic adduct has been in no way proved. Moreover, the mechanism has not been confirmed by recent investigations either[28]. We believe that the formation of the final products can be accounted for by a simpler mechanism, which follows logically from the facts discussed above:



$$>P{-}Cl + CH_2{=}CH{-}C\begin{smallmatrix}\nearrow O\\ \searrow OH\end{smallmatrix} \rightarrow\ >P{-}O{-}\overset{O}{\overset{\|}{C}}{-}CH{=}CH_2 + HCl \rightarrow$$
$$\rightarrow\ >P\begin{smallmatrix}\nearrow O\\ \searrow H\end{smallmatrix} + CH_2{=}CH{-}C\begin{smallmatrix}\nearrow O\\ \searrow Cl\end{smallmatrix} \rightarrow\ >\overset{O}{\overset{\|}{P}}{-}CH_2{-}CH_2{-}\overset{O}{\overset{\|}{C}}{-}Cl\,.$$

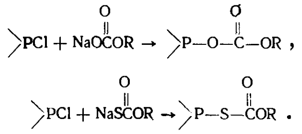
This course of the process explains why the reaction of phosphorochloridites with $\alpha\beta$-unsaturated acids of the type RCH=CHCOOH with substituents at the β-carbon atom takes place in an unusual way: thus crotonic and cinnamic acids do not form the above products and are only converted into their chlorides[29]. Probably in this case the reaction stops at an intermediate stage, since acid phosphites should add less readily to such chlorides owing to the steric and electrostatic effects of the hydrocarbon groups.

Summarising the discussion of the literature data on the reaction of phosphorus(III) acid chlorides with carboxylic acids, the following may be noted. At the present time there is no convincing proof for a particular mechanism of this reaction, but the known facts indirectly confirm that in all the syntheses which have been achieved the primary products are acyl phosphites. In some cases acyl phosphites were isolated in a pure form but usually they are decomposed by hydrogen chloride to acid phosphites and acyl chlorides.

For preparative purposes, acyl phosphites are best synthesised from phosphorus(III) acid chlorides and carboxylic acid salts. Optimum results are obtained when alkali metal salts are employed. Experimentally this method is distinguished by simplicity and ease of isolation of the required products. The reaction is of general importance. On the one hand, aliphatic and aromatic phosphorochloridites[30-34], phosphoramidochloridites[33], and phosphonous acid chlorides[33,35,36] and, on the other hand, salts of various aliphatic and aromatic acids enter into it.

The reaction of phosphorochloridites with formic acid salts is of considerable interest, since it is known that formic anhydrides constitute a little investigated group of compounds in organic chemistry. Unfortunately the formyl phosphites obtained proved to be unstable, decomposing with liberation of carbon monoxide. The second decomposition product is acid phosphite[33]. Since this decomposition is not accompanied by other side processes, formyl phosphites are promising reagents for the synthesis of certain acid phosphites.

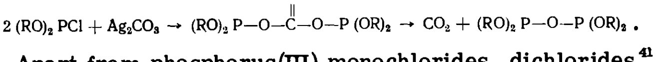
Dialkyl phosphorochloridites react also with salts of alkylcarbonic[37] and alkylthiocarbonic[38,39] acids:



$$>PCl + NaO\overset{O}{\overset{\|}{C}}OR \rightarrow\ >P{-}O{-}\overset{O}{\overset{\|}{C}}{-}OR\,,$$
$$>PCl + NaS\overset{O}{\overset{\|}{C}}OR \rightarrow\ >P{-}S{-}\overset{O}{\overset{\|}{C}}OR\,.$$

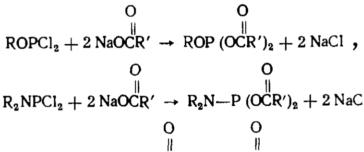
Phosphite-carbonates are of interest for the synthesis of completely esterified phosphorus(III) acids and natural acidophilic alcohols, since phosphorylation by phosphite-carbonates should be accompanied by the liberation of monoalkyl carbonates, which, by virtue of their extreme instability, decompose into alcohols and carbon dioxide—substances which are inert with respect to neutral phosphites.

When dialkyl phosphorochloridites react with silver carbonate, a symmetrical phosphite-carbonate is formed, which is also unstable and is readily decarboxylated to pyrophosphite[40]:



$$2\,(RO)_2PCl + Ag_2CO_3 \rightarrow (RO)_2P{-}O{-}\overset{O}{\overset{\|}{C}}{-}O{-}P\,(OR)_2 \rightarrow CO_2 + (RO)_2P{-}O{-}P\,(OR)_2\,.$$

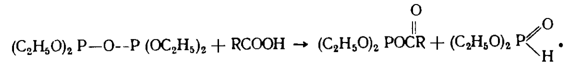
Apart from phosphorus(III) monochlorides, dichlorides[41] and also phosphorus trichloride[42] react with carboxylic acid salts, forming di- and tri-acyl phosphites, for example:



$$ROPCl_2 + 2\,NaO\overset{O}{\overset{\|}{C}}R' \rightarrow ROP\,(O\overset{O}{\overset{\|}{C}}R')_2 + 2\,NaCl\,,$$
$$R_2NPCl_2 + 2\,NaO\overset{O}{\overset{\|}{C}}R' \rightarrow R_2N{-}P\,(O\overset{O}{\overset{\|}{C}}R')_2 + 2\,NaCl\,,$$
$$PCl_3 + 3\,NaO\overset{O}{\overset{\|}{C}}R' \rightarrow P\,(O\overset{O}{\overset{\|}{C}}R)_3\,.$$

3. Reaction of Pyrophosphites with Carboxylic Acids

Acyl alkyl phosphites were obtained for the first time by the acidolysis of tetraethyl pyrophosphites using a method developed by A. E. Arbuzov and Alimov[43]. These investigators showed that pyrophosphite reacts with carboxylic acids with liberation of heat according to the following mechanism:

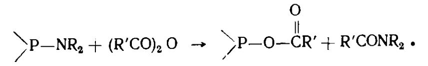


$$(C_2H_5O)_2P{-}O{-}P(OC_2H_5)_2 + RCOOH \rightarrow (C_2H_5O)_2PO\overset{O}{\overset{\|}{C}}R + (C_2H_5O)_2P\Big\langle^{O}_{H}\,.$$

Anderson et al.,[44] who employed tetraethyl pyrophosphite for the synthesis of peptides, also stated that acyl phosphites are formed as intermediates. Despite its ease, this method of synthesis has many disadvantages. Firstly, it is not universal, since frequently it is difficult to separate by distillation the anhydride and the side product (acid phosphite). Secondly only half of the phosphorus bound to the organic group is usefully employed in this method. Moreover, one must remember that the initial pyrophosphites are frequently difficult to obtain. These reasons probably explain why the above method of synthesis of acyl phosphites has not found preparative application.

4. Reaction of Phosphorus(III) Acid Amides with Carboxylic Acids and Their Anhydrides

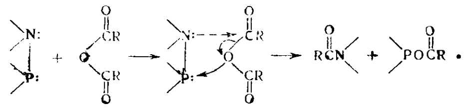
A novel synthesis of acyl phosphites distinguished by a high yield of the desired product is based on the reaction of the amides[45-49] and hydrazides[49] of phosphorus(III) acids with carboxylic acid anhydrides:



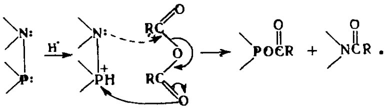
$$>P{-}NR_2 + (R'CO)_2O \rightarrow\ >P{-}O{-}\overset{O}{\overset{\|}{C}}R' + R'CONR_2\,.$$

A series of acyl phosphites and acyl phosphinites have been obtained in this way, but this method can hardly be recommended for preparative purposes, since the second reaction product (the acyl amide or acyl hydrazide) frequently has a boiling point close to that of the required product. In this case the separation of the products is extremely difficult. Moreover, in the reaction of triamide of phosphorous acid with 1, 2, or 3 moles of acetic anhydride, it was not possible to isolate acetyl phosphorodiamidite, diacetyl phosphoroamidite, or triacetyl phosphite respectively[46]. Formyl phosphites cannot be obtained by this method, since formic acid anhydride does not exist. It should also be noted that the amides and even more so the hydrazides of phosphorus(III) acids are in most cases more difficult to obtain than the chlorides (the latter are frequently employed as the starting materials for the synthesis of the amides). Thus the reaction of phosphorus(III) amides and hydrazides with mixed carboxylic acid anhydrides must be regarded as a new reaction of compounds with a phosphorus–nitrogen bond rather than as a preparative method for synthesising acyl phosphites.

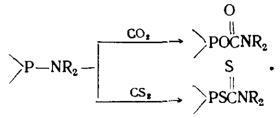
The study of the mechanisms of this process is of considerable interest. Recently the first mechanism was proposed, according to which the carbon in the carbonyl group is subjected to nucleophilic attack by the nitrogen atom with a free electron pair[46]:



This treatment of the mechanism is open to a number of objections. In particular, it contradicts the available data showing the greater nucleophilicity of the phosphorus(III) atom compared with the nitrogen atom in phosphorus(III) amides[50-52]. Bearing in mind what has been said above and also the observations according to which phosphoramidites frequently react in a protonated form[41,53], a different mechanism may be proposed for this reaction:



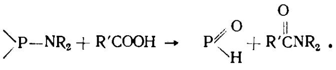
By the reaction of phosphoramidites with carbon dioxide and carbon disulphide, it proved possible to obtain mixed anhydrides of *NN*-substituted carbamic acids and phosphoramidous and phosphorodiamidous acids[54-56]:



However, the attempts to synthesise the trianhydrides of phosphorous and carbamic acids were unsuccessful.

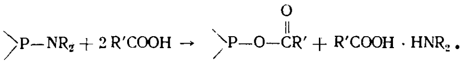
In a study of carbonylation it was established that the reaction takes place successfully only in the presence of proton donors, for example amine hydrochlorides[57]. Probably the mechanism of this process is the same as that considered above for carboxylic acid anhydrides.

One of the preparative methods for the synthesis of carboxylic acid amides is the reaction of phosphoramidites with carboxylic acids[58]:



$$>P{-}NR_2 + R'COOH \rightarrow P\Big\langle^{O}_{H} + R'\overset{O}{\overset{\|}{C}}NR_2\,.$$

A new application of this reaction, permitting the preparation of acyl phosphites, has been recently demonstrated[59]:

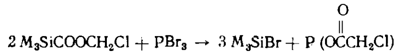


$$>P{-}NR_2 + 2\,R'COOH \rightarrow\ >P{-}O{-}\overset{O}{\overset{\|}{C}}R' + R'COOH\cdot HNR_2\,.$$

Probably this method will be of synthetic value in those cases where phosphorus(III) acid amides are more readily available than their chlorides.

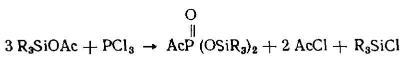
5. Reaction of Acetyltrialkylsilanes with Phosphorous Acid Halides

In 1952 Anderson[60] reported that the exchange of a halogen linked to the phosphorus(III) atom for acyloxy-group takes place readily when trimethylsilyl α-monochloroacetate reacts with phosphorus tribromide:



$$2\,M_3SiCOOCH_2Cl + PBr_3 \rightarrow 3\,M_3SiBr + P(O\overset{O}{\overset{\|}{C}}CH_2Cl)_3\,.$$

Later Orlov and Kaufman[61], who investigated this reaction with phosphorus trichloride, found that triacetyl phosphite is not formed and the process takes place by the following mechanism:



$$3\,R_3SiOAc + PCl_3 \rightarrow Ac\overset{O}{\overset{\|}{P}}(OSiR_3)_2 + 2\,AcCl + R_3SiCl\,.$$

It appears that Anderson's report is incorrect.

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Thus several types of reactions leading to mixed anhydrides of phosphorus(III) and carboxylic acids are known at present. We believe that in most cases the most promising method of synthesising acyl phosphites is based on the reaction of sodium (or potassium) salts of carboxylic acids with phosphorus(III) acid chlorides. The method is fairly general and experimentally simple, giving high yields of the desired products.

III. CHEMICAL PROPERTIES OF ACYL PHOSPHITES

All the reactions of acyl phosphites, which are probably heterolytic processes, can be divided into two large groups on the basis of the reagents employed—electrophilic and nucleophilic. Such subdivision of the available data is of course arbitrary and is used merely to facilitate description.

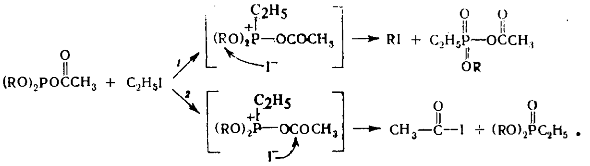
A. REACTIONS WITH ELECTROPHILIC AGENTS

1. Oxidation and Addition of Sulphur

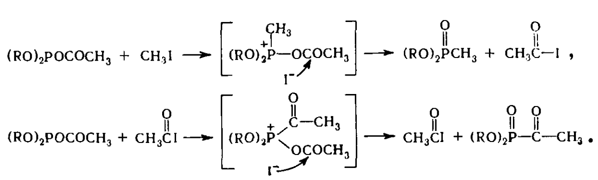
Like all compounds containing a phosphorus(III) atom, acyl phosphites are readily oxidised to acyl phosphates[30], combine with sulphur[43,45], and react with monohalogenocompounds of copper with liberation of heat, forming crystalline products[43,62]. As was to be expected, derivatives containing phosphorus-carbon bonds are very reactive in these processes.

2. The Arbuzov Reaction

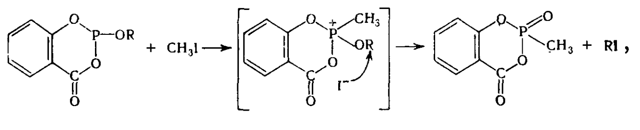
The fundamental process in the chemistry of organophosphorus compounds is the Arbuzov reaction. It has recently been applied to acyl phosphites. Since acyl phosphites contain both alkoxy- and acyloxy-groups at the phosphorus atom, it might have been expected that the process would involve the elimination of either an alkyl or an acyl halide:



In 1951 A. E. Arbuzov and Alimov reported[43] that the reaction of diethyl isovaleroyl phosphite with ethyl iodide gives a low yield of an isomerisation product via mechanism *1*. At the same time there is a high yield of a product the structure of which the authors did not establish. Later Pudovik and coworkers[63,64] showed that the intermediate complex decomposes predominantly via mechanism *2*, and the acid halide liberated reacts in turn with the acyl phosphite:

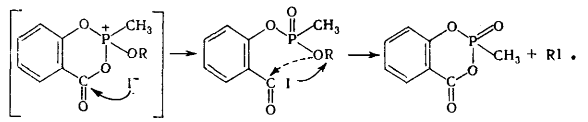


It is interesting that, when methyl iodide is introduced into the reaction, it remains almost completely unchanged. It is quite evident that in this case the process takes place via the Arbuzov mechanism and in the second stage of the reaction the iodide ions attack the more electrophilic centre—the carbon of the carbonyl and not the alkoxy-group. It is noteworthy that in the alkylation of salicylphosphorous acid esters by methyl iodide the overall situation changes. According to Nesterov and Sabirova[65], who achieved this reaction, the iodide ion attacks the carbon of the alkoxy-group which results in the formation of phosphonates in high yields:



where R = CH_3, C_2H_5, or iso-C_4H_9.

The authors of the above investigation believe that this mode of reaction is most likely, since "the C–O bond is polarised in the required direction in the alkoxy-group"[65]. This statement is not altogether clear. Another reaction mechanism, which does not contradict data showing a greater electrophilicity of the carbon atom in the carbonyl group compared with the carbon atom in the alkoxy-group, is more likely:

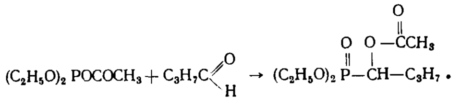


The studies confirming the possibility of the concluding stage of the reaction were discussed above (p. 1052).

Above we considered the interaction of acyl phosphites with acyl halides as an intermediate stage in certain reactions. Later this process was investigated also as an independent reaction, using as the acyl chlorides the chlorides of mono-, di-, and tri-chloroacetic acids[66].

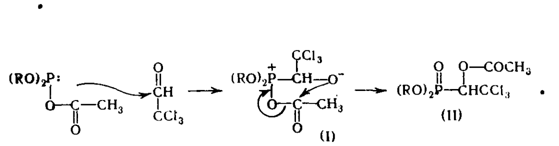
3. Reaction with Aldehydes and Ketones

In 1956 Alimov and Cheplanova reported that the reaction of acetyl diethyl phosphite and butyraldehyde results in the formation of α-acetoxybutyl diethyl phosphonate[67]:

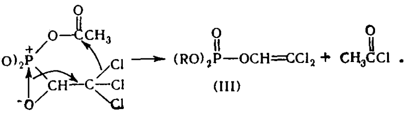


$$(C_2H_5O)_2POCOCH_3 + C_3H_7C\overset{O}{\underset{H}{\lt}} \rightarrow (C_2H_5O)_2\overset{O}{\overset{\|}{P}}-\overset{O-\overset{O}{\overset{\|}{C}}CH_3}{\overset{|}{C}H}-C_3H_7\,.$$

Subsequently other workers extended this reaction to new systems[34,68]. The reaction of α-halogenoaldehydes with acyl phosphites is similar to that of the simplest aldehydes[70,71]:

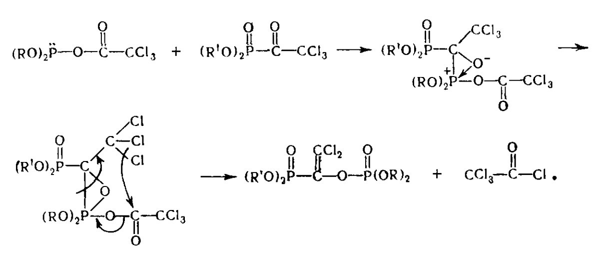


In this case the reaction takes place much more readily (with spontaneous liberation of heat). This was in fact to be expected, bearing in mind that the reaction begins with the nucleophilic attack by the phosphorus(III) atom on the carbon atom in the carbonyl group. The dipolar adduct (I) formed in the first stage of the process has two electrophilic centres: the phosphorus atom and the carbon atom of the carbonyl group. Consequently in the second stage of the reaction the attack by the negatively charged oxygen atom may be directed either to the carbonyl group, with formation of a product having the phosphonate structure (II), or to the phosphorus atom, whereupon the mechanism of the Perkow reaction[71] may obtain with formation of a product having the enol phosphate structure (III):



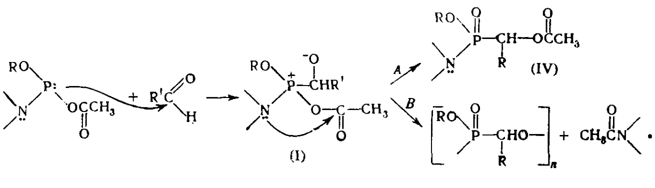
Indeed in some cases, for example in the reaction of acetyl di-isobutyl phosphite with chloral, ββ'-dichlorovinyl di-isobutyl phosphate was isolated together with α-acetoxyphosphonate[71]. It is noteworthy that in the reaction of chloral with dialkyl phosphites, enol phosphates are formed preferentially[72]. This difference in the behaviour of trialkyl phosphites and acyl dialkyl phosphites can probably be explained by the presence in the molecules of the latter of a carbonyl group, which in the second stage of the process may be attacked by the negatively charged oxygen atom in preference to the phosphorus atom.

Pudovik and Gazizov obtained very interesting results in a study of the reaction of acyl dialkyl phosphites with trichloroacetylphosphonic acid esters[66]:



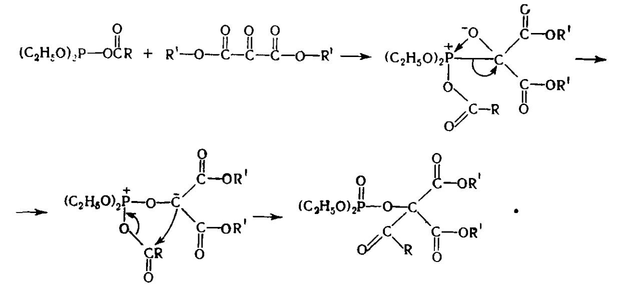
The mechanism of this reaction is different from that with chloral. Evidently the $(RO)_2P{=}O$ group, which replaces a hydrogen atom in chloral, increases the electrophilicity of the phosphonic acid centre. As a result, the attack by the anionic centre is directed to the phosphorus atom and not to the carbon atom in the carbonyl group, and the reaction proceeds via the Perkow mechanism. The occurrence of both competing reactions has been discovered when aldehydes were allowed to react with acetyl phosphoramidites[69].

Possibly in this case the reaction proceeds via a stage involving the formation of a dipolar ion of type (I), which either rearranges under the influence of the nucleophilic attack by the negatively charged oxygen atom on the carbon atom of the carbonyl group with formation of the phosphonate (IV) (mechanism *A*) or decomposes to acetamide and a phosphorus-containing polyester (mechanism *B*):



4. Reaction with α-Ketoacid Esters

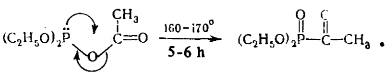
Acyl phosphites react with mesoxalic esters. Probably in this case the phosphorus(III) atom exhibits its nucleophilic properties[73]:



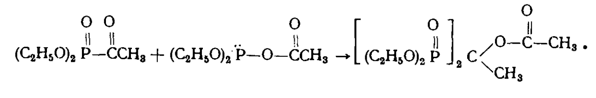
It must be emphasised that in this reaction the attack by the carbanionic centre of the intermediate compound is directed to the carbon atom of the carbonyl and not the alkoxy-group, as happens in the reaction of neutral phosphites with mesoxalic acid esters. Pyruvate and glyoxylate esters react with acyl phosphites similarly to mesoxalic acid esters[74].

5. Thermal Isomerisation

In contrast to acyl phosphates[32,75], acyl phosphites are not readily disproportionated on heating to pyrophosphites and carbon dioxide. However, they can undergo a rearrangement, the mechanism of which is as follows[32]:

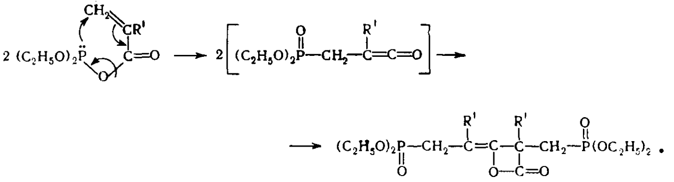


This rearrangement is a kind of intramolecular version of the Arbuzov reaction. The diethyl acetylphosphonate formed reacts further with another molecule of acetyl diethyl phosphite with formation of methylbis(diethylphosphono)methyl acetate:



$$(C_2H_5O)_2\overset{\overset{O}{\|}}{P}-\overset{\overset{O}{\|}}{C}CH_3+(C_2H_5O)_2\ddot{P}-O-\overset{\overset{O}{\|}}{C}CH_3\rightarrow\Big[(C_2H_5O)_2\overset{\overset{O}{\|}}{P}\Big]_2C\begin{smallmatrix}O-\overset{\overset{O}{\|}}{C}-CH_3\\ CH_3\end{smallmatrix}.$$

The isomerisation of acyl phosphites formed by αβ-unsaturated acids takes place in an unusual manner. In the first stage of the reaction a phosphorylated ketone is formed, which, being unstable, undergoes subsequent isomerisation[32]:

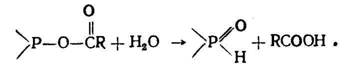


B. REACTIONS WITH NUCLEOPHILIC AGENTS

Acyl phosphites have two electrophilic reaction centres: the carbon atom in the carbonyl group and the phosphorus atom. This property of acyl phosphites leads to the expectation that two series of reaction products may be formed, the structure of which is determined by the mode of attack by the nucleophilic agent.

1. Hydrolysis

When water acts upon acyl phosphites, the latter decompose into the carboxylic and the corresponding phosphorous acids. The reaction is accompanied by the liberation of heat[43,62]:



$$\rangle P-O-\overset{O}{\overset{\|}{C}}R + H_2O \rightarrow \rangle P\overset{O}{\underset{H}{\lessdot}} + RCOOH\,.$$

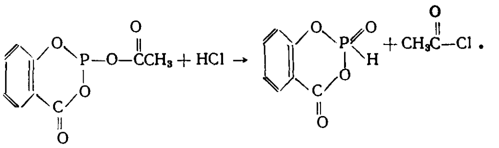
It is noteworthy that the formation of the final products may take place as a result of the attack by the hydroxy-group on both the phosphorus atom and the carbon atom in the carbonyl group. This problem still remains open.

2. Reaction with Acids

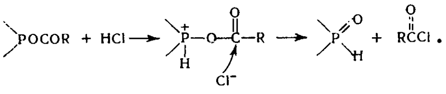
Data have been published on the reaction of certain acyl phosphites with hydrogen chloride. It has been established that salicyl phosphorochloridite hardly changes in the presence of hydrogen chloride. However, butyl salicyl phosphate is cleaved with formation of butyl phosphorodichloridite[76]. The hydrochlorination of diacetyl trifluoromethyl phosphonite, resulting in the formation of acetic acid and dichlorotrifluoromethylphosphine, is formally analogous to this process[35]:

$$CF_3P(OCOCH_3)_2 + HCl \rightarrow CF_3PCl_2 + 2\,CH_3COOH\,.$$

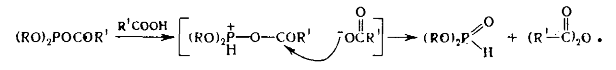
The mechanism of these reactions has not been investigated and the available data do not allow the appropriate analysis. However, we may conclude that the reactions considered are accompanied by the formation of phosphorus–chlorine bonds and are energetically favourable under the given conditions. Another result was obtained for reactions of hydrogen chloride with acetyl salicyl phosphite[77] and acetyl dialkyl phosphites[78]:



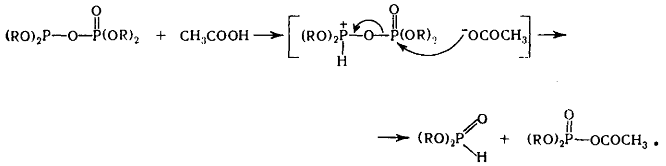
Evidently the latter syntheses proceed via a mechanism similar to that which was adopted for the alkylation of acyl phosphites:



This mechanism is also consistent with the results of the reaction of acyl phosphites with carboxylic[14,33,79]†, dialkylphosphoric[80], and dialkylphosphorodithioic[81] acids:



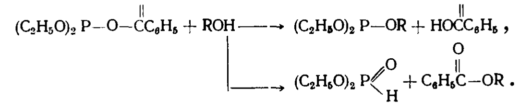
Probably the Arbuzov mechanism operates also in the reaction of neutral subphosphates with acetic acid[82]:



This process can be represented in a different way too: initially there is transacylation to acyl phosphite and dialkylphosphoric acid, which then react with one another to form the products isolated. However, ultimately these mechanisms do not differ significantly.

3. Reaction with Alcohols

One may expect that the alcoholysis of acyl phosphites will lead to the formation of either phosphorus(III) acid esters or carboxylic acid esters. A. E. Arbuzov and Alimov[43] showed that benzoyl diethyl phosphite reacts with alcohols to give a small yield of a phosphorylated product, i.e. of the possible modes of reaction the first actually occurs:



(1)

(2)

Subsequently certain additional data on this reaction were published[30,31,62,76,83,84]. They are mainly concerned with the fact that the reaction of acyl phosphites with alcohols yields both neutral phosphites and dialkyl phosphites. This result was explained by secondary dealkylation of the neutral phosphites formed initially[31,85].

The possibility, in principle, of this reaction at an elevated temperature has been demonstrated[86]. Therefore, in order to prevent the dealkylation side process, it is recommended that neutral phosphites be employed only in the presence of acid acceptors (triethylamine[31,85] or dialkyl phosphoramidites[83,85]). The authors of these hypotheses note themselves that the use of such procedures gives rise to considerable experimental difficulties in the isolation of the required products. Consequently this version of the method does not have fundamental advantages over the alcoholysis of phosphorochloridites, which also requires the application of an acceptor; moreover, phosphorochloridites are more readily available and are usually employed as the starting materials in the synthesis of acyl phosphites.

Thus the procedures for the phosphorylation of alcohols by acyl phosphites described in the early investigations are of no synthetic value.

Subsequently this reaction was studied in greater detail. In the first place the stability of the neutral phosphites with respect to carboxylic acids at room temperature was estimated. For this purpose, the most labile neutral esters (trimethyl phosphite and 1,3-butylene methyl phosphite) were kept at 20°C with acetic acid and the mixture was periodically analysed by gas chromatography. It was

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† In a brief communication[47] it has been stated that acetyl ethylene phosphite reacts with benzoic acid to form benzoyl ethylene phosphite. The conditions of the synthesis and the yield and the constants of the product are not quoted. The reaction of acetyl diethyl phosphite with benzoic acid described in the same paper is striking. The authors assert that transacetylation also takes place in the first stage and subsequently diethyl phosphate and acetyl benzoate are formed. No factual data are given for this reaction either.

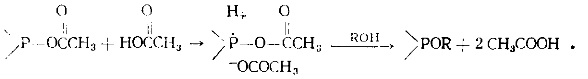
shown[79] that only after 48 h weak peaks due to methyl acetate appeared on the chromatogram. Consequently, under the phosphorylation conditions, acetic acid hardly reacts with neutral phosphites and the side process involving their dealkylation, which had been suggested previously, does not in fact occur.

On the basis of this experiment, it was concluded that acid phosphites are formed via another side process.

In the preceding section of this review, the reaction of carboxylic acids with acyl phosphites was discussed and it was concluded that such reaction takes place significantly more readily than the reaction of acids with neutral phosphites. This finding led to the conclusion[14,79] that in the earlier investigations of the alcoholysis of acyl phosphites the formation of hydrogen phosphites was not associated with the dealkylation of the neutral phosphites but with the deacylation of the phosphorylating agent. The carboxylic acid liberated by the reaction accumulates in the reaction medium and, when its concentration becomes equal to that of the alcohol, it can successfully compete with the latter for the phosphorylating agent. Evidently, in order to develop a preparative method for the synthesis of neutral phosphites, it is necessary to find conditions such that the alcohol reacts faster with the phosphorylating agent. Since acetyl dialkyl phosphites are deactivated by carboxylic acids at an appreciable rate only above 0°C while they react with alcohol also at lower temperatures, at 0°C the synthesis may be successfully employed to prepare neutral phosphites without the introduction of carboxylic acid acceptors. Experiments confirmed this hypothesis and the method thus developed has been used to prepare a series of neutral phosphites, the yield of which was in all cases higher than under conditions where acceptors are employed[33,79,87].

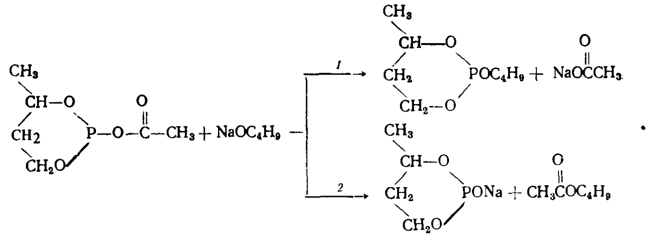
The mechanism of the alcoholysis of acyl phosphites is of considerable interest. In a study of this reaction it was concluded that, when the reactants are mixed, the process does not begin at once but only after an induction period and, once begun, the reaction proceeds exothermically. Hence it was suggested that the alcoholysis does not reduce merely to the reaction of the acyl phosphite and the alcohol but that the carboxylic acid also takes part[79].

We believe that the following mechanism of the alcoholysis is most likely. The process begins with the protonation of the mixed anhydride by the acid, probably due to the free electron pair of the phosphorus atom. The protonation is accompanied by the induction of a considerable positive charge at the phosphorus atom, which is subsequently subjected to nucleophilic attack by the alcohol, terminating with the formation of the neutral phosphite and carboxylic acid; the latter accumulates in the reaction medium and accelerates the process:



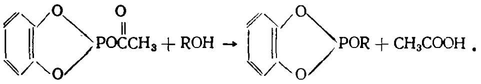
$$>P-O\overset{O}{\overset{\|}{C}}CH_3 + HO\overset{O}{\overset{\|}{C}}CH_3 \rightarrow >\overset{H_+}{\dot{P}}-O-\overset{O}{\overset{\|}{C}}CH_3 \;\; {}^{-}OCOCH_3 \xrightarrow{ROH} >POR + 2\,CH_3COOH\,.$$

This mechanism has been confirmed experimentally by comparing the rates of reaction of acetyl 1,3-butylene phosphite with 2-octanol in the absence and in the presence of triethylamine. It was established that in the first case the process is much faster than in the second[74]. Experiments, in which the effect of the acid on the phosphorylating capacity of acyl phosphites was excluded, indirectly confirm this mechanism. Thus the reaction of acetyl 1,3-butylene phosphite with sodium butoxide results in the formation of a mixture of both phosphorylation and acetylation products, i.e. butyl 1,3-butylene phosphite and butyl acetate were obtained[79]:



On the other hand, the acetate ester could not be isolated in the reaction between acetyl 1,3-butylene phosphite and butanol. Thus, in those cases where the reaction mixture contains an acid which is an effective protonating agent, the reaction proceeds virtually in one way, while in the absence of such acid there are two reaction mechanisms. If the reaction mixture contains an acid, it activates the phosphorylating centre and the reaction involves only that centre. If there is no acid, there is no activation either (or it takes place less effectively via the solvation of the reactant) and both phosphorylation and acylation, which previously took place to a lesser extent, occur.

The alcoholysis of acyl phosphites in the presence of acids is a convenient and effective method for the synthesis of a wide variety of neutral phosphite esters. Particularly satisfactory results were obtained when acetyl *o*-phenylene phosphite was employed[87]:

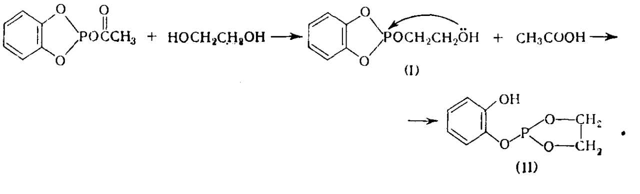


In this synthesis the yield of neutral phosphites reached 90%; this was explained by the enhanced stability (with respect to acetic acid) of the anhydride, which did not change on being kept for 24 h with an equimolar amount of the acid. Since *o*-phenylene phosphites are used industrially as stabilisers for certain materials[88,89], the explanation of the finding that they are formed readily and in high yields is very important. It should also be noted that the esters obtained in this way are purer than those synthesised by other procedures[89,90].

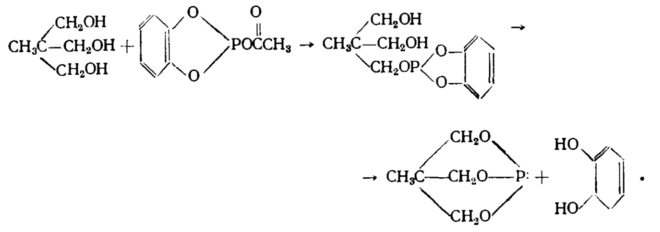
Like monohydric alcohols, glycols readily react with mixed anhydrides of dialkyl(aryl)phosphorous and carboxylic acids without the introduction of acceptors[87]. Diphosphites were obtained in this way in high yields. Esters containing a free hydroxy-group were synthesised in a low yield. This result can be accounted for by the disproportionation of the hydroxyalkyl phosphites (formed initially) under the conditions of their isolation:

$$2>PO(CH_2)_n OH \rightarrow >P-O-(CH_2)_n-O-P< + HO(CH_2)_n OH\,.$$

A similar transphosphorylation reaction was recently investigated for acid hydroxyalkyl phosphites[91]. When acetyl *o*-phenylene phosphite reacted with ethylene glycol in proportions of 1 : 1, ethylene *o*-hydroxyphenyl phosphite (II) was obtained instead of the expected hydroxyethyl *o*-phenylene phosphite (I)[87]:



Intramolecular transesterification takes place very readily also when 2-hydroxymethyl-2-methyl-1,3-propanediol is phosphorylated by acetyl *o*-phenylene phosphite:

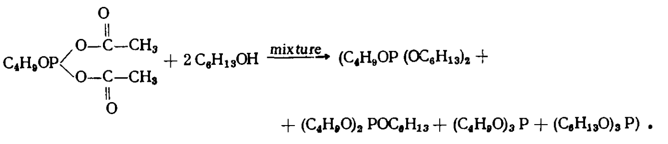


However, in the reaction with an excess of the anhydride the main product is the fully phosphorylated diol. Under analogous conditions, pentaerythritol is phosphorylated to give the tetraphosphite[87].

Acyl phosphites are highly effective in the phosphorylation of hydroxylated polymers. In this case the effect of acids on the process is particularly pronounced. Thus in the phosphorylation of hydroxylated macromolecular compounds [cellulose and poly(vinyl alcohol)] it was virtually impossible to obtain phosphorus-containing polymers when the experiments were carried out without added acid[92], whereas in similar syntheses with added acids such polymers are obtained readily and their phosphorus content reaches 14%.[93,94]

Di- and tri-acyl phosphites are also good phosphorylating agents for alcohols[41]. It might have been supposed that they would prove to be more promising for the synthesis of certain neutral phosphites than monoacetyl phosphites. This hypothesis was based on the following factors.

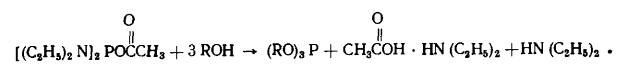
Firstly, the synthesis of di- and tri-acetyl phosphites takes place in one stage and experimentally does not differ from the synthesis of monoacyl phosphites. Secondly, the initial acid dichlorides and phosphorous trichlorides are more readily available than the monochlorides of dialkylphosphorous acid. Unfortunately only symmetrical phosphites could be obtained by this procedure in high yields. All the experiments undertaken to synthesise esters with different groups resulted in a mixture of neutral phosphites[41], for example:



$$C_4H_9OP\left<\begin{matrix}O-\overset{O}{\overset{\|}{C}}-CH_3\\ O-\underset{O}{\underset{\|}{C}}-CH_3\end{matrix}\right. + 2\,C_6H_{13}OH \xrightarrow{\text{mixture}} (C_4H_9OP\,(OC_6H_{13})_2 + (C_4H_9O)_2\,POC_6H_{13} + (C_4H_9O)_3\,P + (C_6H_{13}O)_3\,P)\,.$$

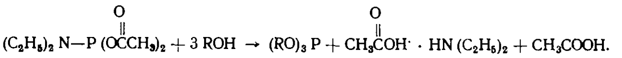
Many workers have concluded that asymmetric neutral phosphites disproportionate during their synthesis and suggested that the tendency towards "ester exchange" is a characteristic of the asymmetric neutral phosphites themselves. The reason for this phenomenon was never elucidated. The first step towards the determination of the mechanism of such disproportionation was taken by the present authors[41], who succeeded in establishing that the disproportionation of asymmetric phosphites takes place only in the presence of acid compounds or at least is sharply accelerated by them.

The results of the alcoholysis of acyl phosphoramidites merit special consideration. The reaction of acetyl *NNN'N'*-tetraethylphosphorodiamidite and alcohol in molar proportions of 1 : 3 at a temperature above 10°C gave a high yield of trialkyl phosphite[33]:



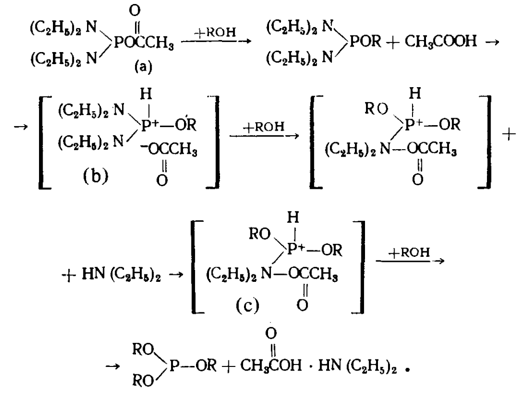
$$[(C_2H_5)_2\,N]_2\,PO\overset{O}{\overset{\|}{C}}CH_3 + 3\,ROH \rightarrow (RO)_3\,P + CH_3\overset{O}{\overset{\|}{C}}OH \cdot HN\,(C_2H_5)_2 + HN\,(C_2H_5)_2\,.$$

Fully esterified phosphorous acid is also formed under these conditions in the alcoholysis of diacetyl *NN*-diethylphosphoramidite[41]:

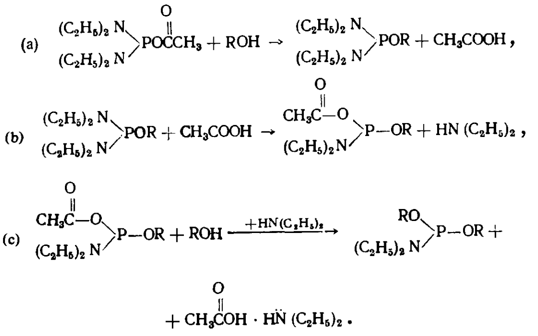


$$(C_2H_5)_2\,N{-}P\,(O\overset{O}{\overset{\|}{C}}CH_3)_2 + 3\,ROH \rightarrow (RO)_3\,P + CH_3\overset{O}{\overset{\|}{C}}OH \cdot HN\,(C_2H_5)_2 + CH_3COOH.$$

The reaction is exothermic and therefore, in order to avoid spontaneous heating, it is necessary to mix the reactants very cautiously with cooling. Such reaction conditions are consistent with the phosphorylation of alcohols by mixed anhydrides but not phosphorus(III) acid amides, which react with alcohols only on heating[95]. Consequently one may conclude that in the phosphorylation by amidoanhydrides, phosphoramidites and acetic acid are formed in the first stage and then interact with formation of new products, which are capable of readily phosphorylating alcohols. Probably these intermediates have the structure of quasiphosphonium salts:

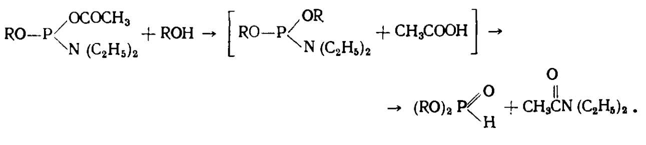


It is interesting that ammonium acetate is isolated only at the end of the reaction after the P–N bonds in the phosphoramidite have been fully replaced by P–O bonds. Probably this finding can be explained by the higher basicity of the phosphoramidite compared with the neutral phosphite, the quasiphosphonium complex of which with carboxylic acid is extremely unstable and readily decomposes into the initial compounds. In our cases the acid isolated is immediately converted into the salt by the diethylamine present in the reaction mixture. Probably the ready formation of neutral phosphites in the alcoholysis of acyl phosphoramidites cannot be represented by another mechanism, including the formation of acyl phosphite by the reaction of phosphoramidite and acetic acid produced in the first reaction stage (the possibility and scope of this reaction were demonstrated above—see Section II, 4):

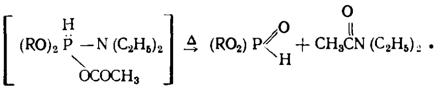


In this case the acetic acid bound in a salt with diethylamine can no longer participate in the formation of the next anhydride bond and the product must be *NN*-dialkylphosphoramidite and not the neutral phosphite, as is in fact observed experimentally. One should also remember that the amine is much more nucleophilic than the alcohol and therefore if the occurrence of stage (b) involving the formation of acyl phosphoramidite and diethylamine is postulated, the amine will react with the phosphoramidite faster than the alcohol.

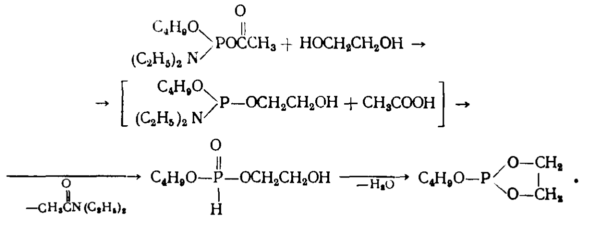
Yet another treatment of the mechanism of the alcoholysis of acetyl phosphoramidites[84] must be rejected. The authors conclude that the reaction of equimolar amounts of the phosphorus-containing reactant and alcohol yields dialkyl phosphite and *NN*-diethylacetamide via the following mechanism:



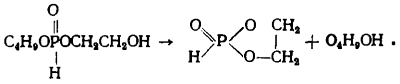
Probably in this case the phosphoramidite and acetic acid formed in the first stage are not produced in a pure form but are present as a quasiphosphonium compound. On heating, this adduct may decompose to acid phosphites and *NN*-diethylacetamide:



It was to be expected that, when the temperature of the process is controlled and a large amount of alcohol is employed, it should result in neutral and not acid phosphites‡. Unfortunately Evdakov et al.[84] did not arrive at this conclusion. Moreover, they carried out the reaction of acetyl butyl *NN*-diethylphosphoramidite with an equimolar amount of glycol (which corresponds to two moles of a monohydric alcohol in terms of the number of hydroxy-groups) and obtained butyl ethylene phosphite—a neutral ester of phosphorous acid. However, on the basis of their general mechanism of alcoholysis, including the formation of an acid phosphite as an obligatory stage, the authors put forward the following scheme for the process:

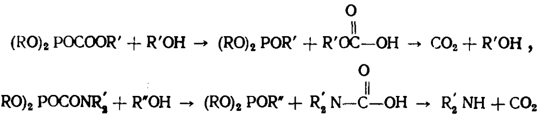


However, this postulate contradicts the logic of the chemistry of phosphites. It is known that diesters of phosphorous acid are not esterified by alcohols under the usual conditions[96,97] and in general the conversion of derivatives of phosphorous acid with a tetracoordinate phosphorus atom to derivatives with a tricoordinate phosphorus atom is extremely difficult. Moreover, the assertion that alkyl β-hydroxyethyl phosphites can be cyclised to alkyl alkylene phosphites contradicts also specific experimental data, since it has been shown that these compounds are cyclised by a transesterification and not a dehydration mechanism[91]:



Thus the inclusion in the mechanism of the alcoholysis of acyl phosphoramidites of a stage involving the formation of an acid phosphite is unjustified. Probably protonation products are always formed§ and, depending on the specific conditions, these are converted into various compounds in accordance with the factors described above.

The range of acyl phosphites employed was very recently extended in a study of the phosphorylation of alcohols. Apart from the mixed anhydrides of phosphorus(III) acids and carboxylic acids, the corresponding derivatives of alkylcarbonic[37] and carbamic[57] acids have begun to be employed. The results obtained are extremely interesting: the synthesis takes place under mild conditions and, what is most important, acid does not accumulate in the reaction mixture:

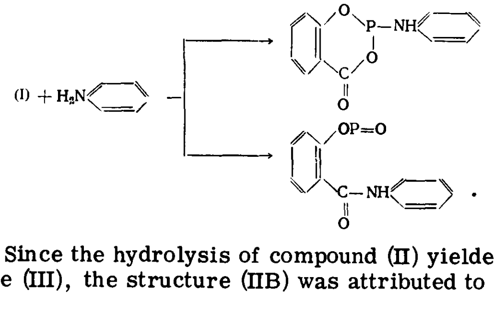


$$(RO)_2POCOOR' + R'OH \rightarrow (RO)_2POR' + R'O\overset{O}{\overset{\|}{C}}-OH \rightarrow CO_2 + R'OH\,,$$

$$(RO)_2POCONR'_2 + R''OH \rightarrow (RO)_2POR'' + R'_2N-\overset{O}{\overset{\|}{C}}-OH \rightarrow R'_2NH + CO_2\,.$$

4. Reactions with Amines and Phosphines

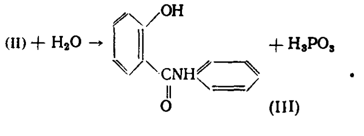
In Section II, 2 it was stated that the reaction of salicylic acid with phosphorus trichloride yields a product to which one of the two structures (IA) or (IB) (see p. 1051) could be attributed. The reaction of compound (I) with aniline led to the isolation of a product (II), the structure of which may also be represented by two formulae, corresponding to those of compound (I):



(IIA)

(IIB)

Since the hydrolysis of compound (II) yielded salicylanilide (III), the structure (IIB) was attributed to the product[8]:



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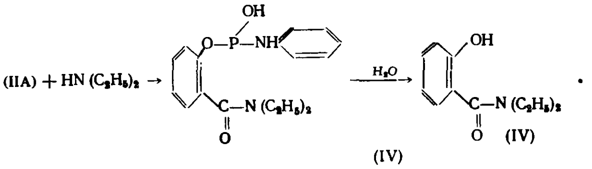
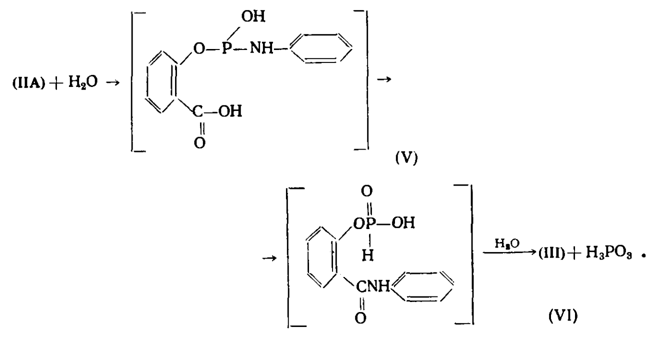
‡ Subsequently[41] acetyl butyl *NN*-diethylphosphoramidite was allowed to react with two moles of butanol at 0°C and tributyl phosphite was obtained in a high yield. The second reaction product is diethylammonium acetate and not *NN*-diethylacetamide.

§ Acid catalysis is probably of general importance in the reactions of phosphorus(III) acid derivatives with nucleophilic agents. Thus in the presence of acetic acid, triamides react with three moles of alcohol and are converted into trialkyl phosphites at 0°C[53], whereas previously, without the use of acid, this synthesis was carried out at a temperature frequently exceeding 100°C.

However, the reaction of (II) with diethylamine and subsequent hydrolysis of the intermediate led to the isolation of *NN*-diethylsalicylamide (IV)[10]. The formation of (IV) is probably possible only when compound (II) includes an anhydride ring, i.e. has the structure (IIA):

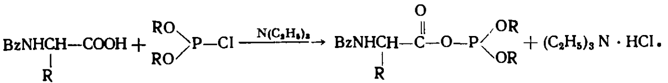


The isolation of salicylanilide in the hydrolysis of (II) is also consistent with the structure (IIA) and may be represented by the following mechanism:



Above we stated that the amides of phosphorus(III) acids react vigorously with carboxylic acids to form carboxamides[58]. Therefore the conversion of (V) into (VI) agrees with expectation. Thus the demonstration of the cyclic structure of compound (I) yields information about the reaction of acyl phosphites and amines.

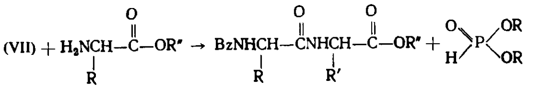
As we have seen above, the reaction of *N*-benzoylated α-aminoacids with phosphorus(III) chlorides leads to the formation of acyl phosphites:



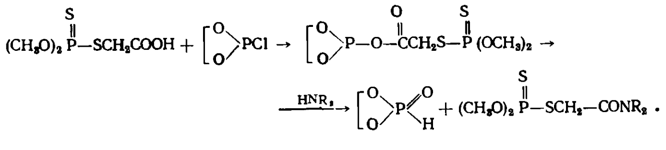
$$\underset{\mid\atop R}{BzNHCH}{-}COOH + (RO)_2P{-}Cl \xrightarrow{N(C_2H_5)_3} \underset{\mid\atop R}{BzNHCH}{-}\overset{O}{\overset{\|}{C}}{-}O{-}P(OR)_2 + (C_2H_5)_3N\cdot HCl.$$

(VII)

These compounds react further with α-aminoacids, forming peptides[16]:



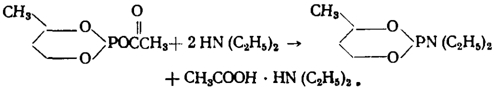
Amine acylation products were obtained in the synthesis of analogues of the insecticide Ragor[98]:



Thus the data quoted show that the ammonolysis of acyl phosphites gives high yields of acylation products and does not result in their phosphorylation. This finding is not trivial, since we know that acyl phosphites react with alcohols to form esters of phosphorous and carboxylic acids, i.e. act as phosphorylating agents.

It would be wrong to seek the cause of the difference between the reactions of acyl phosphites with alcohols and amines only in the different nature of the reactants employed and to use for this purpose one of the familiar concepts, for example those of Pearson[99], which have been recently resorted to in the interpretation of the results of the reactions of other phosphorus-containing mixed anhydrides with alcohols and amines[100].

The above considerations are based on the relevant experiments. An experiment was performed in which the mode of attack by the amine on the phosphorus atom in the acyl phosphite was definitely demonstrated. Indeed, at 0°C acyl phosphites react with twice the equimolar amount of diethylamine, so that one obtains a more than 50% yield of the phosphoramidite and the ammonium salt of the carboxylic acid[78,101], for example:

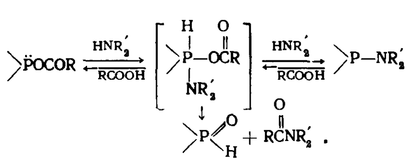


In a parallel experiment without temperature control the diethylamide of the carboxylic acid was obtained in high yield.

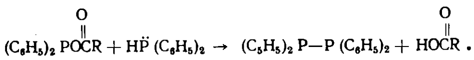
Probably the first stage of the reaction of acyl phosphites with amines involves an addition process similar to that which occurs when certain phosphorus(III) acid fluorides are treated with amines[102].

The addition product, which is essentially a quasiphosphonium salt, can undergo a nucleophilic substitution reaction if the reaction mixture contains an excess of the amine. In the absence of temperature control, the addition product decomposes with formation of the pure acid phosphite and the carboxylic acid amide.

The general scheme should be supplemented by the decomposition of the addition product on treatment with acid to the acyl phosphite and the ammonium salt. The overall process mechanism can be represented as follows:



It is interesting to add to the above that, in contrast to the amine, according to the data of Trippett and coworkers, diphenylphosphine forms with acyl phosphinate diphosphine and a carboxylic acid even when the reactants are present in stoichiometric proportions[36]:

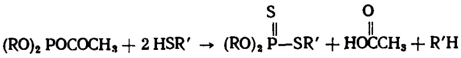


$$(C_6H_5)_2P\overset{O}{\overset{\|}{O}}CR + H\ddot{P}(C_6H_5)_2 \rightarrow (C_6H_5)_2P{-}P(C_6H_5)_2 + HO\overset{O}{\overset{\|}{C}}R.$$

5. Reaction with Mercaptants

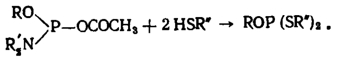
The reaction of acyl phosphites with mercaptants has been very little investigated despite the fact that it has a number of characteristic features compared with the alcoholysis of phosphonimidites. After the acyl phosphites had been treated for a long time with an equimolar amount of a mercaptan at 20°C under conditions excluding radical reactions, new products were not obtained[101,103]. When the reaction was carried out in the presence of triethylamine or sodium mercaptide was employed instead of the mercaptan, phosphorothioites were obtained[101].

Neutral phosphorodithioates were synthesised by treating acyl dialkyl phosphites with an excess of a mercaptan[104]:



$$(\text{RO})_2\text{POCOCH}_3 + 2\,\text{HSR}' \rightarrow (\text{RO})_2\overset{\text{S}}{\overset{\|}{\text{P}}}\text{—SR}' + \text{HO}\overset{\text{O}}{\overset{\|}{\text{C}}}\text{CH}_3 + \text{R}'\text{H}\,.$$

Probably in this case phosphorylation was accompanied by the desulphuration of the mercaptan, i.e. a process which is very familiar in the chemistry of phosphites[105,106]. The reaction of acyl phosphoramidites with mercaptans, which leads to neutral phosphorodithioites but not phosphorothioates, has also been described[104]:

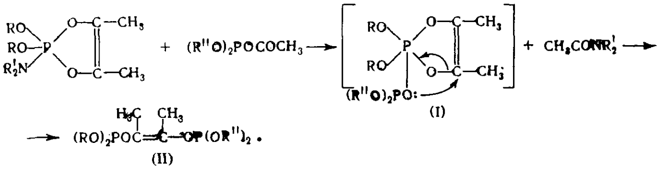


$$\begin{matrix}\text{RO}\\ \text{R}'_2\text{N}\end{matrix}\!\!>\!\text{P—OCOCH}_3 + 2\,\text{HSR}'' \rightarrow \text{ROP(SR}'')_2\,.$$

The authors[104] did not analyse the causes of the difference in the mode of the two formally similar reactions.

6. Interaction with Aminophospholens

Aminophosphoranes with a phospholen ring are an interesting type of nucleophilic agent with several centres capable of undergoing attack by electrophilic agents. The reaction of aminophospholens with acyl phosphites has been described[107] and the following mechanism has been put forward:

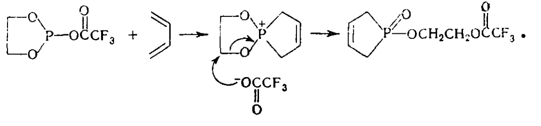


It is suggested that in the first stage the carbon atom of the carbonyl group undergoes nucleophilic attack with formation of acetamide and an intermediate pentacovalent compound(I), which undergoes further rearrangement to the final product (II). It is surprising that Mizrakh et al.[107] discussed the possibility of nucleophilic attack by nitrogen only and on only one electrophilic centre in acyl phosphites—the carbon atom of the carbonyl group. Nevertheless, having concluded that compound (II) is formed (yield 23%), the authors failed to prove rigorously its structure. For example, no data are quoted concerning the presence of a phosphorus(III) atom in the molecule. At the same time the absence of a phosphorus–carbon bond is not demonstrated either, although it is well known that it is always formed when dialkyl phosphite anions are alkylated by unsaturated compounds[108] (this in fact happens in the mechanism proposed). Moreover, it remains obscure why the dialkylphosphite anion attacks the carbon atom involved in the multiple bond and not the more electrophilic carbon atom of the alkoxy-group.

Thus at present it is impossible to include the reaction of acyl phosphites with aminophospholens among the known processes.

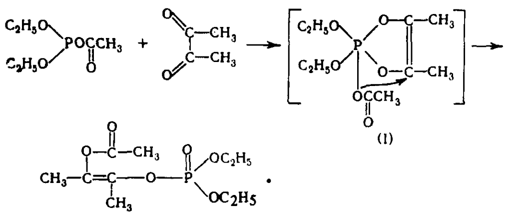
7. Reactions with Dienes

The reaction of acyl phosphites with conjugated dienes, the investigation of which began only very recently[109], can be considered in this section in a somewhat arbitrary fashion, for example:

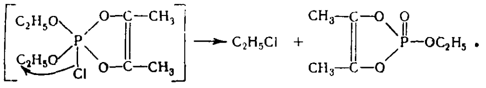


It has been noted that mixed anhydrides containing a trifluoroacetic acid residue react with dienes more readily than the corresponding acetic acid derivatives.

When diacetyl is employed as the diene, the reaction takes place readily also with mixed anhydrides incorporating non-halogenated carboxylic acids[110]:



The intermediate (I), the structure of which had been demonstrated by ^{31}P NMR[110], proved to be unstable, undergoing, according to the authors of the investigation, a rearrangement via the mechanism of the second stage of the Arbuzov reaction. However, the cause of the attack by the anion of the carbon atom of the multiple bond is not explained. At the same time this factor must be investigated in detail, since phospholen, which has a similar structure and is formed in the reaction between diacetyl and dialkyl phosphorochloridite[111], decomposes with elimination of alkyl chloride and not with ring opening:



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Department of Chemical Engineering,
Faculty of Chemistry,
Moscow State University

U. D. C. 547.89 : 616.89-072.8

The Present State of the Chemistry of 1,4-Benzodiazepines

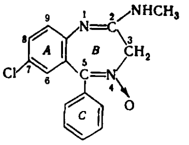
A.V.Bogatskii and S.A.Andronati

Derivatives of 1,4-benzodiazepines have found wide application as minor tranquilisers. Moreover, compounds of this class are of interest for the investigation of problems in stereochemistry, tautomerism, and mutual effects of atoms in heterocyclic systems and also for the determination of the relation between pharmacological activity and structure. This review deals with the methods of preparation and the chemical properties of 1,4-benzodiazepines and also their dihydro- and tetrahydro-derivatives and the stereochemistry and applications of these substances.
The bibliography includes 195 references.

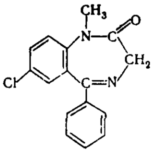
CONTENTS

I. INTRODUCTION

The chemistry of 1,4-benzodiazepines has been attracting increasing interest each year. The reason is that 7-chloro-2-methylamino-5-phenyl-3*H*-1,4-benzodiazepine 4-oxide [Chlordiazepoxide, Librium, Elenium†, and Thymosine† (I)],[1,2] 7-chloro-1-methyl-5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one [Diazepan, Valium, or seduxene† (II)][3] and their derivatives have proved to be exceptionally effective tranquilisers of a new type[4]:



(I)



(II)

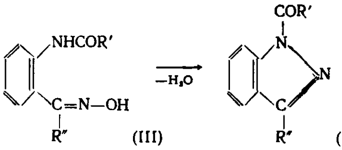
On the other hand, the chemical reactions of these systems and their stereochemistry and tautomerism proved to be unusual. The range of studies carried out so far includes systems resembling (I) and (II) with various substituents in the rings, A, B, and C, systems with non-benzene substituents in the 5-position, tetrahydro-derivatives, and also derivatives of 1,4-benzodiazepine with various functional groups. One review has been published on the chemistry of 1,4-benzodiazepines covering the literature up to 1963.[4] In the general reviews on diazepines[5] and benzodiazepines[6] a number of problems are not dealt with at all, for example the problem of the stereochemistry of 1,4-benzodiazepines and their tautomerism, and extensive new data have now accumulated which were not considered in previous reviews. Moreover, although the first derivative of 1,4-benzodiazepine, namely 4-(*N*-phenylacetamido)-3,4-dihydro-5*H*-1,4-benzodiazepine-3,5-dione was sythesised as early as 1904 by Gärtner[7], the chemistry of these structures has developed essentially only in the last ten years. The present review covers the bibliography up to 1969 inclusive.

II. METHODS OF SYNTHESIS OF 1,4-BENZODIAZEPINE SYSTEMS

1. 3*H*-1,4-benzodiazepines

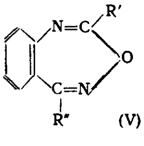
Fully unsaturated 1,4-benzodiazepines were synthesised for the first time in 1959 by Sternbach and coworkers, but the problem has had a fairly long previous history.

In 1891 Auwers and Meyenburg[8] reported that, in the reaction between oximes of *o*-carbamoylaceto- and *o*-carbamoylbenzophenones (III) and a Beckmann mixture, water is split off with formation of acylindazoles (IV). However, these "acylindazoles" were not hydrolysed to indazoles as might have been expected, but were reconverted on hydrolysis into acetamido-oximes, which threw doubt on the proposed structure (IV):



(III) (IV)

Three years later Bischler[9] proposed formula (V) for these substances, whereby they were assigned to the class of benzoxadiazepines. This formula was adopted by all investigators, including Auwers himself, although the latter believed that the proof of structure (V) was insufficiently vigorous[10].



(V)

In 1954 Ried and Stahlhofen[11] observed that benzoxadiazepines combine with two molecules of hydrogen over Raney nickel and are converted into dihydroquinazolines.

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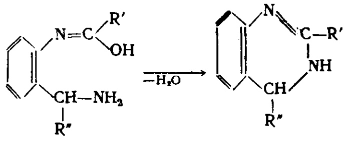
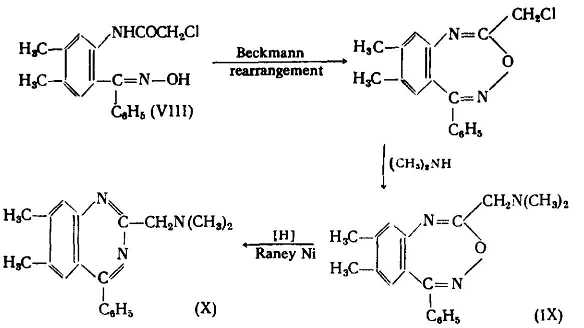
† Tentative spelling (not traced) (Ed. of Translation).

These investigators suggested that compound (V) is hydrogenated to product (VI), which eliminates water and is converted into dihydroquinazoline (VII):



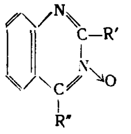
(VI) (VII)

Almost simultaneously Sternbach carried out the following synthesis in order to obtain structures of type (IX), i.e. benzoxadiazepines with basic substituents:



However, on reduction by the method of Ried and Stalhofen the product (IX) gave a high yield of the quinazoline (X) instead of the expected 3,4-dihydroquinazoline of type (VII).

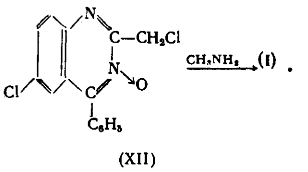
On the basis of the work of Schmitz[12], Katritzky[13], and others in the field of heterocyclic *N*-oxides, Sternbach established that the Auwers compounds have the structure of quinazoline *N*-oxides (XI):



(XI)

This was indicated by the presence of an intense absorption band in the region of 1318–1290 cm^{-1}, which is usually attributed to the N → O bond[14]. Soon structure (XI) was finally proved also chemically[15].

By allowing methylamine to react with 6-chloro-2-chloromethylquinazoline-3-oxide (XII), Sternbach obtained a compound isomeric with the expected 6-chloro-2-methylaminoquinazoline 3-oxide, but differing in its ultraviolet and infrared spectra. A more detailed study showed that this is the 4-oxide of 7-chloro-2-methylamino-5-phenyl-3*H*-1,4-benzodiazepine (I, trivial name—Chlordiazepoxide‡):

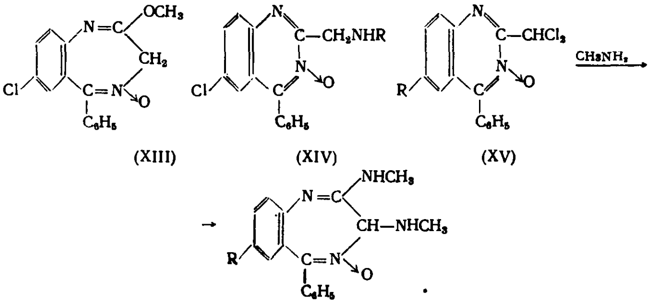


(XII)

According to Sternbach[4], the rearrangement occurring during the reaction of (XII) with methylamine takes place in three stages. The carbon atom in the 2-position of the quinazoline (XII) has a partial positive charge owing to the inductive effect of the N→O group. The first stage is the nucleophilic attack by methylamine on this carbon atom, the second stage includes the dissociation of the C–N bond between the 2-carbon atom and the *N*-oxide nitrogen, and the third stage is the formation of a new C–N bond between the amine oxide nitrogen and the methylene carbon atom with elimination of a chloride ion. The seven-membered ring is in fact formed in this third stage.

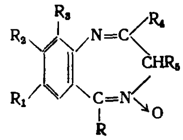
A similar rearrangement with ring expansion takes place when (XII) reacts with ammonia, primary aliphatic amines[2,16], hydrazine[17], and sodium methoxide[18]. In the latter case the product is 7-chloro-2-methoxy-5-phenyl-3*H*-1,4-benzodiazepine 4-oxide (XIII), which is obtained also when diazomethane reacts with compound (XXVIII).[18,19]

In some cases the reaction of (XII) with primary amines also gives 2-aminomethylquinazolines (XIV) as side products[20]. This type of reaction with secondary amines leads to aminoquinazolines. Only the normal substitution product is formed in the reaction of diethylamine and pyridine. The reaction of 2-dichloromethylquinazolines (XV) with methylamine leads to bismethylamino-derivatives of 1,4-benzodiazepines (XVI):[21]



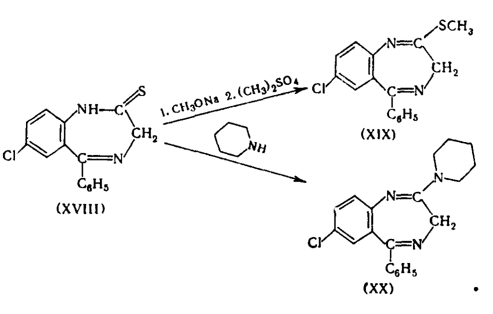
(XVI)

A necessary condition for the rearrangement is the presence of the *N*-oxide group. Without this group, quinazoline reacts with amines to form substitution products. Quinazolines with electron-donating substituents in the 6- and 8-positions also do not undergo the rearrangement. The method described permitted a synthesis of 3*H*-1,4-benzodiazepine *N*-oxides (XVII) with a large number of a wide variety of substituents[1,2,15-37]:



(XVII)

3*H*-1,4-Benzodiazepines without the *N*-oxide group can be obtained by the reduction of the corresponding *N*-oxides or by the reaction of 1,2-dihydro-3*H*-1,4-benzodiazepine-2-thiones with amines or alkylating agents[38]:



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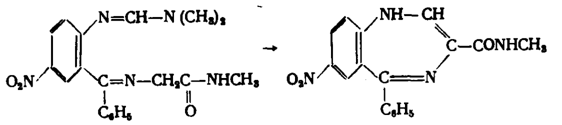
‡ The names Librium and Elenium were given to the hydrochloride of Chlordiazepoxide.

As already stated, 1,4-benzodiazepine derivatives are distinguished from the isomeric quinazolines by their infrared and ultraviolet spectra. In the infrared spectra of 1,4-benzodiazepine there is an intense absorption band in the region 1620–1605 cm^{-1} and a second intense band in the region 1590–1580 cm^{-1}, while quinazoline has only two weak bands in this region[2], at 1605 and 1550 cm^{-1}.

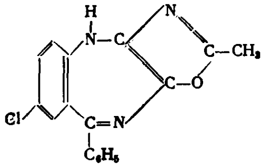
2. 1*H*-1,4-Benzodiazepines

Only two compounds of this series are known. One of these, compound (XXI), was obtained by the cyclisation of the corresponding di-imine (XXII):[39]



(XXII) (XXI)

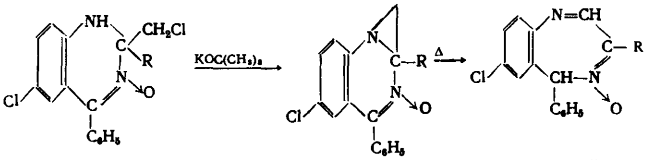
The second derivative (XXIII) is obtained as a side product in the acetylation of 2-amino-7-chloro-5-phenyl-3*H*-1,4-benzodiazepine 4-oxide:



(XXIII)

3. 5*H*-1,4-Benzodiazepines

When acted upon by potassium t-butoxide, the 3-oxides of dihydroquinazolines of type (XXIV) form the *N*-oxides of aziridinoquinazolines (XXV),[40,41] which readily isomerise on heating to derivatives of 5*H*-1,4-benzodiazepines (XXVI):

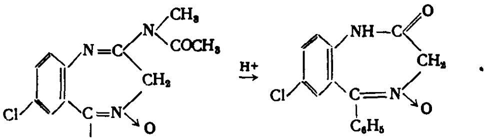


(XXIV) (XXV) (XXVI)

where R = H or CH_3.

4. 1,2-Dihydro-3*H*-1,4-Benzodiazepines

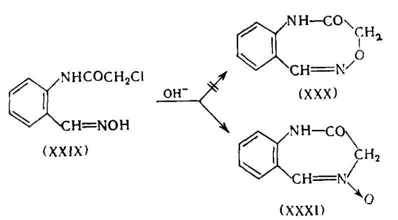
When an inorganic acid is allowed to react with an acetyl derivative of Chlordiazepoxide (XXVII) under mild conditions, the hydrolysis product (XXVIII) [22] is identical with the substance formed when a solution of the hydrochloride of compound (I) is allowed to stand in the cold for a long time§. Alkaline hydrolysis of the acetyl derivative yields the initial 1,4-benzodiazepine (I):



(XXVII) (XXVIII)

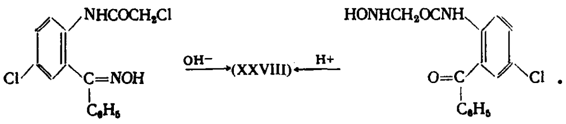
Similar compounds are readily obtained by the reaction of the 3-oxide of 6-chloro-2-chloromethyl-4-phenylquinazolines with alkali[44,45]. This process resembles the rearrangement (described above) which occurs in the course of the synthesis of compounds of type (I) from the corresponding quinazolines. Here the attacking nucleophilic agent is the hydroxide ion[45].

By treating 2-chloroacetamidobenzaldehyde β-oxime (XXIX) with alkali, Auwers[42] obtained a substance, to which he attributed the structure of benzoxadiazocine (XXX), but later it was shown that the substance is in fact the 4-oxide of 1,2-dihydro-3*H*-1,4-benzodiazepin-2-one (XXXI):[47]



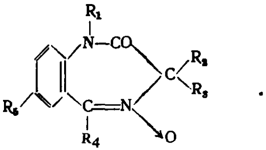
(XXIX) (XXX) (XXXI)

Under these conditions 5-chloro-2-chloracetamidobenzophenone β-oxime (XXXII) cyclises to the *N*-oxide (XXVIII),[42] which is also formed from the hydroxylamine derivative (XXXIII) in an acid medium[48-51]:



(XXXII) (XXXIII)

A number of homologues and analogues of compound (XXVIII) having the general formula (XXXIV) have been synthesised by these methods[22,44-53]:



(XXXIV)

The reduction of the 4-oxide of 7-chloro-1-methyl-5-phenyl-1,2-dihydro-3*H*-1,4-benzodiazepin-2-one yielded compound (II), which also proved to be a tranquiliser and was given the trivial name Diazepam. The high activity of compounds of this kind stimulated the synthesis of analogues and homologues of compound (II).

Several methods are known for the preparation of 1,2-dihydro-3*H*-1,4-benzodiazepin-2-one from aromatic and

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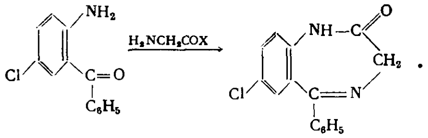
§ Like the 4-oxide of 2-amino-7-chloro-5-phenyl-3*H*-1,4-benzodiazepine, this compound is a product of the metabolism of Librium in the human and dog organisms[43].

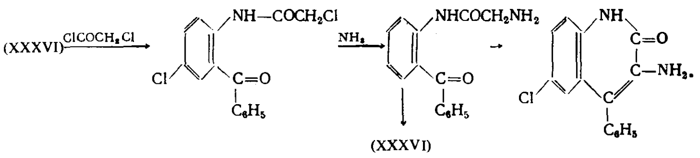
aliphatic-aromatic *o*-aminoketones. The simplest synthesis is based on the condensation of *o*-aminobenzophenones with glycine or its hydrochloride or the hydrochloride of the ethyl ester of glycine[3,54-56]:



(XXXV) (XXXVI)

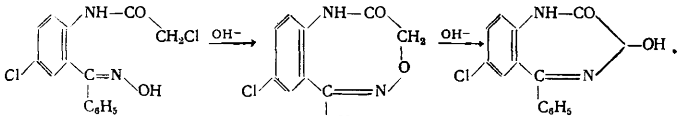
Sometimes the amino-group in glycine is protected by a benzyloxycarbonyl or phthaloyl group[44,57-60]. Syntheses have been described where one obtains initially halogenoacetamidobenzophenone (XXXVII), which is then converted into the amino-derivative (XXXVIII) and cyclised to (XXXVI).[3,23,44,61] Sometimes the dihydroquinolone (XXXIX) is then obtained as a side product.

3-Hydroxy-1,2-dihydro-3*H*-1,4-benzodiazepin-2-ones may be obtained by treating 2-chloroacetamidobenzophenone α-oximes (XL) with alkali, with the intermediate formation of the benzoxadiazocine (XLI), which is readily converted into benzodiazepine:



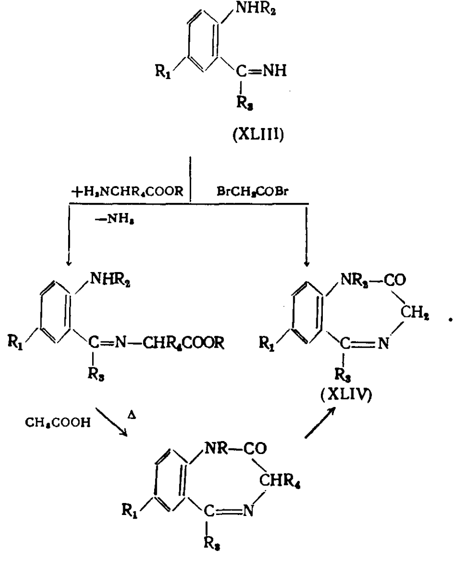
(XXXVI) (XXXVII) (XXXVIII) (XXXIX)

7-Chloro-3-hydroxy-5-phenyl-1,2-dihydro-3*H*-1,4-benzodiazepin-2-one (XLII) [the active principle of the medicinal preparation Oxazepam (or Adumbran)] was synthesised in this way[62]:

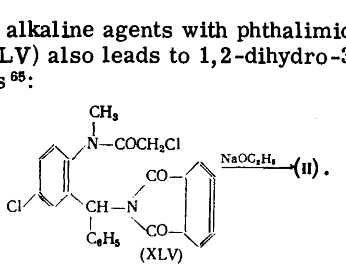


(XL) (XLI) (XLII)

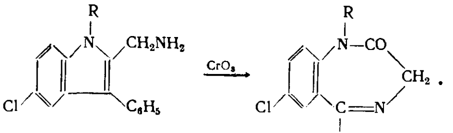
Together with *o*-aminophenones, *o*-aminoketimines (XLIII) may be employed as the starting materials for the synthesis of 1,2-dihydro-3*H*-1,4-benzodiazepin-2-ones.[63] Another way involves the reaction of the ketimines with bromoacetyl bromide, which leads directly to compounds of type (XLIV):[64]



The reaction of alkaline agents with phthalimido-derivatives of type (XLV) also leads to 1,2-dihydro-3*H*-1,4-benzodiazepin-2-ones[65]:



The 1,2-dihydro-3*H*-1,4-benzodiazepine system is formed on oxidation of aminoindoles (XLVI) with chromium trioxide[66]:

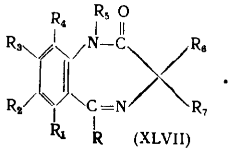


(XLVI)

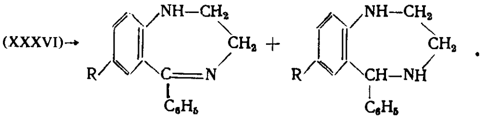
1,2-Dihydro-3*H*-1,4-benzodiazepin-2-ones can also be obtained by the reduction of *N*-oxides of type (XXVIII) or by oxidising tetrahydro-1,4-benzodiazepines or 1,2-dihydro-3*H*-1,4-benzodiazepines.

Substituents in the 1-position are usually introduced by alkylating the benzodiazepinone.

Recently many analogues and homologues of compound (II) having the general formula (XLVII) have been obtained[3,23-25,44,57-94]:



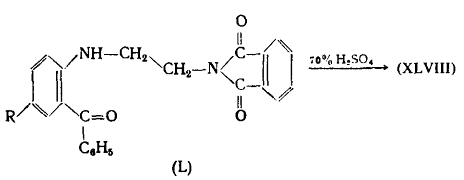
The conversion of the carbonyl group in 1,2-dihydro-3*H*-1,4-benzodiazepin-2-ones into a methylene group leads to 1,2-dihydro-3*H*-1,4-benzodiazepines[82,95-98]. However, when the initial lactams are reduced by lithium, aluminium hydride or hydrogen in the presence of a Raney nickel, tetrahydro-1,4-benzodiazepines (XLIX) are formed in addition to the dihydro-derivatives of type (XLVIII):



(XLVIII) (XLIX)

A more convenient method is the reduction over Raney nickel of the thiones (XVIII),[99,100] which are readily obtained from the corresponding carbonyl compounds.

1,2-Dihydro-3*H*-1,4-benzodiazepine (XLVIII, R = H) may be obtained by the cyclisation of phthalimidoethylaminobenzophenone (L):[95]

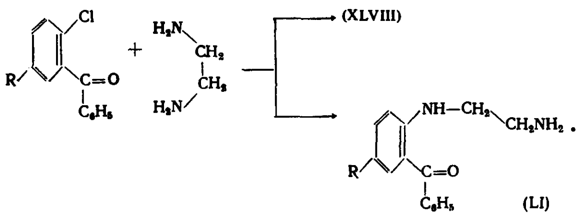


(L)

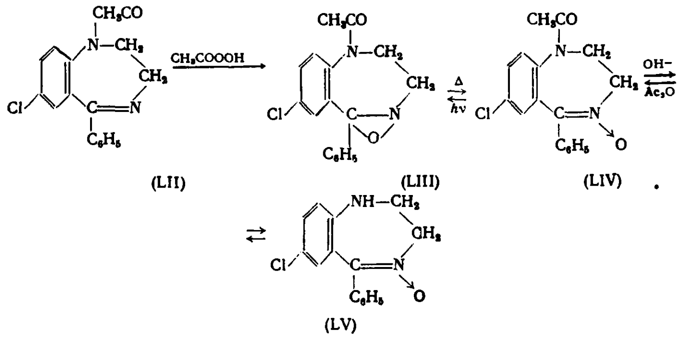
where R = H.

Another version of the reaction considered is the condensation of *o*-aminobenzophenones with aziridine in the presence of aluminium chloride. This reaction has a very low yield[95].

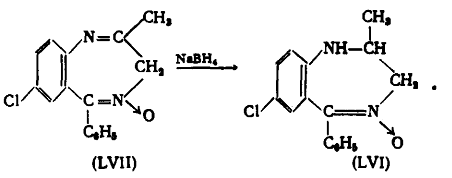
Finally, yet another procedure whereby compounds with a methylene group in the 2-position may be obtained is based on the reaction of *o*-chlorobenzophenones with diamines[101]. Then the yields of the dihydro-derivatives are higher when a nitro-group or CF_3 group is present in the *para*-position relative to the chlorine atom. With 2,5-dichlorobenzophenone, the yield is only 10%. The open-chain compounds (LI) may be formed in this reaction together with 1,4-benzodiazepines (XLVIII):



The 4-oxides of 1,2-dihydro-3*H*-1,4-benzodiazepines were synthesised from the 1-acetyl derivatives (XLVIII). Thus, when 1-acetyl-7-chloro-5-phenyl-1,2-dihydro-3*H*-1,4-benzodiazepine (LII) is treated with peracetic acid, an oxaziridine derivative (LIII) is obtained and then converted on heating into the isomeric *N*-oxide form (LIV). The acetyl group may be eliminated in an alkaline medium[102]:

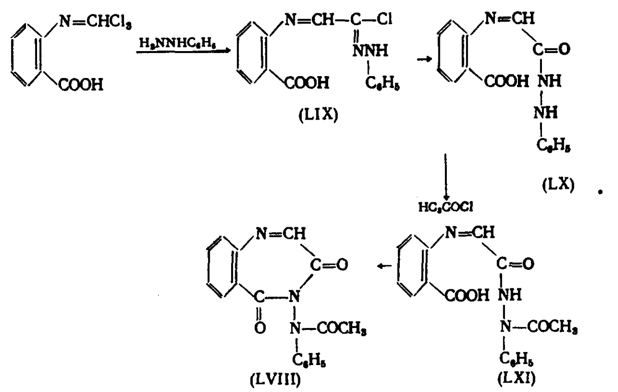


The formation of compound (LVI) on reduction of 7-chloro-2-methyl-5-phenyl-3*H*-1,4-benzodiazepine 4-oxide (LVII) with sodium borohydride has been described[41]:

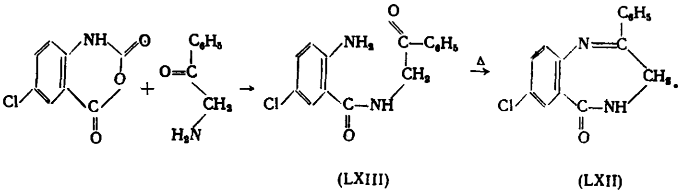


5. 3,4-Dihydro-5*H*-1,4-benzodiazepines

As stated above, the first 1,4-benzodiazepine synthesised was 4-(*N*-phenylacetamido)-3,4-dihydro-5*H*-1,4-benzodiazepine-3,5-dione (LVIII). Trichloroethylidene-anthranilic acid was converted into the phenylhydrazide (LIX) by condensation with phenylhydrazine and then by treatment with water into compound (LX), which reacted with acetyl chloride to give the acetyl derivative (LXI). Its vacuum distillation gave compound (LVIII):[7]



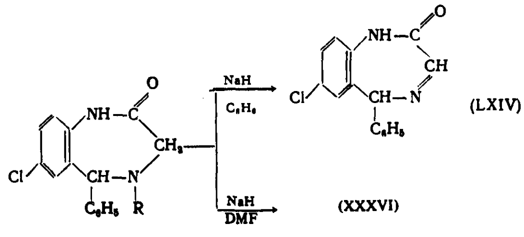
7-Chloro-5-phenyl-3,4-dihydro-5*H*-1,4-benzodiazepin-5-one (LXII) is formed by the cyclisation of compound (LXIII), obtained by the reaction of 5-chloroisatoic anhydride with aminoacetophenone[103,104]:



Similarly 2-(*o*-chlorophenyl)-3,4-dihydro-5*H*-1,4-benzodiazepin-5-one is obtained from ω-amino-*o*-chloroacetophenone and isatoic anhydride[105]. Another method for the preparation of 3,4-dihydro-5*H*-1,4-benzodiazepines consists in the reduction of the homologues and analogues of Chlordiazepoxide with lithium aluminium hydride.

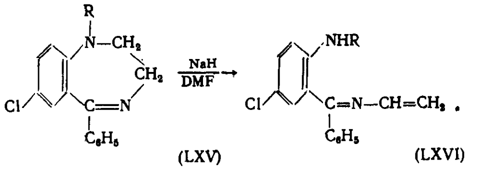
6. 1,2-Dihydro-5*H*-1,4-benzodiazepines

Representatives of this system are fairly unstable, i.e. they readily isomerise to 1,2-dihydro-3*H*-1,4-benzodiazepines. They are obtained by treating 4-tosyl(or methanesulphonyl)tetrahydro-1,4-benzodiazepin-2-ones with sodium hydride[106] or ethoxide[50] in an anhydrous non-polar solvent:



where R = *p*-tosyl, methanesulphonyl, or $OCOCH_3$. When the reaction is carried out in a polar solvent or aqueous solution, the more stable isomer (XXXVI) is formed.

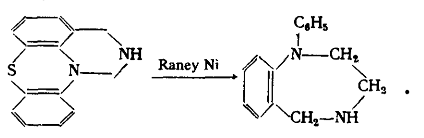
When treated with sodium hydride in dimethylformamide, 1-tosyl(or methanesulphonyl)-1,2-dihydro-3*H*-1,4-benzodiazepines (LXV) form the vinylimines (LXVI) and not the 1,4-benzodiazepine derivatives:


(LXV) (LXVI)

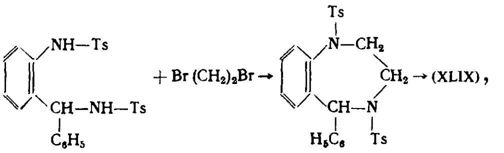
7. 1,2,3,4-Tetrahydro-5*H*-1,4-benzodiazepines

These compounds are largely obtained by the reduction of the corresponding carbonyl derivatives and *N*-oxides by complex metal hydrides or hydrogen in the presence of catalysts (palladium, nickel, and platinum).[95,98,103,107] When acted upon by $LiAlH_4$ and $NaBH_4$, the N→O group is converted into N–OH.

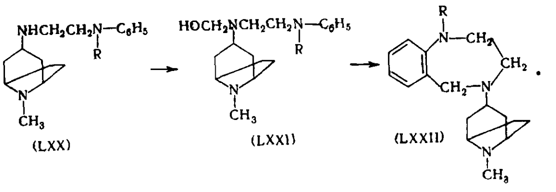
Diazepinophenothiazine (LXVII) undergoes reductive desulphuration on Raney nickel with formation of compound (LXVIII):[108]


(LXVII) (LXVIII)

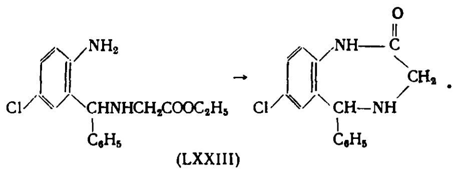
By allowing ethylene bromide to react with the diamide (LXIX), a ditosyl derivative was obtained, which on treatment with sulphuric acid was converted into (XLVIII, R = H).[109]


where R = H.

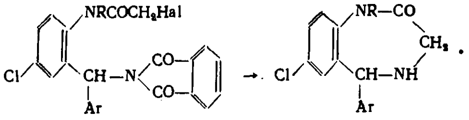
The reaction of formaldehyde and formic acid with tropanylethylenediamine (LXX) gave tropanyl derivatives of 1,4-benzodiazepine[110,111]. It is suggested that compound (LXXI) is formed as an intermediate, the intramolecular rearrangement of which gives tetrahydro-1,4-benzodiazepine (LXXII):


(LXX) (LXXI) (LXXII)

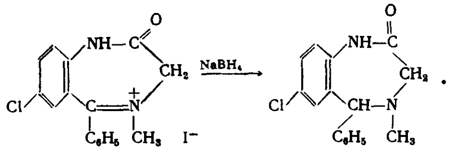
1,2,3,4-Tetrahydro-5*H*-1,4-benzodiazepin-2-ones are obtained from aminoesters of type (LXXIII), which are formed when [*o*-aminophenyl(phenyl)]methylamines are treated with bromoethyl acetate or *o*-aminobenzyl chlorides are treated with glycine ethyl ester[112-115]:


(LXXIII)

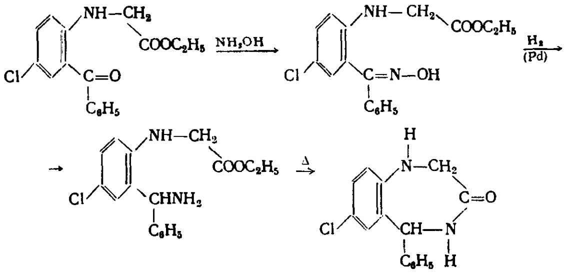
Derivatives of tetrahydro-1,4-benzodiazepin-2-one (LXXV) were synthesised by heating phthalimide derivatives of type (LXXIV) in aqueous potassium carbonate solution and subsequent treatment of the product with hydrobromic acid in acetic acid[116]:


(LXXIV) (LXXV)

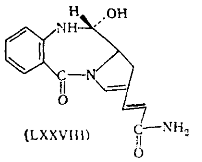
The reaction of $NaBH_4$ with the quaternary salt (LXXVI) leads to the selective reduction of the C=N bond (the carbonyl group is then retained)[44]:

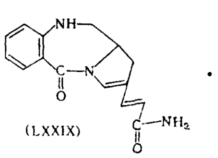

(LXXVI)

7-Chloro-1,2,3,4-tetrahydro-5*H*-1,4-benzodiazepin-3-one (LXXVII) [117] was synthesised from 5-chloro-2-ethoxycarbonylmethylaminobenzophenone according to the following mechanism:

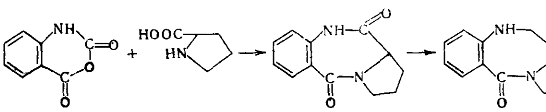

(LXXVII)

The 1,2,3,4-tetrahydro-5*H*-1,4-benzodiazepin-5-one system is a component of the structure of the cytotoxic antibiotic anthramycin (LXXVIII) and its simpler analogue (LXXIX):

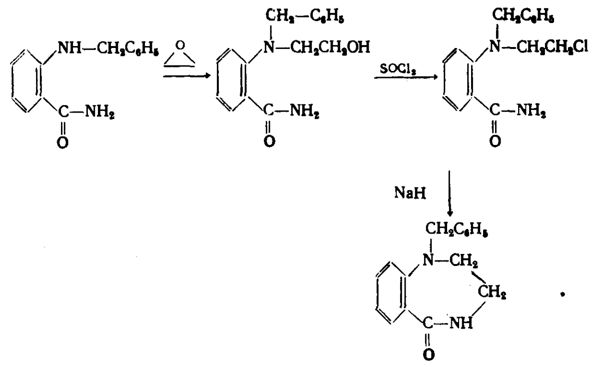

(LXXVIII)


(LXXIX)

The structures of these compounds, their stereochemistry, and intramolecular transformations have been investigated in very great detail and described in a number of papers by Leimgruber and coworkers[118,119]. Compound (LXXX) was synthesised by these investigators as a model using the following procedure:

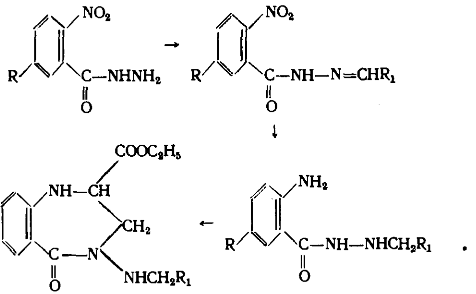

(LXXX)

The synthesis of a compound in the 1,2,3,4-tetrahydro-5*H*-1,4-benzodiazepin-5-one series was first described by Santilli and Osdene[103]. However, later it was established that the substance which they assumed to be 1-tosyl-1,2,3,-4-tetrahydro-5*H*-1,4-benzodiazepin-5-one has in fact the structure of the isomeric oxazoline[104,120]. The same investigators[121] achieved the synthesis of compound (LXXXI) from the amide of *N*-benzylanthranilic acid according to the mechanism



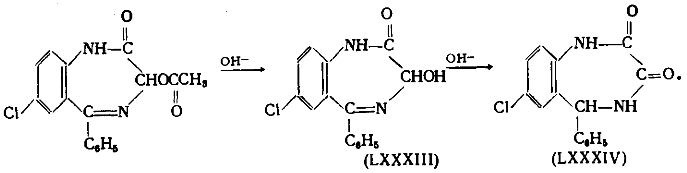
(LXXXI)

A number of various derivatives of 4-arylalkylamino-1,2,3,4-tetrahydro-5*H*-1,4-benzodiazepin-5-ones (LXXXII) were synthesised from *o*-nitrobenzoylhydrazines[122]:



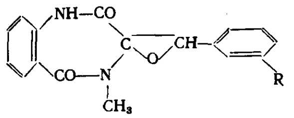
(LXXXII)

1,2,3,4-Tetrahydro-5*H*-1,4-benzodiazepin-2,3-diones are formed when 1,2,3,4-tetrahydro-5*H*-1,4-benzodiazepines and their 2-carbonyl derivatives are oxidised with CrO_3 and also on treatment with alkali of 3-acetoxy-1,2-dihydro-3*H*-1,4-benzodiazepin-2-one via the intermediate 3-hydroxy-derivative[123]:



(LXXXIII) (LXXXIV)

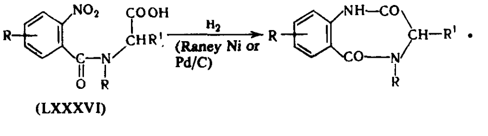
Cyclopenin (LXXXVa) and cyclopenol (LXXXVb), metabolites of the fungi *Penicillium cyclopium* Westling and *Penicillium viridicatum* Westling[124,125], are derivatives of 1,2,3,4-tetrahydro-5*H*-1,4-benzodiazepin-2,5-dione[126]. The structure of (LXXXVa) was confirmed by synthesis[127,128]:



(a—R=H; b—R=OH).

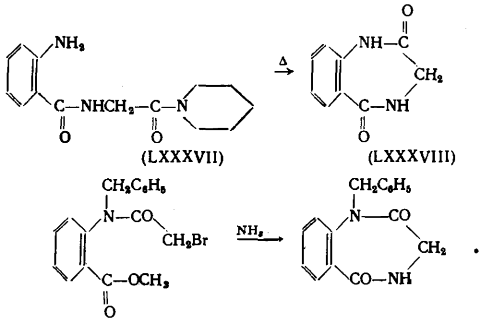
(LXXXV)

There are several synthetic procedures for the preparation of the 2,5-diones. One of these consists in the reductive cyclisation of *o*-nitrobenzamides of type (LXXXVI):[129–133]



(LXXXVI)

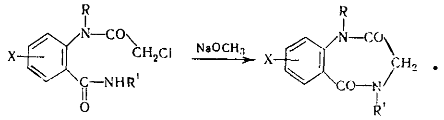
The amide of *o*-aminohippuric acid (LXXXVII) splits off piperidine on heating in acetic acid and is converted into the 2,5-dione (LXXXVIII). Its 1-benzyl derivative (XI) is obtained by treating with ammonia the methyl ester of *N*-benzyl-*N*-bromoacetylanthranilic acid (LXXXIX):[134,135]



(LXXXVII) (LXXXVIII)

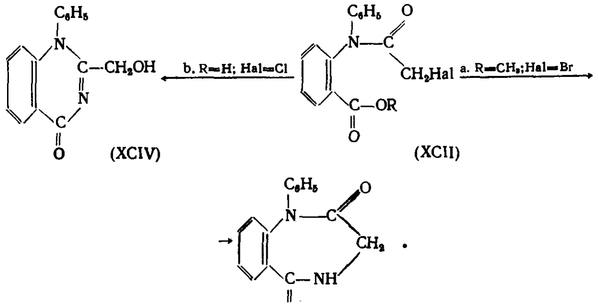
(LXXXIX) (XC)

A similar process takes place when *o*-chloroacetamidobenzamides (XCI) are treated with bases such as sodium methoxide and potassium carbonate[136–138]:



(XCI)

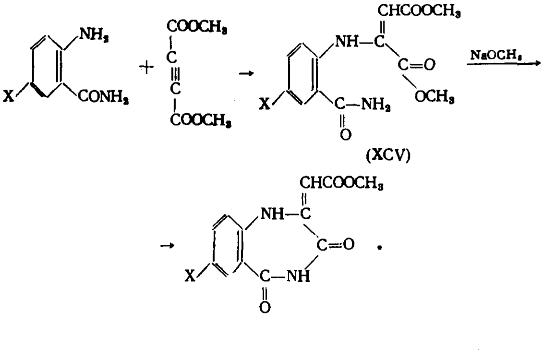
However, it has been observed[139,140] that in certain cases the reaction yields a quinazoline and not a benzodiazepine derivative. Thus, like compound (LXXXIX), the methyl ester (XCII, R = CH_3, Hal = Br), gives 1-phenyl-1,2,3,4-tetrahydro-5*H*-1,4-benzodiazepine-2,5-dione (XCIII), while *N*-acetyl-*N*-phenylanthranilic acid (XCII, R = H, Hal = Cl) cyclises to the isomeric quinazolinone (XCIV):



(XCIV) (XCII)

(XCIII)

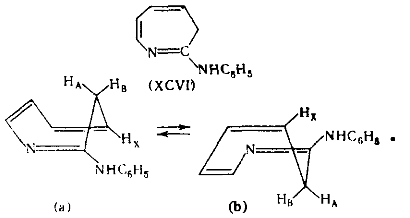
1,2,3,4-Tetrahydro-5*H*-1,4-benzodiazepin-3,5-diones were obtained by the Michael reaction from anthranilic acid amides and the dimethyl ester of acetylenedicarboxylic acid via the intermediate compound (XCV):[141,142]



(XCV)

III. STEREOCHEMISTRY OF 1,4-BENZODIAZEPINES

In 1967 Mannschreck et al.[143] investigated by NMR the intramolecular mobility of various azepines and diazepines, including 2-phenylamino-3*H*-1,4-azepine [Dibenzamil (XCVI) and similar compounds]. According to their data, in deuterated acetone compound (XCVI) (and similar substances) exist in the boat form, which undergoes inversion at a temperature as low as −55° ± 7°C between two conformations (a) and (b) 258 times per second. The free energy of activation for the process (a)⇌(b) proved to be 10.2 ± 0.4 kcal mole^{-1}. An approximately the same barrier (17 kcal mole^{-1}) was found also for 7-chloro-1-methyl-5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one:



(XCVI)

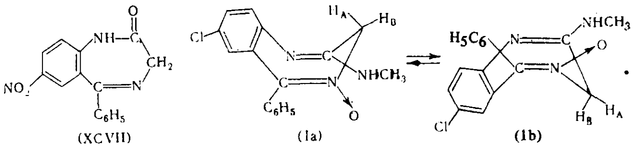
(a) (b)

Somewhat later Nuhn and Bley[144,145] found that at room temperature the methylene protons located near the 3-C atom of compound (II) gives rise in the spectrum to a typical AB-quartet with $\Delta\nu = 144$ Hz (spectrometer with $\nu_0 = 100$ MHz) and $J_{HH'} = 10.5$ Hz. At a temperature as low as 32°C the lines of the quartet begin to blur and at 127°C the protons of the methylene group contribute to a singlet peak.

Thus at room temperature the Diazepam (II) molecule exists in a conformation which does not undergo inversion and the conformational inversion of the system begins only at 32°C. The conformational stability of compounds (XCVII) and (I) is lower. The inversion of their conformations begins at −65° and −10° respectively.

The values of ΔH^* are respectively 15.9 ± 0.4 kcal mole^{-1} for (II), 10.9 ± 1.1 kcal mole^{-1} for (I), and 11.0 ± 0.3 kcal mole^{-1} for (XCVII), while the ΔS^* are 5.1 ± 1.0 kcal mole^{-1} deg^{-1} for (II), 3.4 ± 4.5 kcal mole^{-1} deg^{-1} for (I), and 13.3 ± 0.9 kcal mole^{-1} deg^{-1} for (XCVII).

The higher conformational stability of compound (II) compared with (XCVII) and (I) can be accounted for by an increase in the rigidity of the system on introduction of a methyl substituent in the 1-position of the benzodiazepine ring:

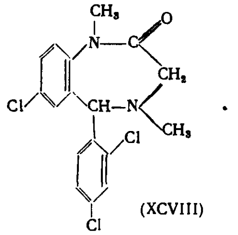


(XCVII) (Ia) (Ib)

It is also interesting that the lowest entropy of activation is observed for compound (I), which indicates a lower probability of the formation of a transition state in this case, probably because the nature of the transition state for substance (I) differs significantly from that of the transition state formed on conformational inversion of compounds(II) and (XCVII). It is not difficult to see that in the transition state formed by the inversion of conformation (I) considerable electrostatic repulsion may occur, which evidently effects the probability of the formation of such a system.

By comparing the spectra with Dreiding's models, Nuhn and Bley concluded that the most probable conformation of the above systems is the boat form¶. Consequently the above investigators arrived at the general conclusion that compounds (I), (II), and (XCVII) have a non-polar conformation, which is probably the boat form, and inversion of the type (Ia)⇌(Ib) is observed after definite temperature barriers have been overcome.

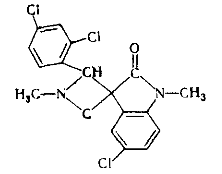
Karle and Karle[147] showed by X-ray diffraction that 7-chloro-5-(2,4-dichlorophenyl)-1,4-dimethyl-4,5-dihydro-3*H*-1,4-benzodiazepin-2-one (XCVIII) crystallises in the triclinic space group with two molecules in the unit cell, the dimensions of which are as follows: $a = 8.84$ Å; $b = 10.18$ Å; $c = 10.80$ Å; $\alpha = 93°51'$; $\beta = 112°31'$; $\gamma = 101°39'$.



(XCVIII)

The nitrogen atom in the 1-position is planar while that in the 4-position is pyramidal, which contributes to the difference between their basicities.

The $-\overset{|}{\underset{|}{C}}-\overset{|}{\underset{\substack{\| \\ O}}{C}}-\underset{\substack{| \\ CH_3}}{N}-\overset{|}{\underset{|}{C}}-$ group is almost planar but is rotated by 50°C relative to the condensed benzene ring. On the basis of the above calculations of the bond lengths and valence angles in the molecule, the authors[147] assert that the configuration of the compound corresponds to a distorted "boat", the 5-phenyl and 4-methyl groups being in the *trans*-positions with respect to one another:



It follows from the above that only the first steps have been taken in the study of the stereochemistry of the systems under consideration. Despite the valuable information obtained recently, important problems such as the question of the preferred conformation of the ring and the factors influencing the stability of the conformation have still not been resolved unambiguously. Further study of the problem will help in the development of the chemistry of 1,4-benzodiazepines and will undoubtedly promote further development of modern stereochemistry.

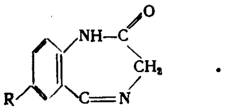
IV. PROPERTIES OF 1,4-BENZODIAZEPINES

1. Certain Characteristics of the Structure and Tautomerism of 1,4-benzodiazepine

The study of the infrared spectra of lactams of type (XCIX) leads to the conclusion that in the crystalline state and in concentrated solutions these compounds form association complexes via intermolecular hydrogen bonds.

¶ 7-Chloro-5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one and its *N*-oxide exist in the same preferred conformation[146].

The interaction of (XCIX) with the molecules of polar solvents (chloroform, pyridine) also has a distinctive effect. The electronic influence of the substituent in the 7-position on the absorption frequency of the carbonyl group can be readily traced in the spectra of crystalline specimens of compound (XCIX).



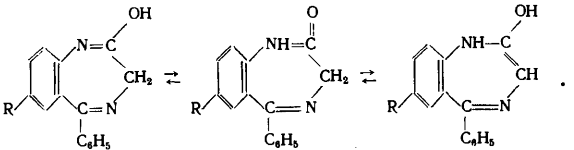
(XCIX)

The carbonyl band in the spectrum of the compound with R = NO_2 is displaced by 20 cm^{-1} towards higher wave numbers compared with the spectrum of the compound with R = CH_3 and by about 10 cm^{-1} compared with the spectrum of the compound where R = Cl.[148]

An electron-accepting substituent, for example a nitro-group, increases the polarisation of the carbonyl group and displaces the carbonyl absorption band towards higher wave numbers, as happens in other examples known from the chemistry of the aromatic series[149]. An electron-donating substituent causes the opposite shift of the absorption band, while substituents with $-J$ and $+C$ effects (halogens) have an intermediate influence. It has been found that the relative changes in the shift of the carbonyl absorption bands as a function of the substituent in the 7-position are satisfactorily correlated with Hammett's σ constants.

Usually investigators[2] regard the bands at 1620–1605 cm^{-1} and 1580–1590 cm^{-1} as characteristic of this system, but this assertion is so far insufficiently supported by evidence although empirically it is probably reliable.

Three tautomeric forms may be suggested for compounds of type (XCIX):



(a) (XCIX) (b)

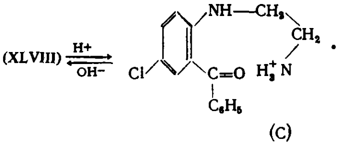
In the crystalline state and in acid and neutral solutions, (XCIX) exists in the lactam form, as shown by the infrared spectra and the chemical properties of the compound. In the presence of bases the lactim or enol forms may be produced, which has been demonstrated by ultraviolet spectroscopy at different pH of the medium. The changes in the position of the long-wavelength absorption band (λ_{max} = 320–370 nm) are of greatest interest. The bathochromic shift of this band in alkaline and acid media (to λ_{max} = 350–370 nm) compared with the neutral medium (λ_{max} = 320 nm) may be accounted for by an increase in the conjugation chain, which occurs as a result of the quaternisation of the fourth nitrogen atom (in an acid medium) and the formation of the lactim form (XCIXa) (in an alkaline medium).

The choice of structure (a) in preference to (b) was made on the basis of the finding that the ultraviolet spectra of 1-substituted and unsubstituted benzodiazepines are identical in neutral and alkaline media.

2. Hydrolysis of 1,4-Benzodiazepines

Acid hydrolysis under mild conditions of the *N*-oxides of 3*H*-1,4-benzodiazepines or their acetyl derivatives leads to the *N*-oxides of 1,2-dihydro-3*H*-1,4-benzodiazepin-2-ones.[22,150]. Under more severe conditions, 7-chloro-2-methylamino-5-phenyl-3*H*-1,4-benzodiazepine is hydrolysed to 2-amino-5-chlorobenzophenone, glycine, and methylamine[2].

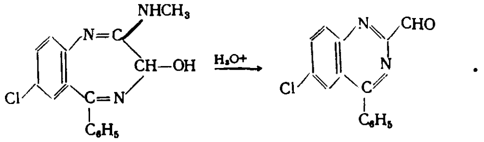
The acid hydrolysis of 1,2-dihydro-3*H*-1,4-benzodiazepines (XLVIII) takes place with the opening of the seven-membered ring and the formation of the salt (C), which on treatment with alkali cyclises to the initial compound[95]:



(C)

where R = Cl.

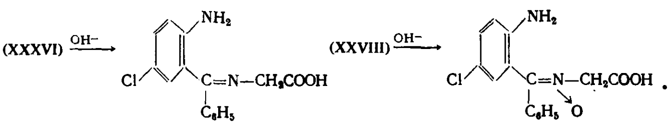
7-Chloro-3-hydroxy-2-methylamino-5-phenyl-3*H*-1,4-benzodiazepine (CI) is hydrolysed by acids to quinazoline-aldehyde (CII):[151]



(CI) (CII)

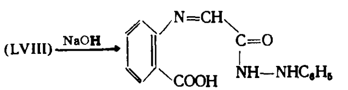
When treated with hot 75% sulphuric acid, the 2,5-dione (LXXXVIII) is converted into anthranilic acid[134].

Alkaline hydrolysis of 1,2-dihydro-3*H*-1,4-benzodiazepin-2-ones (XXXVI) and their 4-oxides (XXVIII) leads to the aminoacid salts (CIII) and (CIV) respectively, which, however, react differently with acids: compound (CIII) decomposes into *o*-aminobenzophenone and glycine and compound (CIV) cyclises to the initial product[22,44]:



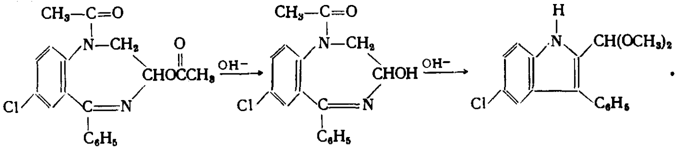
(CIII) (CIV)

1,2,3,4-Tetrahydro-5*H*-1,4-benzodiazepine-2,5-diones (LXXXVIII) are not decomposed by alkali, in contrast to the 3,5-dione (LVIII), which is readily cleaved by a hot sodium hydroxide solution to the phenylhydrazide (CV):[7,134]



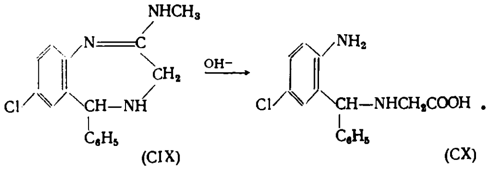
(CV)

The alkaline hydrolysis of 3-acetoxy-1-acetyl-1,4-benzodiazepine (CVI) gives the 3-hydroxy-derivative (CVII), while under more severe conditions it rearranges to the indole derivative (CVIII):[153]

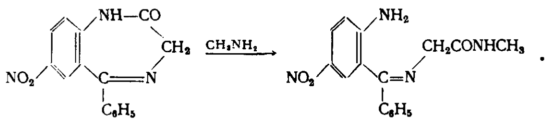


(CVI) (CVII) (CVIII)

When an aqueous alcoholic solution of compound (CIX) is refluxed with barium hydroxide, an aminoacid derivative (CX) is formed[2]:



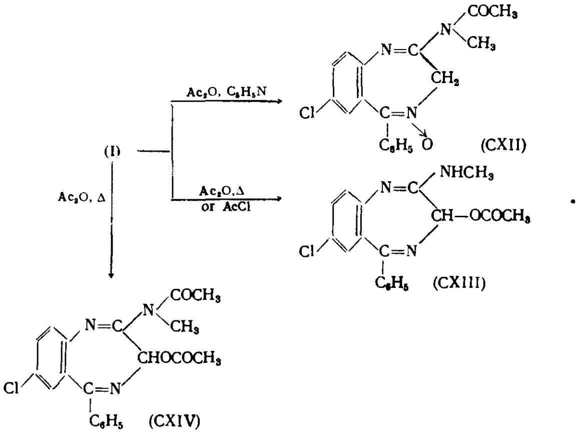
It has been shown for 7-nitro-5-phenyl-1,2-dihydro-$3H$-1,4-benzodiazepin-2-one (XCVII) that the seven-membered ring is opened when acted upon by methylamine[39]†:



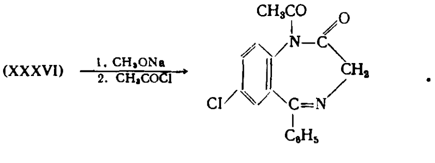
The heterocyclic ring in the 2,5-dione (LXXXVIII) is cleaved under the same conditions[134].

3. Acylation of 1,4-Benzodiazepines

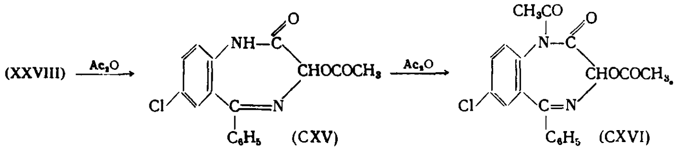
When benzodiazepines of the "Chlordiazepoxide" type are acetylated, various derivatives are obtained depending on the reaction conditions[151,154]. Thus the acetylation of compound (I) with acetic anhydride in pyridine at room temperature leads to the 2-acetyl derivative (CXII). When Chlordiazepoxide is treated with hot acetic anhydride or acetyl chloride in dimethylformamide, a rearrangement of the Polonovskii type takes places with formation of the 3-acetoxy-derivative (CXIII). Prolonged heating of compound (I) with acetic anhydride gives the 3-acetoxy-2-acetyl derivative (CXIV):



1,2-Dihydro-$3H$-1,4-benzodiazepin-2-ones are capable of being acetylated when their sodium salts are acted upon by acetyl chloride[155]:



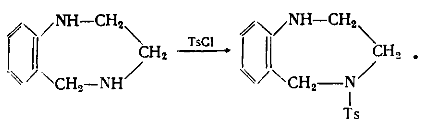
Like compound (I), on treatment with acetic anhydride the N-oxides of 1,2-dihydro-$3H$-1,4-benzodiazepin-2-ones (XXVIII) undergo a rearrangement in which the N-oxide oxygen atom migrates to the carbon atom in the 3-position forming 3-acetoxy-1,2-dihydro-$3H$-1,4-benzodiazepin-2-ones (CXV). Further reaction with acetic anhydride leads to compound (CXVI): [123,156]



When 1,2-dihydro-$3H$-1,4-benzodiazepin-2-ones (XXXVI) are treated wtih a mixture of acetic and peracetic acids and acetic anhydride, 3-acetoxy-derivatives (CXVI) are immediately obtained[157].

Other reactions of compounds of type (XXXVI) on treatment with acylating agents will be discussed below.

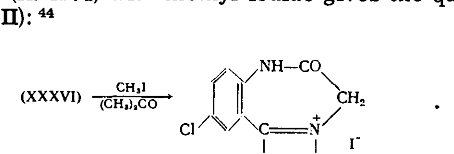
1,2-Dihydro-$3H$-1,4-benzodiazepines are acylated in the 1-position by acid anhydrides and chlorides[92,98,153]. It is interesting that the acylation of 1,2,3,4-tetrahydro-$5H$-1,4-benzodiazepine with p-toluenesulphonyl chloride in pyridine gives only the 4-tosyl derivative[105], which indicates a higher basicity of the nitrogen atom in the 4-position:



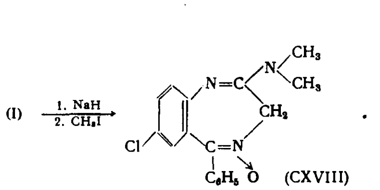
4. Alkylation and Alkoxylation of 1,4-Benzodiazepines

1,4-Benzodiazepines are alkylated preferentially in the 1- and 4-position when they or their sodio-derivatives are treated with the usual alkylating agents[3,22,44]. The methylation of the 2,5-dione (LXXXVIII) gives a mixture of the 1-methyl and 1,4-dimethyl derivatives[107].

Owing to the different basicities of the two nitrogen atoms in 1,2,3,4-tetrahydro-$5H$-1,4-benzodiazepin-2-ones, 1- or 4-alkyl or 1,4-dialkyl derivatives may be obtained depending on the reaction conditions[76]. The reaction of compound (XXXVI) with methyl iodide gives the quaternary salt (CXVII): [44]



On treatment with methyl iodide in the presence of sodium hydride, Chlordiazepoxide (I) is converted into the 2-dimethylamino-derivative (CXVIII): [158]



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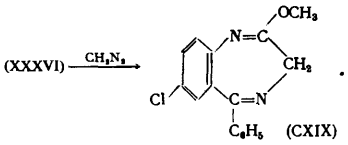
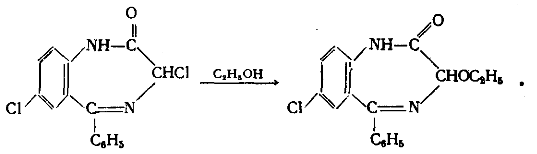
† The corresponding amidine is also formed as a side product in this reaction[152].

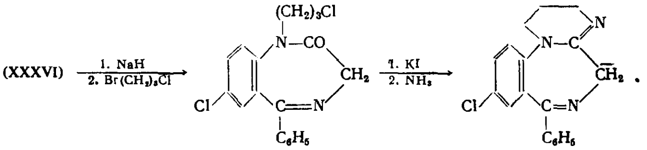
When compounds (XXVIII) and (XXXVI) react with diazomethane, the *O*-methyl derivatives of the 3*H*-1,4-benzodiazepine system (CXIX) are formed:[17,159]



3-Halogeno-derivatives of 1,4-benzodiazepines are converted into the 3-ethoxy-derivatives when acted upon by ethanol[45]:



By alkylating 1,2-dihydro-3*H*-1,4-benzodiazepin-2-ones unsubstituted in the 1-position, a large number of compounds of this series with various substituents at the N_1 atom‡ were obtained. In many cases this method is used to synthesise more complex condensed systems. For example dihydroimidazo- and tetrahydropyrimido-[1,2-*a*]-1,4-benzodiazepines were obtained in this way[161,162]:



5. Oxidation of 1,4-Benzodiazepines

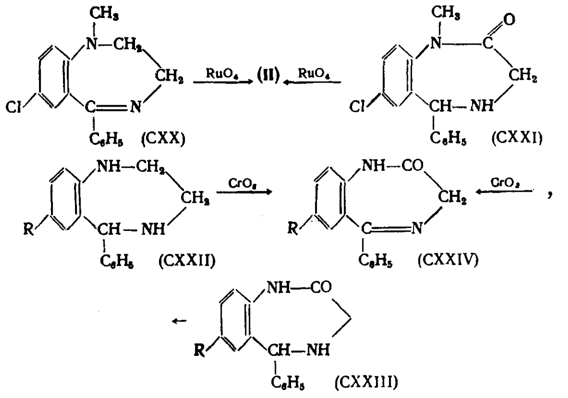
Several examples of the oxidation of these substances by peroxides have been described. 1,2-Dihydro-3*H*-1,4-benzodiazepin-2-ones may be converted into the 4-oxides by treatment with hydrogen peroxide[22]. 1,4-Benzodiazepin-2-ones unsubstituted in the 1-position (XXVI, CXIV) react with peracetic acid to form the 4-oxides.

Under these conditions, 1-acetyl-7-chloro-5-phenyl-1,2-dihydro-3*H*-1,4-benzodiazepine (LII) forms the oxaziridino derivative (LIII), which on heating is converted into the *N*-oxide (LIV).

2-Acetylmethylamino-3*H*-1,4-benzodiazepines are oxidised by peracetic acid to compounds of type (XXVIII).[150]

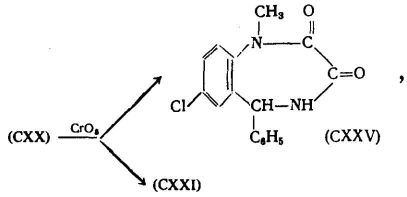
Mercury(II) oxidises 4,5-dihydro-3*H*-1,4-benzodiazepin-4-ols to *N*-oxides of type (I).[163]

When acted upon by RuO_4, CrO_3, SeO_2, or AgO, dihydro- and tetrahydro-1,4-benzodiazepines (CXX and CXXI) and tetrahydro-1,4-benzodiazepin-2-ones (CXXII and CXXIII) are converted into dihydro-1,4-benzodiazepinones (II) and compound (CXXIV) [112,164,165] respectively:



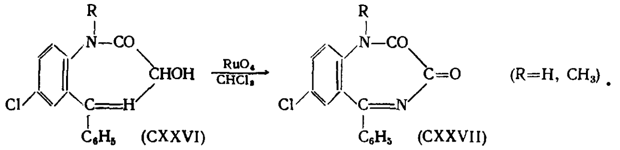
where R = H.

However, it should be noted that 1-alkyltetrahydro-1,4-benzodiazepines are oxidised to the dihydrobenzodiazepinones only by RuO_4, while CrO_3, SeO_2, and AgO oxidise compounds (CXX) to the monocarbonyl (CXXI) or dicarbonyl (CXXV) derivatives of tetrahydro-1,4-benzodiazepines:

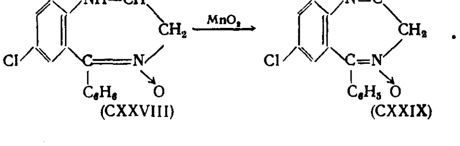


where R = CH_3.

3-Hydroxy-1,2-dihydro-3*H*-1,4-benzodiazepin-2-ones (CXXVI) are oxidised by ruthenium tetroxide to the unstable *α*-dicarbonyl derivatives (CXXVII):[165]



When 7-chloro-2-methyl-5-phenyl-1,2-dihydro-3*H*-1,4-benzodiazepine 4-oxide (CXXVIII) is oxidised with MnO_2, the 4-oxide of 7-chloro-2-methyl-5-phenyl-3*H*-1,4-benzodiazepine (CXXIX) is obtained:



6. Reduction of 1,4-Benzodiazepines

The *N*-oxides of 1,4-benzodiazepines are reduced to the corresponding deoxy-compounds by phosphorus trichloride or hydrogen in the presence of Raney nickel[2].

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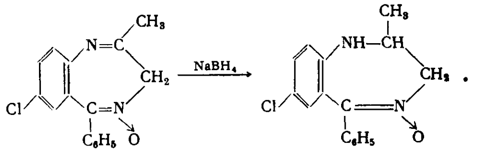
‡ It proved possible to synthesise in this way all the metabolites of 7-chloro-1-(diethylaminoethyl)-5-(2-fluorophenyl)1,2-dihydro-3*H*-1,4-benzodiazepin-2-one observed previously in the urine of patients receiving this preparation[160,161].

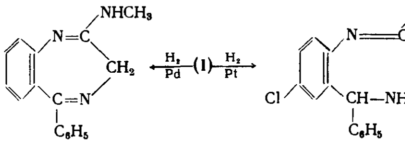
The *N*-oxide group is reduced to N–OH by complex hydrides [$LiAlH_4$, $NaBH_4$, $(CH_3)_4NBH_4$], hydrogen on a platinum catalyst and in the presence of Raney nickel, and also by Grignard reagents. Apart from the *N*-oxide group, the adjacent C=N double bonds are also reduced and in the case of *N*-oxides of 1,4-benzodiazepines $LiAlH_4$ reduces the carbonyl group to the methylene group[2,98,163].

The 4-oxides of 5*H*-1,4-benzodiazepines are reduced by complex hydrides to 1,2,3,4-tetrahydro-5*H*-1,4-benzodiazepines[41]. In contrast to other 1,4-benzodiazepine *N*-oxides, compound (CXXX) is reduced by sodium borohydride to (CXXXI), i.e. in this case a selective reduction of the C=N bond in the 1,2-position without involvement of the N→O group is observed[41]:



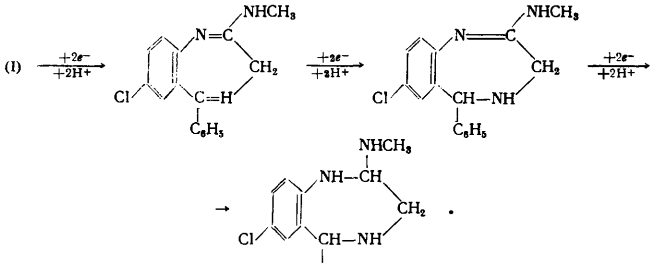
(CXXX) (CXXXI)

Chlordiazepoxide (I) is reduced in different ways by hydrogen on palladium and platinum catalysts: in the first case the reduction proceeds with elimination of chlorine from the 7-position and the oxygen from the N→O group, while in the second case the N→O group and the adjacent C= N bond are reduced[2]:



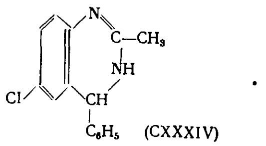
(CXXXII)

The attempts to reduce further compound (CXXXII) by hydrogen in the presence of platinum were unsuccessful. Compound (I) is reduced at a dropping mercury electrode in three stages, which corresponds to three polarographic waves[166]:



(CXXXIII)

In the first stage the *N*-oxide group is reduced, in the second stage the azomethine bond in the 4,5-position, and in the last case the double bond in the 1,2-position. However, it proved impossible to isolate compound (CXXXIII) by the preparative electrochemical reduction of (CXXXII) owing to its instability and ready conversion into the dihydroquinazoline (CXXXIV) with elimination of methylamine[167]:

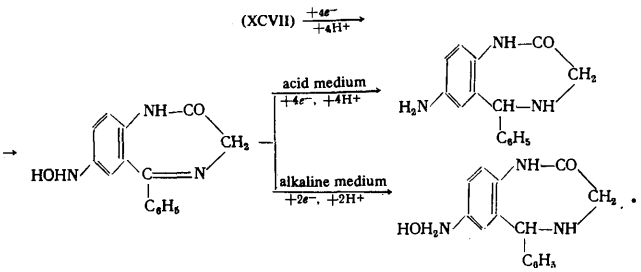


(CXXXIV)

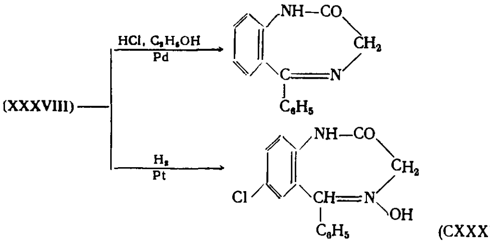
The azomethine group is reduced polarographically in 1,2-dihydro-3*H*-1,4-benzodiazepin-2-ones of type (II).[168-171]

The mechanism of the reduction of 7-nitro-5-phenyl-1,2-dihydro-3*H*-1,4-benzodiazepin-2-one (CXVII)§ is more complex, since this compound contains another polarographically active group (NO_2). In the first stage, corresponding to the first wave, the nitro-group is reduced to the hydroxyamino-group. In the second stage (second wave) in an acid medium the azomethine bond and the hydroxyamino groups are reduced, the latter to the amino-group.

In an alkaline medium only the azomethine bond is reduced in this stage[169,170]:

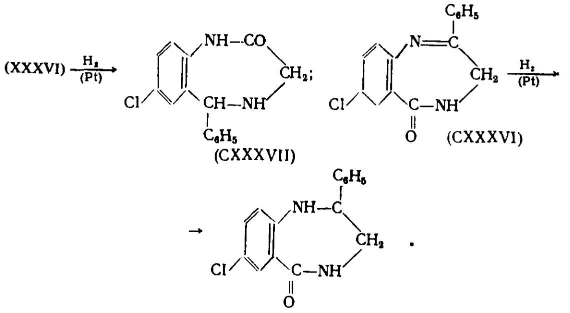


The benzodiazepinone (XXVIII) is also reduced on a palladium catalyst with elimination of chlorine and *N*-oxide oxygen atoms, whereas treatment with hydrogen in the presence of platinum results in the formation of compound (CXXXV):[22,44,172]



(CXXXV)

Compounds (XXXVI) and (CXXXVI) are reduced on a platinum catalyst to the 1,2,3,4-tetrahydro-5*H*-1,4-benzodiazepinones (CXXXVII) and (CXXXVIII) respectively[22,103]:



(CXXXVII) (CXXXVI) (CXXXVIII)

When compounds (XXXVI) and (LXXXVIII) are reduced with lithium aluminium hydrides, a mixture of dihydro- and

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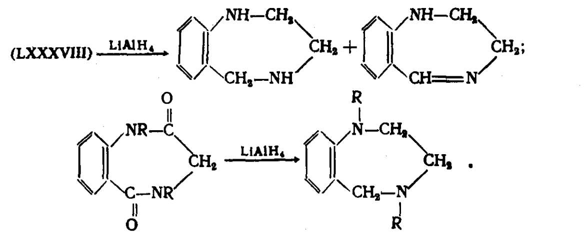
§ The active ingredient of the familiar sedative "Mogadon" ["Mogadan", "Nitrazepam", "Eunoctine" (tentative spelling—Ed. of Translation)].

tetrahydro-derivatives is formed, while 1,4-disubstituted diones give only the tetrahydro-derivatives (CXL): [95,107,134]



(CXXXIX) (CXL)

Dihydro-derivatives of 1,4-benzodiazepines of type (XLVIII) are reduced to tetrahydro-1,4-benzodiazepines by lithium aluminium hydride and hydrogen on platinum and palladium catalysts[95].

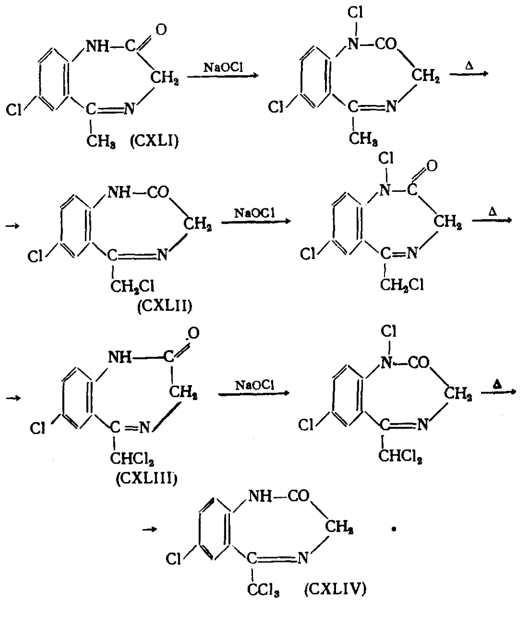
7. Nitration of 1,4-Benzodiazepines

Benzodiazepines unsubstituted in ring *A* are nitrated in the 7-position. When 7-substituted 5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-ones are nitrated, derivatives with the nitro-group in ring *C* occupying the *meta*-positions are obtained[173]. Consequently the 1,4-benzodiazepine system behaves as an electron acceptor in relation to the benzene ring. Further nitration leads to the substitution of hydrogen by a nitro-group in the 9-position[174] and in the nitration of tetrahydro-1,4-benzodiazepines substitution also takes place in ring *C*, but this time in both the *meta*- and *para*-positions and not the *meta*-position only.

8. Halogenation of 1,4-Benzodiazepines

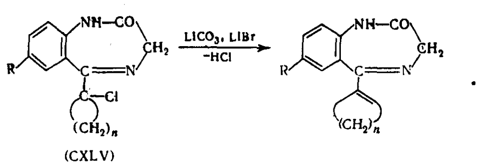
1,2-Dihydro-3*H*-1,4-benzodiazepin-2-ones with a very mobile chlorine atom in the 1-position can be obtained by the reaction of the lactams (CXLI) with organic or mineral hypochlorites[175].

The chlorine atom readily migrates to the carbon atom of the substituent in the α-position relative to the seven-membered ring provided that there is at least one hydrogen atom at this carbon atom. If there are two or three such hydrogen atoms, they are all successively substituted by chlorine atoms:



The chlorine atoms in compounds of type (CXLII), (CXLIII), and (CXLIV) can be readily replaced, by the usual procedures, by a CN group or amino-residues.

When chloro-derivatives of type (CXLV) in solution in dimethylformamide are refluxed with lithium carbonate or bromide, a molecule of HCl is split off with formation of a double bond in the αβ-position of the substituent at C_5:

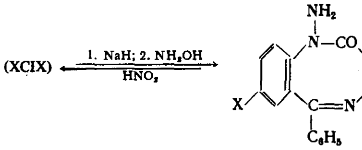


(CXLV)

There are data showing the successful halogenation of 1,2-dihydro-3*H*-1,4-benzodiazepin-2-ones by *N*-halogeno-compounds[176]. However, according to Bell's results[50], the bromination of compound (XXXVI) by *N*-bromosuccinimide does not give the required 3-bromo-derivative. The latter was obtained by the action of *N*-bromosuccinimide on an isomer of compound (XXXVI)—7-chloro-5-phenyl-1,2-dihydro-5*H*-1,4-benzodiazepin-2-one[50].

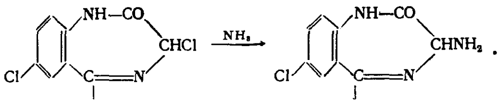
9. Amination of 1,4-Benzodiazepines

The sodium salts of lactams of type (XCIX) can react with chloramine to form 1-amino-derivatives (CXLVI), [177] which are readily deaminated by nitrous acid:



(CXLVI)

3-Amino-derivatives (CXLVIII) are obtained when solutions of 3-chloro-1,2-dihydro-3*H*-1,4-benzodiazepin-2-ones (CXLVII) are treated with ammonia:



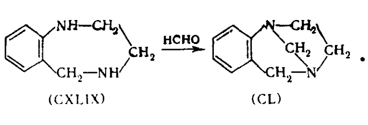
(CXLVII) (CXLVIII)

1,4-Benzodiazepines with an amino-group in the 7-position are obtained from the 7-nitro-derivatives by reduction with hydrogen in the presence of Raney nickel[25] and also by the Hofmann degradation of 7-carbamoyl-1,4-benzodiazepines. Aminobenzodiazepines may be converted into the corresponding hydroxy-, cyano-, and halogeno-derivatives via diazo-compounds.

10. Other Reactions

The reaction of 1,4-benzodiazepin-2-ones with P_2S_5 (in boiling pyridine) leads to the substitution of carbonyl oxygen by sulphur, i.e. to the formation of 1,4-benzodiazepine-thiones, from which methylthio-derivatives have been obtained by reaction with dimethyl sulphate[38,158].

Tetrahydro-1,4-benzodiazepine (CXLIX) undergoes condensation with formaldehyde, forming a bridge-type compound (CL): [110]

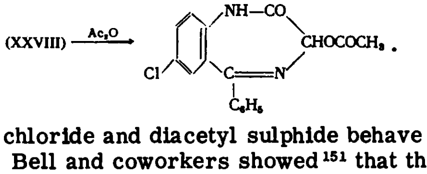


(CXLIX) (CL)

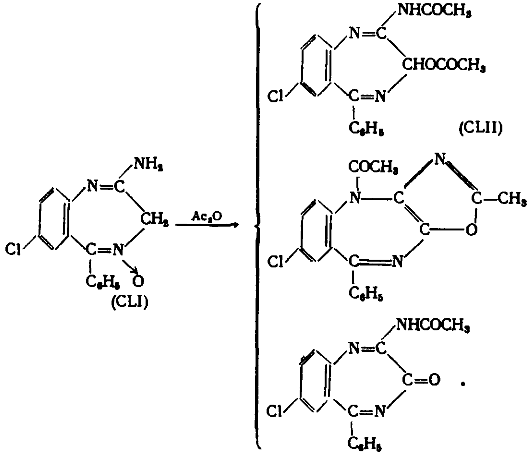
1,4-Benzodiazepines readily form coordination compounds with Lewis acids. Thus it has been observed that 1,2-dihydro-3*H*-1,4-benzodiazepin-2-ones react with SiF_4 to give 1 : 1 adducts. The SiF_4 molecule is probably coordinated to the 4-N atom[178].

11. Rearrangements and Isomerisation

The rearrangement of *N*-oxides of 1,4-benzodiazepines of the Polonovskii type¶ under the influence of acetic anhydride leads to the formation of derivatives with the acetoxy-group in the α-position relative to the nitrogen atom of the *N*-oxide group[123]:

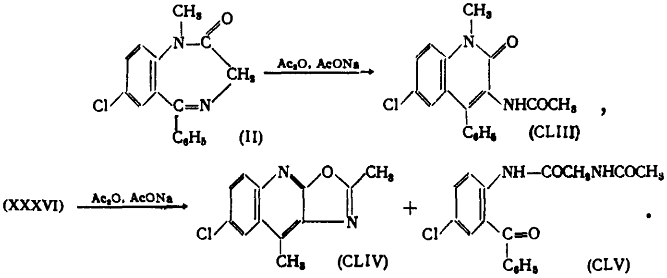


Benzoyl chloride and diacetyl sulphide behave analogously[181]. Bell and coworkers showed[151] that the 4-oxide of 2-amino-7-chloro-3*H*-1,4-benzodiazepine (CLI) forms three compounds on heating with acetic anhydride; the authors suggest that the last two are formed from the diacetyl derivative (CLII):



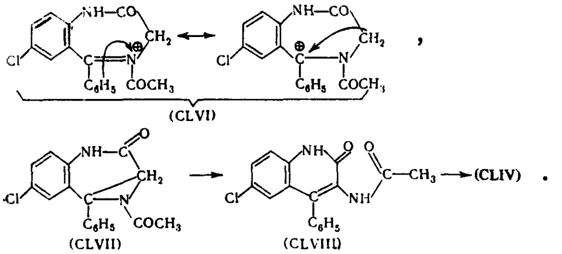
(CLI) (CLII)

The reaction of acetic anhydride with 7-chloro-1-methyl-5-phenyl-1,2-dihydro-3*H*-1,4-benzodiazepin-2-one (II) in the presence of sodium acetate leads to an intramolecular rearrangement with formation of 3-acetamido-6-chloro-1-methyl-4-phenyl-2-(1*H*)-quinolone (CLIII).[182] The corresponding 1,4-benzodiazepinone without the methyl group at the nitrogen atom rearranges under these conditions to the tricyclic compound (CLIV) and at the same time the seven-membered ring is cleaved with formation of compound (CLV):



(II) (CLIII) (CLIV) (CLV)

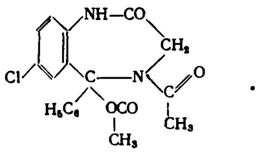
The formation of compound (CLIV) can be accounted for as follows. The mesomeric acetylated ion (CLVI), formed when acetic anhydride reacts with compound (XXXVI) via the unstable intermediate (CLVII), is converted into acetamidoquinolone (CLVIII), which is cyclodehydrated under the reaction conditions to compound (CLIV):



(CLVI)

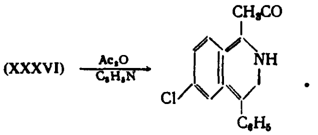
(CLVII) (CLVIII)

The formation of compound (CLIII) from (II) can be explained similarly. The second intermediate (CLIX) is postulated to account for the formation of compound (CLV) and the mesomeric acetylated ion (CLVI):



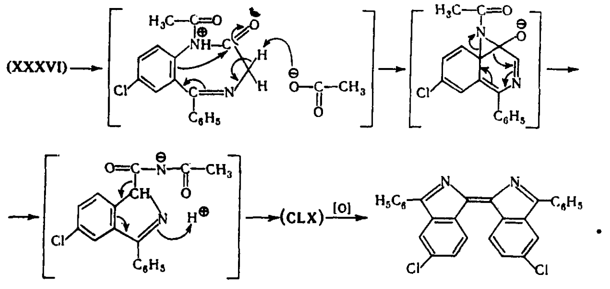
(CLIX)

When acted upon by acetic anhydride in the presence of pyridine, compounds of type (XXXVI) are converted into isoindole derivatives (CLX):[183]



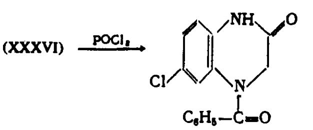
(CLX)

It is suggested that this reaction also proceeds via a stage involving the formation of an acetylated ion:



A certain amount of the "dimer" is formed as a result of the oxidative dimerisation of the isoindole.

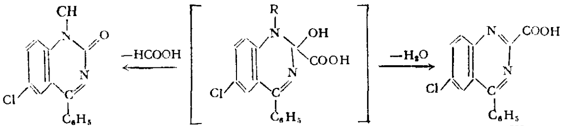
1-Alkyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-ones also rearranges to isoindoles when acted upon by bases in an anhydrous medium[184]. When compounds (XXVIII) are treated with phosphorus oxychloride or *p*-toluenesulphonyl chloride, a rearrangement of the Beckmann type takes place with formation of 4-benzoyl-6-chloro-3,4-dihydro-1*H*-quinoxalin-2-one:[185]



¶ The mechanism of the rearrangement has been discussed in a number of papers (see, for example, Refs. 179 and 180).

1,2-Dihydro-3*H*-1,4-benzodiazepine-2,3-diones rearrange to the quinozoline derivatives in the presence of acids[165].

It is suggested that the rearrangement of compound (CXXX) in the presence of acids takes place with participation of an intermediate (CLXI), which splits off formic acid (R = CH_3) or water (R = H) and gives 6-chloro-1-methyl-4-phenyl-1,2-dihydroquinazolin-2-one (CLXII) or 6-chloro-4-phenylquinazolinecarboxylic acid (CLXIII) respectively:

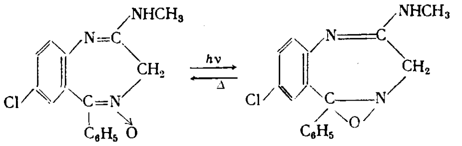


(CLXII) (CLXI) (CLXIII) ,

where R = CH_3 or H.

When 1,2-dihydro-5*H*-1,4-benzodiazepin-2-ones are acted upon by bases (alkalis, alkoxides, or triethylamine), they isomerise to 1,2-dihydro-3*H*-1,4-benzodiazepin-2-ones[50].

The photoisomerisation of 1,4-benzodiazepines has been described[186]. When a dilute solution of compound (I) in isopropyl alcohol is illuminated, the two absorption maxima in the ultraviolet spectra at λ_{max} = 245 and 265 nm characteristic of the substance disappear and are replaced by a band with a lower intensity at λ_{max} = 278 nm. It is suggested that this involves the formation of an epoxide, as happens in the conversion of nitrones into oxaziridines[187,188]:



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V. APPLICATIONS OF 1,4-BENZODIAZEPINES

The development of the chemistry of 1,4-benzodiazepine systems is in many ways due to their practical applications. We may recall that the first studies by Sternbach of compounds of this class were undertaken to find substances acting on the central nervous system. The first preparation of this class—Chlordiazepoxide (Librium or Elenium) (I)—already proved to be an unusually effective tranquiliser[189]. Apart from this effect, compound (I) exhibits a muscle relaxing and anticonvulsive activity.

The tranquilising action of 1,4-benzodiazepines is not only accompanied by the inhibition of the central nervous system but there is at the same time a stimulating effect. All these factors led to the isolation of 1,4-benzodiazepines as a new important group of psychotropic preparations—minor tranquilisers.

All derivatives of the Chlordiazepoxide type, i.e. 4-oxides of 3*H*-1,4-benzodiazepine, and also 1,2-dihydro-3*H*-1,4-benzodiazepin-2-ones exhibit an effect on the central nervous system similar to that of Librium. The presence or absence of basic groups in the 2-position of the ring and also of the amine oxide group does not involve a loss of psychopharmacological activity[4].

Probably the 1,4-benzodiazepine ring itself and possibly also its conformation play the most significant role in physiological activity[190].

As effective tranquilisers, 1,4-benzodiazepines have found wide application in the treatment of epilepsy, alcoholism[191], various psychological disorders[4], and tetanus; their use before and after operations as sedatives has been indicated. Among the widely employed preparations enumerated above, Valium (Diazepam), which gives excellent results in 50% of psychotic and 80% of psychoneurotic cases[192] may be particularly recommended. The latest published data suggest that the above effects are not optimal, since the study of this series of physiologically active substances has only just begun[193].

Unfortunately so far other applications of these preparations have been little investigated, although, in view of the presence of an interesting conjugated system in their molecules, they are not without interest for the chemistry of dyes and possibly also in other practical fields. Certain data on this problem have been published recently[194]: a series of cyanine dyes derived from 1,4-thiazepines, diazepines, and selenazepines have been obtained.

Probably 1,4-benzodiazepine derivatives are capable of giving rise to new possibilities in both theory and practice, which will be discovered in further investigations of this interesting group of substances[195].

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Mechnikov Odessa State
University

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Synthesis and Chemical Reactions of Metal-containing Macromolecules

S.L.Davydova, N.A.Plate, and V.A.Kargin (deceased)

The synthesis of polymers containing "non-organic" elements has been discussed in the literature, the most exhaustive monographs being those of Andrianov[1], Nametkin and coworkers[2], Gefter[3], and others. There have also been a large number of publications concerning the problem of the synthesis of polymers containing alkali metals, alkaline earth metals, heavy metals, and transition metals.

The present review deals with the most important studies on the synthesis and chemical reactions of metal-containing polymers of various types. Metal-containing polymeric compounds are understood as organometallic polymers with organic principal chains containing a direct carbon-metal bond (regardless of the type of metal), saltlike compounds, in particular those with macromolecule-oxygen-metal bonds, and also complex polymeric compounds containing, for example, coordinated atoms of 3*d* transition metals.

Wherever possible the reactivities of metal-containing molecules and their low-molecular-weight analogues have been compared. The review mentions unsuccessful attempts to prepare metal-containing macromolecules and their reaction products[4]; the studies where the formation of these compounds was inferred only from the change in the colour of the reaction mixture[5] and also those where the possibility of metallation was admitted merely in principle[6] are not included.

In the preceding review on the synthesis of metal-containing polymers[7], the problems of their reactivity were hardly dealt with owing to the lack of sufficient factual data at the time.

The bibliography includes 111 references.

CONTENTS

I. INTRODUCTION

Metal-containing polymers as well as low-molecular-weight organometallic and complex compounds are interesting primarily from the standpoint of the reactivity of the bond formed by the metal. The bonds between the metal and the polymer chain may be of fundamentally different types. Covalent polymer–metal bonds are extremely reactive and this has been used in many chemical reactions involving macromolecules.

Coordinate bonds of the type $C-O-M \leftarrow O$, $C-O-M \leftarrow N$, etc. are particularly interesting, since they are formed in many of the most important biochemical systems. The nature of bonds of this kind changes significantly as a function of the metal and the ligand coordinated to it; the coordination centres are as a rule quasiaromatic systems.

The saltlike metal–polymer bond, for example $C-O-M$ or $CO-O-M$, is widely used in ion exchange; many publications have dealt with metal-containing polymers of this type[8] and therefore we shall not consider them in detail.

Dative polymer–metal π interaction is assumed, for example, for copper(I), silver(I), and gold(I) acetylides in which electrons are transferred from the bonding π_n acetylene orbitals to the *d* orbitals of the metal and from the latter to the unoccupied antibonding π_g orbitals of acetylene; a recent review by Sladkov and Ukhin[9] dealt with this problem.

Depending on the nature of the polymer–metal bond, various applications of metal-containing compounds are possible.

When a fairly stable bond (for example a saltlike bond) is formed by the metal with polymers, the latter may be used and have been used to detect and separate traces of metal ions and to separate ions quantitatively to achieve a high degree of purification of water and organic solvents. Here we have the entirely realistic problem of the application of salt forming polymers for medical and agricultural purposes associated with the introduction and elimination of metals from organisms.

When a reactive metal–polymer bond is formed, as happens in true organometallic compounds, the polymers may be used as catalytic systems for chemical reactions of different kinds. One of the most important fields in the modern physical chemistry of polymers is concerned with the search for macromolecular catalysts and the study of the mechanism of their action. The long-chain structure of the molecule containing in the chain active centres capable of interacting with one another, with the additional possibility of altering the shape of the molecule sorbing selectively particular reactants, makes polymer catalysis noteworthy not only from the theoretical (simulation of biocatalysis) but also from the practical standpoint of the achievement of particular oxidation–reduction, polymerisation, hydrolytic, etc. reactions. Effective catalysts of this type may be both organometallic polymers and complex polymeric compounds obtained by the coordination of variable-valence metal ions to polymeric ligands of a wide variety of types.

Recently polymeric substances have been employed with increasing frequency in medical practice and therefore increasing attention has been devoted to the problems of the synthesis and investigation of new polymeric systems with physiological activity and a set of properties necessary for their employment in medical practice (blood substitutes, oxygen-transferring agents, medicinal preparations, materials for artificial internal organs). In their theoretical aspect, the studies on macromolecular compounds are coming into increasingly close association with the investigation of biopolymers and the simulation of biological systems, where complex-forming polymers as model systems are already of particular interest.

II. ORGANOMETALLIC POLYMERS DERIVED FROM GROUP I, II, AND III METALS. THE USE OF LITHIUM-CONTAINING POLYMERS FOR THE INITIATION OF POLYMERISATION AND THE PREPARATION OF POLYFUNCTIONAL POLYMERS

Recently most attention has been devoted to the study of the chemical reactions of macromolecules of two types: containing alkali metals (mainly lithium) and heavy metals (mainly tin). This can be understood if one remembers the wide range of reactions of which low-molecular-weight organolithium compounds are capable, on the one hand, and also the great interest in low-molecular-weight organotin compounds as stabilisers for a wide range of polymers, antiseptics, etc., on the other.

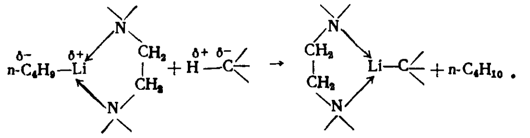
Among all the possible syntheses of organometallic polymers derived from Group I, II, and III metals, the following may be employed: (1) direct replacement of a hydrogen atom for a metal atom, for example by metallic lithium[10] ($RH + Li \rightarrow RLi + H$); (2) metallation consisting in the reaction of a metal, for example lithium, with a halogeno-derivative of the polymer[11] ($RX + 2Li \rightarrow RLi, LiX$); (3) metallation of polymeric hydrocarbons by lithium alkyls[12] ($RH + R'Li \rightarrow RLi + R'H$); (4) exchange reaction between a low-molecular-weight organolithium compound, for example $N\text{-}C_4H_9Li$, or C_6H_5Li, and a halogeno-derivative of the polymer[13] ($RX + R'Li \rightarrow RLi + R'X$); (5) addition of the metal hydride to a double bond of the polymeric hydrocarbon[5].

The first reaction has not been achieved for polyolefins owing to the lack of sufficiently reactive C–H bonds (the energies of the $-\overset{|}{\underset{|}{C}}-H$ bonds in polyethylene and in polypropylene are 128 and 80 kcal mole^{-1} respectively).

The use of the second reaction for the introduction of lithium into polyolefins is also difficult for the following reasons: judging from the literature data[14], an increase of the yield of the organolithium compound containing the metal at a saturated secondary carbon atom may be expected only when the reaction temperature is reduced and this involves the necessity to carry out the reaction under heterogeneous conditions, since both components (the polymer and metallic lithium) are insoluble in the reaction medium at low temperatures.

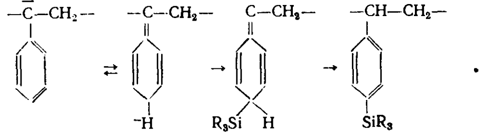
In order to introduce the metal into aryl-containing polymers by the third method, the authors of the review, Yampol'skaya, and Okhlobystin employed the reaction of the complex of butyl-lithium with *NNN'N'*-tetramethylethylenediamine, which is familiar in the chemistry of low-molecular-weight compounds; the starting materials employed in this reaction were acetic polystyrene and aryl-containing polyolefins–copolymers of α-methylstyrene and α-methyl-*p*(*m*)-methylstyrene and propene[15].

The high reactivity of the complex of n-butyl-lithium with *NNN'N'*-tetramethylethylenediamine can be accounted for by the increase in the ionic character of the C–M bond owing to the vigorous solvation of the lithium atom. The metallation of aryl-containing polymers by hydrogen–metal exchange takes place as a result of nucleophilic attack by the anion of the complex on the benzene hydrogen (in styrene polymers and copolymers of α-methylstyrene and propene) or on the methyl group attached to the arene ring [for poly-*p*-methylstyrene and copolymers of α-methyl-*p*(*m*)-methylstyrene and propene]:



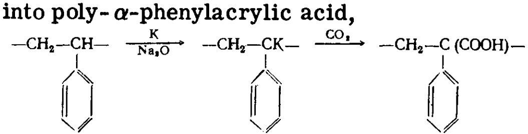
Although the formation of metal derivatives is in fact complicated by competing reactions, nevertheless the degree of metallation is quite sufficient for further reactions of such polymers with compounds containing the appropriate functional groups[16].

Chalk subsequently investigated the metallation of polystyrene by the butyl-lithium–*NNN'N'*-tetramethylethylenediamine complex[17] and compared it with the metallation of a low-molecular-weight model (toluene)[13] under the same conditions. With the aid of successive trimethylsilylation and treatment with dimethyl sulphate or D_2O, it was shown that, whereas toluene is substituted by lithium mainly in the side chain (up to 90.8%) and only slightly in the ring (the yields of derivatives substituted in the *meta-*, *para-*, and *ortho*-positions were 5.3, 1.8, and 2.0% respectively), polystyrene is substituted by lithium almost exclusively in the ring (20–25%) and only slightly in the chain (1–2%), regardless of the duration of the reaction; the substitution takes place to the extent of 80% in the *para*-position and to the extent of 20% in the ortho-position. The author proposes the following mechanism of such "anomalous" course of the reaction:



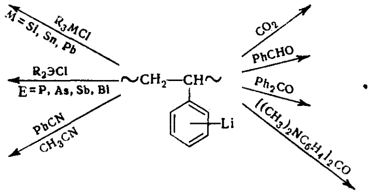
We believe that these results can be explained by the steric hindrance to the reaction in the benzyl-position of the polystyrene chain (see p. 1093).

Poly-α-potassiostyrene, which is subsequently converted into poly-α-phenylacrylic acid,



was obtained by Morton and Taylor[19] by the action of metallic potassium on polystyrene, but these data were not confirmed subsequently.

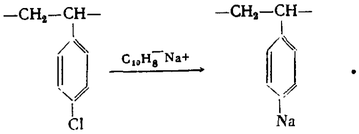
The fourth method has been most widely used for the metallation of polyhydrocarbons; here the principal investigations have been carried out by Braun and coworkers[7]. They discussed comprehensively the metallation of halogen-containing polymers in a number of publications[20–23]; they investigated a large number of reactions of polylithiostyrene:



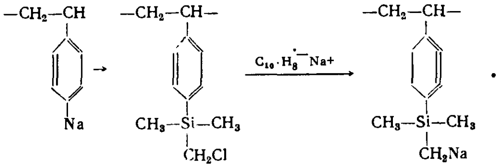
Apart from the reactions indicated in the above scheme, the reactions of poly-*p*-lithiostyrene with O_2, SO_2, nitroso- and nitro-compounds, phenyl isocyanate and thiocyanate, orthoformic ester, pyridine, dimethylformamide, etc. have been described. Braun also obtained an insoluble lithium-substituted polystyrene starting with a cross-linked (degree of cross-linking 2%) polymer of iodostyrene and styrene with a high content of the latter. Then he replaced lithium by residues of nicotine, comphor, camphorsulphonic acid, and other organic groups[21], as well as groups containing "non-organic" elements[22]; by allowing the copolymer to react with sulphur powder, he obtained mercaptopolystyrene[23]. Thus the chemical reactions of lithium-substituted polystyrene made it possible to introduce virtually any functional group into polystyrene. It has been noted that in the reaction of butyl-lithium with iodinated polystyrene, the order of addition of the reactants is very important (polymer to a solution of the organometallic compound and not vice versa) in order to prevent the cross-linking of the chains[21].

Lithium derivatives of polystyrene have also been obtained by Leavitt and Matternas[24] by the metallation of poly-*o*- or poly-*p*-bromostyrene; to suppress the Wurtz–Fittig reactions, the metallation was carried out at a high concentration of butyl-lithium and a low temperature (−35°); subsequently the lithium-substituted polystyrene was substituted by tin with the aid of R_3SnCl.

Greber and coworkers[5] carried out a series of studies on the metallation of halogen-containing polymers (for poly-*p*-chlorostyrene and its copolymer with styrene) by sodionaphthalene in tetrahydrofuran or dimethoxyethane:

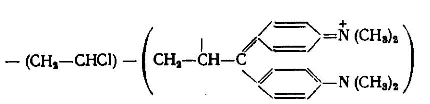


The authors employed the metallated polymers obtained as polymeric initiators of polymerisation or for the introduction of functional groups (for example the dimethylchloromethylsilyl group), which are in turn capable of undergoing further metallation:



By this type of metallation of poly(vinyl chloride), Greber prepared a polyhydrocarbon of unknown structure with a high content of cyclopropane groups. Fig. 1 shows that, in the metallation of poly-*p*-chlorostyrene, 2 g-atoms of sodium are consumed for each g-atom of chlorine; this implies that the Wurtz side reaction (interchain cross-linking) hardly occurs under these conditions[5].

Several attempts have been made to achieve the reaction of poly(vinyl chloride) or poly(vinyl bromide) with organometallic compounds such as diethylzinc[25], trityllithium and its analogues[26], and sodionaphthalene[26]. The reaction of poly(vinyl chloride) with butyl-lithium was investigated in greatest detail by Shiina and Minoura[6]. It leads to only partial metallation of the polymer, since in this case the competing reactions are as for halogenopolystyrenes, butylation and dehydrochlorination. The lithium-substituted fraction of poly(vinyl chloride) was employed in polymerisation initiated by CO_2, Michler's ketone, etc. For example the polymeric analogue of Malachite Green was obtained:



The authors note that the attempts to carry out the reaction of poly(vinyl chloride) with phenyl-lithium and sodionaphthalene were unsuccessful[6].

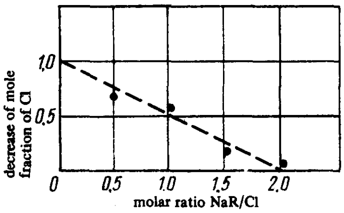
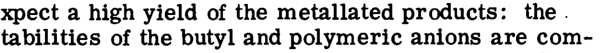


Figure 1. Metallation of poly-*p*-chlorostyrene (M = 78 000) with $NaC_{10}H_8$.

It has been found that the metallation of halogen-containing polymers, for example polychlorotrifluoroethylene, may be achieved by treatment with a solution of the given metal in liquid ammonia; lithium, sodium, calcium, barium, and magnesium have been used[27]. The introduction of sodium may be achieved also with the aid of a solution of sodionaphthalene in dimethoxyethane[28]. Examination under the electron microscope of a polymer film after its immersion for 2–3 s in the metallating solution shows that the metallating component penetrates to a depth of 10^{-4} cm. Metallation of this kind increases the adhesion of adhesives to films of the above type.

The exchange reaction between a low-molecular-weight compounds RLi, for example n-butyl lithium or phenyllithium, and polymers were carried out by the authors of the review and Yampol'skaya[29] for halogeno-derivatives of polyolefins:

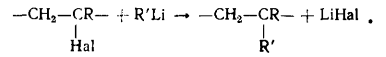


$$-\underset{\displaystyle Hal}{CH_2C}(R)-CH_2-CH(R)- + R'Li \rightleftarrows -CH_2-\underset{\displaystyle Li}{C}(R)-CH_2-CH(R)- + R'Hal\,,$$

where R = H or CH_3 and R′ = n-C_4H_9 or C_6H_5.

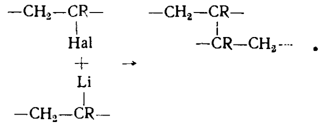
Chlorinated and brominated polyethylene and chlorinated polypropylene were employed as halogen-containing polyolefins. The reaction involving the substitution of a halogen by lithium is reversible; its equilibrium position is determined by the relative stabilities of the corresponding carbanions. Therefore in the reaction of halogenopolyolefins with n-butyl- and phenyl-lithium one cannot expect a high yield of the metallated products: the stabilities of the butyl and polymeric anions are comparable and the phenyl anion is actually more stable than the polymeric anion. Indeed the amount of lithium in the polymeric molecule, determined by direct titration, proved to be low (lithium-substituted polyethylene containing 0.85% of lithium was obtained from chlorinated polyethylene containing 24.5% of chlorine, i.e. only 22% of the chlorine present was replaced by lithium). To increase the degree of metallation, it is necessary to employ an excess of the organolithium compound; moreover, the rate of reaction increases in the presence of highly solvating solvents, for example tetrahydrofuran (THF).

Being reversible, the reaction is complicated by the competing process involving the nucleophillic substitution of the halogen by the group R′ of the organolithium compound:

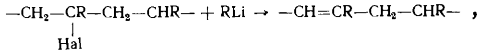


$$-CH_2-\underset{Hal}{CR}- + R'Li \rightarrow -CH_2-\underset{R'}{CR}- + LiHal\ .$$

The side condensation reaction can also lead to the formation of cross-linked products of the following type:



As a result of second side reaction, dehydrochlorination under the influence of the nucleophillic organometallic compound:



$$-CH_2-\underset{Hal}{CR}-CH_2-CHR- + RLi \rightarrow -CH=CR-CH_2-CHR-\ ,$$

double bonds appear in the chlorinated polyethylene. The degree of metallation of brominated polyethylene by n-butyl-lithium is very insignificant; dehydrobromination is the dominant reaction in this case.

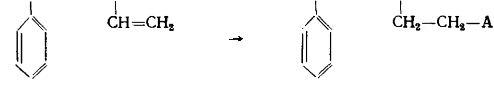
The reaction of chlorinated polypropylene is more unambiguous—when treated with phenyl- and n-butyl-lithium, it undergoes only condensation and dehydrochlorination reactions. This is in fact understandable, since an increase in the mobility of the chlorine atom at the tertiary carbon atom in the chlorinated polypropylene molecule leads to an increase of the proportion of dehydrohalogenation at the expense of metallation.

As mentioned previously (see, p. 1084), lithium-containing polymers react with various organic compounds such as dialkyl(aryl)chlorophosphines, trialkyl(aryl)chlorosilanes, trialkyl(aryl)chlorostannanes, carbonyl compounds, etc., with formation of the corresponding derivatives[30].

The high reactivity of metallated polyethylene and the copolymers of polyethylene and polypropylene with styrene permitted their application as polymeric initiators in the ananionic polymerisation of many monomers; methyl methacrylate, acrylonitrile, isoprene, and styrene. As a result of this reaction, copolymers with polyolefinic main chains and side chains comprising units of the grafted comonomers were obtained; the reaction is complicated by the homopolymerisation of the monomers by the excess n-butyl-lithium[31].

The hydrometallation of polyhydrocarbons and their derivatives was in fact achieved in the 1950's when Morton and coworkers[32] showed that alfin catalysts can cause, apart from the polymerisation of dienes, a side reaction involving the metallation of the macromolecule formed.

This method of metallation of polymers has been achieved by the addition of, for example, organoaluminium hydrides to unsaturated polymers, in particular a copolymer of styrene and butadiene[33]:



and enabled Greber and coworkers[33] to prepare a series of aluminium-containing polymers; the metallation kinetics (bromometry) are presented in Fig. 2.[33]

The same workers[34] demonstrated the intermediate formation also of another kind of metallated polymer—with a C=N–M bond, for example:

$$-CH_2-\underset{C\equiv N}{CH}- \xrightarrow{+RMgCl} -CH_2-\underset{RC=N-MgCl}{CH}-\ ,$$

by the reaction of lithium alkyls or alkyl(aryl)magnesium halides with copolymers containing nitrile groups (acrylonitrile-styrene).

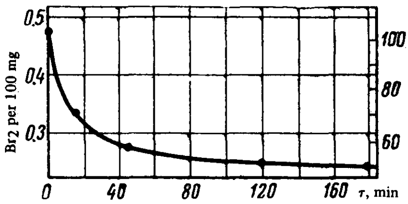
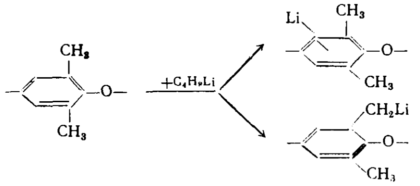


Figure 2. Decrease with time of the degree of unsaturation of the butadiene-styrene copolymer during metallation.

Greber employed metallated aluminium-containing polymers as macromolecular Ziegler catalysts (in a mixture with transition metal chlorides: $TiCl_4$, $TiCl_3$, $VOCl_2$, etc.).[35]

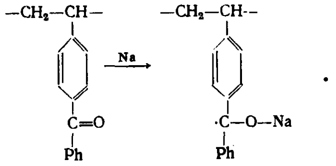
Hulot et al.[36], who repeated and revised Greber's data, investigated the interaction of unsaturated polymers (a styrene-butadiene copolymer and polyisopropene) with dibutylaluminium hydride and titanium tetrachloride as a function of the reaction conditions (effect of the order of addition and the relative amounts of the reactants and also temperature). They showed that a soluble and homogeneous polymeric catalyst of the Ziegler type is obtained only following the exhaustive metallation of the polyhydrocarbon by dialkylaluminium hydride at 130°C and subsequent reaction with titanium tetrachloride. The polymeric initiator thus obtained was used in the polymerisation of ethylene; graft copolymers containing 80% of the styrene-butadiene copolymer and 20% of the grafted monomer were also synthesised.

Chalk and Hay[37] achieved the metallation of polymers containing oxygen, namely substituted polyphenylene oxide; they employed poly-2,6-dimethyl-1,4-phenyl ether:



With the aid of butyl-lithium, both the ring (about 20%) and the alkyl group (about 80%) are metallated. The mode of metallation depends on the duration and temperature of the reaction. The authors believe that the use of potassio- and sodio-derivatives for this purpose leads to the preferential metallation of the alkyl substituents (demonstrated by trimethylsilylation). The authors believe that the initial stage of the process is ring-metallation, assuming that this stage is accompanied by the migration of the substituent to the benzyl position.

Other oxygen-containing metallated polymers (polymeric metal ketyls) were described by Braun and Löflund[38]. They were prepared by treating poly-*p*-vinylbenzophenone with sodium powder; the solutions of sodiopoly-*p*-vinylbenzophenone were employed as polymeric initiators of the radical polymerisation of vinyl monomers, for example acrylonitrile[38]:



The type of reaction between inorganic salts and polymeric epoxyethane is not entirely clear, although it can be classified as an interaction between a metal and an oxygen-containing polymer[39]. The proof of the occurrence of such interaction is the appreciable lowering of the degree of crystallinity of the polymer in the presence of 10–30% KI (the two substances being completely compatible) (Fig. 3) quoted by the authors.

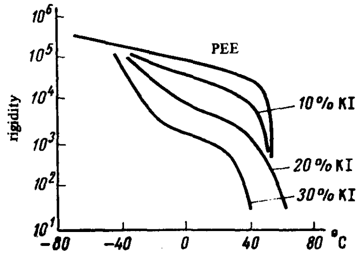
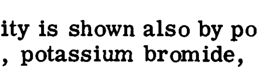


Figure 3. Dependence of the modulus of rigidity on KI content in polyepoxyethane (PEE).

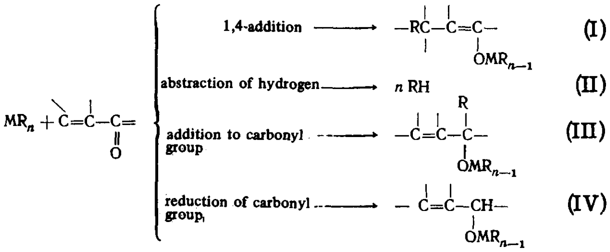
The finding that in the adduct investigated there is one salt molecule for nine polymer units suggests that ion-dipole interaction takes place but it is not clear which ion is directly linked to the chain:



$$-CH_2-CH_2-\underset{KI^-}{\overset{+}{O}}-CH_2-CH_2- \; .$$

A similar capacity is shown also by potassium fluoride, potassium chloride, potassium bromide, rubidium fluoride, and rubidium iodide, but not lithium chloride and lithium bromide; probably other polyethers, for example polyoxypropylene, are also capable of undergoing reactions of this kind[39].

An interesting mechanism for the reaction between organometallic compounds and ketones (at a low-molecular-weight level) has been put forward by Tsuruta and coworkers[40]. The reactions of a large number of organometallic compounds (RLi, RMgX, AlR_3, ZnR_2, $CaZnR_4$) with $\alpha\beta$-conjugated ketones such as phenyl vinyl (and also isopropenyl, β-styryl, isopropylidene, and benzylidene) ketone and methyl phenyl ketone have been investigated. It was found that, when $(C_4H_9)_2Zn$ and $(n\text{-}C_4H_9)_3Al$ are used, the principal stages are 1,4-addition and abstraction of hydrogen; other possible reactions (reduction of the carbonyl group, addition to the carbonyl group) take place to a lesser extent:



The contributions of the reactions (calculated from the amount of hydrocarbon produced by a particular mechanism) depend markedly on the nature of the organometallic compound:

Organometallic compound	Reaction (I)	Reaction (II)	Reaction (III)	Organometallic compound	Reaction (I)	Reaction (II)	Reaction (III)
RLi	1	1	1	ZnR_2	1	2	—
RMgX	1	1	1	$CaZnR_4$	1	2	—
AlR_3	1	3	—				

Metallation reactions of a similar type can undoubtedly be carried out also at a macromolecular level.

In conclusion of the section, we may point to another class of polymetallated oxygen-containing polymers, namely metal-containing derivatives of cellulose. Its alkoxides, not containing an excess of the alkali metal, are obtained by treatment with sodium in ammonia[41] or by an exchange reaction with sodium alkoxide[42]; however, the mechanism of the reaction of cellulose with metals leading to the formation of metal-containing derivatives in solutions of the complexes of these metals has not as yet been adequately elucidated. Cellulose metallated in this way is highly reactive in alkylation, etherification, and other reactions[42].

One may conclude that the reactivity of polymeric organometallic compounds is on the whole lower than that of their low-molecular-weight analogues. This is probably due to the great scope for the delocalisation of the charge in the polymeric cryptocarbanion (see p. 1092) and also the factors complicating the reactions and specific to polymers, which have been discussed on p. 1092.

III. ORGANOMETALLIC POLYMERS DERIVED FROM HEAVY METALS. METALLATED POLYMERS AND STABILISATION

The introduction of heavy metals such as mercury, thallium, tin, or lead into polymers has been mentioned in the literature from 1957†. The introduction of mercury into polymers was investigated in fair detail by Smirnov[43] and later by Traylor[44], who mercuated polystyrene with mercury(II) acetate; mercury-containing polymers have been obtained by the action of mercury(II) butyrate on polystyrene and poly-α-vinylthiophen[45]. The substitution of polystyrene and poly-α-vinylthiophen by thallium(III) isobutyrate takes place similarly to mercuration[46]. The substitution of cellulose derivatives by mercury and thallium has been investigated by Rogovin and coworkers[47];

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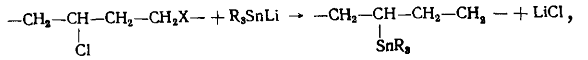
†We shall not consider the phenomenon of association, which is well known in the chemistry of organometallic compounds of the type $[R_xM]_n$.

recently they obtained the corresponding tin and lead derivatives[48].

The sulphonated copolymers of styrene and divinylbenzene have been mercurated with mercury(II) perchlorate[49]. Polymers and copolymers of butadiene are oxymercurated by mercury(II) acetate at the double bond and also in the allyl position[50]. The reactivity of the mercurated specimens was investigated in acylation by acetyl chloride and benzenesulphonyl chloride.

In order to modify chlorinated polyethylene and poly(vinyl chloride), the authors of the review and Purinson[51] introduced organotin groups, having developed special methods for the synthesis of such tin-substituted polymers. Dimetallic mixed organic derivatives of lithium and tin, capable of reacting with chlorine atoms, for example triphenylstannyllithium or tributyl stannyllithium, were chosen for the introduction of R_3Sn groups into polymeric molecules:



$$-\mathrm{CH_2}-\underset{\mathrm{Cl}}{\mathrm{CH}}-\mathrm{CH_2}-\mathrm{CH_2X}- + \mathrm{R_3SnLi} \rightarrow -\mathrm{CH_2}-\underset{\mathrm{SnR_3}}{\mathrm{CH}}-\mathrm{CH_2}-\mathrm{CH_2}- + \mathrm{LiCl}, \qquad (\mathrm{I})$$

where X = H or Cl and R = C_6H_5 or n-C_4H_9.

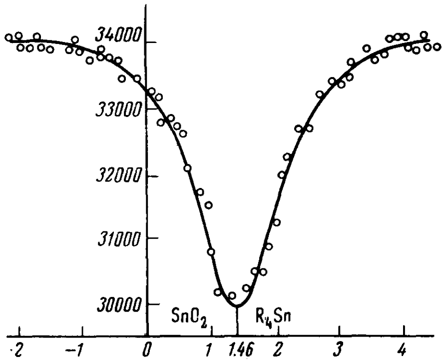
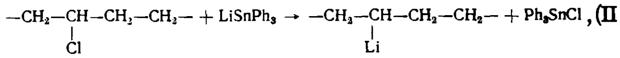


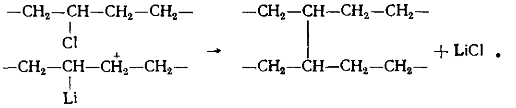
Figure 4. Mössbauer spectrum of triphenylstannated chloropolyethylene.

The structure of triphenylstannylated chloropolyethylene was confirmed by Mössbauer (gamma-resonance) absorption spectroscopy without recoil[52]. The isomeric shifts relative to SnO_4 in the Mössbauer spectra of the stannated polymers correspond to compounds of the type R_4Sn (Fig. 4). The stannation reaction via mechanism (I) is accompanied by a reaction in which lithium is introduced into chloropolyethylene by triphenylstannyllithium:



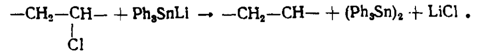
$$-\mathrm{CH_2}-\underset{\mathrm{Cl}}{\mathrm{CH}}-\mathrm{CH_2}-\mathrm{CH_2}- + \mathrm{LiSnPh_3} \rightarrow -\mathrm{CH_2}-\underset{\mathrm{Li}}{\mathrm{CH}}-\mathrm{CH_2}-\mathrm{CH_2}- + \mathrm{Ph_3SnCl}, \qquad (\mathrm{II})$$

which results in the formation of an insoluble fraction via the interaction of the lithium-substituted chloropolyethylene with the initial chloropolyethylene:



$$\begin{array}{c} -\mathrm{CH_2}-\underset{\mathrm{Cl}}{\mathrm{CH}}-\mathrm{CH_2}-\mathrm{CH_2}- \\ + \\ -\mathrm{CH_2}-\underset{\mathrm{Li}}{\mathrm{CH}}-\mathrm{CH_2}-\mathrm{CH_2}- \end{array} \rightarrow \begin{array}{c} -\mathrm{CH_2}-\mathrm{CH}-\mathrm{CH_2}-\mathrm{CH_2}- \\ | \\ -\mathrm{CH_2}-\mathrm{CH}-\mathrm{CH_2}-\mathrm{CH_2}- \end{array} + \mathrm{LiCl}\,. \qquad (\mathrm{III})$$

We may note that cross-linking can also occur via the formation of macroradicals without the intermediate formation of the lithium-containing polymer:



$$-\mathrm{CH_2}-\underset{\mathrm{Cl}}{\mathrm{CH}}- + \mathrm{Ph_3SnLi} \rightarrow -\mathrm{CH_2}-\dot{\mathrm{C}}\mathrm{H}- + (\mathrm{Ph_3Sn})_2 + \mathrm{LiCl}\,. \qquad (\mathrm{IV})$$

Reactions (II), (III), and (IV), which compete with the triphenylstannation reaction (I), take place to a considerable degree in heptane (for chloropolyethylene) or in tetrahydrofuran [for poly(vinyl chloride)]; in such cases fully soluble stannated polymers are formed[52].

Among all the possible chemical reactions of stannated poly(vinyl chloride), its interaction with hydrogen chloride, simulating the mechanism of the stabilisation of poly(vinyl chloride) by organotin compounds, is of greatest interest. The reaction of triphenylstannylated poly(vinyl chloride) in tetrahydrofuran with dry hydrogen chloride supplied at a constant rate was investigated. The kinetics of the dehydrochlorination of various specimens of triphenylstannylpoly(vinyl chloride) are presented in Fig. 5. The rate of dehydrochlorination was determined from the change in the amount of chloride ions bound by the polymer (curve *1*) and from the content of chloride ions in the gaseous reaction products absorbed by water (curve *2*). The dearylation of polymeric organotin compounds has also been investigated by the nuclear gamma-resonance method[30].

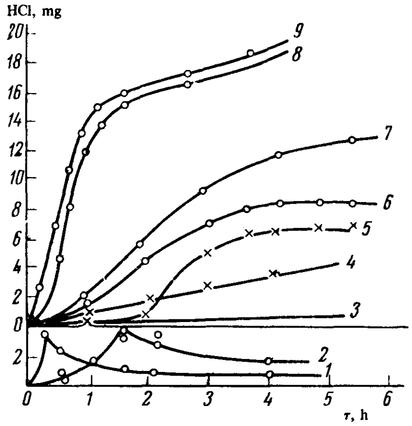
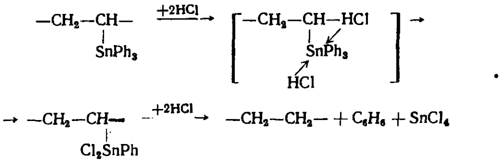


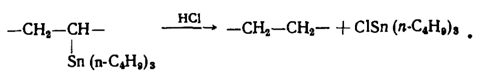
Figure 5. Kinetics of the dehydrochlorination of triphenylstannylpoly(vinyl chloride) (SPVC): 1) 0.05 g of SPVC, bound HCl; 2) 0.05 g of SPVC, free HCl; 3) mixture of 0.05 g of SPVC and 1 g of PVC, bound HCl; 4) mixture of 0.05 g SPVC and 1 g of PVC, free HCl; 5) 0.05 g of SPVC, total HCl; 6) 0.05 g of PVC, free HCl; 7) mixture of 0.05 g of SPVC and 1 g of PVC, total HCl (experimental); 8) 1 g of PVC, free HCl; 9) mixture of 0.05 g of SPVC and 1 g of PVC, total HCl (calculated).

According to the mechanism adopted by the authors, substituents at the tin atom are not split off one by one but in pairs: initially the two phenyl groups and then the third phenyl group and the polymer chain together; the intermediate formation of a hexacoordinate complex with tin is postulated:



$$-CH_2-\underset{SnPh_3}{CH}- \xrightarrow{+2HCl} \left[\begin{array}{c}-CH_2-CH-HCl\\ SnPh_3\\ HCl\end{array}\right] \rightarrow -CH_2-\underset{Cl_2SnPh}{CH}- \xrightarrow{+2HCl} -CH_2-CH_2- + C_6H_6 + SnCl_4$$

However, the analogous reaction of tri-n-butylstannated poly(vinyl chloride) with dry hydrogen chloride takes place in virtually only one stage with formation of tri-n-butyltin chloride and polyethylene [52]:

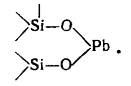


$$-CH_2-\underset{Sn(n\text{-}C_4H_9)_3}{CH}- \xrightarrow{HCl} -CH_2-CH_2- + ClSn(n\text{-}C_4H_9)_3 \,.$$

Since it is known that alkyl substituents are split off from the tin atom with greater difficulty than aryl substituents and the difficulty increases with increase in their chain length, it is understandable why phenyl groups are split off before the polymer chain, whereas in the case of butyl substituents such a sequence no longer holds. The overall study of the reactions of triphenyl and tri-n-butyltin derivatives of poly(vinyl chloride) with hydrogen chloride enabled the authors to make certain conclusions concerning the mechanism of the stabilisation of poly(vinyl chloride) by low-molecular-weight organotin compounds [30].

In conclusion of the section dealing with polymers metallated by heavy metals, the following point may be noted. There is no doubt that in the step involving the stabilisation of any polymer by compounds of heavy metals the latter are incorporated in the chain. Thus it was shown recently [53] that the basic lead sulphates $PbO.PbSO_4$, $3PbO.PbSO_4.H_2O$, and $4PbO.PbSO_4$ enter into complex formation reactions with the double bonds of poly(vinyl chloride), which appear in the latter on heating, and this leads to a weakening of the colour of the polymer owing to the breakdown of the double bond conjugation chain. It was noted that the introduction of various metal compounds into polymers, for example polyorganosiloxanes, significantly lowers the rate of their depolymerisation and decomposition. Therefore it was suggested that various metal compounds be introduced into polymer compositions; studies of this kind are listed in detail in a review by Balykova and Rode [54].

Thus Rafikov and coworkers [55] showed that the stabilising effects of titanium and iron acetylacetonates, alkoxyacetylacetonates, and also oxides on the thermal degradation of polydimethylsiloxane is due to their reaction with macromolecular chains, which leads to the formation of new high-molecular-weight compounds with metal atoms in the siloxane chain. Basic cerium acetylacetonate probably reacts with the terminal groups of the siloxane chains, forming new –Ce–O–Si– bonds [56]. The effect of many metals (metal oxides) on the thermal stability of polyalkylarylsiloxanes and their resistance to thermal oxidation has been demonstrated by Atkins et al. [57], who suggested that the treatment of the polymer with PbO leads to the formation of structures of the type



The interaction with salts, oxides, or alkoxides of metals of different Groups in the processing of polymers may be regarded as similar examples of the metallation of polymer chains: thus crystals, mainly of basic salts, insoluble in the rubber are formed in carboxylate rubbers obtained by the copolymerisation of butadiene with acrylic acids and in vulcanisation by divalent metal oxides or hydroxides [58]; the list of examples of this kind may be extended.

Whereas the polymeric derivatives of light metals can find application in the introduction into the chain of a wide variety of functional groups for the purpose of extensive chemical modification of polymers, polymeric derivatives of heavy metals are of course much less suitable for this. Therefore the number of studies on chemical reactions with participation of heavy metals is also significantly smaller. Almost all the investigations of polymer derivatives of heavy metals described in the literature deal mainly with problems of polymer stabilisation in one form or another.

IV. TRANSITION METAL COMPLEXES WITH MACROMOLECULAR LIGANDS

Two fundamentally different classes of macromolecular complexes are known [59]. Macromolecules the main chain of which contains the metal and fragments when the latter is eliminated may be obtained by the polycoordination of polyvalent ions to polydentate low-molecular-weight ligands. Regardless of the type of ligand, polymeric complexes of this kind are called polycoordination polymers; they have been extensively described by Marvell, Korshak, Vinogradova and coworkers, Baylar, Berlin, and others [60].

Macromolecules containing the metal in side chains can be prepared by the coordination of transition metal ions to macromolecular ligands already synthesised; in this case the metal can be readily removed or replaced by another without the breakdown of the main chain of the macromolecule. Polymeric complexes of this type, which will henceforth be referred to as complexes with macromolecular ligands, include in fact also the ion-exchange resins capable of the formation of chelates; the latter were investigated by Sansoni, Hering, and others [61].

In principle, all the complexes with macromolecular ligands discussed in the literature were obtained by the reaction of the complex-forming groups of the macromolecule with metal ions [59]. The few investigations in which a complex in the finished form, for example an acid metal-complex dye, are introduced into a poly(vinyl alcohol) [62] or Wofatit matrix [63], are an exception.

The reactivity of complexes with macromolecular ligands of various types is determined by the fact that both the metal–ligand bonds and the polymeric ligands can take part in chemical reactions.

1. Reactions with Participation of the Metal–Ligand Bond

The reactivity of the metal–macromolecular ligand coordinate bond is shown in the catalysis of a number of organic and inorganic reactions, in its participation in the so called ligand exchange reactions, and also redox reactions with participation of complexes having macromolecular ligands.

Usually the problem of the effect of the ligand on the reactivity of the M–L bond is treated as the effect of the coordination with the ligand on the catalytic activity of M^{n+}. The nature of the ligand is known to have a significant influence on the catalytic properties of the metal ions; a particularly marked influence is observed for enzymes and their models [64]. The nature of the ligand can influence not only the reactivity of the metal-containing catalyst but also the mode of the reaction catalysed[65]. An explanation of the causes of the effect of the ligand on the catalytic properties of the complexes, including polymeric complexes, should be sought in the effect of several factors. The nature of the M–L bonds affects the donor–acceptor properties of the metal ion: an increase in the amount of ionic character of this bond entails an increase in the electron-accepting and a decrease in the electron-donating capacity of the metal; the formation of dative $M \rightarrow L$ bonds increases the charge of M, increasing thereby its electron-accepting capacity. It may be that in some cases ligands participate in the catalytic process itself. Thus in oxidation–reduction reactions there is a possibility of electron transfer via a ligand bridge; in some cases the coordinated ligands may form hydrogen bonds with the solvent, influencing thereby the mutual orientation of the reactants[65].

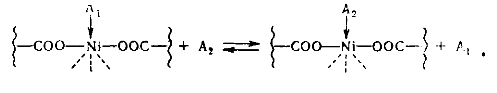
An attempt was made to employ complexes with ion exchangers (for example, resins based on polystyrene) containing iminodiacetic acid groups[66] as heterogeneous catalysts. The authors think that the advantages of using polymeric complexes for catalysis compared with low-molecular-weight complexes consist in the ease of separation of the catalyst from the reaction medium and, what is more important, in the fact that during the catalytic reaction very low but constant concentrations of metal ions in equilibrium with the polymeric complex are established:

$$\sim[fM] \rightleftarrows \sim[f^{n-}] + [M^{n+}]\ .$$

A review has already been devoted to the problem of using macromolecular complexes as heterogeneous catalysts for chemical reactions[67]. On the whole, one may conclude that, although certain macromolecular complexes do in fact show an enhanced catalytic activity compared with their low-molecular-weight analogues, nevertheless the employment of heterogeneous catalysts of this type is greatly impeded by diffusion phenomena, the inhomogeneity of the composition of the ligand, the non-uniform content of the metal, and similar factors complicating the study of the process.

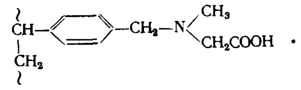
The capacity of such complexes to exchange ligands, which is based on the use of coordination vacancies in the transition metal incompletely saturated by the polymeric ligand, may be regarded as one of the effects of the reactivity of the metal–macromolecule coordinate bond.

Helfferich[68] was virtually the first to use for ligand exchange acidic cation exchangers in the nickel-form. Subsequently Latterel and Walton[69] showed that the nickel-forms of ion exchangers with carboxylic acid residues may be employed to separate many amines (A_1 and A_2):



Siegel and Degens[70] isolated aminoacids from their mixtures with the aid of sorption–desorption on the copper chelate complex of Chelex 100,[100] which consists of a polystyrene matrix with iminodiacetic acid groups. They also examined the reactivity of the Fe^{3+}-, Co^{2+}-, Ni^{2+}-, and Zn^{2+}-forms of Chelex 100 in relation to the sorption of amines, phenols, and also purine and pyrimidine bases, unsaturated hydrocarbons, sugars, peptides, humic acids, and other interesting natural compounds.

Hering and Heilmann[71] separated quantitatively glycine and β-alanine on poly-*N*-(*p*-vinylbenzyl)-*N*-methylaminoacetic acid in the nickel- and copper-forms (other metals were also employed):



Rogozhin and Davankov[72] obtained dissymetric complex forming ion-exchange sorbents of similar structure with optically active α-aminoacid groups. In many cases it proved possible to achieve a quantitative separation of the optical isomers by the chromatography of the ligands on these sorbents in the presence of complex-forming metal ions. Since their separation is based on stereoselective effects in the complex formation process, this method is an example of a new principle of the cleavage of racemates[72]. The sequence in which the ligands emerge from the chromatographic column is directly related to the stability of the complexes formed by them with participation of the stationary polymeric ligand. Therefore chromatography of the ligands may be employed in the study of the kinetics of labile mixed complexes[73].

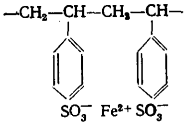
We shall consider in greater detail how the reactivity of complexes with macromolecular ligands is reflected in their redox properties. All metal-containing redox polymers are obtained by combining a polymeric matrix with specific substances capable of oxidation and reduction. Three main classes of such compounds are distinguished[61], the coupling of which to the matrix involves (1) the formation of covalent bonds and is thus essentially irreversible, (2) the coupling is to some extent reversible and can involve some form of complex formation, (3) the substance being an oxidising or a reducing agent is linked to the polymeric matrix by adsorption forces, via the formation of clathrate compounds, etc. Since in the last class of compounds the metal atoms are linked to the polymer chain by forces weaker than those of covalent or coordinate bonds, we shall consider only the first two classes of metal-containing redox polymers.

By combining ferrocene with diazotised poly-*p*-aminostyrene, Sansoni and Sigmund[74] obtained a polymer the apparent normal potential of which is 0.415 V and the redox capacity is 5.4 mequiv. g^{-1}. Fe^{II} and Fe^{III} polyvinylferrocenes have been reported[75]. Arimoto and Haven[76] oxidised the polymer (molecular weight of the order of 50 000) by suspending it in a solution of cerium sulphate, the polymer being gradually converted into a water-soluble pale blue Fe^{III} form, which can be reduced by any reducing agent to an insoluble yellow form containing iron(II). Partially sulphonated polyvinylferrocene is soluble in water and may be oxidised but the sulphonated molecule is unstable in the oxidised state and rapidly loses iron ions. Sansoni and Sigmund's ferrocene polymers[74] constitute essentially an example of the irreversible binding of a molecule with redox properties to a polymer already synthesised.

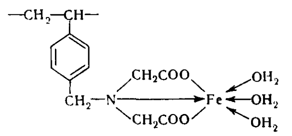
Examples of the formation of polycoordination compounds with the aim of synthesising redox polymers having reversible properties may be found in studies in which ion-exchange resins were saturated by inorganic cations. Thus Sansoni[74] also obtained oxidation–reduction cation exchangers by saturating Amberlite IR-120, Dowex-50, and Wofatit by the following redox systems: Fe^{2+}/Fe^{3+}, Sn^{2+}/Sn^{4+}, Ce^{3+}/Ce^{4+}, and Ti^{3+}/Ti^{4+}. Mills and Dickenson treated Duolite A-3 with a solution of copper sulphate until the resin became completely saturated and then with an excess of sodium hydrosulphite until the complete reduction of copper ions to the metal.

Similarly silver ions on Duolite A-2 resin were reduced by the same reagent to metallic silver; after such treatment the resin reacts with oxygen and eliminates it from liquid media[77].

M^n/M^{n+1} redox systems fixed in a suitable manner in a macromolecular matrix (the so called redoxites) or linked ionogenically to the ion-exchange resin (the so called redox ion exchangers) are of significant interest for preparative and analytical chemistry, since, when they are employed, the reduced (oxidised) substances are not contaminated by the reduction product of the reducing (oxidising) agent. The industrial application of systems of this kind was hindered for a long time by the fact that the usual reducing agents (Fe^{2+}, Sn^{2+}, and others) do not exhibit a high reducing capacity on ion-exchange resins. Hering[78] was the first to use for complex formation at a polymeric level the principle, familiar from inorganic chemistry, of a change in the redox potential of the metal ion following the addition of complex-forming agents or following a change in the pH (which in most cases is also explained by the formation of complexes with hydroxide ions). The formation of complexes of macromolecular ligands with metal ions can result in the formation of both reducing and oxidising agents, the reactivity of which greatly exceeds that of the free metal ions. We may quote a specific example of a change in the normal redox potential of the Fe^{2+}/Fe^{3+} system when it is combined with a resin containing iminodiacetic acid groups. According to Hering[78], the reducing capacity of Fe^{2+} increases markedly when the iron ions are not fixed on strongly acidic cation exchangers, which are capable of binding Fe^{2+} only in the ionic form, such as, for example,



but on resins of the type of Dowex-A-1 or Dowex-50W which are capable of complex formation:



The Fe^{2+}/Fe^{3+} oxidation–reduction system, the normal potential of which is +0.78 V, is known to be a weak oxidising agent. The normal potential of the Fe^{2+}/Fe^{3+} system on a resin containing iminodiacetic acid groupings may be calculated from the Nernst equation:

$$E = E_0 + RT/nF \lg C_{ox}/C_{red} = +0{,}78 + (0.058 \cdot \lg 10^{-11}/10^{-6}) = +0.49\text{v}.$$

It is evident from the data presented that, when a polymeric matrix is employed, the weakly oxidising Fe^{2+}/Fe^{3+} system becomes a powerful reducing agent. The fact that the reducing capacity of the Fe^{2+}-form of the iminodiacetic acid resin is sufficient to reduce the oxygen dissolved in water merits particular attention[78]. When Ag^+ ions form complexes with the same Dowex-A-1 resin, the normal oxidation–reduction potential of the Ag^0/Ag^+ system shifts to positive values; thus the Ag-form of Dowex-A-1 resin is a more powerful oxidising agent than the Ag^0/Ag^+ system.

2. Reactions of a Coordinated Macromolecule

Little information has been published about the reactions of a coordinated macromolecular ligand, but the reactivity of coordinated low-molecular-weight compounds has now been investigated fairly widely. Thus there is a large number of specific examples of the effect of coordination on the reactivity of molecules, for example bidentate singly-charged ligands such acetylacetone, acetoacetic ester, aminoacid esters, salicylaldimines, etc. have been quoted in a review by Jones and Connor[79].

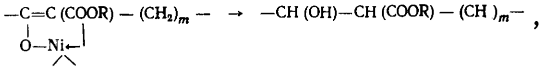
Since coordination leads to a redistribution of electron density in the ligand molecule and to a change of interatomic distances and valence angles, which entails a change in the polarity and strength of the bonds, it follows naturally that in the general case it cannot fail to influence the reactivity of the ligand. It is known that coordination usually, if not always, weakens the bonds (frequently those adjoining the coordinate bond) within the molecule and lowers the frequencies of the corresponding stretching vibrations. Such decrease of the frequency $\Delta\nu$ is determined by the acceptor capacity of the complex-forming cation, which is confirmed by the observed parallel variation of $\Delta\nu$ and the electron-accepting properties of cations, determined by an independent procedure[80]. During complex formation, coordination via the interaction of the unpaired electrons of the ligand and the free orbitals of the metals shifts the electron density of the ligand towards the metal, as a result of which the ligand becomes more electrophilic. The situation becomes more complicated when dative interaction with the reverse transfer of negative charge to the ligand contributes appreciably to the formation of the $M \rightarrow L$ bond; in the formation of such an $M \leftarrow L$ bond the effect of coordination extends to a large number of electrons and the antibonding orbitals of the ligand are involved in the binding, which entails a weakening of the bonds in the ligand.

Siling and Gel'bshtein[65] quote the following references concerning the reactivity of ligands in complexes: (a) data on the chemical reactions of coordinated organic molecules (see, for example, Jones and Connor[79]); (b) infrared spectroscopy (see, for example, Nakamoto[80]); (c) data on the acid dissociation constants of the complexes and free ligands (see, for example, Grinberg[81]); (d) data on catalytic activity in reactions with participation of coordinated organic molecules (see, for example, Langenbeck[82]) or macromolecules[67].

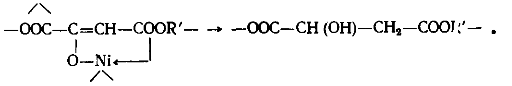
The first attempts at investigation of the reactions of a coordination macromolecular ligand dealt with transesterification and hydrogenation. A study of the transesterification kinetics of acetoacetic ester and its copper complex showed[83] that transesterification with butanol takes place in both polar and non-polar solvents; the rate constants for the reaction and the activation energies and entropies were determined. However, the polymeric ligand (I) and the copper complex obtained on its basis have very low reaction rates.

The hydrogenation of polymeric ketoesters on a Raney nickel catalyst may be quoted as an example of reactions of a coordinated macromolecule which take place more effectively.

It has been shown[85] that macromolecular ligands of the β-ketoester type (I and II) can undergo hydrogenation in the coordinated (Ni^{2+}) state, being converted into poly-β-hydroxyesters; the reaction takes place with liberation of Ni^{2+} ions, probably in consequence of the breakdown of the resonance in the quasiaromatic ring of the coordination centre:

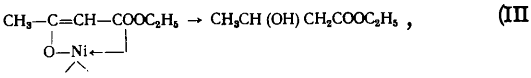

(I)

$$-C{=}C(COOR)-(CH_2)_m- \rightarrow -CH(OH)-CH(COOR)-(CH\,)_m- ,$$

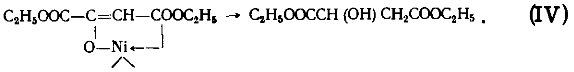

(II)

$$-OOC-C{=}CH-COOR'- \rightarrow -OOC-CH(OH)-CH_2-COOR'- .$$

Nickel complexes of acetoacetic ester [complex (III)] and oxaloacetic ester [complex (IV)], which may be regarded as low-molecular-weight analogues of the macromolecular complexes (I) and (II), also enter into the hydrogenation reaction with formation of β-hydroxybutyric and malic acid esters[86]:


(III)

$$CH_3-C{=}CH-COOC_2H_5 \rightarrow CH_3CH(OH)CH_2COOC_2H_5 ,$$


(IV)

$$C_2H_5OOC-C{=}CH-COOC_2H_5 \rightarrow C_2H_5OOCCH(OH)CH_2COOC_2H_5 .$$

It has been established that the hydrogenation of complexes (I)–(IV) under asymmetrising Akabori conditions (Raney nickel catalyst subjected to preliminary modification by an asymmetric compound) leads to optically active reaction products (Table).

Asymmetric hydrogenation of coordinated ligands of the ketoester type.

Initial ketoester and polyketoester complexes	Modifying agent (0.5 h, pH 5.1, 0°C)	Yield of hydroxy-ester or polyoxy-ester, %	$[\alpha]^{20}_{589}$
$(CH_3COCHCOOC_2H_5)_2Ni$	—	95	0.0
	L-glutamic or (+)-tartaric acid	92	—2.0
	—	100	0.0
$[-(CH_2)_m-COCH(COOC_2H_5)]_2Ni$	L-glutamic or (+)-tartaric acid	96	+1.2
	—	100	0.0
$(C_2H_5OOCCOCHCOOC_2H_5)_2Ni$	L-glutamic acid	98	—1.3
	—	100	0.0
$(-OOCCOCHCOOR')]_2Ni$	L-glutamic acid	92	+8.6

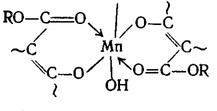
It may be supposed that in the hydrogenation of nickel complexes by hydrogen under pressure at an elevated temperature the initial complex breaks down with simultaneous (or subsequent) coordination of the substrate containing groups capable of chelation to the surface of the heterogeneous catalyst; this results in the formation of an intermediate mixed substrate–metal–modifying agent chelate. Such fixation of the conformation of the transition state and the steric limitation of the accessibility of unsaturated bonds to hydrogen lead to preferential formation of one of the optical isomers of polyoxyesters and hydroxyesters[87]. On the other hand, the hydrogenation of copper complexes of poly-β-ketoesters or acetoacetic ester does not lead to identified reaction products, only the decomposition of the complexes with liberation of the metal on the surface of the catalyst is observed[88]. The use of synthetic polymers as carriers for the active phase of the catalyst for non-stereospecific hydrogenation has been described by Sokol'skii and coworkers[89]. Thus palladium and platinum were deposited on poly(ethylene terephthalate) to be used subsequently in the hydrogenation of unsaturated alcohols (the reactivity of catalysts of this kind increased by a factor of 5–6 compared with palladium black). We attempted to employ the products of the asymmetric hydrogenation of (I) and (II) (above) as polymeric modifying agents in asymmetric induction from polymer to polymer[84]. It was shown that, like the Akabori catalyst[90], the metal-containing polymeric catalyst exhibits a definite stereospecific control in the hydrogenation of polymeric ketoesters.

In conclusion of the section on the synthesis of complexes with macromolecules and their chemical reactions, we may note that certain difficulties arise in the interpretation of these processes.

The steric factor plays an important role in the formation of complexes with macromolecules and their reactions. To calculate the energy of formation of low-molecular-weight complexes, formulae are employed in which account is taken of the radius of the complex-forming ion and the ligand[91] and it is assumed that the ligands approach closely the metal ion. On the other hand, in the formation of complexes with macromolecular ligands, the metal ions cannot in all cases approach the ligand owing to its large dimensions and the wide variety of its conformations. The so called critical ratios of the radii r_M/r_L or r_L/r_M make it possible to infer for low-molecular-weight compounds the highest coordination number n allowed by given steric factors[91], whereas for macromolecular ligands it is not always clear what value of r_L should be adopted.

A characteristic feature of a low-molecular-weight complex is a rigorous geometrical disposition of the functional groups of the ligand relative to the metal. On the other hand, for polymeric complexes the geometrical and stoichiometric relations may be significantly altered, which of course entails a change in the reactivity of both the coordinate metal–ligand bond and of the coordinated macromolecule. In polymeric complex compounds there is a possibility of the formation in the same macromolecule of coordination centres of various symmetries, frequently extremely strained, and, as shown by Tolmachev and coworkers[92], with various magnetic characteristics. Moreover, in complexes with bi- and poly-dentate macromolecular ligands part of the metal ions may be held by the usual Coloumbic forces without forming a coordinate bond and frequently retaining their counterions or forming 1 : 1 coordination centres (for example, instead of 1 : 2), such cases being quoted by Marinsky and coworkers[93] for the polymeric analogues of iminodiacetic acids.

A coordination number $n = 6$ is known to obtain usually for complex-forming metals. When 1 : 2 coordination centres are formed with macromolecular bidentate ligands, the residual vacancies in the complex-forming ion may be saturated, for example, by solvent molecules or by other ligands (the ligand exchange quoted above is based on this principle, p. 1089). As an example of the formation of a mixed macromolecule–metal–solvent complex, we may quote the coordination centre of the manganese complex of a poly-β-ketoester[59]:



Naturally the degree of coordination unsaturation of the centres cannot fail to influence significantly the reactivity of the given class of polymeric compounds.

Even these few examples show that the concepts adopted in the chemistry of low-molecular-weight complexes may be extended to macromolecular objects only when account is taken of the fine structure of the macromolecular ligand and the polymeric complex formed from it. Therefore one of the tasks at the present stage of the investigation of the synthesis and chemical reactions of complexes with macromolecules is the accumulation and systematic arrangement of factual data in order to discover the specific features of this field.

V. FACTORS DETERMINING THE PROPERTIES OF VARIOUS TYPES OF POLYMER–METAL BONDS

To estimate the reactivity of any type of compounds, the following procedures have been employed[94]: (a) examination of various charge densities, bond orders, bond polarisibilities, etc. (b) determination of the energies of the reactants and the transition state. Only the second procedure is valid, since any treatment without taking into account the transition state is not sufficiently precise. Nevertheless up to the present time the procedure involving a comparative semiquantitative estimation of the reactivities of various compounds is still mainly used in the chemistry of organometallic compounds.

In discussions of the problems of the reactivity of organometallic compounds attention is concentrated on the behaviour of the C–M bond. Although the understanding of the nature of this bond is in fact most important for the understanding of the properties of the organometallic compound, other factors also play a certain role. These include certain steric characteristics of the organic substituent, the possibility of intra- and inter-molecular coordination with participation of the metal, effect of the solvent employed, etc.[94] These factors of course play a significant role also for polymeric organometallic compounds in which the multiplicity of chain conformations, solvation of the macromolecules, and interchain coordination may actually become of decisive importance in a particular reaction. To assess the properties and reactivities of organometallic compounds, the concept of electronegativity is sometimes employed[95]; nowadays it is believed that this criterion is neither a qualitative nor a quantitative characteristic of the chemical bond[96].

The main common factors determining the reactivity of organometallic compounds with a metal–carbon σ-bond, including polymeric organometallic compounds, are the nature of the metal and the stability of the organic cryptocarbanion.

One of the procedures whereby the nature of the metal–carbon bond in organometallic compounds may be inferred consists in the determination of the effective charges of the linked atoms. The effective charges may be calculated from the X-ray absorption spectra and frequently dipole moments are adduced to assess the effective charges and the electronegativities; sometimes the effective charges are determined from the ratio of the bond moment to the product of the elementary charge and the bond length[96]

Various methods have been employed to elucidate the problem of the relative stabilities of the carbanions of saturated low-molecular-weight hydrocarbons[97]. Thus the equilibria $RX + R'M \rightleftharpoons RM + R'X$ or $RMg + R'Hg \rightleftharpoons RHg + R'Mg$ have been investigated; a polarographic scale has been proposed for the determination of the CH acidity from the equation $\alpha E_{1/2} = f(pK_a)$ and the equilibrium ionisation constant of the CH acid has been used to assess the relative stability of the corresponding carbanion[97]. On the whole, one may assume that the higher is the acidity of the hydrocarbon, the greater the concentration of the charge in the corresponding carbanion, and the lower the nucleophilicity of the corresponding organometallic compound.

Unfortunately no studies on the determination of the effective charges of metals in polymeric metal-containing compounds or on the determination of the stability of macromolecular carbanions are described in the literature.

In the general case there are two limiting possibilities in the formation of bonds in complex compounds[98]: (a) formation of covalent bonds by utilising the unshared pairs of, for example, an oxygen-containing ligand; when two electrons are delocalised to an equal extent between two atoms, for example O and M, a negative charge is transferred to the metal (so that its resultant charge may actually become negative) with formation of a positive charge at the oxygen atom; (b) the ligand molecules are held around the metal ion by ion–dipole interaction forces only.

The true position for both low-molecular-weight and macromolecular complexes is intermediate between these two limiting mechanisms and in molecules of complex compounds the metal–ligand bond is to some degree covalent with unequal sharing of the electrons.

It is known[98] that the majority of transition metal complexes are of the type ML_4 or ML_6; the first usually has a square or tetrahedral form and the complexes of the second type are almost always octahedral (in polymeric complexes these postulates may not in fact hold, see p. 1091).

When a non-transition metal forms an octahedral complex, for example SnR_4X_2 by the reaction of triphenylstannated poly(vinyl chloride) with hydrogen chloride (p. 1088), the metal (tin) utilises one *s*, three *p*, and two *d* orbitals of the valence shell from which six sp^3d^2 hybrid orbitals oriented along the three coordinate axes are formed. In the formation of an octahedral transition metal complex, a similar hybridisation takes place, but here the *d* orbitals of the inner shell are employed. Thus, in the transition metals of the First Period (iron, nickel cobalt, and manganese), d^2sp^3 hybridisation involves only two 3*d*, one 4*s*, and three 4*p* orbitals. Many characteristic features of transition metal complexes are due precisely to the fact that a metal atom still has residual 3*d* orbitals not participating in the hybridisation and formation of valence bonds.

One may assume that the reactivities of both organometallic and complex compounds, including macromolecular complexes, are determined by the same factors—the nature of the metal and the nature of the organic component of the molecule. Probably, the most striking feature of the properties of coordination compounds is the coordination unsaturation of the metal due to the 3*d* or 4*f* vacant orbitals, as already stated above.

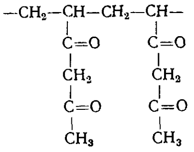
VI. CHARACTERISTICS OF THE CHEMICAL REACTIONS OF METAL-CONTAINING MACROMOLECULES DUE TO THEIR POLYMERIC NATURE

The field of chemical reactions in polymer chains is not at the present time simply the field of the synthesis of new macromolecular compounds which are difficult or even impossible to obtain by the polymerisation or polycondensation of low-molecular-weight substances. It is closely related to the problem of the reactivity of macromolecules and goes far beyond the framework of the concepts applied to it in the classical scheme of the individual branches of the chemistry of macromolecular compounds.

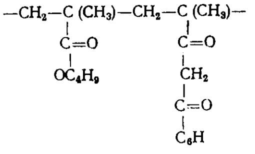
We shall examine the effect of the macromolecular nature of polymeric metal-containing compounds on their reactivity, following the classification of the characteristics of the reactions involving polymers proposed by one of the authors [99].

As already stated on p. 1085 the chemical modification of a polymer chain by substitution of lithium leads to the possibility of ionic grafting of a number of monomers on polylithiopolyethylene and polylithiostyrene. The study [100] of the kinetics of the anionic polymerisation of styrene and isoprene on these macromolecular initiators showed that in polar media the rate of polymerisation is higher than in the presence of the corresponding low-molecular-weight initiator (butyl-lithium): for the polymerisation of styrene on polylithiopolystyrene (PLPS), the ratio of the effective rate constants for chain propogation $k_{\mathrm{PLPS}}/k_{\mathrm{C_4H_9Li}}$ is 2.5 at 25°C and 3.9 at 10°C. The increase of the rate of polymerisation of styrene initiated by the macromolecular initiator ("live polystyrene") may be accounted for as due to the effect of the association of the growing polystyrene chains via intermolecular interaction between them, since they are formed in the immediate vicinity of one another owing to the presence of active centres in the same chain of the lithium-substituted polymer. In the microphase comprising such growing polymer chains the local concentration of the monomer may prove to be higher than its average concentration in the bulk phase (the concentration effect); the reaction takes place within such aggregate, which exhibits an enhanced selective permeability in relation to monomer molecules [16]. The effect of the polymeric nature of the system to be metallated influences the substitution of lithium in polystyrene compared with its low-molecular-weight analogue (toluene) [17] (p. 1083). In this case the so called chain effect is of decisive importance, namely the steric inaccessibility of the benzyl position in the polystyrene chain.

The formation of complexes between macromolecular ligands of the poly-β-diketone type with 3*d* transition metals is convenient for the demonstration of the change in the reactivity of a functional group owing to the chain effect. It was found that the effectiveness of the formation of coordination centres depends on the distribution of the complex-forming groups in the chain. Thus Fig. 6 shows the effectiveness of the binding of Ni^{2+} (expressed as a percentage) for two polymeric ligands: ligand (I) obtained by the polymerisation of methyl vinyl ketone with simultaneous acetylation and containing diketone groups in each unit and ligand (II) obtained by the ester condensation of poly(butyl methacrylate) with acetophenone and not necessarily containing diketone groups in each macromolecular unit:



$-CH_2-CH(COCH_2COCH_3)-CH_2-CH(COCH_2COCH_3)-$ (I)



$-CH_2-C(CH_3)(COOC_4H_9)-CH_2-C(CH_3)(COCH_2COC_6H)-$ (II)

In the polymeric ligand (I) only 45% of the functional groups are employed for the binding of Ni^{2+} and this proportion remains constant regardless of the excess of Ni^{2+} ions in the medium [99]. On the other hand, in the polymeric ligand (II) up to 70% of the complex-forming groups are employed; in the presence of a small excess of ions the effectiveness of complex formation is low but increases with the concentration of the metal in solution.

Examination of the Stuart–Briegleb models shows that in the given case the chain effect is shown by the steric hindrance to the complex-formation process; with low-molecular-weight analogues, all the functional groups of the ligand are of course employed in the formation of the complex.

The chain effect was shown fairly notably in a comparative study of the stabilities (β_2) of the poly-β-ketoester (I) and acetylacetonate (II) complexes of the same metals [101]:

$\lg\beta_2$ for (I)	$\lg\beta_2$ for (II)	$\lg\beta_2$ for (I)	$\lg\beta_2$ for (II)
Mn^{2+} 7.10	Mn^{2+} 10.50	Ni^{2+} 7.55	Ni^{2+} 13.50
Co^{2+} 7.35	Co^{2+} 12.60	Cu^{2+} 8.00	Cu^{2+} 18.40

The defectiveness of the coordination centres formed, the distortion of the geometry of the coordination centres, and mixed complex formation with participation of the solvent (p. 1091) all lead to a greater lability of the L–M bond compared with the stoichiometric and geometrically regular acetylacetone complexes. One cannot exclude the possibility that this property of macromolecular and manganese complexes in fact makes them active‡, for example in the polymerisation of butadiene [67]: the corresponding acetylacetonates exhibit only a slight activity under these conditions.

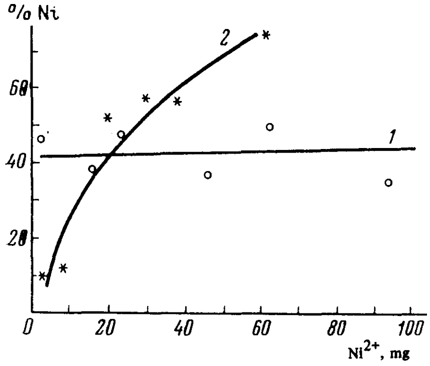


Figure 6. Effectiveness of the binding of Ni^{2+} (%) by polymeric ligands of types (I) (curve *1*) and (II) (curve *2*).

An interesting example of the influence of the concentration effect, which is a direct consequence of the presence of the polymer chain, on the catalytic activity of polymeric complexes in the decomposition of hydrogen peroxide was demonstrated by Kabanov et al. [102] They observed that, by virtue of the local concentration of H_2O_2

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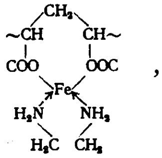
‡There is of course no direct relation between the thermodynamic stability constant of the complexes and their catalytic activity due to the homolytic splitting of the L–M bond; here it would be more correct to compare the thermal stabilities of the complexes and their activities; however, the K_{st} data presented may also be of definite interest.

in the vicinity of the coordination centres of the mixed iron(II) chelate with poly(acrylic acid) and ethylenediamine,



the catalase activity of the latter exceeds that of the low-molecular-weight analogue (Fe^{2+}, malonic acid, ethylenediamine) by several powers of 10.

The study of the interaction of copper(II) salts and polymethacryloyl-lysine by Moravetz et al.[103] showed that the polymer tends to form complexes even at a comparatively low pH, where the content of the complex in solutions of the monomeric analogue is low. This phenomenon may be understood if each spiral of the ligand macromolecule is regarded as a specific region of a concentrated solution of the polyaminoacid, which for this reason forms complexes effectively independently of the formation of 20-membered rings (the concentration effect). The concentration effect is shown in the fact that the macromolecular ligand behaves apparently as a more powerful complex-forming agent than its low-molecular-weight analogue.

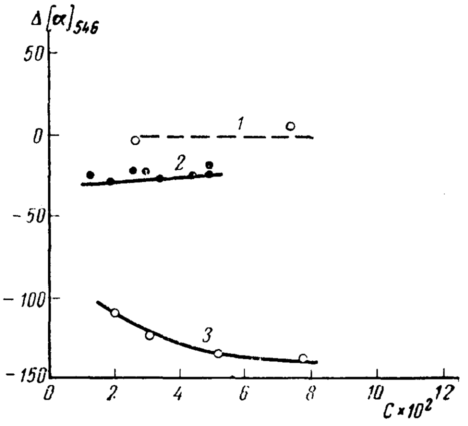


Figure 7. Dependence of the change $\Delta[\alpha]$ of a reaction mixture of triethylenediaminecobalt(III) and a polymeric anion on the concentration of the latter:
1) sodium acetate; 2) sodium polyacrylate;
3) sodium polymethacrylate.

Another consequence of the presence of the polymer chain is the conformation effect. Thus the study of optical rotatory dispersion in a system comprising a polymeric anion (polyacrylate, isotactic, syndiotactic, or atactic polymethacrylate, polyphosphate, polystyrenesulphonate) and an optically active cation $[Coen_3]^{3+}$ or $[Niphen_3]^{2+}$ showed that in such a system the nature of the polymeric ligand is more important. Fig. 7 shows that $\Delta[\alpha]$ falls with increasing polymethacrylate concentration but increases slightly as the concentration of polyacrylate rises, remaining unchanged in the presence of acetate. This is probably associated with different types of metal–polymeric ligand outer sphere interaction, which depends on the charge density along the chain and consequently on the chain–coil conformational transitions[104].

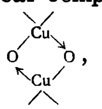
The configurational effect involving a change in the reactivity of the functional groups in the macromolecule compared with the low-molecular-weight ligands may be divided into several subtypes according to Plate's classification[99]. A striking example, where the presence of a group already involved in complex formation next to a free complex-forming group influences (unfavourably) the formation of the next coordination centre along the chain, is provided by the nickel complexes of polyacryloylacetone discussed above (p. 1093) (the so called "neighbour effect").

Another subtype of the configurational effect is shown in the influence of electrostatic interactions in the macromolecule on the rates of chemical reactions and on the equilibrium concentrations of the resulting complexes owing to the additional attraction (repulsion) of the reacting groups. The above example of the reaction of an optically active complex cation and a polyanion shows that not only the nature of the ionised groups but also the degree of their neutralisation is important[104].

Leyte and coworkers[105,106] observed the formation of mononuclear or dinuclear copper complexes in solutions of polymethacrylic acids as a function of the degree of neutralisation of the polymeric ligand; they expressed the binding of the Cu^{2+} by the polymeric acid in terms of the ratio

$$f = \frac{\text{equivalent concentration of ionised polymeric acid}}{\text{equivalent concentration of } Cu^{2+}}$$

When the charge of the polyelectrolyte was low ($f = 1.3$), the formation of the dinuclear complexes



in which, as in copper acetate, copper ions form a structure with D_{4h} symmetry having two polymeric ligands along the C_4 axis, was demonstrated with the aid of spectroscopic and static magnetic data.

With increase of the charge of the polyanion to $f = 3.3$, the dinuclear complexes dissociate into mononuclear species in which the central ion is surrounded in a distorted octahedron by polymeric ligands with negative charges. It is interesting that an analogous relation between the nature of complex formation with copper and the degree of neutralisation of a macromolecular ligand was observed by Japanese investigators[107] for polyglutamic acid.

The influence of different microstructures of the polymer chain on the rate of a chemical reaction with participation of the macromolecule, as happens in the formation of diastereoisomers in the chemistry of low-molecular-weight organic compounds, may be regarded as yet another consequence of the configurational effect.

The influence of the chain microstructure reduces in principle to the occurrence of a favourable (or unfavourable) disposition of neighbouring units in a transition state of known geometry. Complex-formation reactions with polymeric ligands of the acrylic and methacrylic types, for which there exist reliable methods whereby polymers microtactic to different degrees may be obtained, have been most thoroughly investigated. Moravetz et al.[103] were some of the first investigators to turn their attention to the dependence of the chelating capacity of polymethacrylic acid in relation to copper or magnesium ions on its stereoregularity. They started with the hypothesis that, if complex formation involves neighbouring sections of the chain, the steric configuration of the latter should influence the stability of the complexes formed; on the other hand, when complex formation involves remote COOH groups, the complex formation equilibrium should be relatively insensitive to the configuration of the microligand. It was found that, in relation to Cu^{2+}, the isotactic polymer is three times more reactive than the syndiotactic polymer, whereas in relation to Mg^{2+} the opposite relation obtains:

k_b (isotactic)	k_b (syndiotactic)
13.4—18.0 Cu^{2+} (degree of ionisation 0.5-0.9)	1.6—6.1 (degree of ionisation 0.3-0.9)
9—14 Mg^{2+} (degree of ionisation 0.25-0.75)	15—24 (degree of ionisation 0.25-0.75)

$$k_b = [M_b^{2+}]/[M_f^{2+}](CO\ddot{O})_p\ ,$$

where M_b and M_f are the concentrations of bound (b) and free (f) cations and $(COO)_p$ is the concentration of ionised carboxy-groups in the polymer.

This is in fact understandable since copper ions form complexes with a definite geometry of the coordination centre, which are particularly stable when the ligand is the isotactic polymer, whereas magnesium ions form relatively unstable complexes with a less well defined geometry of the coordination centre; in the latter case the complexes of the syndiotactic polymer are actually somewhat more stable than those with the isotactic polymer.

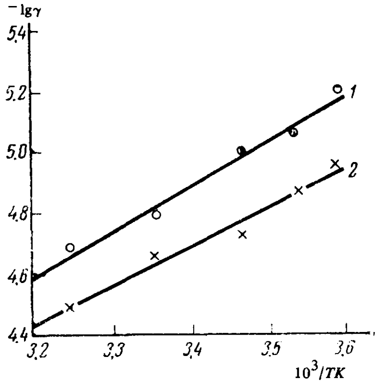
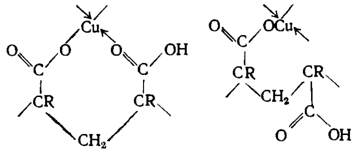


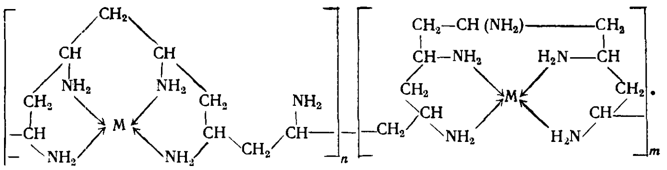
Figure 8. Kinetics of complex formation by isotactic (line *1*) and syndiotactic (line *2*) polymethacrylic acids with Cu^{2+}.

Geuskens et al.[108] re-examined the differences between the reactivities of polymethacrylic acid in relation to copper ions as a function of the microtactic character of the polymeric ligand chain:



Kinetic data show (Fig. 8) that in the temperature range 5–35°C isotactic polymethacrylic acid is more reactive than its syndiotactic isomer: the rate of complex formation involving the first-isomer is higher by a factor of 1.5 than for the second; the activation energies are 6 and 7 kcal $mole^{-1}$ respectively.

The polymeric nature of the macromolecular ligand is shown particularly clearly in the so called "synthetic muscle model"; in the chemistry of low-molecular-weight complexes there are simply no analogues. Teyssie et al.[109] investigated the formation of transition metal complexes of polyvinylamine and obtained complexes soluble in water over a wide range of pH and ionic strengths; with the aid of a wide variety of research techniques, they showed that the formation of complexes with Cu^{2+}, Ni^{2+}, Co^{2+}, and Zn^{2+} greatly influences the dimensions and shape of the polymeric ligand molecules:



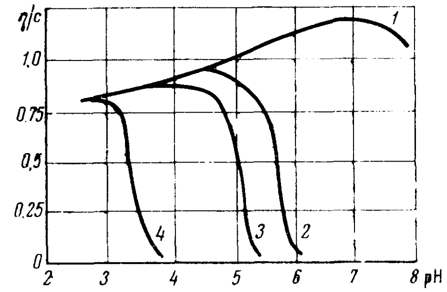
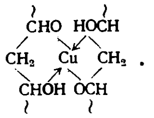


Figure 9. Variation of the viscosity of polyvinylamine solutions in complex formation with transition metal ions: 1) polyvinylamine; 2) Zn^{2+}; 3) Ni^{2+}; 4) Cu^{2+}.

The three condensed cyclic structures produced by complex formation give rise to very powerful contraction of the macroligand molecule, which has been clearly demonstrated by a viscometric technique (Fig. 9). The authors explain the colossal decrease of the viscosity of polyvinylamine solutions in the presence of 3*d* transition metal ions by a change in chain conformation during the complex formation step.

The work of Kuhn et al.[110] provides a still more unusual example of the effect of the polymer chain on complex formation. Employing the principle of reversibly contracting fibres already known from biochemistry, they showed that a partially neutralised and cross-linked copolymer of poly(vinyl alcohol) and polyacrylic acid contracts under the influence of a number of salts (Ca^{2+}, Mg^{2+}, Cu^{2+}) and is reversibly extended in the presence of EDTA; the reversible shift of the system is determined by the presence of the competing ligands poly(vinyl alcohol) and EDTA. We may note here that DNA and RNA nucleoprotein filaments also contract when the above salts are added to the medium and become extended when a suitable complex-forming agent is introduced. The "contracting polymeric systems" of Kuhn[110] operating on the principle of complex formation and oxidation–reduction simultaneously are also extremely interesting. On treatment with Cu^{2+} ions, the gel of poly(vinyl alcohol) swollen in water (100% H_2O and 10% of the polymer) forms a coloured complex with simultaneous intense contraction of the gel fibres (recorded dynamometrically):



If the system is then acted upon by H_2/Pt, the central metal ion is reduced to Cu^+ and the coordination centre breaks down; the gel fibres are decolourised and resume their former dimensions. On the other hand, the effect of O_2/Pt leads to the oxidation of the metal ion to Cu^{2+}, complex formation, and the dyeing and contraction of the gel fibres (Fig. 10).

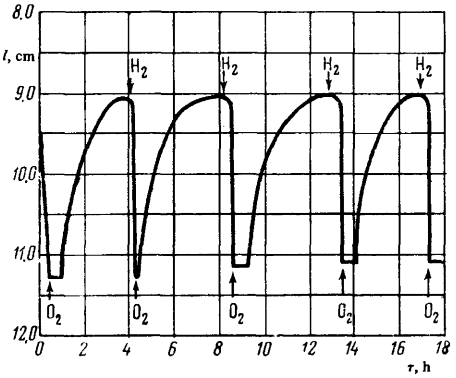


Figure 10. Variation of the length of a poly(vinyl alcohol) fibre on reversible oxidation–reduction in the presence of Cu^{2+} ions.

Kuhn's system has no analogies in the chemistry of low-molecular-weight compounds and is a striking example of the influence of the chain structure on the reactivity of the complex-forming molecule. We may note that Kuhn's system imitates the redox reactions of DNA complexes, for example with Fe^{2+} or Cu^{2+}, where the reduction of central atoms causes a weakening of the bonds between the complementary chains and its oxidation gives rise to the stabilisation of the two-tier conformation of DNA.[111]

All the findings described in this last section show that chemical reactions already known for low-molecular-weight analogues can be achieved on polymeric coordinated and non-coordinated ligands. At the same time the characteristics of the chemical reactions of macromolecules due to their polymeric nature are fairly remarkable, the effect of the polymeric chain on the reactivity of polymeric compounds of this type being most striking.

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Topchiev Institute of
Petrochemical Synthesis,
USSR Academy of Sciences,
Moscow