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REARRANGEMENT OF RADICALS IN SOLUTION

R. Kh. Freidlina, V. N. Kost, and M. Ya. Khorlina

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INTRODUCTION

The number of known organic reactions which are accompanied by rearrangement is continuously growing. Such reactions constitute, in a sense, the philosopher's stone for theoretical organic chemistry.

Hückel[1] believes that rearrangements lie outside the scope of structural theory, which cannot explain them or predict their course. Nevertheless, this theory enabled Baker[2] to classify rearrangements (in 1933) on the basis of a combined structural and chemical principle. He distinguishes "diad", "triad", "tetrad", etc. rearrangements, those involving rings, and rings and chains, as well as carbon–carbon, carbon–oxygen, etc. rearrangements, depending on the type of molecule, the nature of the migrating groups, the nature of the rearrangement centres, and the number of atoms in the chain linking two such centres. All the rearrangements discussed by Baker are heterolytic since homolytic rearrangements in solution were not known at that time.

It has been stated that radical rearrangement in solution is impossible or limited in extent. Thus, Dewar[3] suggested that isomerisation of aliphatic radicals did not occur because stable π complexes are not formed. In fact, the absence of rearrangement in the neopentyl residue when sodium reacts with neopentyl chloride has been quoted as proof of the radical mechanism of the Wurtz reaction[4].

Even in recent times some reviews and monographs specifically devoted to the chemistry of radicals either completely neglect the problems of radical rearrangement or regard such rearrangement as a relatively rare phenomenon. Thus, in a symposium dedicated to the memory of M. S. Kharasch, Kutschke and Steacie failed to mention the possibility of rearrangement of free radicals in their list of free-radical reactions in the gas phase. Walling[6] writes: "It seems a safe generalisation that radical rearrangements are less common than those of the corresponding carbonium ions". However, the experimental data accumulated to date show that radical rearrangement occurs widely. Semenov believes rearrangement to be a general property of radicals[7].

Investigations of free radicals in liquid and gas phases have been largely carried out in isolation[5]. Study of free radicals in the gas phase has been mainly confined to the simplest short-lived radicals (methyl, ethyl), and concerned almost exclusively with kinetic problems. Studies in the liquid phase concerned a large number of complex

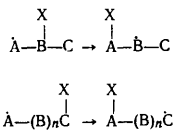
radicals, including stable radicals, and dealt with their structure, their chemical reactions, and new methods for their synthesis. At present, the two fields of study are converging, but the differences between them, both as regards the conditions employed and the approach of the investigators to the problem, still remains very considerable.

This review concerns radical rearrangements in the liquid phase. The general literature on this problem is extremely meagre. We can quote only one small review, in Japanese [8], and a short description of certain problems of radical rearrangement in solution given in the monographs [6,7] quoted above. We shall also consider the structural-chemical principles for classifying rearrangements, designating them as 1,2-, 1,3-, ... 1,5-migration of an atom or group [8]. The numbers denote the mutual disposition of the rearrangement centres.

Among the various factors governing the occurrence of radical rearrangements in solution, the main role appears to be played by the possibility of rearrangement of a less stable radical to one which is more stable under the given conditions [for example, rearrangement of the primary radical $(C_6H_5)_3CCH_2$ to the more stable tertiary radical $(C_6H_5)_2CCH_2C_6H_5$]. Recently, however, examples of rearrangements have been found in which the stabilities of the initial and final radicals do not differ very much (for example, the rearrangement $C_6H_5CH_2^{14}CH_2^{\cdot} \rightarrow \dot{C}H_2^{14}CH_2C_6H_5$), but in these cases the yields of the rearrangement products are small. An important factor in the rearrangement appears to be the ability of the substance the radical stabilises in the reaction to effect chain transfer. The use of less effective chain-transfer agents lengthens the life of the radical and favours rearrangement.

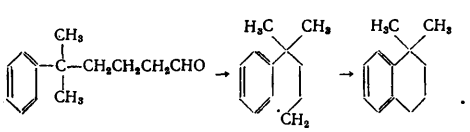
Intramolecular radical rearrangements may be regarded as reactions of the radical with itself. Radical rearrangements may then be divided into three principal groups, according to three types of reactions in which radicals participate.

1. Substitution reactions. These embrace a large number of true rearrangements with migration of various atoms or groups, which may be schematically represented as follows:



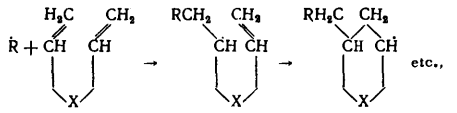
where X is the migrating atom or group.

2. Addition reactions. In our case these will be ring-closure reactions, for example, the formation of tetralin in the peroxide-catalysed decarbonylation of phenyldimethylpentanal [9]:



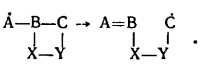
Rearrangements of this type have also been observed in the polymerisation of diene compounds with non-conjugated double bonds, particularly in 1,5- and 1,6-positions (when the formation of 5- and 6-membered rings is possible).

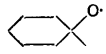
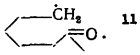
These reactions are important in the synthesis of macromolecular compounds with heterocyclic residues in the chain, for example:



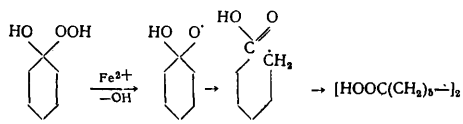
where X = C, N, O, P, Si, Sn. A review of these reactions has been published recently [10].

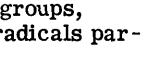
3. Decomposition reactions. This group includes rearrangements with ring rupture as well as some of allylic type. Bond rupture at the β-atom with the formation of a new α,β double bond is characteristic of such rearrangements:



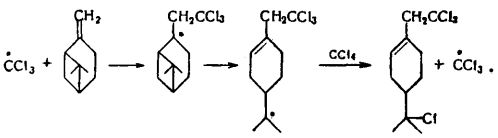
These reactions often take place in radicals with a weakened β,γ-bond; for example, alkoxy radicals with the structure  rearranged to  . [11]

Decomposition of α-hydroxycyclohexyl hydroperoxide in the presence of Fe^{2+} salts results in the formation of α,ω-decanedicarboxylic acid [12]:

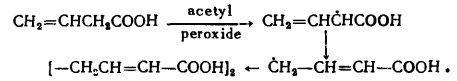


The 5-membered ring in the corresponding hydroxy--radicals opens in the same way [11]; for example, the oxychloride  rearranges to the ω-chloro-derivative

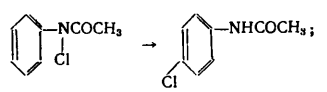
O
||
$CH_3CCH_2CH_2CH_2CH_2Cl$. Rearrangements with rupture of a strained ring, for example a 4-membered one, take place even in hydrocarbon radicals. Thus the free-radical addition of carbon tetrachloride and other polyhalogenomethanes to pinene takes place as follows [13]:



Oxidative dimerisation of vinylacetic acid [14] may be quoted as an example of an allylic rearrangement:



It is evident from the above that intermolecular free--radical rearrangements, where there is no true radical rearrangement, are not included here. For example: the rearrangement of chloroacetanilides [15]:



rearrangement of alkoxystyrenes[16], for which the following mechanism has been proposed[17]:

$$CH_2=C(OR)C_6H_5 + \dot{R} \rightarrow RCH_2\dot{C}(OR)C_6H_5 \rightarrow RCH_2C(=O)C_6H_5 + \dot{R};$$

certain allylic rearrangements:

$$CH_2=CH-CHBrR + Br \rightarrow BrCH_2CH-CHBrR \rightarrow CH_2Br-CH=CHR + Br;$$

etc. Apparently, the free radicals, if they are formed in these reactions, do not undergo rearrangement.

Reactions of types 2 and 3 have been little studied, and this review will deal with rearrangements of type 1, which are accompanied by the migration of hydrogen, chlorine, and aryl and alkyl groups.

I. RADICAL REARRANGEMENTS WITH HYDROGEN MIGRATION

Radical rearrangements with hydrogen transfer are among the most important to be considered. The principal laws governing radical-substitution reactions (for example, radical chlorination), the characteristic features of the ability of individual groups in the molecule to undergo homolytic substitution, and the comparative radical stability series have all been deduced on the assumption that the radical centre, at least in saturated molecules, is not displaced along the molecular chain. However, in a number of studies it has been asserted or assumed that radical rearrangement takes place with migration of a hydrogen atom from an adjacent (1,2-migration) or more distant carbon atom to one bearing an unpaired electron.

A. 1,2-Migration of Hydrogen

Contradictory views have been expressed on the possibility of free-radical rearrangement with 1,2-hydrogen migration. In 1936 the rearrangement of the isopropyl to the n-propyl radical ($CH_3\dot{C}HCH_3 \rightarrow CH_3CH_2\dot{C}H_2$) was described[18]. These data, however, were questioned by Kharasch and his coworkers[19,20], since according to their results alkyl radicals do not isomerise in solution.

1,2-Migration of hydrogen in radicals of the type $RCH_2\dot{C}HCOOH$ was suggested to resolve the contradiction which arose when the action of a chlorine atom[21] and a methyl radical[22] on isobutyric acid was compared. In the first case the substitution was in the β-position (formation of β-chloroisobutyric acid), in the second in the α-position (formation of tetramethylsuccinic acid).

The photochemical reaction between sulphonyl chloride and propionic acid[21] also results in a β-substituted product ($HOSO_2CH_2CH_2COOH$). Kharasch and Brown[21] explained the formation of β-substituted products by rearrangement with 1,2-migration of hydrogen, for example as follows:

$$(CH_3)_2CHCOOH + Cl \rightarrow (CH_3)_2\dot{C}COOH + HCl$$

$$(CH_3)_2\dot{C}COOH \rightarrow (CH_3)_2\dot{C}H-COOH \xrightarrow{Cl_2} ClCH(CH_3)_2-COOH + Cl.$$

Later, Brown himself admitted[22] the weakness of this hypothesis and pointed out that the polar character of the attacking atom or radical plays an important role in determining the site of the attack. Consequently, the initial assumption that the chlorine atom and methyl radical must attack at the same site in the molecule is unjustified.

1,2-Rearrangement with hydrogen transfer was postulated to explain the anomalies observed in certain reactions of organomagnesium compounds in the presence of $CoCl_2$. Thus when n-butylmagnesium bromide reacts with γ-chloropropylbenzene in the presence of cobalt chloride, *trans*-β-methylstyrene (and not allylbenzene) and *trans*-2-butene (and not 1-butene) are obtained[23]. The formation of these products was explained by 1,2-migration of hydrogen in the radicals,

$$C_6H_5CH_2CH_2\dot{C}H_2 \rightarrow C_6H_5CH_2\dot{C}HCH_3,$$

$$CH_3CH_2CH_2\dot{C}H_2 \rightarrow CH_3CH_2\dot{C}HCH_3,$$

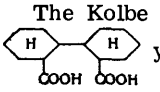
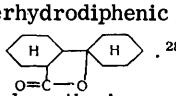
followed by their disproportionation. Slaugh[24], however, believes that the formation of *trans*-β-methylstyrene and *trans*-2-butene is more plausibly explained by the migration of the double bond (rather than 1,2-transfer of hydrogen).

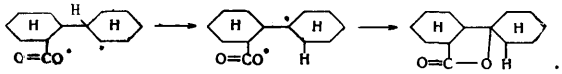
Recently[25] the behaviour of the primary butyl radical under various conditions has been studied in detail. In particular, the reaction between butyl bromide and magnesium in the presence of cobalt bromide was found to yield approximately equal quantities of 1-butene and 2-butene. Since the isomerisation of 1-butene to 2-butene requires more severe conditions, the author explained the formation of 2-butene by the migration of hydrogen in the radical (without specifying from which carbon atom the hydrogen migrates). It should be noted that in the case of both the γ-phenylpropyl and n-butyl radicals the formation of unsaturated compounds with a non-terminal double bond may be explained by 1,3-migration of hydrogen with subsequent disproportionation of the isomerised radicals (see following section).

The decarbonylation of β-phenyl-β-(*p*-methoxyphenyl)-propionaldehyde yielded α-phenyl-α-(*p*-methoxyphenyl)-ethane[26]. The authors suggested that this reaction may involve the 1,2-migration of hydrogen in the radical:

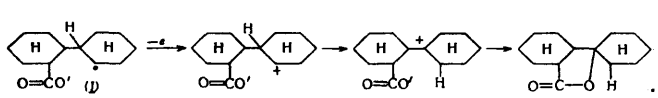
$$p\text{-}CH_3OC_6H_4(C_6H_5)CH\dot{C}H_2 \rightarrow p\text{-}CH_3OC_6H_4(C_6H_5)\dot{C}-CH_3.$$

Later this hypothesis was checked by Curtin and Cauer[27], who on decarbonylation of β-deutero-β-phenyl-β-(*p*-methoxyphenyl)propionaldehyde obtained only the compound $p\text{-}CH_3OC_6H_4CD(C_6H_5)CH_3$, which indicates the absence of migration of either the aryl group or deuterium.

The Kolbe electrolysis of perhydrodiphenic acids  yields the lactone  .[28] The authors[28] suggested that this involves the isomerisation of the radical with 1,2-migration of hydrogen:



It is also possible that the 5-membered lactone may arise due to ionic migration of hydrogen in the carbonium ion formed by the oxidation of the intermediate radical (I):



Thus, although 1,2-migration of hydrogen was postulated in the studies quoted above, its occurrence was not proved. Special investigations were undertaken to settle this question. The most definite results, showing the absence of 1,2-migration of hydrogen in radicals both in the gas and in the liquid phase, were obtained in work with tracer atoms (deuterium, tritium).

Brown and Russell[30] chlorinated photochemically 2-deuteroisobutane at -15°. They obtained both t-butyl chloride and isobutyl chloride and, correspondingly, both deuterium chloride and hydrogen chloride, which means that the reaction proceeds *via* two pathways:

$$(CH_3)_2CDCH_3 + Cl_2 \xrightarrow[-15°]{h\nu} \begin{cases} HCl + (CH_3)_2CDC\dot{H}_2 \\ DCl + (CH_3)_2\dot{C}CH_3. \end{cases}$$

The DCl : HCl and t-butyl chloride : isobutyl chloride molar ratios were found to be the same in two experiments, confirming that isomerisation with hydrogen migration, $(CH_3)_2CDC\dot{H}_2 \rightarrow (CH_3)_2\dot{C}CH_2D$ or $(CH_3)_3\dot{C} \rightarrow (CH_3)_2CHC\dot{H}_2$, does not take place, and that the exchange reaction

$$(CH_3)_2CDC\dot{H}_2 + (CH_3)_2CDCH_3 \rightarrow (CH_3)_2CDCH_2D + (CH_3)_2\dot{C}$$

is also absent.

Slaugh[24] studied the behaviour of the 2-phenylethyl radical in the presence of tritium-labelled toluene-ω-thiol. If the primary radical (II) rearranges to the secondary radical (III), the ethylbenzene formed should contain tritium at the "benzyl" atom in the hydrocarbon:

$$\begin{array}{l} C_6H_5CH_2C\dot{H}_2 \xrightarrow{C_6H_5CH_2ST} C_6H_5CH_2CH_2T \\ \text{(II)} \quad \downarrow \\ C_6H_5\dot{C}HCH_3 \xrightarrow{C_6H_5CH_2ST} C_6H_5CHTCH_3. \\ \text{(III)} \end{array}$$

The reaction product was treated with *N*-bromosuccinimide:

$$C_6H_5CHTCH_3 + C_4H_4O_2NBr \rightarrow C_6H_5CHBrCH_3 + C_4H_4O_2NT$$

The activity of the succinimide corresponded to 1.8% rearrangement, but the author believes that it is due to the exchange reaction between the succinimide and the tritium-labelled toluene-ω-thiol.

Kornblum and coworkers[31] studied the possibility of 1,2-migration of hydrogen from carbon to oxygen in the system $H-\overset{|}{C}-\dot{O}$. They investigated the liquid-phase pyrolysis (at 100°) of optically active 2-octyl nitrite and obtained optically active 2-octanol. They believe that the reaction proceeds in a manner analogous to the scheme proposed by Rice[32] for the gas-phase pyrolysis of alkyl nitrite:

$$C_6H_{13}CH(CH_3)ONO \rightarrow C_6H_{13}CH(CH_3)\dot{O} + NO$$
$$C_6H_{13}CH(CH_3)\dot{O} + C_6H_{13}CH(CH_3)ONO \rightarrow C_6H_{13}CH(CH_3)OH + C_6H_{13}\dot{C}(CH_3)ONO$$
$$C_6H_{13}\dot{C}(CH_3)ONO \rightarrow C_6H_{13}C\overset{O}{\diagdown\!\!\diagup}CH_3 + NO.$$

The formation of optically active 2-octanol demonstrates the absence of rearrangement of radical (IV) to radical (V), since this would have resulted in racemisation†:

$$\begin{array}{ll} C_6H_{13}CH\dot{O} & C_6H_{13}\dot{C}-OH \\ \quad | & \quad | \\ \quad CH_3 & \quad CH_3 \\ \text{(IV)} & \text{(V)} \end{array}$$

In another investigation[33] a study was made of the thermal decomposition of an optically active peroxide in the presence of thiophenol at 125°:

$$C_6H_5CH(CH_3)OOC(CH_3)_3 + C_6H_5SH \xrightarrow{125°} C_6H_5CH(CH_3)OH.$$

Optically active phenylmethylmethanol was obtained, which again points to the absence of 1,2-migration of hydrogen in the radical

$$\begin{matrix} H_5C_6 \\ H_3C \end{matrix}\!\!\diagup\!\!\diagdown CH\dot{O}.$$

Proof of the absence of 1,2-migration of hydrogen in radicals may also be derived from many investigations undertaken for the solution of other problems. For example, the homolytic addition of carbon tetrachloride or bromotrichloromethane to olefines of the type $R-CH_2CH=CH_2$ takes place as follows:

$$RCH_2CH=CH_2 + \dot{C}Cl_3 \rightarrow RCH_2\dot{C}HCH_2CCl_3,$$

and even in the case where R = phenyl[34]; the product $RCHXCH_2CH_2CCl_3$ (X = halogen) is not formed, showing that there is no isomerisation of the radical $C_6H_5CH_2.CHCH_2CCl_3$ to the more stable substituted benzyl radical $C_6H_5CHCH_2CH_2CCl_3$.

From the above data, it is evident that up to the present there has not been a single reliable demonstration of 1,2-migration of hydrogen in radicals.

B. MIGRATION OF HYDROGEN TO MORE DISTANT CARBON ATOMS WITH FREE VALENCIES

The migration of hydrogen to a more distant radical centre has been observed in many cases. However, it has often proved impossible to establish unambiguously from which carbon atom the hydrogen migrates.

1,3-Migration of hydrogen. There are few reliable data showing 1,3-migration of hydrogen in a hydrocarbon radical in solution.

Reutov and Shatkina[29] found that the propyl radical formed on thermal decomposition of n-butyryl peroxide (labelled in the α-position) undergoes rearrangement in solution with 1,3-migration of hydrogen:

$$CH_3CH_2\overset{14}{C}H_2 \rightarrow \dot{C}H_2CH_2\overset{14}{C}H_3.$$

The yield of the rearranged product amounts to 4.0 ± 0.5%.

It is possible that in the reactions (mentioned above) between butyl bromide and magnesium in the presence of cobalt halides[25], resulting in a mixture of 1-butene and

† It is possible that the formation of equimolar quantities of 2-octanol and 2-octanone is due to disproportionation of the radicals:

$$2C_6H_{13}\overset{CH_3}{\underset{|}{C}}HO\cdot \rightarrow C_6H_{13}\overset{CH_3}{\underset{|}{C}}HOH + C_6H_{13}COCH_3;$$

however, this does not alter the main conclusion.

2-butene, the formation of 2-butene is due to the 1,3-migration of hydrogen $CH_3CH_2CH_2\dot{C}H_2 = CH_3\dot{C}HCH_2CH_3$ with subsequent disproportionation of the secondary radicals. It seems to us that the behaviour of the phenoxybutyl radical (described in the same paper), which breaks down with the formation of 1-butene, can also be interpreted in terms of a 1,3-migration of hydrogen:

$$C_6H_5OCH_2CH_2CH_2\dot{C}H_2 \rightarrow C_6H_5OCH_2\dot{C}HCH_2CH_3 \rightarrow C_6H_5\dot{O} + CH_2{=}CHCH_2CH_3.$$

1,3-Migration of hydrogen from carbon to nitrogen may take place in the reduction with benzyl radicals of aromatic nitro- and nitroso-compounds to amines[35]. The following reaction scheme has been proposed:

$$ArN{=}O + Ph\dot{C}H_2 \rightarrow Ar\dot{N}OCH_2Ph$$

$$Ar\dot{N}OCH_2Ph \xrightarrow{rearrangement} ArNHO\dot{C}HPh \rightarrow Ar\dot{N}H + PhCHO$$

$$Ar\dot{N}H + Ph\dot{C}H_2 \rightarrow ArNHCH_2Ph \qquad Ar\dot{N}H + Ph\dot{C}H_2 \rightarrow ArNH_2 + Ph\dot{C}H_2.$$

1,5-Migration of hydrogen. Kosiakoff and Rice[36] suggested that the thermal decomposition of higher hydrocarbons results in the formation of long-chain radicals which can isomerise. They suggested, for example, that in the decomposition of n-hexane the primary radical 1-hexyl can isomerise to the secondary radical 2-hexyl:

$$\begin{matrix} CH_2{-}CH_2 \\ | \\ CH_2{-}\dot{C}H_2 \end{matrix} \diagdown CH_2{-}CH_3 \rightleftarrows \begin{matrix} CH_2CH_2 \diagdown \dot{C}H{-}CH_3, \\ | \\ CH_2{-}CH_3 \end{matrix}$$

i.e. with 1,5-migration of hydrogen in the radical. Since the activation energy of such a process is undoubtedly much less than that for decomposition of the radical, equilibrium between the two radicals is probably established. Assuming that at 600° under low pressure n-hexane decomposes according to the scheme:

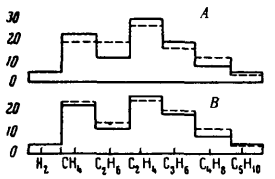
$$R + C_6H_{14} \rightarrow \begin{matrix} \nearrow CH_3(CH_2)_4\dot{C}H_2 \\ \rightarrow CH_3(CH_2)_3\dot{C}HCH_3 \\ \searrow CH_3(CH_2)_2\dot{C}HCH_2CH_3, \end{matrix}$$

$$CH_3CH_2CH_2CH_2CH_2\dot{C}H_2 \rightarrow 2C_2H_4 + \dot{C}_2H_5 (C_2H_6),$$

$$CH_3CH_2CH_2CH_2\dot{C}HCH_3 \rightarrow C_3H_6 + C_2H_4 + \dot{C}H_3 (CH_4),$$

$$CH_3CH_2CH_2\dot{C}HCH_2CH_3 \rightarrow \begin{matrix} \nearrow C_4H_8 + \dot{C}_2H_5 (C_2H_6) \\ \searrow C_5H_{10} + \dot{C}H_3 (CH_4), \end{matrix}$$

the authors calculated the yield of the possible products of the thermal decomposition of n-hexane both in the absence and in the presence of free-radical isomerisation with 1,5-migration of hydrogen. The results obtained are clearly shown in the Figure. It is evident that assumption



Thermal decomposition of n-hexane. Continuous line — experimental; broken line — calculated. *A*) Rearrangement not allowed for; *B*) rearrangement allowed for.

of radical isomerisation substantially improves the agreement between the calculated and experimental data. In the case of radicals with longer chains, obtained for example by the cracking of n-octane[36] and n-hexadecane[37], the possibility of the isomerisation of intermediate radicals is even greater and the improvement in the calculated yields becomes still more notable when isomerisation is taken into account.

Grob and Kammüler[38] demonstrated liquid-phase 1,5-migration of hydrogen in a radical. In an attempt to investigate the possible isomerisation of radical (VI) to radical (VII),

$$\underset{(VI)}{C_6H_5CH_2(CH_2)_3\dot{C}H_2} \rightarrow \underset{(VII)}{C_6H_5\dot{C}H(CH_2)_3CH_3},$$

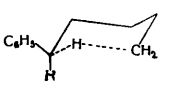
they studied the pyrolysis of ϵ-phenylcaproyl peroxide at 85° in the presence of dry sand. The following were the products: CO_2, ϵ-phenylcaproic acid, δ-phenylpentyl ether, ϵ-phenylcaproate, n-pentylbenzene, 1,10-diphenyldecane, 5,6-diphenyldecane, and polymeric material. The formation of 5,6-diphenyldecane (yield 4.5%) may be due to the intramolecular rearrangement of radical (VI) to radical (VII) with subsequent recombination of the rearranged radicals. However, the formation of this compound may be interpreted as due to the action of radicals present in the reaction mixture on n-pentylbenzene with subsequent recombination of the 1-phenylpent-1-yl radicals:

$$\dot{R} + C_6H_5CH_2(CH_2)_3CH_3 \rightarrow RH + C_6H_5\dot{C}H(CH_2)_3CH_3,$$

$$2C_6H_5\dot{C}H(CH_2)_3CH_3 \rightarrow [CH_3(CH_2)_3\underset{\displaystyle C_6H_5}{\underset{|}{C}}H{-}]_2.$$

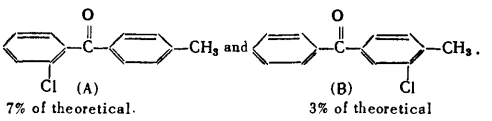
The formation of 5,6-diphenyldecane by the action of radicals (generated in the breakdown of t-butyl peroxide) on n-pentylbenzene is known. Grob and Kammüler quote the following evidence in support of intramolecular rearrangement in this process. When the peroxide is pyrolysed in cumene (at 110°–120°), it might be expected that outside the solvent "cage" the radicals would react with the more reactive cumene and not with n-pentylbenzene the concentration of which in solution is low. Thus the yield of 5,6-diphenyldecane should fall if the compound were formed as a result of the secondary reaction with n-pentylbenzene. Experiment shows that the yield of 5,6-diphenyldecane increases when the reaction is carried out in cumene. The reason for the increase is not clear [possibly it is due to the higher temperature (110°–120°) in cumene (85° without cumene)].

It is interesting to compare this with the fact that decomposition of δ-phenylvaleryl peroxide does not result in products derived from 1,4-migration of hydrogen[39]. It is possible that the $C_6H_5(CH_2)_3\dot{C}H_2$ and $C_6H_5(CH_2)_4\dot{C}H_2$ radicals behave differently because in the latter case a conformation favouring rearrangement may be assumed:



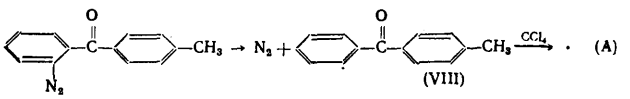
1,5-Migration of a hydrogen atom bound to an aromatic nucleus has been suggested to explain the formation of isomeric products in the decomposition of 2-(4-methylbenzoyl)aryldiazonium salts[40]. The decomposition of aryldiazonium halides of this structure was carried out in

carbon tetrachloride at pH 7.2. Among other products, the following chloro-derivatives were obtained:



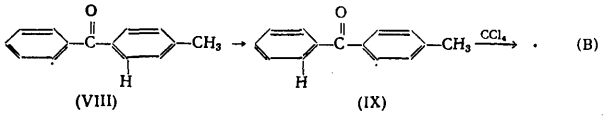
7% of theoretical. 3% of theoretical

The following reaction has been suggested to explain the formation of chloro-derivative (A):



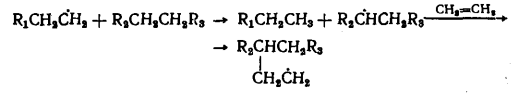
(A)

Chloro-derivative (B) was assumed to arise through rearrangement of radical (VIII) to radical (IX) *via* 1,5-migration of hydrogen with subsequent reaction of radical (IX) with carbon tetrachloride:

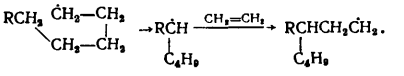


(B)

It is noteworthy that radical rearrangement with 1,5-migration of hydrogen appears to play a major role in the radical polymerisation of ethylene and other olefines as well as in the polymerisation of dienes and other unsaturated compounds (see, for example, refs. 41 and 42). In recent years data have been obtained suggesting that polyethylene molecules synthesised by radical polymerisation under pressure have side chains. Depending on the reaction conditions, polyethylene with long or short side chains can be obtained. The physicomechanical properties of polyethylene depend to a large extent on the nature of branching in the molecule. It has been suggested[41] that there may be two mechanisms leading to chain branching in the molecule. Long side chains are formed as a result of intermolecular hydrogen transfer:



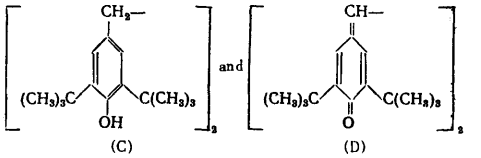
and short side chains are formed *via* intramolecular hydrogen transfer. Assuming that the formation of 5- and 6-membered rings in the transition state is sterically favoured, Roedel[41] suggested that the intramolecular rearrangement is effected mainly by 1,5-migration of hydrogen in the radical:



Study of the infra-red spectra of polyethylene containing short side chains[42] has shown that the number of methyl and ethyl groups in the polyethylene specimens examined was the same. This has been interpreted as showing that pendant methyl side groups are not formed in polyethylene. The short side chains are supposed to arise mainly by 1,5-migration of hydrogen in the radical; 1,3- and 1,4-migrations are also believed to be possible.

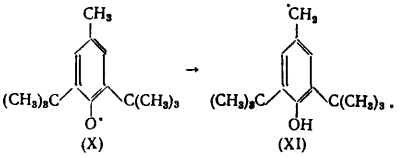
A number of other observations have been interpreted as proof that radicals can isomerise *via* hydrogen transfer from a carbon atom to a non-neighbouring atom with an unpaired electron, but it was impossible to establish from which particular carbon atom the hydrogen migrated.

1,6-Migration of hydrogen from carbon to oxygen in a radical has been invoked to explain the formation of compounds (C) and (D) in the oxidation of 4-methyl-2,6-di-t-butylphenol:



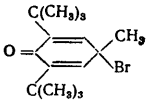
(C) (D)

The formation of these products is supposed to be due to the rearrangement of radical (X) to radical (XI):



(X) (XI)

When the bromo-compound



reacts with mercury, the same compounds, (C) and (D), are formed which confirms the occurrence of this rearrangement.

Thus the ability of radicals to isomerise in solution *via* hydrogen migration to a non-neighbouring atom is now definitely established. However, such isomerisation has been little studied. In particular, the influence of the structure of the radical, the nature of the solvent, the temperature, and other conditions on this reaction is unknown, and no quantitative data characterising the process are available.

The possibility of rearrangement, *via* hydrogen migration, of initially formed radicals must undoubtedly be taken into account in studies on the mechanism of radical substitution, on the reactivity and stability of radicals in solution, and in many other problems.

II. RADICAL REARRANGEMENT WITH CHLORINE MIGRATION. 1,2-MIGRATION OF CHLORINE

Studies on chemical reactions of polychlorohydrocarbons containing the trichloromethyl group have shown that this group is active in homolytic reactions[44]. Thus when $\alpha,\alpha,\alpha,\omega$-tetrachloroalkanes are allowed to react with organomagnesium compounds in the presence of cobalt chloride, the CCl_3 group is attacked and compounds with the structure $Cl(CH_2)_nCCl_2CCl_2(CH_2)_nCl$ are formed. The reaction of $\alpha,\alpha,\alpha,\omega$-tetrachloroalkanes with copper and nickel takes place similarly. The process apparently goes *via* a stage in which a chlorine atom or a tetrachloroalkane molecule undergoes homolytic scission:

$$\dot{R} + CCl_3(CH_2)_nCl \rightarrow RCl + \dot{C}Cl_2(CH_2)_nCl,$$

$$2Cl(CH_2)_n\dot{C}Cl_2 \rightarrow Cl(CH_2)_nCCl_2{-}CCl_2(CH_2)_nCl.$$

It must be emphasised that the removal of a chlorine atom from the trichloromethyl group takes place under

extremely mild conditions. It is possible that the ease of this removal from a CCl_3 group in a polychlorohydrocarbon radical is even greater, by analogy with the greater mobility of hydrogen in hydrocarbon radicals than in the molecules of saturated hydrocarbons[45,46]. The ease of removal of the chlorine atom and the stability of radicals in which a carbon atom with an unpaired electron is bound to two chlorine atoms[47], should favour the rearrangement of radicals of type (A) to radicals of type (B):

$$\underset{\text{(A)}}{CCl_3\dot{C}<} \rightarrow \underset{\text{(B)}}{\dot{C}Cl_2CCl<}$$

In a number of investigations of this rearrangement the radicals of the above structure were obtained by the homolytic addition of various compounds to olefines containing a polyhalogenomethyl group. The addition of hydrogen bromide, bromotrichloromethane, bromine, and thiophenol to substances with the structure $XCCl_2CY=CH_2$ (where X = Cl, F, H, CH_3; Y = Cl, H, Br, CH_3) has been studied. The results obtained are collected in Tables 1–3.

Table 1 gives some data on the reaction between hydrogen bromide and a number of polyhalogenoalkenes in the presence of benzoyl peroxide or under illumination with ultra-violet light. It is well known that the addition of hydrogen bromide to olefines in the presence of peroxides takes place *via* a chain radical mechanism. The purely homolytic character of the reactions described in Table 1 is emphasised by the fact that in the absence of radical-process initiators there is no reaction between hydrogen bromide and the compounds listed in the table. The chain character of the reaction is confirmed by the fact that addition of negligible quantities of inhibitors brings the reaction to a complete stop. Addition of HBr was carried out by saturating a solution of 0.5 g of benzoyl peroxide in 0.1–0.6 mole of polyhalogenoalkene at 50°–70°. In the general case the reaction results in a mixture of products:

$$\text{(I)}\quad XCCl_2CY{=}CH_2+HBr \xrightarrow{Bz_2O_2} \begin{cases} XCCl_2CHYCH_2Br \\ HCClXCYClCH_2Br & 1 \\ \dot{C}ClX{=}CYCH_2Br & 2 \\ HCClXCYClCH_2Cl & 3 \end{cases}$$

Thus in the case of example 4 in Table 1, where X = Cl and Y = Cl compounds 1′, 2′, and 3′ were obtained:

$$CCl_3CCl{=}CH_2+HBr \xrightarrow{Bz_2O_2} \begin{cases} CHCl_2CCl_2CH_2Br & 1' \\ CCl_2{=}CClCH_2Br & 2' \\ CHCl_2CCl_2CH_2Cl & 3' \end{cases}$$

The following mechanism has been proposed for this process:

$$Bz_2O_2 \rightarrow C_6H_5\dot{}$$

$$C_6H_5\dot{} + HBr \rightarrow C_6H_6 + Br$$

$$CCl_3CCl{=}CH_2 + Br \longrightarrow CCl_3\dot{C}ClCH_2Br \qquad \text{(a)}$$

$$\underset{\text{(A)}}{CCl_3\dot{C}ClCH_2Br} \xrightarrow{\text{rearrangement}} \underset{\text{(B)}}{\dot{C}Cl_2CCl_2CH_2Br} \qquad \text{(b)}$$

$$\dot{C}Cl_2CCl_2CH_2Br + HBr \longrightarrow HCCl_2CCl_2CH_2Br + Br \qquad \text{(c)}$$

$$\left.\begin{matrix} CCl_3\dot{C}ClCH_2Br \\ \text{or} \\ \dot{C}Cl_2CCl_2CH_2Br \end{matrix}\right\} \longrightarrow CCl_2{=}CClCH_2Br + Cl \qquad \text{(d)}$$

$$CCl_3CCl{=}CH_2 + Cl \longrightarrow \underset{\text{(A′)}}{CCl_3\dot{C}ClCH_2Cl} \qquad \text{(e)}$$

$$\underset{\text{(A′)}}{CCl_3\dot{C}ClCH_2Cl} \xrightarrow{\text{rearrangement}} \underset{\text{(B′)}}{\dot{C}Cl_2CCl_2CH_2Cl} \qquad \text{(f)}$$

$$\dot{C}Cl_2CCl_2CH_2Cl + HBr \longrightarrow HCCl_2CCl_2CH_2Cl + Br \qquad \text{(g)}$$

This scheme is analogous to that proposed by Kharasch for the "peroxide effect", but stages (b) and (f) involve the rearrangement of radicals (A) and (A′) to radicals (B) and (B′), and the elimination of a chlorine atom in stage (d) leads to the propagation of a chain reaction [stages (e), (f), and (g)], which is completely analogous to the main process [stages (a), (b), and (c)] resulting from the presence of bromine atoms in the system. Elimination of chlorine, which stabilises the intermediate radicals, is encountered quite frequently in homolytic reactions[48–51].

Introduction of fluorine or hydrogen to a trihalogenomethyl group in unsaturated compounds (Nos. 5 and 7 in Table 1 and No. 3 in Table 3) impedes the rearrangement of radicals and, in addition to the rearranged products, non-rearranged addition products are also formed. Table 2 gives some data on the reaction of bromotrichloromethane, bromine, and mercaptans with 3,3,3-trichloropropene. The

TABLE 1. Addition of hydrogen bromide to polychloroolefines in the presence of benzoyl peroxide or under ultra-violet illumination.

No.	Polychloroolefine	Reaction products (yield, % of theoretical)				% rearrangement**	Reference
		not rearranged	rearranged	rearranged Cl-addition product	unsaturated products		
1	$CCl_3CH{=}CH_2$		$CCl_2H{-}CHCl{-}CH_2Br$ 77			100	52
2*	$CCl_3CH{=}CH_2$		$CHCl_2{-}CHCl{-}CH_2Br$ 88			100	53
3	$CCl_3C(CH_3){=}CH_2$		$CHCl_2{-}C(CH_3)Cl{-}CH_2Br$ 59	$CHCl_2{-}C(CH_3)Cl{-}CH_2Cl$ 11	$CCl_2{=}C(CH_3){-}CH_2Br$ 15	100	54
4	$CCl_3CCl{=}CH_2$		$CHCl_2{-}CCl_2{-}CH_2Br$ 34	$CHCl_2{-}CCl_2{-}CH_2Cl$ 14	$CCl_2{=}CCl{-}CH_2Br$ 15	100	55
5	$CHCl_2{-}CH{=}CH_2$	$CHCl_2{-}CH_2{-}CH_2Br$ 5	$CH_2Cl{-}CHCl{-}CH_2Br$ 46			90	56,57
6	$CH_2Cl{-}CCl_2{-}CH{=}CH_2$		$CH_2ClCHCl{-}CHCl{-}CH_2Br$ 73			100	57
7*	$CFCl_2{-}CH{=}CH_2$	$CFCl_2CH_2CH_2Br$ 39	$CFClH{-}CClH{-}CH_2Br$ 18			30	53
8	$CHCl_2{-}CCl{=}CH_2$	$CHCl_2{-}CClH{-}CH_2Br$ 30				0	55
9	$CHCl_2{-}C(CH_3){=}CH_2$	$CHCl_2{-}CH(CH_3){-}CH_2Br$ 34	$CH_2Cl{-}C(CH_3)Cl{-}CH_2Br$ ~30		$CHCl{=}C(CH_3){-}CH_2Br$ ~12	~50	57

* Experiments carried out under illumination with ultra-violet light.

** Calculated from the proportions of the addition products.

TABLE 2. Addition of various reagents to 3,3,3-trichloropropene.

No.	Reagent	Initiator	Solvent	Temp., °C	Reaction products (yield, % of theoretical)				Reference
					not rearranged	rearranged	rearranged Cl-addition product	unsaturated	
1	$BrCCl_3$	$(C_6H_5CO)_2O_2$		100		$BrCCl_2CHCl-CH_2Cl$, 18	$BrCCl_2CHCl-CH_2Cl$ 14	$CCl_2=CH-CH_2Cl_2$ 26	52
2	Br_2		CH_3COOH	20	$CCl_2CHBr-CH_2Br$ 80				58
3	Br_2	illumination with incandescent lamp (150 W)	$CHCl_3$		$CCl_2CHBr-CH_2Br$ 70	$CCl_2Br-CHCl-CH_2Br$* 30			58
4	Br_2	$(C_6H_5CO)_2O_2$	CCl_4	80	$CCl_2CHBr-CH_2Br$ 47	$CCl_2Br-CHCl-CH_2Br$* 53			58
5	C_6H_5SH**			115	$CCl_2CH_2CH_2SC_6H_5$ 27				59
6	C_6H_5SH	illumination with incandescent lamp (150 W)		80—90		$CHCl_2CHCl-CH_2SC_6H_5$ 30		$CCl_2=CHCH_2SC_6H_5$ 11	59
7	$C_6H_5CH_2SH$	ditto		110—115		$CHCl_2-CClH-CH_2SCH_2C_6H_5$ 11		$CCl_2=CH-CH_2-S-CH_2C_6H_5$ 39	59
8	$n\text{-}C_6H_{13}SH$	»		110—115				$CCl_2=CHCH_2SC_6H_{13}\text{-}n$ 30	60

* Yield given as a percentage of total products.

** Reaction carried out in the presence of sulphur as inhibitor of the homolytic process.

first of these compounds add to trichloropropene solely by a chain radical mechanism. The addition of bromine to 3,3,3-trichloropropene may be heterolytic when the reaction is carried out in a polar solvent (acetic acid) and in the absence of initiators (No.2 in Table 2). Under these conditions a non-rearranged addition product with the structure $CCl_3CHBrCH_2Br$ is formed. When the reaction is carried out in a non-polar solvent under illumination (No.3 in Table 2) or in the presence of benzoyl peroxide (No. 4 in Table 2), a mixture of rearranged ($BrCCl_2CHClCH_2Br$) and non-rearranged compounds is formed.

In exactly the same way the addition of thiophenol to trichloropropene can be effected by both a heterolytic (in the presence of sulphur as an inhibitor of the homolytic process, No.5 in Table 2) and a homolytic (No. 6 in Table 2) mechanism. In the first case a non-rearranged product with the structure $CCl_3CH_2CH_2SC_6H_5$ is formed, and in the second a rearranged product and an unsaturated compound ($HCCl_2CHClCH_2SC_6H_5$ and $CCl_2=CHCH_2SC_6H_5$). The last is obtained in a slight yield. When thiophenol is replaced by toluene-ω-thiol (No. 7 in Table 2) or n-hexanethiol (No. 8 in Table 2), the principal products are $CCl_2=CHCH_2SCH_2C_6H_5$ and $CCl_2=CHCH_2SC_6H_{13}$ respectively. It is interesting that in these reactions the chlorine eliminated instead of being bound to the trichloropropene reacts with toluene-ω-thiol and n-hexanethiol to form hydrogen chloride.

A number of factors affect the chemical behaviour of the radicals in solution; this is reflected particularly in the relative yields of products 1,2, and 3 (scheme I) and those of the non-rearranged products. The most important of these factors are the relative stabilities of the initial and rearranged radicals, the relative rates of their reaction with the chain-transfer agent (HBr, Br_2, C_6H_5SH), etc. Comparison of the results of the reactions (Tables 1 and 2) leads to certain conclusions on the relation between the structure of the radical and its ability to rearrange with 1,2-migration of chlorine.

The reactions listed in Table 1 were carried out under comparable conditions with the same chain-transfer agent — hydrogen bromide. The results obtained show that rearrangement leads to the formation of more stable radicals. For example, the reaction of 2,3,3-trichloroprop-1-ene (No. 8 in Table 1) with hydrogen bromide takes place without rearrangement, since, in conformity with the general rule, the initial secondary radicals $CHCl_2\dot{C}ClCH_2Br$ are more stable than the primary radicals $\dot{C}HClCCl_2CH_2Br$, which would be formed as a result of rearrangement. Radicals in which the unpaired electron is associated with the group $\dot{C}Cl_2-\overset{|}{C}-$ are more stable than secondary radicals of the type $-\overset{|}{C}-\dot{C}H-\overset{|}{C}-$ or $-\overset{|}{C}-\dot{C}Cl-\overset{|}{C}-$, and also more stable than tertiary radicals. Accordingly, radicals (A), (B), and (C) rearrange to (A'), (B'), and (C') (Nos. 1, 3, and 4 in Table 1).

$$\underset{(A)}{CCl_3\dot{C}HCH_2Br} \rightarrow \underset{(A')}{\dot{C}Cl_2CHClCH_2Br},$$

$$\underset{(B)}{CCl_3\dot{C}ClCH_2Br} \rightarrow \underset{(B')}{\dot{C}Cl_2CCl_2CH_2Br},$$

$$\underset{(C)}{CCl_3\dot{C}(CH_3)-CH_2Br} \rightarrow \underset{(C')}{\dot{C}Cl_2CCl(CH_3)CH_2Br}.$$

Primary radicals bound to chlorine are somewhat more stable than secondary radicals bound to hydrogen; thus radicals (D) rearrange to (D'):

$$\underset{(D)}{CHCl_2\dot{C}HCH_2Br} \rightarrow \underset{(D')}{\dot{C}HClCHClCH_2Br}. \qquad \text{(No. 5, Table 1)}$$

It is therefore readily seen why the secondary radical (E) rearranges to the more stable secondary radical (E'):

$$\underset{(E)}{CH_3CCl_2\dot{C}HCH_2Br} \rightarrow \underset{(E')}{CH_3\dot{C}ClCHClCH_2Br}. \qquad \text{(No. 6, Table 1)}$$

Reactions of 3,3,3-trichloropropene with various substances which can function as chain-transfer agents are compared in Table 2. Examination of the data shows that, in all cases where the reaction is carried out in the presence of radical initiators (Nos.1, 3, 4, 6, and 7), the initial radicals $CCl_3\dot{C}HCH_2Y$ (Y = CCl_3, Br, C_6H_5S) rearrange to the more stable radicals $\dot{C}Cl_2CHClCH_2Y$. The different chain-transfer agents resulted merely in a change of the relative yields of products of types 1, 2, and 3 (scheme I, p. 7). This also confirms that the main factor determining the occurrence of rearrangement is the greater stability of the rearranged radical.

In some of the cases investigated, "normal" addition products were obtained together with the rearranged products:

(1) $CCl_3CH=CH_2 + Br_2 \rightarrow CCl_3CHBrCH_2Br$ (No. 4, Table 2)
$BrCCl_2CHClCH_2Br$,

(2) $CFCl_2CH=CH_2 + HBr \rightarrow CFCl_2CH_2CH_2Br$ (No. 7, Table 1)
$HCFClCHClCH_2Br$,

(3) $CFCl_2CBr=CH_2 + HBr \rightarrow CFCl_2CHBrCH_2Br$ (No. 3, Table 3)
$CFCl=CClCH_2Br$,

(4) $CHCl_2-CH=CH_2 + HBr \rightarrow CHCl_2-CH_2CH_2Br$ (No. 5, Table 1)
$CH_2Cl-CHCl-CH_2Br$,

(5) $CHCl_2-C(CH_3)=CH_2 + HBr \rightarrow CHCl_2-C(CH_3)H-CH_2Br$ (No. 9, Table 1)
$CH_2Cl-CCl(CH_3)-CH_2Br$.

In all cases except the first, the formation of non-rearranged products by simultaneous heterolytic addition reactions is eliminated from consideration since these reactions do not occur in the absence of benzoyl peroxide and illumination. Furthermore, addition of traces of inhibitors suppresses the formation of both the rearranged and non-rearranged products. It is possible that the initial radicals $CFCl_2\dot{C}HCH_2Br$, $CFCl_2\dot{C}BrCH_2Br$, $CHCl_2\dot{C}HCH_2Br$, and $CHCl_2\dot{C}(CH_3)CH_2Br$, and the corresponding rearranged radicals $\dot{C}FClCHClCH_2Br$, $\dot{C}FClCBrClCH_2Br$, $\dot{C}HClCHClCH_2Br$, and $\dot{C}HClCCl(CH_3)CH_2Br$ have comparable lifetimes, which results in a mixture of rearranged and non-rearranged products.

During studies of 1,2-migration of chlorine in radicals the interesting homolytic transformation of 3,3,3-trichloro-2-bromoprop-1-ene to the isomeric 1,1,2-trichloro-3-bromoprop-1-ene was investigated[61] (No. 1 in Table 3). The compound ($CCl_3CBr=CH_2$) isomerises on standing after an induction period (over 1–2 days) or on illumination (without heating) with a mercury-vapour lamp (over several minutes):

$$CCl_3CBr=CH_2 \rightarrow CCl_2=CClCH_2Br.$$

The radical chain mechanism of this rearrangement has been demonstrated by the following observations. The rearrangement is initiated by illumination of the substance with ultra-violet light and is inhibited by the addition of small quantities of such inhibitors as hydroquinone and dimethylaniline. The homolytic isomerisation of this compound differs from the heterolytic anionotropic isomerisation, which is of the allylic type:

$$CCl_3CBr=CH_2 \xrightarrow{h\nu} CCl_2=CClCH_2Br$$
$$CCl_3CBr=CH_2 \xrightarrow{SbCl_5} CCl_2=CBrCH_2Cl.$$

The following scheme has been proposed for the homolytic isomerisation.

(III)
$$Br + CCl_3CBr=CH_2 \xrightarrow{a} CCl_3\dot{C}BrCH_2Br$$
$$\uparrow \qquad\qquad\qquad\qquad b \downarrow$$
$$Br + CCl_2=CClCH_2Br \xleftarrow{c} \dot{C}Cl_2CBrClCH_2Br.$$

The results of other studies on isomerisation of this type are given in Table 3.

Compounds of the type $XCCl_2CBr=CH_2$ (where X = CH_3, F) can also isomerise on illumination with ultra-violet light or on heating with benzoyl peroxide:

$$XCCl_2CBr=CH_2 \rightarrow XCCl=CClCH_2Br.$$

3,3-Dichloro-2-bromobut-1-ene (No. 2, Table 3) isomerises heterolytically under the action of $SbCl_5$ with the formation of the allylic isomer 1,3-dichloro-2-bromobut-2-ene, whereas on illumination with ultra-violet light it

TABLE 3. Homolytic isomerisation of compounds of the type $XCCl_2CBr=CH_2$.

No.	Polyhalogenoalkene	$SbCl_5$-catalysed anionotropic isomerisation	Homolytic isomerisation	Interaction with various reagents: reagent	products: unsaturated	products: addition products	yield, % of theoretical	% rearrangement	Reference
1	$CCl_3CBr=CH_2$*	$CCl_2=CBr-CH_2Cl$	$CCl_2=CCl-CH_2Br$**	C_6H_5SH	$CCl_2=CCl-CH_2SC_6H_5$	–	55	100	61
				C_6H_5SH	$CCl_2=CCl-CH_2SC_6H_5$	–	30	100	60
				C_6H_5SH+S	–	$CCl_2CHBr-CH_2SC_6H_5$	38	0	
2	$CH_3CCl_2CBr=CH_2$*	$CH_3CCl=CBr-CH_2Cl$	$CH_3CCl=CCl-CH_2Br$**	$HBr+(C_6H_5CO_2)_2$	$CH_3CCl=CCl-CH_2Br$	–	90	100	62
3	$CFCl_2-CBr=CH_2$*		$CFCl=CCl-CH_2Br$*** + dimer* (C)	HBr (u.v. light)	$CFCl=CCl-CH_2Br$ (A)	$CFCl_2-CHBr-CH_2Br$+ (B) +dimer* (C)	78 (B); 3 (A); 9 (C);	4****	63
				heating with $(C_6H_5CO_2)_2$	$CFCl=CClCH_2Br$ (A)	dimer* (C)	46 (A); 49 (C);	100****	

* After an induction period Nos.1 and 2 undergo homolytic isomerisation to $CClX=CCl-CH_2Br$ (X = Cl, CH_3); on standing No.3 is converted to dimer (C) with the structure $CH_2Br-CBr(CFCl_2)-CH_2-CCl=CFCl$; on interaction with dialkylamines Nos.1, 2, and 3 form amines with the structure $CXCl=CBr-CH_2NR_2$(X = Cl, F, CH_3).

** Illumination with ultra-violet light.

*** Heating or illumination with ultra-violet light.

**** Yield of dimers not taken into account.

isomerises homolytically to 2,3-dichloro-1-bromobut-2--ene. Ultra-violet light causes the homolytic isomerisation of 3-fluoro-3,3-dichloro-2-bromoprop-1-ene (No. 3 in Table 3) to 1-fluoro-1,2-dichloro-3-bromoprop-1-ene, a dimer which probably has the structure $CH_2BrCBr(CFCl_2)-CH_2CCl=CClF$ being formed at the same time.

Such isomerisation of compounds of the type $XCCl_2CBr=CH_2$ is due to the fact that radicals with the bond system $-\overset{|}{C}-\overset{|}{C}-Br$ readily split off the bromine atom, then becoming stabilised by rearrangement to unsaturated compounds [reaction *c*, scheme (III)]. Thus compounds with the structure $XCCl_2CBr=CH_2$ (where X = Cl, CH_3) do not undergo homolytic addition, even of extremely effective chain-transfer agents such as hydrogen bromide and thiophenol (Nos. 1 and 2 in Table 3); in all cases the initially formed radicals of the type $XCCl_2\dot{C}BrCH_2Y$ (where X = Cl, CH_3; Y = Br, C_6H_5S) isomerise to $X\dot{C}ClCClBrCH_2Y$ which become stabilised by splitting off bromine and rearranging to unsaturated compounds of the type $XCCl=CClCH_2Y$. Only when hydrogen bromide is added to 3-fluoro-3,3--dichloro-2-bromoprop-1-ene under ultra-violet illumination (No. 3 in Table 3) is a saturated addition product ($CFCl_2CHBrCH_2Br$) obtained together with the unsaturated compound ($CFCl=CClCH_2Br$). The former, however, is formed from the non-rearranged radical, and the rearranged radical is stabilised solely by eliminating bromine and undergoing conversion to an unsaturated compound:

$$CFCl_2CBr=CH_2 + Br \rightarrow CFCl_2\dot{C}BrCH_2Br \quad (F)$$

(IV)
$$CFCl_2\dot{C}BrCH_2Br \xrightarrow{heat} \dot{C}FClCClBrCH_2Br \quad (F')$$
$$\downarrow HBr \qquad\qquad \downarrow$$
$$CFCl_2CHBrCH_2Br + Br \qquad CFCl=CClCH_2Br + Br.$$

1,2-Migration of chlorine is observed also in other reactions. Thus Urry and Eiszner[64] obtained a 60% yield of tetra(chloromethyl)methane in the reaction between diazomethane and carbon tetrachloride under illumination. The reaction must be based on a radical chain mechanism, since it is very slow in the dark, becomes faster on illumination, and is inhibited by diphenylamine. In stages (1), (2) and (3) [scheme (V)] the mechanism proposed for the formation of tetrachloromethylmethane involves rearrangement with migration of a chlorine atom from the trichloromethyl group (and then from the dichloromethyl and monochloromethyl groups) to a neighbouring carbon atom with an unpaired electron.

(V)
$$\dot{C}Cl_3 + CH_2N_2 \rightarrow CCl_3\dot{C}H_2 + N_2,$$
$$CCl_3\dot{C}H_2 \rightarrow \dot{C}Cl_2-CH_2Cl, \quad (1)$$
$$\dot{C}Cl_2-CH_2Cl + CH_2N_2 \rightarrow CH_2CCl_2-\dot{C}HCl + N_2,$$

$$\dot{C}H_2CCl_2-CH_2Cl \rightarrow CH_2Cl-\dot{C}Cl-CH_2Cl, \quad (2)$$

$$CH_2Cl-\dot{C}Cl-CH_2Cl + CH_2N_2 \rightarrow CH_2Cl-\underset{\displaystyle CH_2}{\overset{|}{C}}Cl-CH_2Cl + N_2,$$

$$CH_2Cl-\underset{\displaystyle \dot{C}H_2}{\overset{|}{C}}Cl-CH_2Cl \rightarrow CH_2Cl-\underset{\displaystyle CH_2Cl}{\overset{|}{\dot{C}}}-CH_2Cl, \quad (3)$$

$$CH_2Cl-\underset{\displaystyle CH_2Cl}{\overset{|}{\dot{C}}}-CH_2Cl + CH_2N_2 \rightarrow CH_2ClC-\underset{\displaystyle CH_2Cl}{\overset{|}{\underset{\displaystyle CH_3}{\overset{|}{C}}}}-CH_2Cl + N_2,$$

$$CH_2Cl-\underset{\displaystyle CH_2Cl}{\overset{|}{\underset{\displaystyle \dot{C}H_2}{\overset{|}{C}}}}-CH_2Cl + CCl_4 \rightarrow (CH_2Cl)_4C + \dot{C}Cl_3.$$

It might be supposed that in the reaction between diazomethane and carbon tetrachloride the C–Cl bond is ruptured and the biradical $\cdot CH_2^{\cdot}$ "inserted", which should also result in the formation of tetra(chloromethyl)methane. However, since CH_3CCl_3 and CH_2ClCCl_3 do not react with diazomethane under these conditions, this hypothesis was rejected.

Diazomethane reacts similarly with bromotrichloromethane, chloroform, and methyl trichloroacetate[64]. Methyl diazoacetate reacts with chloroform, carbon tetrachloride, and bromotrichloromethane with the formation of rearranged products[65]:

$$CHN_2COOCH_3 + XCCl_3 \rightarrow \underset{(G)}{CCl_3CHCOOCH_3} + (X) \; (X = H, Cl, Br),$$

(VI)
$$\underset{(G)}{CCl_3-\dot{C}HCOOCH_3} \rightarrow \underset{(G')}{\dot{C}Cl_2CHCl-COOCH_3}$$

$$\dot{C}Cl_2-CHCl-COOCH_3 \; (G') \begin{cases} \xrightarrow{XCCl_3} CCl_2X-CHCl-COOCH_3 + \dot{C}Cl_3 \; (X = H, Br) \\ \xrightarrow{-H} CCl_2=CCl-COOCH_3 \qquad (X = Cl, Br). \end{cases}$$

It must be emphasised that although the secondary radical (G) in scheme (VI) is stabilised by the neighbouring methoxycarbonyl group, it is nevertheless less stable than the (G′) radical which contains the $\dot{C}Cl_2$ group.

Reaction between olefines and sulphonyl chloride in the presence of t-butyl peroxide proceeds as follows[66]:

$$RCH=CH_2 + SO_2Cl_2 \begin{cases} \longrightarrow RCHClCH_2Cl \\ \longrightarrow (RCHClCH_2)_2SO_2. \end{cases}$$

The authors suggested that the reaction involves rearrangement of the radicals with 1,3-migration of chlorine from sulphur to carbon:

$$RCH=CH_2 + \dot{S}O_2Cl \rightarrow R-\dot{C}HCH_2SO_2Cl$$

$$\searrow \text{rearrangement}$$

$$RCHClCH_2SO_2CH_2\dot{C}HR \xleftarrow{RCH=CH_2} RCHClCH_2\dot{S}O_2$$
$$\downarrow SO_2Cl_2$$
$$(RCHClCH_2)_2SO_2 + \dot{S}O_2Cl.$$

Assuming that rearrangement of polyhalogenoalkyl radicals results in the formation of more stable radicals, the following table of relative stabilities has been set up:

$$CCl_3\dot{C}H_2 < \dot{C}Cl_2CH_2Cl \; [64]$$

$$CH_2ClCCl_2\dot{C}H_2 < CH_2Cl\dot{C}ClCH_2Cl \; [64]$$

$$(CH_2Cl)_2CCl\dot{C}H_2 < (CH_2Cl)_2\dot{C}CH_2Cl \; [64]$$

$$\dot{C}HClCCl_2CH_2Br < CHCl_2\dot{C}ClCH_2Br \; [55]$$

$$CCl_3\dot{C}HCH_2X < \dot{C}Cl_2CHClCH_2X \; (X=Cl \; [52], Br \; [52], CCl_3 \; [53], SC_6H_5 \; [50])$$

$$CCl_3\dot{C}HCOOCH_3 < \dot{C}Cl_2CHClCOOCH_3 \; [65]$$

$$CCl_3\dot{C}ClCH_2Br < \dot{C}Cl_2CCl_2CH_2Br \; [55]$$

$$CCl_3\dot{C}BrCH_2Y < \dot{C}Cl_2CClBrCH_2Y \; (Y=Br \; [58], SC_6H_5 \; [60])$$

$$CH_3CCl_2\dot{C}HCH_2Br < CH_3\dot{C}ClCHClCH_2Br \; [67]$$

$$CCl_3\dot{C}(CH_3)CH_2Br < \dot{C}Cl_2CCl(CH_3)CH_2Br \; [64]$$

$$CHCl_2\dot{C}HCH_2Br \leqslant \dot{C}HClCHClCH_2Br \; [56,57]‡$$

$$CHCl_2\dot{C}(CH_3)CH_2Br < \dot{C}HClC(CH_3)Cl-CH_2Br \; [57]‡$$

$$CFCl_2\dot{C}HCH_2Br \leqslant \dot{C}FClCHClCH_2Br \; [63]‡$$

$$CFCl_2\dot{C}BrCH_2Br \leqslant \dot{C}FClCClBrCH_2Br \; [63]‡$$

‡ Under the given conditions these radicals have comparable life-times. Sufficient data for an actual estimate of their stabilities are not available, but it appears that the stabilities of radicals in the left-hand column are less than or close to the stabilities of those in the right-hand column.

From this table, the radicals can be arranged in the following series with respect to their stability:

$$R\dot{C}H_2 < R_2\dot{C}H < R_3\dot{C} \leqslant R\dot{C}HCl < R_2\dot{C}Cl < R\dot{C}Cl_2,$$

where R are polyhaloalkyl radicals. The agreement between the left-hand side of this stability series and the related series for hydrocarbon radicals (primary < secondary < tertiary) emphasises the correctness of the hypothesis that the principal factor governing the occurrence of rearrangement is the formation of radicals which are more stable under the given conditions.

The available experimental evidence shows that the rearrangement involves intramolecular migration of a chlorine atom. For example, in the homolytic addition of HBr to 3,3,3-trichloropropene the process may be represented by scheme (A):

(A)
$$\begin{array}{ccc} Br + CCl_3CH{=}CH_2 & \longrightarrow & CCl_3\dot{C}HCH_2Br \\ \uparrow & & \downarrow \text{rearrangement} \\ Br + HCCl_2CHClCH_2Br & \xleftarrow{HBr} & \dot{C}Cl_2CHClCH_2Br. \\ & (III) & \end{array}$$

An alternative possibility is the migration of a chlorine atom to the reaction point and its subsequent addition to the double bond with the formation of a rearranged radical, as in scheme (B):

(B)
$$\begin{array}{ccccc} Br + CCl_3CH{=}CH_2 & \rightarrow & CCl_3\dot{C}HCH_2Br & \longrightarrow & CCl_2{=}CHCH_2Br + Cl \\ \uparrow & (I) & & & \downarrow \quad (II) \\ Br + HCCl_2CHClCH_2Br & \xleftarrow{HBr} & & & \dot{C}Cl_2CHClCH_2Br. \\ (III) & & & & \end{array}$$

However, the chlorine atom is known to add on very much more readily to compounds of type (I) than to those of type (II) and consequently process (B) cannot explain the observed preferential formation of the rearranged compound (III).

The fact that in a number of cases rearrangement does not yield any product which could be ascribed to intermolecular migration of chlorine constitutes the principal proof that the migration of the chlorine atom is intramolecular. Some examples of rearrangements of this type, which result in almost quantitative yields of a single product, are given below:

$$CCl_3CBr{=}CH_2 \xrightarrow{h\nu} CCl_2{=}CClCH_2Br,$$
$$CH_3CCl_2CBr{=}CH_2 \xrightarrow[HBr]{Bz_2O_2} CH_3CCl{=}CClCH_2Br,$$
$$CCl_3CH{=}CH_2 + HBr \xrightarrow{Bz_2O_2} HCCl_2CHClCH_2Br.$$

In addition to intramolecular migration of chlorine, intermolecular migration is also possible in a number of cases. This always leads to the formation of side products, as for example in scheme (C) which describes the homolytic addition of thiols to 3,3,3-trichloropropene with the formation of the rearranged compounds (V) (pathway *a*, *b*, *c*) and the unsaturated compounds (IV) plus hydrogen chloride (pathway *a*, *d*, *e*):

(C)
$$\begin{array}{ccccc} \dot{S}R + CCl_3CH{=}CH_2 & \xrightarrow{a} & CCl_3\dot{C}HCH_2SR & \xrightarrow{d} & CCl_2{=}CH{-}CH_2SR + Cl \\ & & & & (IV) \\ & & \downarrow b \text{ rearrangement} & & Cl + HSR \xrightarrow{e} HCl + \dot{S}R \\ \dot{S}R + HCCl_2CHClCH_2SR & \xleftarrow[c]{HSR} & \dot{C}Cl_2CHClCH_2SR. & & \\ (V) & & & & \end{array}$$

III. RADICAL REARRANGEMENTS WITH MIGRATION OF ARYL GROUPS

A. 1,2-Migration of Aryl Groups

A number of free-radical rearrangements involving 1,2-migration of aryl groups are known. The first such rearrangement, for the neophyl radical, was described by Urry and Kharasch[67] in 1944. They found that when phenylmagnesium bromide is allowed to react with 1-chloro-2-phenyl-2-methylpropane(neophyl chloride) in the presence of cobalt chloride, hydrocarbons (I)–(IV) are formed in 55% yield, which corresponds to 50% rearrangement. The following scheme was proposed:

$$C_6H_5MgBr + CoCl_2 \rightarrow C_6H_5CoCl + MgBrCl,$$
$$2C_6H_5CoCl \rightarrow C_6H_5C_6H_5 + 2CoCl',$$
$$C_6H_5C(CH_3)_2CH_2Cl + CoCl' \rightarrow C_6H_5C(CH_3)_2\dot{C}H_2 + CoCl_2,$$
$$C_6H_5C(CH_3)_2\dot{C}H_2 \xrightarrow{\text{ether}} \underset{(I)}{C_6H_5C(CH_3)_2CH_3},$$
$$C_6H_5C(CH_3)_2\dot{C}H_2 \xrightarrow{\text{rearrangement}} \dot{C}(CH_3)_2CH_2C_6H_5,$$
$$C_6H_5CH_2\dot{C}(CH_3)_2 \rightarrow \begin{cases} \underset{(II)}{C_6H_5CH_2\overset{CH_3}{\overset{|}{C}}{=}CH_2} + \underset{(III)}{C_6H_5CH_2CH(CH_3)_2} \\ \underset{(IV)}{C_6H_5CH{=}\overset{CH_3}{\overset{|}{C}}{-}CH_3} + III. \end{cases}$$

An analogous rearrangement takes place in the decarbonylation of β-phenylisovaleraldehyde catalysed by di-t-butyl peroxide, which results in approximately identical yields of t-butylbenzene and isobutylbenzene[68]. Seubold[69] studied the effect of dilution and temperature on the rearrangement in this reaction. He found that the ratio of the reaction products (isobutylbenzene : t-butylbenzene) to a large extent depends on the concentration of the aldehyde and only little on the temperature (see Table 4).

The dependence of the extent of rearrangement on the concentration suggests that the rearrangement involves the formation of a free neophyl radical with subsequent migration of the phenyl group, resulting in the formation of the phenylisobutyl radical:

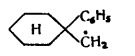
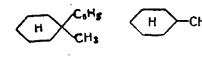
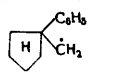
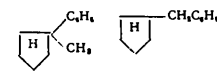
$$R_1\dot{C}O \xrightarrow{k_1} \dot{R}_1 + CO,$$
$$\dot{R}_1 + R_1CHO \xrightarrow{k_2} R_1H + R_1\dot{C}O,$$
$$\dot{R}_1 \xrightarrow[k_3]{\text{rearrangement}} \dot{R}_2,$$
$$\dot{R}_2 + R_1CHO \xrightarrow{k_4} R_2H + R_1\dot{C}O,$$
$$\frac{(R_2H)}{(R_1H)} \simeq \frac{d(R_2H)}{d(R_1H)} = \frac{k_3}{k_2(R_1CHO)}.$$

Another possibility, by analogy with heterolytic rearrangements, is that the phenyl group participates in the reaction

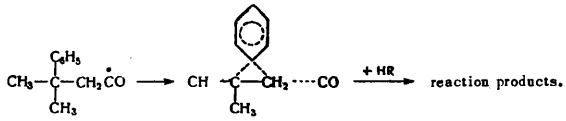
TABLE 4.

Temp., °C	Molar concn. of aldehyde in chlorobenzene	% rearrangement
130	6.4	51
130	1	80
130, 150	without solvent	57±3
170	ditto	63±3

TABLE 5. Decarbonylation of aldehydes (RCHO) on heating to 130°–150°.

No.	R	Migrating group	Temperature, °C	Products (overall yield, %)	% rearrangement	Reference
1	$C_6H_5C(CH_3)_2CH_2$	C_6H_5	130	$C_6H_5C(CH_3)_2CH_3$, $C_6H_5CH_2CH(CH_3)_2$ 71	57±3	68,69
2	$CH_3C_6H_4C(CH_3)_2CH_2$	p-$CH_3C_6H_4$	130	$CH_3C_6H_4C(CH_3)_2CH_3$, $CH_3C_6H_4CH_2CH(CH_3)_2$, $CH_3C_6H_4CH_2C(CH_3)=CH_2$, $CH_3C_6H_4CH=C(CH_3)_2$ 55	48–49	78
3	$(C_6H_5)_2C(CH_3)CH_2$	C_6H_5		$[C_6H_5CH_2C(CH_3)C_6H_5]_2$ 34	100	26
4	$(C_6H_5)_2C(CH_3)CH_2$	C_6H_5	140	$(C_6H_5)_2CHCH_2C_6H_5$, $(C_6H_5)_2C=CHC_6H_5$ 24.3	96	27
5	$(C_6H_5)_2C(CH_3)CH$	C_6H_5		$(C_6H_5)_2CHCH(CH_3)C_6H_5$, $(C_6H_5)_2C=C(CH_3)C_6H_5$ 33	100	26
6	p-$NO_2C_6H_4C(C_6H_5)_2CH_2$	p-$NO_2C_6H_4$	140	p-$NO_2C_6H_4CH=C(C_6H_5)_2$ unidentified p-nitrophenyl-hydrocarbon 4	80	27
7		C_6H_5	140	 47	89	70,79
8		C_6H_5	140	 74	63	70,79
9	$CH_3OC_6H_4CD(C_6H_5)CH_3$	C_6H_5 or $CH_3OC_6H_4$	140	$CH_3OC_6H_4CD(C_6H_5)CH_3$ 45–50	0	27
10	$C_6H_5{}^{14}CH_2CH_3$	C_6H_5	145–150 (in chlorobenzene)	$C_6H_5{}^{14}CH_2{}^{(14)}CH_3$, $C_6H_5{}^{14}CH{=}{}^{(14)}CH_2$ 67.8	3.3±0.1	24
11	$C_6H_5CH_2C(CH_3)_2$	C_6H_5		$C_6H_5CH_2CH(CH_3)_2$	0	78

through a bridge-type transition state, for example as follows:



Here the proportion of the reaction product should not depend on the concentration of the hydrogen donor, in this case aldehyde. It is noteworthy that the 1,1-dimethyl-2--phenylethyl radical obtained by the decarbonylation of the corresponding aldehyde does not rearrange to the neophyl radical (No. 11 in Table 5).

Later[9,24,70] it was shown that the extent of rearrangement during the decarbonylation of aldehydes decreases on addition of a hydrogen donor, for example, toluene-ω-thiol or thiophenol, to the reaction mixture. Such a reaction may be represented as follows:

$$RSH + \dot{A} \rightarrow R\dot{S} + AH,$$
$$R\dot{S} + R_1CHO \rightarrow RSH + R_1\dot{C}O,$$
$$R_1\dot{C}O \rightarrow \dot{R}_1 + CO,$$
$$\dot{R}_1 \xrightarrow{RSH} R_1H + R\dot{S}$$
$$\dot{R}_1 \xrightarrow{\text{rearrangement}} \dot{R}_2,$$
$$\dot{R}_2 + RSH \rightarrow R_2H + R\dot{S},$$

where R = C_6H_5, $C_6H_5CH_2$.

The chain transfer constants for mercaptans are known to be much higher than for aldehydes[71,72], *i.e.* mercaptans are better hydrogen donors in free-radical reactions than aldehydes. This confirms the data obtained by Slaugh[24], who found that the side chain of the ethylbenzene obtained in the decarbonylation of 3-phenylpropionaldehyde in the presence of tritium-labelled toluene-ω-thiol contained tritium. Thus addition of the mercaptan shortens the life

of the radical so that the latter does not have time to undergo rearrangement. Seubold[69] explains the absence of rearrangement in the peroxide-catalysed chlorination of t-butylbenzene[73] by the fact that the rate of the reaction of the neophyl radical with chlorine is higher than the rate of the rearrangement.

The small temperature dependence of the relative yields of the reaction products shows that the activation energy for the rearrangement and for the removal of hydrogen from the aldehyde are approximately the same. For the latter process, $E = 7-8$ kcal mole^{-1}§. Seubold[69] also quotes the heat of migration of the phenyl group in the neophyl radical:

$$\dot{H} + C_6H_5C(CH_3)_2\dot{C}H_2 \rightarrow C_6H_5C(CH_3)_2CH_3 + 95.5 \text{ kcal mole}^{-1}$$

(it is assumed that this quantity is the same as in neopentane),

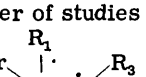
$$C_6H_5CH_2CH(CH_3)_2 \rightarrow C_6H_5CH_2\dot{C}(CH_3)_2 + \dot{H} - 86.5 \text{ kcal mole}^{-1}$$

(as in isobutane),

$$\frac{C_6H_5C(CH_3)_2CH_3 \rightarrow C_6H_5CH_2CH(CH_3)_2 - 0.3 \text{ kcal mole}^{-1},}{C_6H_5C(CH_3)_2\dot{C}H_2 \rightarrow C_6H_5CH_2\dot{C}(CH_3)_2 + 8.7 \text{ kcal mole}^{-1}.}$$

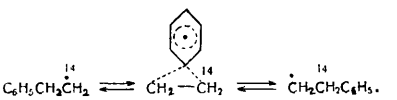
Apart from the above examples, the rearrangement of the neophyl radical was also observed in the decomposition of β-phenylisovaleryl peroxide[74], when bromine was allowed to react with the silver salt of β-phenylisovaleric acid. Here, however, contradictory results were obtained: Berr[75] and Wilt[76] state that there is no rearrangement in the reaction, whereas Smith and Sellas[77] found the extent of rearrangement to be 52%. In general, the extent of rearrangement should depend on the relative rate of the rearrangement of the radical with respect to the rates of the competing reactions (substitution, disproportionation, etc.). The dependence of the extent of rearrangement on the rates of the competing reactions is particularly evident (as described above) in the case of the neophyl radical (dependence on the hydrogen donor concentration, absence of rearrangement in the chlorination of t-butylbenzene, etc.).

From a comparison of the extent of rearrangement in a series of similar reactions, assuming that the rates of the competing reactions change little within a given series, the qualitative dependence of the rate of isomerisation on the structure of the radicals can be determined.

A number of studies on the rearrangement of radicals of the type  , where R_1 and R_2 = H, CH_3, Ar, and R_3 and R_4 = H, Alk are summarised in Tables 5 and 6. Great care must be exercised in comparing radicals which were obtained in different reactions and consequently had different lifetimes. Even in a series of similar reactions, as for example in the decarbonylation of aldehydes, the radicals formed in the intermediate stage are stabilised at different rates and sometimes even by different pathways because of the differences in the structure of the aldehydes and their transfer constants. For instance, in the decarbonylation of phenylisovaleraldehyde (No. 1 in Table 5) the radicals react by removing a hydrogen atom from the aldehyde, whereas in the decarbonylation of β,β-diphenylbutyraldehyde (No. 3 in Table 5) the radicals dimerise; under these conditions triphenylethyl radicals (No. 4 in Table 5) are stabilised mainly by disproportionation.

Rearrangement depends markedly on the degree of substitution at the β-carbon atom, the quantity of rearranged products increasing with increase in the number of substituents. This increase may be due to a number of factors: steric strain in the initial radical, the tendency to form a more stable radical (the rearrangement of a primary to a secondary or tertiary radical), etc. (*cf.* Nos. 1, 10, and 11 in Table 5 and 1, 2, and 3 in Table 6).

In the case of the phenylethyl radical (No. 10 in Table 5 and No. 1 in Table 6) structural factors favouring rearrangement are lacking. Here rearrangement may be effected by the formation of a bridge-type transition state, in which the unpaired electron is delocalised over the benzene ring:



As a result, 50% rearrangement might be expected. However, in practice this equilibrium is not attained and the yields of rearranged products prove to be much lower. Thus when [2-^{14}C]-3-phenylpropionaldehyde is decarbonylated, rearrangement takes place to the extent of only a few per cent. As with the neophyl radical, the rearrangement depends on dilution and on the addition of mercaptan, which is interpreted as proof that the reaction goes *via* the free [^{14}C]-2-phenylethyl radical. In this case the extent of rearrangement increases with the temperature. Thus, unlike the case of the neophyl radical, the activation energy for the migration of the phenyl group in the phenylethyl radical is somewhat higher than the energy required for the removal of a hydrogen atom from the aldehyde.

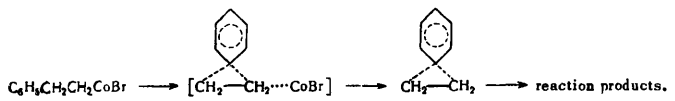
The appreciable rearrangement in the reaction of 2-phenylethyl bromide with magnesium in the presence of cobalt bromide (No. 1 in Table 6) may be explained by the

TABLE 6. Rearrangements in Grignard reactions in the presence of cobalt salts.

No.	R	Reaction	Products (overall yield, %)	% rearrangement	Reference
1	$C_6H_5CH_2\overset{14}{C}H_2$	RBr+Mg+CoBr$_2$	$C_6H_5CH{=}CH_2$, $C_6H_5CH_2CH_3$ 44	19—20	80
2	$C_6H_5\overset{CH_3}{\underset{|}{C}}HCH_3$	RBr+Mg+CoBr$_2$	$C_6H_5\overset{CH_3}{\underset{CH_3}{C}}H$, $C_6H_5\overset{CH_3}{\underset{|}{C}}{=}CH_2$; $C_6H_5CH_2CH_2CH_3$; $C_6H_5CH{=}CHCH_3$, $C_6H_5CH_2CH{=}CH_2$ 17	40	80
3	$C_6H_5\overset{CH_3}{\underset{CH_3}{C}}CH_2$	RCl+C_6H_5MgBr+CoCl$_2$	$C_6H_5C(CH_3)_2CH_3$, $C_6H_5CH_2\overset{CH_3}{\underset{|}{C}}{=}CH_2$; $C_6H_5CH_2CH(CH_3)_2$, $C_6H_5CH{=}C\overset{CH_3}{\underset{CH_3}{<}}$ 55	50	67
4	$CH_3C_6H_4\overset{CH_3}{\underset{CH_3}{C}}CH_2$	RCl+C_6H_5MgBr+CoCl$_2$	p-$CH_3C_6H_4\overset{CH_3}{\underset{CH_3}{C}}CH_3$, p-$CH_3C_6H_4CH_3$, p-$CH_3C_6H_4CH{<}\overset{CH_3}{\underset{CH_3}{}}$; p-$CH_3C_6H_4CH_2\overset{CH_3}{\underset{|}{C}}{=}CH_2$; p-$CH_3C_6H_4CH{=}\overset{CH_3}{\underset{|}{C}}CH_3$ 54.6	36	78

§ Signs of the heats have been changed throughout to conform with English notation (Ed. of Translation).

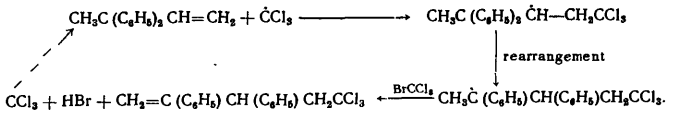
long lifetime of the radical in this reaction. It is also possible that decomposition of phenylethylcobalt halide proceeds in step with the rearrangement, for example[80]:



The question of the formation of non-classical transition states may be resolved by studying the stereospecificity of group migration.

The rearrangement is also considerably influenced by the nature of the substituent at the β-carbon atom. Curtin and coworkers[26,27] studied the decarbonylation of a number of aryl-substituted aldehydes (Nos. 3, 4, 5, 6, and 9 in Table 5). Their results show that when the methyl groups of the neophyl radical are replaced by phenyl groups, the capacity of the radicals to undergo rearrangement increases. Thus, in the decarbonylation of β,β-diphenylbutyraldehyde, β,β,β-triphenylpropionaldehyde, and β,β,β-triphenyl-α-methylpropionaldehyde, only rearranged products were obtained. Rearrangement of the β,β,β-triphenylethyl radical was also observed in the thermal decomposition of $(C_6H_5)_3CCH_2CN{=}NCCH_2C(C_6H_5)_3$, resulting in the formation of β,β,α-triphenylethane and triphenylethylene in approximately equal amounts[81].

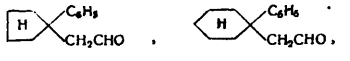
A rearrangement was also found to occur[82] in the peroxide-catalysed addition of butyraldehyde to 3,3-diphenylbut-1-ene, the reaction yielding 2,3-diphenyloctan-4-one. A similar rearrangement was observed[83] in the reaction of this diphenylbutene with bromotrichloromethane in the presence of benzoyl peroxide:



It is interesting that in the homolytic addition of butane thiol or thiolacetic acid to the same diphenylbutene there is no migration of the phenyl group.

The presence of the p-methoxyphenyl group in α-phenyl-α-(p-methoxyphenyl)ethyl radical (No. 9 in Table 5) suppresses rearrangement, the only product of the reaction being α-phenyl-α-(p-methoxyphenyl)ethane.

Very few data are available on the effect of other substituents. Wilt and Philip[70,79] studied the effect on the rearrangement of the incorporation of the cyclopentyl and cyclohexyl rings in the aldehyde molecule. They found that, in the t-butyl peroxide catalysed decarbonylation of aldehydes with structures



the size of the ring appreciably influences the extent of rearrangement (Nos. 7 and 8 in Table 5). The effect of temperature and mercaptans is shown in Table 7. The marked influence of toluene-ω-thiol on the rearrangement

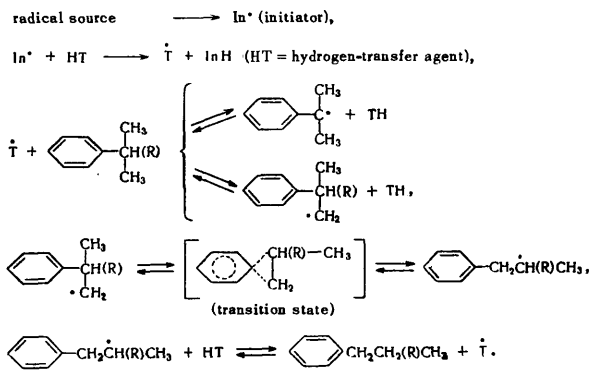
TABLE 7.

R	% rearrangement at various temperatures			
	140°	190°	132° (in chlorobenzene)	160° (20 mole % toluene-ω-thiol)
1-Phenylcyclopentyl	63	71	92	3
1-Phenylcyclohexyl	89	91	94	50

was interpreted by the authors as a confirmation of the free-radical mechanism, the following radicals participating in the reaction:

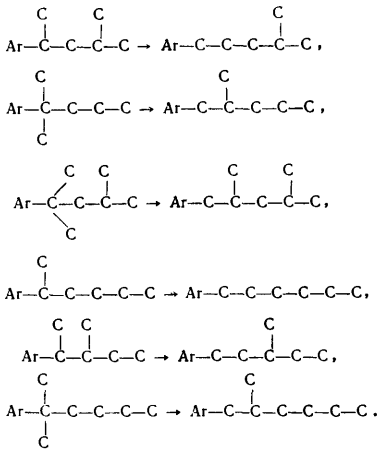
The percentage rearrangement was calculated from the proportions of the hydrocarbons formed, which were obtained in 64–74% yield in the case of the cyclopentyl derivative, and in 21–47% in the case of the cyclohexyl derivative.

The concept of 1,2-migration of the phenyl group was used to explain the isomerisation of certain alkylbenzenes during pyrolysis at high pressure[84,85]. When isopropylbenzene, p-isopropyltoluene, and s-butylbenzene were passed through a heated copper tube (816 atm, 479°–528°), n-propylbenzene, p-n-propyltoluene, and n-butylbenzene (the last in small yield) were obtained respectively, as well as other products[85]. Quite recently Slaugh and Raley[85] found that when these alkylbenzenes are pyrolysed in an autoclave in the presence of effective chain-transfer agents, the yields of the rearranged alkylbenzenes increase. Chain-transfer agents such as C_6H_5SH, H_2S, etc. are either introduced directly or are formed as a result of pyrolysis of halogen- or sulphur-containing promoters. The authors believe the best promoters to be organic bromo-derivatives. The following mechanism was proposed for this isomerisation:

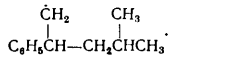


The relatively difficult removal of a hydrogen atom from the β-position in isopropylbenzene appears to be facilitated by the removal of the resulting radical from the equilibrium system by the 1,2-migration of the phenyl group followed by further reactions of the isomeric radical.

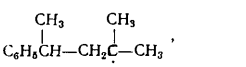
Similar isomerisations with 1,2-migration of the aryl group were also observed in the thermal alkylation (410–420 atm, 400°–485°) of alkylbenzene with olefines[86-88], in the following systems:



For example, alkylation of ethylbenzene with isobutene[86] yielded 2-methyl-4-phenylpentane and 1-phenyl-4-methylpentane, the formation of which is explained by the migration of the phenyl group in the radical



The latter may arise either as a result of 1,4-migration of hydrogen in the radical intermediate formed during the alkylation,



or by the removal of hydrogen from the α-methyl group in 2-methyl-4-phenylpentane (*cf.* isomerisation of alkylbenzenes).

B. Radical Rearrangements with 1,2-Migration of Aryl Groups from Carbon to Oxygen

According to thermochemical calculations, rearrangement of alkoxy radicals ($R_3C-\dot{O}$) with migration of substituents to oxygen should be accompanied by a gain in energy[89]. However, in practice such rearrangements are observed only in radicals containing three aryl groups: $Ar_3C-\dot{O} \rightarrow Ar_2\dot{C}-OAr$. Kharasch *et al.*[90] concluded that the formation of the diphenyl ether of benzopinacol in the thermal decomposition of triphenylmethyl peroxide[91] and triphenylmethyl hyponitrite[92], and in the decomposition of triphenylmethyl hydroperoxide in the presence of ferrous salts, goes *via* the rearrangement of the free radical:

$$(C_6H_5)_3C-\dot{O} \rightarrow (C_6H_5)_2\dot{C}-OC_6H_5 \rightarrow \text{dimer.}$$

Direct confirmation of the formation of free radicals when hydroperoxides are decomposed in the presence of ferrous salts was obtained by Kharasch and his coworkers[93] in the reactions of t-butoxy and α-cumyloxy radicals. In the presence of butadiene, products expected for a reaction between radicals and an olefine were obtained:

$$ROOH + Fe^{2+} \rightarrow R\dot{O} + FeOH^{2+},$$
$$R\dot{O} + CH_2{=}CH{-}CH{=}CH_2 \rightarrow (ROC_4H_6)^{\cdot};$$
$$2\,(ROC_4H_6)^{\cdot} \rightarrow (ROCH_2CH{=}CHCH_2{-})_2,$$
$$2\,(ROC_4H_6)^{\cdot} \rightarrow ROCH_2CH{=}CHCH_2CH\,(CH{=}CH_2)\,CH_2OR.$$

To determine the relative capacity of aryl groups for migration, Kharasch and his coworkers[94] studied the thermal decomposition of t-butyltriarylmethyl peroxides in cumene solution. The following reaction scheme was proposed:

$$(C_6H_5)_2COOC(CH_3)_3 \rightarrow (C_6H_5)_2C\dot{O} + (CH_3)_3C\dot{O},$$
$$(CH_3)_3C\dot{O} + C_9H_6C(CH_3)_2H \rightarrow C_6H_5(CH_3)_2\dot{C},$$
$$[\text{and also } CH_4 + (CH_3)_2CO \text{ or } (CH_3)_2COH],$$
$$2\,(C_6H_5)_2C\dot{O} \rightarrow 2C_6H_5O(C_6H_5)_2\dot{C} \rightarrow [C_6H_5O(C_6H_5)_2C{-}]_2,$$
$$[C_6H_5O(C_6H_5)_2C{-}]_2 + C_6H_5(CH_3)_2\dot{C} \rightarrow C_6H_5O(C_6H_5)_2C{-}C(CH_3)_2C_6H_5 +$$
$$+ C_6H_5O(C_6H_5)_2\dot{C}.$$

The extent of rearrangement was determined by the hydrolysis of the reaction product with subsequent estimation of the phenols. Before hydrolysis the product contained only slight quantities of phenols. The rearrangements of the radicals $ArC(C_6H_5)_2\dot{O}$ (where Ar = p-$CH_3C_6H_4$, α-naphthyl, p-biphenylyl) were investigated in this way, and the capacity for migration of the groups in the given compounds was assessed from the proportions of the aryloxy derivatives. The mobilities of the phenyl and tolyl radicals proved to be approximately the same. The rate of migration of the α-naphthyl and p-biphenylyl groups is six times greater than that of the phenyl group.

Attempts were also made to compare the capacities for migration of p-nitrophenyl and phenyl groups. The following compounds were obtained in the thermal decomposition of nitrophenyldiphenylmethyl hydroperoxide[95]: phenol, p-nitrophenol, p-nitrobenzophenone, p-nitrophenyldiphenylmethanol, and biphenyl. The large quantity of p-nitrophenol and the absence of benzophenone suggest that the rate of migration of the nitrophenyl group is high compared with that of the phenyl group, but the mechanism of the reaction remains obscure. The results obtained in the thermal decomposition of t-butyl p-nitrophenyldiphenylmethyl peroxide are no more definite[94]:

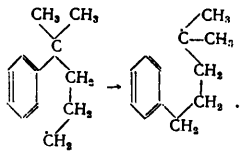
$$p\text{-}NO_2C_6H_4C(C_6H_5)_2{-}O{-}O{-}\ t\text{-}C_4H_9.$$

The results obtained in studies on carbon–carbon rearrangements lead to analogous conclusions about the capacity for migration of certain aryl groups. For example, the proportions of the rearranged and non-rearranged products in the decarbonylation of phenylisovaleraldehyde and p-tolylisovaleraldehyde (Nos. 1 and 2 in Table 5) are similar; this is also the case in the reactions of neophyl chloride and p-methylneophyl chloride with a Grignard reagent in the presence of cobalt chloride (Nos. 3 and 4 in Table 6). It is therefore concluded that the capacities of the phenyl and p-tolyl groups for 1,2-migration are the same. In the decarbonylation of β,β-diphenyl-β-p-nitrophenylpropionaldehyde (No. 6 in Table 5) α-p-nitrophenyl-β,β-diphenylethylene was obtained in 3.3% yield, which constituted approximately 80% of the nitrohydrocarbon monomer fraction. The authors therefore suggested that the p-nitrophenyl group migrates more readily than the phenyl group.

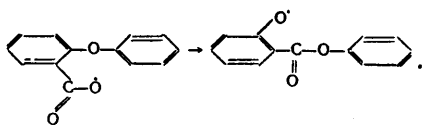
C. Migration of Aryl Groups to a More Distant Radical Centre

There are indications that migration of the phenyl group in free radicals to more distant atoms may be possible.

Winstein *et al.*[9] observed the 1,4-rearrangement in the peroxide-catalysed decarbonylation of 5-methyl-5-phenylhexanal:

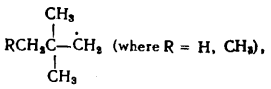


The rearrangement was inferred from the presence of 2-methyl-5-phenylpentane [$C_6H_5CH_2CH_2CH_2CH(CH_3)CH_3$]. In the thermal decomposition of 2-phenoxybenzoyl peroxide[96] phenyl salicylate was obtained, the formation of which the authors explained by the migration of the phenyl group in the free radical:

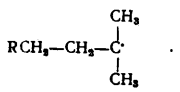


IV. RADICAL REARRANGEMENTS WITH MIGRATION OF ALKYL GROUPS

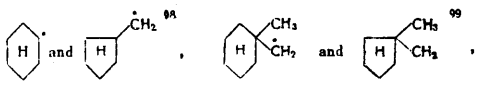
In contrast to carbonium ions in which migration of alkyl groups is frequently observed, hydrocarbon radicals in solution are very stable to such rearrangement. Thus neopentyl[97] and neohexyl[78,98] radicals,



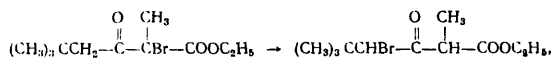
obtained in various ways, do not rearrange to t-pentyl and t-hexyl radicals:



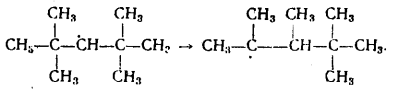
Radicals with the structures



formed in the peroxide-catalysed decomposition of the corresponding aldehydes, also do not undergo isomerisation in which there is a change in the carbon framework. In fact, the absence of migration of the methyl group in the isomerisation of the α-bromoacetoacetic ester[100] containing the neopentyl group,

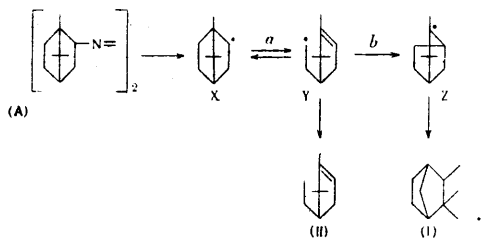


is quoted as proof that the reaction may proceed by a radical mechanism. However, the products obtained in the bromination of 2,2,4,4-tetramethylpentane under ultraviolet illumination (200°) and in the reaction of 3-chloro-2,2,4,4-tetramethylpentane with a Grignard reagent in the presence of $CoBr_2$ are explained by postulating the rearrangement of the initially formed secondary radical to the tertiary radical[101]:

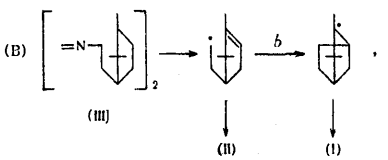


In this case the rearrangement may be due to the structure of the radical in which the methyl groups screen the carbon atom with a free valency; the lifetime of the radical is thereby increased and hence the probability of the rearrangement. It is not impossible, however, that the change in the carbon framework in the above example may be due to a number of other factors, unrelated to homolytic migration of the methyl group (for example, ionic isomerisation of the reaction products).

Isomerisation of alkyl radicals involving rupture of the C–C bond requires considerable activation energy. This is apparently the reason for the low probability of such isomerisation in the liquid phase (at a moderate temperature). At higher reaction temperatures, the migration of alkyl groups becomes more probable. Thus, in the peroxide catalysed decomposition of at 140°–150°, the bornyl radical formed does not undergo a rearrangement involving rupture of the C–C bond[102]. If, however, the bornyl radical comes from 2,2′-bisazocamphane, the decomposition of which requires temperatures up to 255°–290° (in hexadecane), then homolytic rearrangement (of the Wagner–Meerwein type) of the radical does occur[102]. In addition to disproportionation products of the initially formed bornyl radical, , isocamphane (I) (mixture of stereoisomers) and trimethylethylcyclopentene (II) were isolated in the reaction. The authors explain their formation by the following scheme:

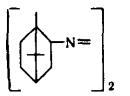


Here the molar ratio (I) : (II) = 0.035 : (> 0.01). To obtain experimental confirmation of this hypothesis, the authors studied the decomposition of the azo-compound (III) under the same conditions and again isolated compounds (I) and (II), the formation of which was represented as follows:

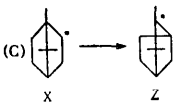


the molar ratio being (I) : (II) = 0.5 : 2.1.

A C–C bond is ruptured in stage *a*, *b* and a new one formed. However, in the decomposition of 2,2′-bisazocamphane,

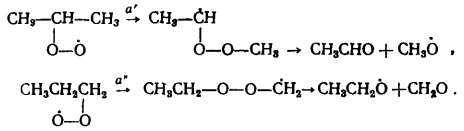


there is also the possibility that the bornyl radical may rearrange as follows:



i.e. radical X rearranges to Z, omitting the stage in which radical Y is formed [scheme (A)]. Otherwise the ratio (I) : (II) in reactions (A) and (B) should be the same.

The probability of such rearrangements becomes greater in the gas phase (at a high temperature)[7,9]. Thus, according to Semenov and his coworkers[7], the appearance of formaldehyde and acetaldehyde in the gas-phase oxidation of propane is due to isomerisation with C–C bond rupture of the normal and branched-chain peroxy radicals formed in the oxidation. The scheme proposed by Semenov and his coworkers includes migration of an alkyl group in stages *a′* and *a″*:



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THE STEREOCHEMISTRY AND MECHANISM OF DEHYDRATION OF CYCLOHEXANE DERIVATIVES

N. Ya. Grigor'eva and V. F. Kucherov

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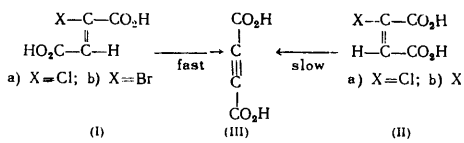
INTRODUCTION

Since van't Hoff formulated the principles of the stereochemistry of tetravalent carbon, the attention of chemists has constantly been attracted to problems connected with the steric course of the fundamental chemical reactions, such as addition, elimination, and replacement, and with the differences in reactivity between geometric isomers. From a formal examination of the tetrahedral models of van't Hoff, it appeared natural that in substitution the entering atoms or group of atoms should occupy the same position as the leaving group, and that addition and elimination reactions should proceed most readily when the entering or leaving groups are as close as possible. This

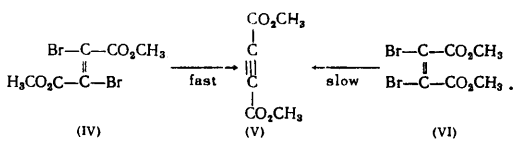
concept was formulated by van't Hoff, and strongly supported by Wislicenus[1], as the *cis*-principle of steric elimination and addition. Wislicenus gave no experimental confirmation of his ideas, but he used them extensively as a general method for establishing the configuration of unsaturated compounds[1,2].

Michael[3,4] approached the study of steric behaviour in addition and elimination reactions in a different way. Taking as a basis his studies on the halogenofumaric and halogenomaleic acids, the configurations of which had been established independently, he showed that on being treated with alkali solutions the halogenofumaric acids (Ia, b) eliminate hydrogen halide to form acetylenedicarboxylic acid (III) (*trans*-elimination) more readily than the corresponding halogenomaleic acids (IIa, b) (*cis*-elimination).



(I) (III) (II)

Generalising Michael's observations, Pfeifer[5] suggested that the greater ease with which the elements of the hydrogen halide are eliminated when these are in the *trans*-position might be used to determine the configurations of unsaturated compounds (*trans*-principle of steric elimination). The validity of this principle was confirmed by Lossen[6], who found that when dimethyl dibromofumarate (IV) is debrominated with zinc, the reaction proceeds much more readily than the debromination of the diester of dibromomaleic acid (VI).



(IV) (V) (VI)

Shavanne[7], who held similar views, showed that *trans*-elimination can be much faster than *cis*-elimination, as exemplified by the isomeric *cis*- and *trans*-dichloroethylenes.

However, notwithstanding these and many similar reports, the idea that spatially adjacent groups are more readily eliminated was widely used to determine the configuration of compounds right up to the thirties. Thus, the configurations of the isomeric aldoximes and ketoximes, determined by Hantzschand Werner[8,9] on the basis of the *cis*-principle of the elimination of water with the formation of the corresponding nitrile, were not corrected until 1924–1925 (Meisenheimer[10]). The configurations of the amines of the terpene series established by Wallach[11] on the basis of the principle of preferential elimination of spatially adjacent groups was reexamined by Read *et al.*[12] as late as 1934. The configurations of the isomeric alicyclic alcohols, also adopted on the basis of this principle (Semmler[13], Wallach[14], and Zeitschel[15]) were corrected by Vavon and Barbier[16-18] in 1931.

Sufficient experimental evidence had accumulated in the early thirties to show that the *trans*-principle is valid for elimination reactions in solution (alkaline dehydrohalogenation, acid-catalysed dehydration of alcohols, conversion of oximes to nitriles, deamination of amines by nitrous acid, etc.). However, it was also known that the *cis*-elimination principle applies to pyrolytic reactions (the Chugaev reaction, pyrolysis of some esters, and cleavage of quaternary ammonium bases).

An understanding of the reasons for the differences in reaction stereochemistry became possible only with the development of the transition-state theory and of electronic theories in organic chemistry. A consideration of modern ideas on the steric principles of chemical reactions therefore presupposes elucidation of the relation between the stereochemistry and the reaction mechanism. This relationship appears, for example, because electron displacements in a system reacting in a definite way can only arise when the reaction groups are appropriately oriented (in the English literature this principle is formulated as "the steric requirements of the reaction"; for example, the *trans*-orientation of groups in bimolecular eliminations). The steric arrangement of the molecule can materially affect the reaction rate within the limits of a given mechanism (steric and synartetic acceleration); the change in reaction mechanism produced by structural factors is an extreme expression of such an effect.

The object of the present review is to examine the stereochemistry of direct and indirect dehydration† of alicyclic six-membered hydroxy-compounds. This limitation is made for two reasons: firstly, within the scope of a comparatively short review it is impossible to consider the literature on the dehydration of all organic compounds: secondly, it is in the case of six-membered alicyclic compounds that the steric principles of dehydration have been studied in greatest detail.

The overwhelming majority of the dehydration reactions of alicyclic alcohols that have been investigated may be divided into two main groups, reactions in solution and intramolecular pyrolysis reactions without a solvent or catalyst. The structure of the corresponding transition states forms the basis of the division of dehydration reactions into two groups. In the first group this structure is an open one and solvent molecules as well as ions in solution may take part in its formation. In the second group the transition state is closed (cyclic). The latter reactions are always unimolecular. We shall therefore examine the main stereochemical features of reactions of both types in turn.

I. IONIC DEHYDRATION REACTIONS IN SOLUTION

The interpretation of the mechanism of these reactions as a special case of nucleophilic elimination was developed and experimentally confirmed by the Ingold–Hughes[19-22] school as early as the 1930's. The following are the main conclusions. Nucleophilic elimination reactions may proceed either by a unimolecular or by a bimolecular mechanism (E1 or E2)‡, according to the structure of the initial

† By "indirect dehydration" is understood elimination of the elements of the acid from the esters of the corresponding hydroxy-compounds.

‡ In recent years it has been shown that elimination reactions are not quite correctly represented by E1 and E2 mechanisms; because of solvent participation, these reactions are in fact polymolecular. However, since this solvent participation does not change the spatial direction of electron transfer, and therefore the stereochemical reaction requirements, we shall use the interpretations of Ingold on E1 and E2 elimination mechanisms.

molecule and the experimental conditions employed. The bimolecular E2 mechanism is characteristic of elimination reactions occurring in the presence of a strong base[19,22]. It may be represented by the following scheme:

$$Y^- + H-C_\beta R_2-C_\alpha R_2-X \longrightarrow Y\cdots H\cdots C_\beta R_2\cdots C_\alpha R_2\cdots X \longrightarrow YH + CR_2=CR_2 + X^-, \quad (1)$$

according to which a hydrogen atom is removed as a proton by means of the nucleophilic reagent (for example, the base Y^-), and simultaneously the $C_\beta - H$ bond electrons liberated are transferred to the octet of the C_α atom, and the electron-acceptor group X is eliminated as an anion. The E2 mechanism therefore implies that the formation of the new and the rupture of the old bonds are synchronous processes, the one facilitating the other. From the foregoing, it follows that a reaction proceeding by the E2 mechanism may be represented by a second-order kinetic equation: $V = K_2[Y^-][HCR_2-CR_2X]$.

The second possible elimination mechanism is the unimolecular E1 mechanism[20,22], which occurs in two steps:

$$\left.\begin{array}{l} HCR_2-CR_2X \xrightarrow[\text{slow}]{} HCR_2-C^+R_2+X^- \\ HCR_2-C^+R_2 \xrightarrow{\text{fast}} H^+ + CR_2=CR_2 \end{array}\right\}. \quad (2)$$

The first slow step is a unimolecular heterolysis (in which the nucleophilic reagent does not take part), as a result of which a carbonium ion is formed; this loses a proton by interaction with the solvent or with another nucleophilic reagent and is stabilised as an olefine. Since the reaction rate depends on the slowest step, the rate of an E1 reaction is independent of the concentration of the base and is represented by a first-order kinetic equation: $V = K_1[HCR_2CR_2X]$.

The kinetic method is therefore the main experimental procedure used to distinguish between E1 and E2 elimination mechanisms, and it has been developed in detail for this purpose by Ingold's school. In 1947 Cristol[23] suggested the use of kinetic results together with the analysis of the final mixture of products for the investigation of the steric course of elimination reactions, and a number of important general quantitative principles have been established by this means.

When the reaction mechanism cannot be decided unambiguously by the kinetic method, useful results may be obtained by the tracer method, developed for this purpose by Skell and Hauser[24]. With this method it is possible, for example, to distinguish between second-order bimolecular reactions and so-called elimination reactions of the conjugate base of the substrate (E1*cB*)[22]:

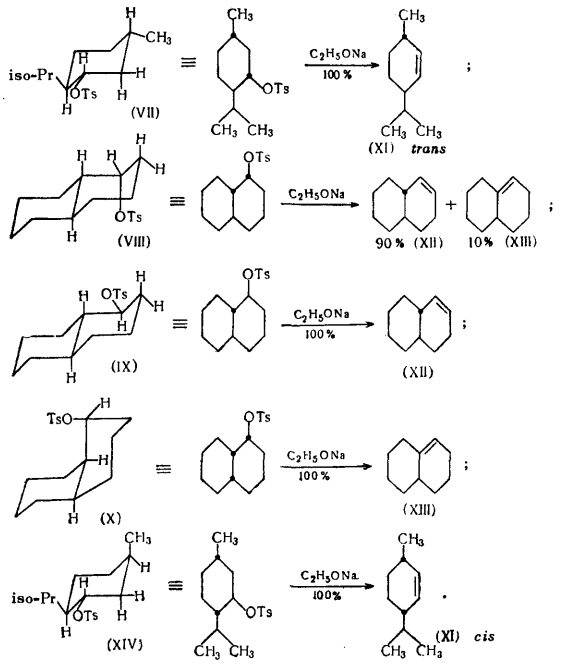
$$\left.\begin{array}{l} Y^- + HCR_2-CR_2X \rightleftarrows YH + C^-R_2-CR_2X \\ C^-R_2-CR_2X \rightarrow X^- + CR_2=CR_2 \end{array}\right\} \quad (3)$$

Such reactions are two-stage and include a reversible bimolecular step in which the conjugate base (carbanion) is formed; this then eliminates an electron-acceptor group as an anion and forms an olefine. The reversibility of the first stage of this reaction is utilised to verify it experimentally. If an E1*cB* mechanism operates in the presence of YH enriched with YD, the initial product HCR_2CR_2X unreacted after a definite time must be enriched with DCR_2CR_2X. In contrast, with the synchronous E2 mechanism the unreacted compound should not contain deuterium.

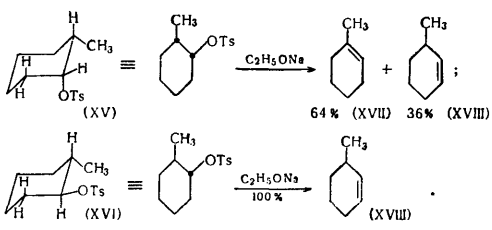
This method also found an interesting application in the elucidation of reaction mechanisms when the stereochemistry of the initial molecule does not allow the elimination mechanism expected from the experimental conditions (see below).

1. Stereochemistry of Bimolecular Dehydration Reactions

Preferred orientation in bimolecular dehydrations. In 1940 Hückel *et al.*[25] first clearly formulated the principle that the steric course of a reaction depends on its mechanism. Having analysed a large amount of experimental material, they showed that the *trans*--principle is rigidly followed in elimination reactions occurring in the presence of a strong base (they considered such reactions to be bimolecular). Of other reactions, they examined one of the types of indirect dehydration — the cleavage of the *p*-toluenesulphonates (tosylates) of *l*-menthol (VII) and the isomeric decalols (VIII)–(X)§ by sodium ethoxide. Since it was later rigorously proved[26,27] that the E2 mechanism applies to the cleavage of tosylates by strong bases, this reaction is a convenient example for examination of the stereochemistry of bimolecular indirect dehydration:

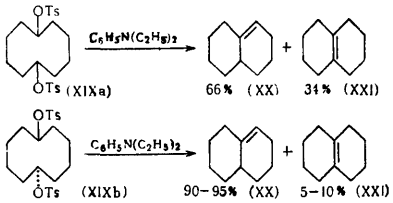


As the examples given show, the *p*-toluenesulphonic acid residue is eliminated together exclusively with the hydrogen situated *trans* to it. This was confirmed by Hückel *et al.*[28,29] with the isomenthyl tosylates (XIV) and also with those of the *cis*- and *trans*-2-methylcyclohexanols (XV) and (XVI):



§ Here and throughout the review hydrogen atoms in the *cis*-position are denoted by heavy dots.

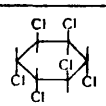
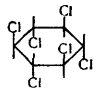
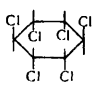
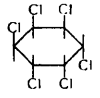
An interesting application of the concept of *trans*-orientation in the bimolecular cleavage of tosylates is the conversion of the tosylates of the isomeric cyclodecane-1,6-diols (XIXa, b) under the action of diethylaniline, which has been investigated by Cope and Holzman[30]:



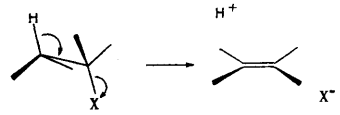
It was established that the *cis*-isomer (XIXa) thus forms a mixture of $\Delta^{1,9}$- and $\Delta^{9,10}$-octalins (XX) and (XXI) in the ratio 2:1, but the *trans*-isomer (XIXb) forms a mixture of the same products in the ratio (10–20):1. Since the authors showed that the isomeric octalins were not mutually interconvertible, they interpreted the reaction as stereospecific elimination: the first molecule of *p*-toluenesulphonic acid is eliminated more rapidly than the second, and the configuration of the isomeric tosylates of 9-decalol thus formed determines the structure of the final reaction products; *trans*-9-decalol tosylate yields a considerable quantity of $\Delta^{9,10}$-octalin (XXI), but the *cis*-isomer forms mainly $\Delta^{1,9}$-octalin (XX), in accordance with the elimination principle.

Cristol *et al.*[31] made a quantitative study of bimolecular indirect dehydration using dehydrochlorination of the isomeric hexachlorocyclohexanes. As the results in Table 1 show, the β-isomer, whose structure permits only *cis*-elimination of hydrogen chloride, is cleaved by bases at a rate about 10^4 times slower than the isomeric compounds, and the energy of activation of the dehydration reaction is about 10 kcal mole^{-1} higher.

TABLE 1. Dehydrochlorination of isomeric hexachlorocyclohexanes.

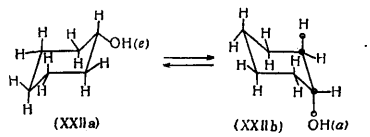
Initial compound	K at 30°	E_{act}, kcal mole^{-1}
α 	0.500	18.5
β 	$2.11 \cdot 10^{-5}$	31.0
γ 	0.151	20.6
ε 	0.182	21.4

The reasons for preferential *trans*-orientation in bimolecular elimination have been discussed by Hughes, Ingold, and their coworkers[32]; they showed that "in the transition state for bimolecular elimination from the HCR_2-CR_2X system, the energy of repulsion between the electron pairs can be reduced to a minimum, if the electrons of the $C_\beta-H$ bond enter the C_α atom octet on the side remote from X. The result of this steric course in the transfer of electrons is *anti*-elimination¶" (E2 rule).



The general applicability of the E2 rule to elimination reactions has been repeatedly confirmed on various examples[22,32,33], and it has been shown that the most favourable conformation of the molecule to undergo *anti*-elimination is that in which the four participating centres are coplanar.

Role of reaction conformations of cyclic alcohols in dehydration. The application of the E2 rule to the dehydration of alicyclic hydroxy-compounds requires primarily a detailed examination of their structures. According to the theory of conformational analysis[34], the hydroxy-compounds of the cyclohexane series consist of an equilibrium mixture of two chair conformations (XXIIa, b) with the hydroxy-groups arranged equatorially or axially:



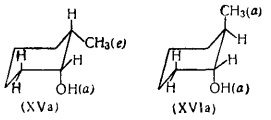
Under ordinary conditions, the preferred conformation is (XXIIa), its potential energy being about 2 kcal mole^{-1} lower than that of conformation (XXIIb). However, this preferred conformation does not meet the steric requirements of bimolecular dehydration, whereas the second, energetically less suitable, conformation (XXIIb), with an axial hydroxy-group at C_1 and an axial hydrogen atom at C_2, has the coplanar arrangement of the four reaction centres (indicated by circles) and the antiparallel arrangement of the leaving groups† necessary for bimolecular dehydration.

Examination of the conformation of cyclohexane derivatives led Barton[33] to suggest that these compounds enter into chemical reactions in the conformation which more nearly meets the steric requirements of the given reaction; he termed these the reaction conformations for the particular reaction. If the reaction conformation is the less stable one, the corresponding reaction is preceded by the conversion from the preferred to the reaction conformation. Therefore, in bimolecular dehydration the reaction conformation is the one with *trans*-diaxial arrangement of the

¶ By "*anti*-elimination" is understood an arrangement of the leaving groups such that the angle between them is close to 180°. The term "*trans*-antiparallel elimination" is used in the same sense.

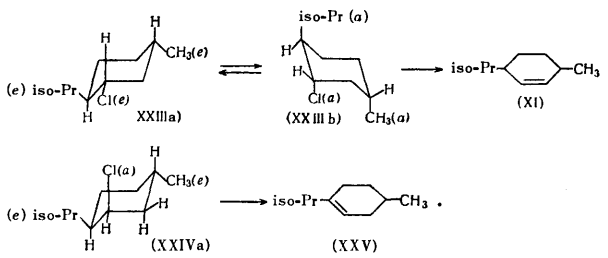
† It should be borne in mind that for some substituted cyclohexanols the conformation with an axial hydroxy-group may also be energetically preferred.

leaving groups[33,35], that is, conformation (XVa) for *cis*-2--methylcyclohexanol and (XVIa) for *trans*-2-methylcyclohexanol:



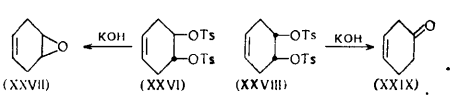
(XVa) (XVIa)

The idea that elimination in the cyclohexane derivative series is effected from the *trans*-diaxial conformation was confirmed by a study of bimolecular dehydrochlorination, one of the most interesting examples being the dehydrochlorination of menthyl- and neomenthyl chlorides (XXIII) and (XXIV) (Hughes, Ingold, and Rose[36]) with sodium ethoxide:



Having studied the kinetics of the conversion, these workers showed that menthyl chloride (XXIII) undergoes bimolecular dehydrochlorination forming Δ^2-menthene at concentrations of EtO^- greater than 1.0 *N* ($k_2^{124.9^\circ} = 0.68 \times \times 10^{-5}$), while neomenthyl chloride (XXIV) is converted by bimolecular dehydrochlorination to Δ^3-menthene (XXV) at concentrations of EtO^- about 0.1 *N* ($k_2^{124.9^\circ} = 131 \times 10^{-5}$). The marked difference between the rates was explained by comparing the reaction conformations of both epimers in the dehydrochlorination reaction. As the schemes presented show, only the energetically less suitable conformation (XXIIIb) can be the reaction conformation in bimolecular elimination from menthyl chloride, the product being the thermodynamically less stable Δ^2-menthene (XXV). In contrast, for neomenthyl chloride the reaction conformation is the energetically‡ favoured conformation (XXIVa), which leads to the thermodynamically more stable Δ^3-menthene (XXV) by *trans*-diaxial elimination.

Examination of the role of reaction conformations in indirect bimolecular dehydrations also permits certain details of the stereochemical features of this reaction to be understood. Thus, for example, in a study of cleavage with potassium hydroxide of the isomeric *cis*- and *trans*--Δ^4-cyclohexene-1,2-diols[37], it was found that the *trans*--isomer (XXVI) is converted to the corresponding epoxide (XXVII), but the *cis*-isomer (XXVIII) forms Δ^3-cyclohexenone (XXIX) at a rate 6 to 7 times faster than that for the corresponding saturated diols:

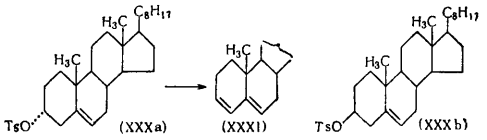


(XXVII) (XXVI) (XXVIII) (XXIX).

‡ From the point of view of conformational analysis the conformation with the maximum number of equatorial substituents is energetically more suitable.

The authors explain this in the following way. For compounds of the cyclohexene series, in the transition state the *meta*-diaxial interaction of the tosyl groups with hydrogen atoms is absent, and consequently the steric requirements of bimolecular dehydration are more easily met.

The necessity for *trans*-diaxial orientation of the leaving groups in bimolecular dehydration has been shown most clearly with polycyclic compounds; because of the rigid articulation in these, the transformation of rings, with all the axial groups becoming equatorial and *vice versa*, is excluded. The published experimental results deal mainly with the base-catalysed cleavage of the tosylates of steroid hydroxy-compounds. Thus, the tosylate of epicholesterol (XXXa) with an axial 3α-hydroxy-group and a hydrogen atom at C_4 readily eliminates *p*-toluenesulphonic acid to give $\Delta^{3,5}$-cholestadiene[27] in 75–80% yield, when it is heated with sodium ethoxide in ethanol.

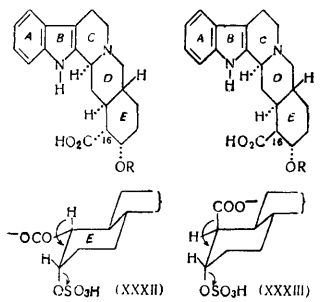


(XXXa) (XXXI) (XXXb)

The cholesteryl tosylate (XXXb), epimeric at C_3 and having an equatorial hydroxy-group, only undergoes a substitution reaction[38] under the conditions described.

The epimeric steroid compounds with the hydroxy-group at C_{12} behave similarly; elimination of *p*-toluenesulphonic acid, which occurs even on shaking with alkaline aluminium oxide[39], is characteristic of the 12α-isomers of these compounds (with an axial hydroxy-group).

The base-catalysed cleavage of the sulphuric esters of yohimbic (XXXII) and corynanthic (XXXIII) acids[40], which are epimeric at C_{16}, is an interesting example of bimolecular dehydration in the polycyclic alkaloid series.

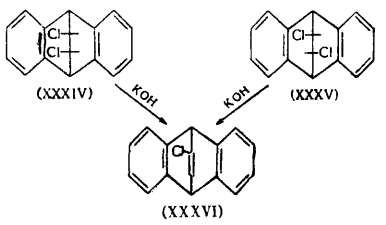


(XXXII) (XXXIII)

Here, as a result of *trans*-diaxial elimination, the ester (XXXII) eliminates only sulphuric acid, but the epimeric ester (XXXIII) undergoes simultaneous decarboxylation.

A striking confirmation of the necessity of a *trans*--coplanar arrangement of leaving groups for the normal course of bimolecular indirect dehydration was obtained by

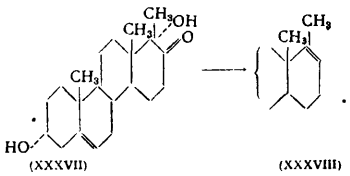
Cristol *et al.*[41] in studies on the alkaline dehydrochlorination of *cis*- and *trans*-11,12-dichloro-9,10-dihydro-9,10-ethyleneanthracene (XXXIV) and (XXXV).



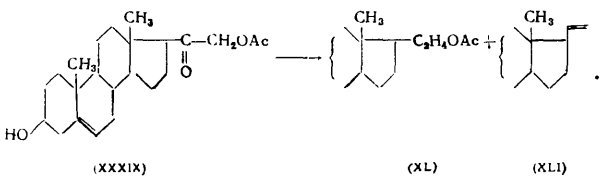
Because of the steric peculiarities of bridge systems of this type, the chlorine atoms at C_{11} and the hydrogen at C_{12} cannot be coplanar, that is, even the isomer (XXXIV) with the removable elements of hydrogen chloride *trans*-oriented does not satisfy the steric requirements of bimolecular dehydration. A consequence is the extraordinary low rate at which (XXXIV) is dehydrochlorinated ($K_2^{110^\circ} = 6.39 \times 10^{-5}$), which is about the same as the rate of *cis*-dehydrochlorination of β-hexachlorocyclohexane (see p. 21) and 10^4 times slower than the rate for the normal *trans*-diaxial dehydrochlorination (*cf.* Table 1).

A similar retardation of indirect dehydration due to the impossibility of a *trans*-diaxial orientation of the leaving groups was noted with *cis*-12-chloro-9,10-dihydro-9,10-ethanoanthracene 11-tosylate[42] and *endo*-*cis*-2,3-dichloronorbornane[43].

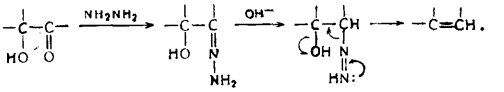
Bimolecular elimination under Kishner--reaction conditions. A special case of bimolecular dehydration arises when α-hydroxy-ketones are reduced under Kishner conditions. As early as 1940, Ruzicka and Meldahl[44] showed that the reduction of 17a-methyl-Δ^5-D-homoandrostene-3α,17a-diol-17-one (XXXVII) is accompanied by the elimination of water and leads to the anomalous product (XXXVIII), without oxygen-containing functional groups at C_{17}.



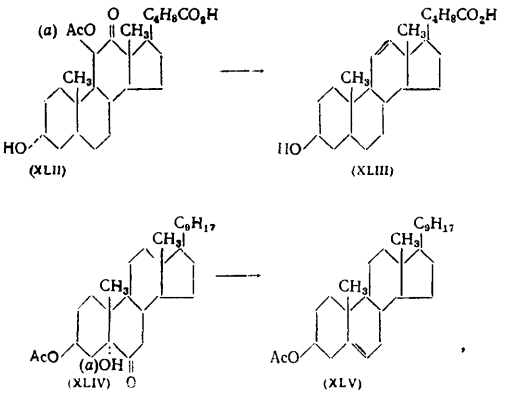
Barton *et al.*[45] found that the Kishner reaction proceeds similarly with the 21-acetate of Δ^5-pregnene-3β,21-diol-20-one (XXXIX), forming $\Delta^{5,20}$-pregnadien-3β-ol (XLI) in addition to the normal reduction product (XL). To explain the



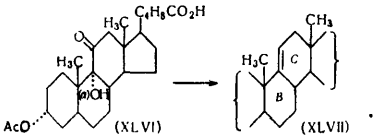
formation of the anomalous product (XLI), Barton suggested that bimolecular elimination occurs in addition to the main reaction:



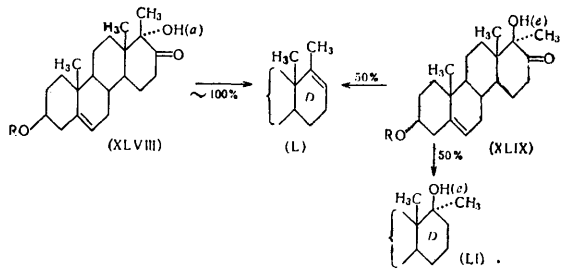
From the proposed mechanism, α-hydroxy-ketones with an axial hydroxy-group would be expected to undergo elimination under Kishner conditions with particular ease. This was confirmed by Long and Gallagher[46] with 3α-hydroxy-11β-acetoxy-12-oxocholanic acid (XLII) and by Barton and Robinson[47] with Δ^{22}-ergostene-3β,5α-diol-6-one-3β-acetate (XLIV):



and also by Heymann and Fieser[48] with 3α-acetoxy-9α-hydroxy-11-oxocholanic acid (XLVI):

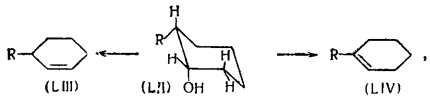


A characteristic difference in the behaviour of epimeric compounds, as exemplified by the hydroxy-ketones (XLVIII) and (XLIX), has been described by Turner[49]:



Kishner reduction of the 18α-hydroxy-ketone (XLVIII) with an axial hydroxy-group gives the elimination product (L) almost quantitatively, but the 18β-hydroxy-ketone (XLIX) with an equatorial hydroxy-group gives the normal reduction product (LI) (~50%) in addition to the $\Delta^{5,17}$-diene (L).

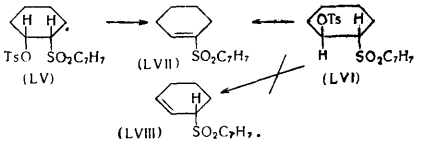
Structure of the initial molecule and the steric effect in bimolecular dehydration. The foregoing experimental results on the stereochemistry of bimolecular dehydration amply confirm Ingold's E2 rule, according to which the main factor determining the course of this reaction is the antiparallel orientation of the groups eliminated from the initial molecule. However, when the conformation of the initial molecule, for example (LII), permits elimination in two different ways:



other factors affecting the mode of elimination, and consequently the ratio of the isomeric products (LIII) and (LIV) formed in this reaction, must be considered. Of these Ingold[32,50] considers the polar factor to be the main one, that is, the possibility of stabilising the transition state leading to the corresponding olefine by hyperconjugation. According to Ingold, the main component in the mixture of isomers should therefore be the cycloolefine (LIV), the formation of which is in accordance with Zaitsev's extended rule[51].

Brown[52,53] investigated another aspect of the problem: he showed conclusively that steric factors — size of substituent and of the attacking base — play a significant part in determining the ratio of isomers in addition to the polar factor.

The effect of the structure of the initial molecule is not limited merely to determining the preferred mode of elimination within the framework of the E2 rule. Recently, Bordwell[54], using the base-catalysed cleavage of the tosylates of the isomeric *cis*- and *trans*-2-*p*-toluenesulphonylcyclohexanols (LV) and (LVI), showed that when the molecule of the hydroxy-compound contains a strong electron-acceptor group, the polar factor (participation in the elimination of a hydrogen atom activated by this group) determines the mode of indirect dehydration, even when this mode is opposite to that expected from the principle of *trans*-diaxial elimination:

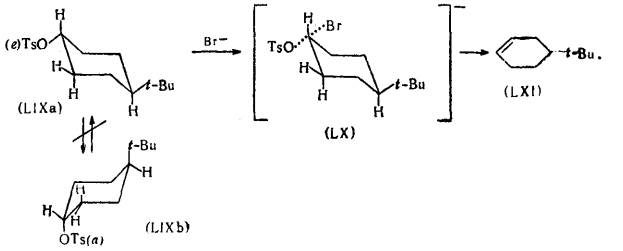


It was found that both isomeric tosylates are converted to the same primary cleavage product, the $\alpha\beta$-unsaturated sulphone (LVII), and the β,γ-unsaturated sulphone (LVII) is not formed in the reaction. This indicates that the elimination of the *trans*-tosylate (LVI) proceeds as a *cis*-elimination. A similar principle was found in the base-catalysed cleavage of *trans*-2-*p*-toluenesulphonylcyclopentyl tosylate, 1-*p*-toluenesulphonylprop-2-yl tosylate[55] and the barium salt of *trans*-2-sulphocyclopentyl hydrogen sulphate[56]. Here and in the cases described above (pp. 21 and 23) *cis*-elimination under conditions of bimolecular elimination is not in accord with the steric requirements of the E2 mechanism.

Since these reactions are much slower and require greater activation energies than *trans*-elimination under similar conditions, Ingold[57] suggested that the additional energy is used in "bending" the molecule and ensuring that its geometry is as close as possible to the geometrical requirements of the E2 mechanism. Ingold believes that the elimination itself proceeds according to the scheme proposed for the bimolecular reaction. Unfortunately, it has not yet been possible to verify Ingold's views experimentally.

The opposite view on the mechanism of *cis*-dehydration in the presence of a strong base has been put forward by Cristol, who suggested that reactions of this kind proceed not by an E2 but by an E1*cB* mechanism (see p. 20). As has been shown above, this mechanism can be verified experimentally by deuterium exchange. The application of this method to the dehydrochlorination of β-hexachlorocyclohexane[58] has shown that the transition state in this reaction is in fact a carbanion. However, this cannot be considered to be the general *cis*-elimination mechanism under conditions of bimolecular dehydration, since examination of the cleavage kinetics[59] and deuterium exchange[60] of the tosylate of *trans*-2-*p*-toluenesulphonylcyclohexanol (LVI) has shown that under the reaction conditions not even an unstable carbanion is formed.

A third possible mechanism has been suggested by Winstein[61] for the cleavage with bromide ions (second-order kinetics) of *trans*-diequatorial-4-*t*-butylcyclohexyl tosylate (LIXa), for which transition to the diaxial conformation (LIXb) is hindered (see p. 25):



This scheme includes attack of the Br^- base ion at the C_1 atom with the formation of the transition state (LX), which can easily be converted to Δ^3-*t*-butylcyclohexene (LXI) by simultaneous elimination of H^+, Br^-, and OTs^-.

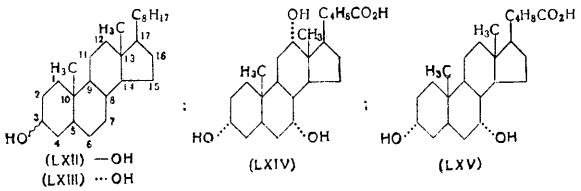
As none of these three mechanisms gives an entirely satisfactory explanation of the known experimental facts, the problem of the mechanism of *cis*-elimination under the conditions of bimolecular indirect dehydration cannot be regarded as solved.

2. Stereochemistry of Unimolecular Dehydration Reactions

From the general ideas on the mechanism of unimolecular elimination reactions (see p. 20) it follows that these reactions can occur in ionising solvents in the absence of a strong base. Such conditions exist in the acid-catalysed dehydration of alcohols, and also in the solvolysis of their tosylates in weak nucleophilic solvents (hydrolysis, acetolysis, alcoholysis, etc.). Since kinetic studies[32,62] have afforded rigorous proof that reactions of this type are unimolecular, they may be used as suitable examples in an examination of the stereochemical features of unimolecular dehydration.

Vavon and Barbier[16] showed that in the alkylcyclohexanol series the *cis*-isomers are dehydrated under milder thermal conditions and more rapidly than the *trans*-isomers. Their experimental results (Table 2) give a sufficiently clear idea of this difference in behaviour.

The dependence of dehydration rate on configuration has been repeatedly confirmed both in the monocylic-alcohol and in the hydroxy-steroid series[33]. As has been shown above, in the discussion on bimolecular reactions *trans*--dehydration proceeds most readily when the eliminated atomic groups occupy axial positions. This also holds for unimolecular dehydration[67,68]; a characteristic example is the dehydration of the epimeric cholestanol [3β(*e*)-OH group]§ (LXII) and epicholestanol [3α(*a*)–OH group] (LXIII) on heating for 60 h with sulphuric acid[68,69]. Here the epimer (LXIII) with an axial hydroxy-group



forms a mixture of 2- and 3-cholestenes in 60% yield, but the epimer (LXII) reacts to the extent of only 28%.

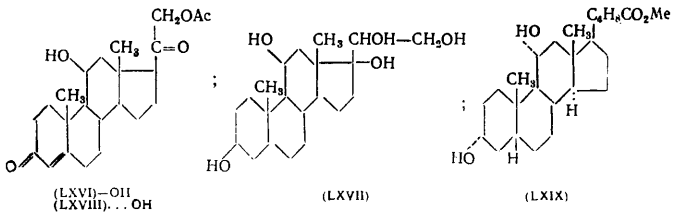
Acid catalysed dehydration in the steroid series also proceeds readily when the axial hydroxy-group at C_7 participates, as has been shown for cholic (LXIV) and chenodeoxycholic (LXV) acids[70-72]. Detailed studies have also been made on the dehydration of 11-hydroxy--steroids[73], which proceeds readily with natural

TABLE 2. Dehydration of isomeric alkylcyclohexanols.

Alcohol	Time required for 25% dehydration, min			
	77°	120°	140°	160°
Cyclohexanol			155	
2-Methylcyclohexanol, *cis*			10	
trans				78
2-Ethylcyclohexanol, *cis*			9	
trans			43	
2-Propylcyclohexanol, *cis*			11	
trans				30
2-Isopropylcyclohexanol, *cis*			9	
trans				24
2-Butylcyclohexanol, *cis*				7
trans				15
4-Isopropylcyclohexanol, *cis*	not examined			
trans				48
4-Butylcyclohexanol, *cis*				15
trans				
Neomenthol			185	38
Menthol			10	30
Isoborneol	5			
Borneol				37

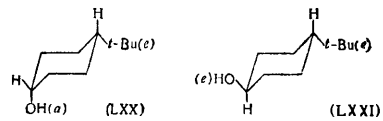
§ In accordance with the accepted nomenclature for steroid compounds, the substituent above the plane of the rings is termed the "β" -substituent and is denoted by a continuous line; the substituent below the plane is termed "α" and is denoted by a dotted line.

compounds containing the 11β(*a*)–OH group. Thus, corticosterone acetate (LXVI)[74] and allopregnane-3β,11β,17,20,21--pentaol (LXVII)[75,76] are readily dehydrated by heating for 0.5 h with a mixture (1 : 9) of hydrochloric and acetic acids, but the 11α(*e*)-hydroxy-compounds, 11α-epicorticosterone acetate (LXVIII) and the methyl ester of 3α,11α-dihydroxycholanic acid (LXIX)[46] are not dehydrated under these conditions.



Preferential *trans*-elimination is also characteristic of the indirect dehydration that occurs in the solvolysis of the tosylates of cyclic alcohols; this has been observed in studies on the ethanolysis and acetolysis[77] of the tosylates of the isomeric menthols[78-80], decalols[79-82], cholestanols[83,84], and ergostanols[83].

Chemical conformational analysis according to Winstein. In 1940 Hückel[85] suggested that the known difference in the rates of solvolysis of the tosylates of isomeric alcohols could be used to determine their configurations, and in 1955 Winstein and Holness examined the possibility of quantitatively evaluating the conformational composition of these compounds on the basis of differences in their rates of solvolysis[86]. Their method is based on the following principle. The observed unimolecular solvolysis rate is related to the mole fractions of the conformations in the initial compound containing axial or equatorial hydroxy-groups by the equation $K = K(e)N(e) + K(a)N(a)$, where K is the constant of the observed first-order reaction rate, $K(e)$ and $K(a)$ are the respective rate constants for the solvolysis of compounds containing only one conformation with either an (*e*)- or an (*a*)-hydroxy-group, these being the same in different compounds; $N(e)$ and $N(a)$ are the mole fractions of the (*e*)- and (*a*)-conformations. This equation can only be applied successfully if the conformationally homogeneous compounds, for which $N(e)$ or $N(a)$ is zero can be obtained. As examples of such compounds the authors examined *cis*- and *trans*-4-t-butylcyclohexanols (LXX) and (LXXI), for which the conformations with an equatorial arrangement of the *t*-butyl group are more favoured by 5.4–5.8 kcal mole^{-1} than the corresponding rotational isomers. It is highly probable that this value ensures conformational homogeneity, so that for (LXX) $N(e) = 0$, and for (LXXI) $N(a) = 0$.

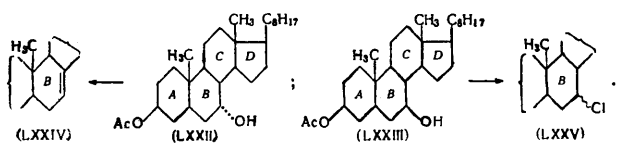


Winstein determined the values of $K(e)$ and $K(a)$ from an examination of the solvolysis of the tosylates of the alcohols (LXX) and (LXXI); these were then used to evaluate the conformational composition of cyclohexanol [$N(a)$ = = 19 ± 7%] and some of its homologues. This approach to

the quantitative evaluation of the conformational composition of compounds was critically examined by Hückel and his coworkers [87-89], who showed conclusively that the solvolysis rate depends substantially on the experimental conditions (solvent, reaction time, presence of additives, temperature). Even when solvolysis is effected under standard conditions, quantitative conformational analysis on the basis of Winstein's equation leads to considerable errors [89], firstly, because solvolysis is not always a rigorously unimolecular reaction, and, secondly, because the structure of the initial molecule significantly affects the rate of solvolysis. Therefore $K(e)$ and $K(a)$ are not constant for different compounds. These limitations do not change the qualitative hypotheses on the relation between mechanism and steric orientation in the elimination reaction, but they exclude the possibility of a quantitative approach to these phenomena.

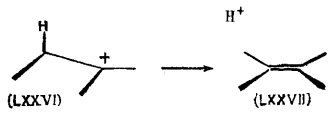
Limitation of steric specificity in unimolecular dehydration. Although *trans*-elimination markedly predominates over *cis*-elimination in unimolecular dehydration, this reaction is not so rigorously stereospecific as bimolecular dehydration, in which the rate of *cis*-elimination is many times less than the rate of *trans*-elimination, and the difference in the activation energies of the two processes exceeds 10 kcal mole^{-1}. [31] Moreover, as has been shown above (see p.24), dehydration by the bimolecular mechanism does not occur if the configuration of the initial molecule does not allow *trans*--antiparallel elimination. In contrast, as can easily be seen from the examples above, the rate of *trans*-elimination in unimolecular dehydrations is only a few times the rate of *cis*-elimination, which proceeds by the same mechanism.

A striking example of the absence of well defined steric selectivity under unimolecular reaction conditions is the dehydration of hydroxy-compounds with phosphorus oxychloride and pyridine [90] or thionyl chloride and pyridine [91]. Notwithstanding the comprehensive experimental data on this question, a sufficiently clear preponderance of *trans*--diaxial elimination has been observed in only a few cases. Thus, Fieser [92] showed that *trans*-diaxial elimination is preferred for the monoacetates of Wintersteiner's epimeric diols (LXXII) and (LXXIII); the 7α-epimer[(a)-OH] (LXXII) is readily converted to Δ^7-cholestenol (LXXIV), but the 7β-epimer (LXXIII) [(e)-OH] undergoes substitution only.



Similar reactions have been observed by Barton [93] with lanostane-3β,7α-diol acetate, and by Davis and Petrow [94,95] with the isomeric cholestane-3,5,6-triols. However, in other reported cases the results obtained cannot be explained by preferential *trans*-elimination. Thus, the dehydration of 11α- and 11β-hydroxy-compounds of the steroid series with $POCl_3$ in pyridine proceeds equally smoothly with both isomers, permitting a double bond to be introduced into the $\Delta^{9,11}$-position [96-99].

The lack of rigorous stereospecificity in the unimolecular dehydration reaction is easy to understand if its mechanism is considered. Reactions of this type are known to start with ionisation, the transition state being a planar carbonium ion (LXXVI). If this ion is capable of prolonged existence, it assumes a planar form and in this limiting case elimination is independent of the initial spatial configuration.



If the elimination is completed before the leaving group X^- is removed a sufficient distance from the planar ion, *anti*(*trans*)-elimination will occur preferentially. If, however, nucleophilic groups, suitably arranged to maintain the configuration of the carbonium ion until the elimination is completed, are present, *syn*(*cis*)-elimination (E1 rule) [22] will occur.

Unimolecular dehydration reactions can therefore only be used to determine the configuration of the initial compounds with great caution, and the explicit claim frequently encountered in the literature (Barton [33], Barton and Rosenfelder [67]) that *trans*-elimination is the rule in ionic elimination reactions is justified only when the structural details of the initial compound and the mechanism of the given ionic reaction have been fully considered.

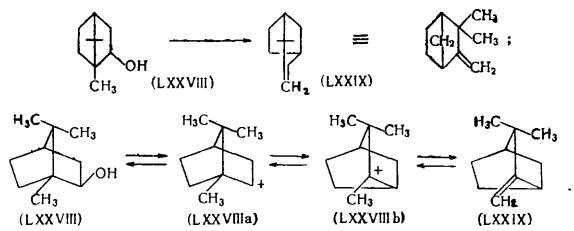
Apart from the lack of stereospecificity in this reaction, the use of multistage unimolecular reactions to obtain information about the configuration of the relevant compounds is complicated by the further consideration that the intermediate carbonium ion may undergo a variety of rearrangements. Thus, in nearly all the acid-induced dehydrations mentioned above the cycloolefines¶ formed isomerise with respect to the double bond, and in some cases the carbon framework of an initial molecule with a given structure and configuration may undergo extensive rearrangement. A particularly interesting example of a conversion of this type is the Wagner–Meerwein rearrangement, which frequently accompanies dehydration.

Stereochemistry of the Wagner-Meerwein rearrangement. A detailed examination of the extensive published work on this rearrangement, which has played such a large part in the development of modern ideas in theoretical organic chemistry, is outside the scope of this review. Here we shall only consider those stereochemical features that are directly related to the mechanism and the stereochemistry of unimolecular dehydration.

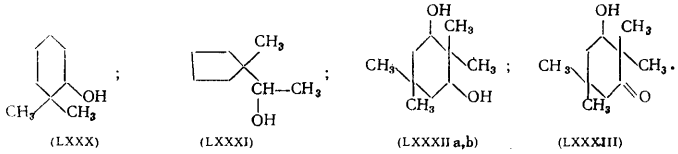
In his classical work Meerwein [100] showed that the rearrangement of the cyclic framework that occurs, for example, in the dehydration of isoborneol (LXXVIII) to camphene (LXXIX), and which had been studied by Wagner [101] using terpene alcohols, is quite general and can be

¶ Isomerisation with respect to the double bonds also occurs in solvolysis of the tosylates, because *p*-toluenesulphonic acid accumulates in the reaction mixture. To avoid this, Hückel [85] suggested that the solvolysis of tosylates should be carried out in the presence of sodium bicarbonate or calcium carbonate.

effected in monocyclic systems having a *gem*-dimethyl substituent adjacent to the carbon atom carrying the hydroxy-group:

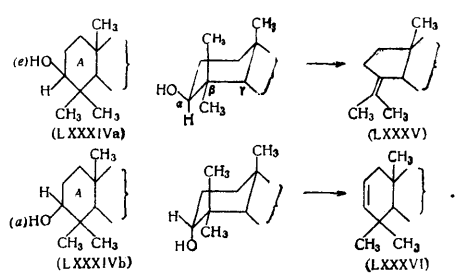


Examples of such compounds are 2,2-dimethylcyclohexanol (LXXX), 1-methyl-1-(α-hydroxyethyl)cyclopentane (LXXXI)[100], the isomeric *cis*- and *trans*-2,2,5,5-tetramethylcyclohexane-1,3-diols (LXXXIIa,b)[102], and 2,2,5,5-tetramethylcyclohexan-1-ol-3-one (LXXXIII)[103], dehydration of which is accompanied by the Wagner–Meerwein rearrangement.



Somewhat later Ruzicka and coworkers showed that a similar rearrangement occurs in the dehydration of triterpenoid compounds containing the 2,2-dimethylcyclohexanol fragment, for example, oleanolic acid[104], lupanol[105], α-amyrin[106,107], and α-amyrenonol[107,108]. Similar examples are known in the steroid series[109–112].

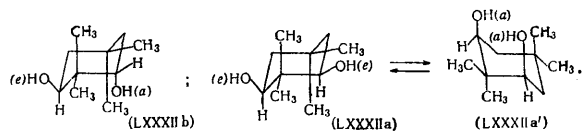
Barton[33] has examined the stereochemistry of systems that undergo the Wagner–Meerwein rearrangement, and from an analysis of a large amount of experimental work he showed that this rearrangement proceeds more readily if an equatorial hydroxy-group takes part in the reaction. To illustrate this conclusion, we shall examine the conformation of ring *A* in α-amyrin (LXXXIVa), which is common to the triterpenoids studied by Ruzicka and contains an equatorial hydroxy-group, and ring *A* in epiamyrin (LXXXIVb), containing an axial hydroxy-group:



From these molecular models it is clear that the presence of an (*a*)–OH group (epiamyrin) ensures the conditions necessary for normal *trans*-diaxial dehydration with the formation of product (LXXXVI), but dehydration in which an (*e*)–OH group participates (α-amyrin) is accompanied by rearrangement of the carbon framework.

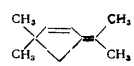
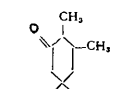
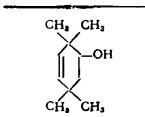
From the steric principles established in the polycyclic series for the Wagner–Meerwein rearrangement, the conformation with the (*e*)–OH group is the one expected to favour this rearrangement in monocyclic compounds. This is confirmed by the conversions of the isomeric *cis*- and *trans*-2,2,5,5-tetramethylcyclohexanediols (LXXXIIa,b) (Allan *et al.*[102]). When subjected to acid-catalysed dehydration, both isomers form a mixture of cyclic products containing 1,1-dimethyl-4-isopropenyl-Δ^2-cyclopentene (LXXXVII), 2,3,5,5-tetramethylcyclohexanone (LXXXVIII), and 2,2,5,5-tetramethyl-Δ^3-cyclohexenol (LXXXIX), the proportions depending on the configuration of the initial alcohols (Table 3).

The results may be explained by examining the conformations of the isomeric diols. The *trans*-diol exists in only one possible conformation (LXXXIIb) with one axial and one equatorial hydroxy-group.



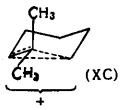
Accordingly, on dehydration 50% of it undergoes a Wagner–Meerwein rearrangement with participation of the equatorial hydroxy-group and 50% reacts with participation of the axial hydroxy-group [normal dehydration to (LXXXIX) and Nametkin† rearrangement followed by dehydration leading to the ketone (LXXXVIII)]. The *cis*-diol (LXXXIIa), which can participate in the last two reactions only in its energetically less suitable diaxial conformation (LXXXIIa′), must be more prone to Wagner–Meerwein rearrangement, for which the reaction conformation is the energetically favoured one (LXXXIIa). This conclusion agrees well with the experimental results.

TABLE 3.

		% of *trans*-diol (LXXXIIb)	% of *cis*-diol (LXXXIIa)
	(LXXXVII)	53	88
	(LXXXVIII)	30	12
	(LXXXIX)	17	

† Barton[33] showed that the Nametkin rearrangement[113–115] proceeds more easily if the hydroxy-group participating in it occupies an axial position.

The stereospecificity of the Wagner–Meerwein rearrangement accompanying unimolecular dehydration cannot be explained if it is assumed that the transition state for this reaction is the classical carbonium ion (LXXVIIIa)[116], which then rearranges to the ion (LXXVIIIb) (see p. 27). With such a mechanism both epimeric alcohols should form the same carbonium ion, and the reaction should be independent of the configuration of the initial compound. In order to explain the stereospecificity of the Wagner–Meerwein rearrangement, it has therefore been suggested that it is effected through a non-classical ion in which the positive charge is distributed over the possible reaction centres[117].


(XC)

Delocalisation of charge is known to lower the potential energy of a system. Therefore, if the non-classical ion interpretation is correct, reactions in which rearrangement occurs would be expected to have lower activation energies, that is, greater velocities, than reactions that proceed without rearrangement.

The acceleration effect on the rate of direct and indirect dehydration reactions in which rearrangement occurs can be observed experimentally‡. This is illustrated by the following figures:

Solvolysis at 80° in 80% aqueous ethanol:

bornyl chloride (no rearrangement) $K_1 = 1.5 \times 10^{-7}$

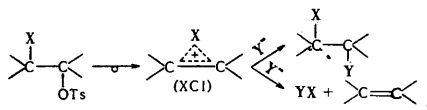
isobornyl chloride (rearrangement) $K_2 = 1.4 \times 10^{-2}$

As has been pointed out in the discussion on bimolecular dehydrations, the synchronous primary reaction step — here ionisation and rearrangement of bonds — is most easily achieved when four coplanar reaction centres participate in it. Since $C_{\alpha,\beta,\gamma}$ atoms and the hydroxy-group at C_α participate in the Wagner–Meerwein rearrangement, the steric requirements are best met when an equatorial hydroxy-group takes part in the reaction.

The physical reality of the non-classical carbonium ion as a transition state in dehydration reactions has been demonstrated experimentally on several examples by deuterium exchange; these are outside the scope of this review[119–122].

Winstein and coworkers have published a series of papers devoted to a systematic study of substitution and elimination reactions, including the non-classical carbonium ion; with them may be included the investigations of other workers on the participation of adjacent groups in solvolysis of 2-substituted cyclohexyl tosylates[123].

This participation is reflected in changes in the solvolysis rate, in configuration, and even in the structure of the reaction products; essentially, the electron pair of the C_2–X bond participates in the ionisation at C_1, which determines the rate of solvolysis; the non-classical intermediate ion (XCI) is then solvated by the nucleophilic solvent, or it interacts with the anion:

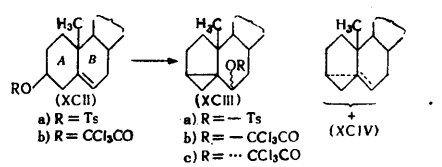

(XCI)

Reactions in which adjacent groups participate show rigorous stereospecificity, as would be expected from the hypothesis that the formation of the carbonium ion and the reaction of the nucleophilic substituent X with the cationic centre are synchronous; these reactions are characteristic only of *trans*-substituted cyclohexyl tosylates.

Alt and Barton[124] examined the conformations of compounds in which adjacent groups participate and showed that here the *trans*-diaxial positions of the "leaving" and "participating" groups were the most favourable; they suggested that this should be used to establish the configurations of isomeric bromohydrins and oxides.

We are unable to review all the experimental work on the participation of adjacent groups, but one particular aspect, *i*-steroid rearrangement, should be considerdd here.

Stereochemistry of *i*-steroid rearrangement. In 1932 Stoll[83] found that boiling with alcohol or with acetic acid and potassium acetate converts the tosylates of steroid hydroxy-compounds containing a $\Delta^{5,6}$ double bond and a 3β-hydroxy-group (cholesterol, ergosterol, stigmasterol) (XCII) to derivatives of the isomeric hydroxy-compounds, which differ from the corresponding derivatives of the epi-series. Wallis *et al.*[125,126] showed that the compounds formed have the "*i*-steroid structure" (XCIIIa).


(XCII) a) R = Ts b) R = CCl_3CO

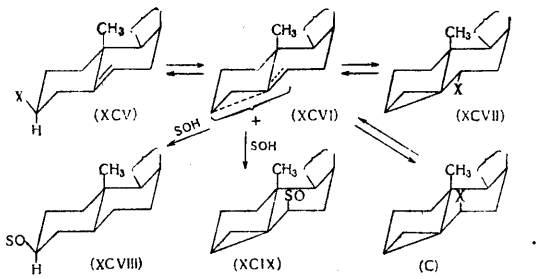
(XCIII) a) R = — Ts b) R = — CCl_3CO c) R = ··· CCl_3CO

(XCIV)

From a comparison of the kinetics of the process (unimolecular reaction $K_1^{50°} = 7.9 \times 10^{-3}$) with the kinetics of solvolysis of cyclohexyl tosylate ($K_1^{50°} = 0.111 \times 10^{-3}$), Winstein[127] suggested that the $\Delta^{5,6}$ double bond participates in the solvolysis as an adjacent group, and he concluded that the ion (XCIV) is the transition state[126–130] in this reaction. In further studies on the mechanism of this reaction Kosower and Winstein[131] examined the methanolysis and hydrolysis of cholesteryl trichloroacetate (XCIIb), the epimeric (at C_6) *i*-cholesteryl trichloroacetate (XCIIIb) and epi-*i*-cholesteryl trichloroacetate (XCIIIc), and they showed that all these compounds yield the same reaction mixture

‡ In the English literature this effect is called "synartetic acceleration", in the American "anchimeric acceleration".

containing 88–89% of *i*-cholesterol. The results unambiguously indicate that the same cation (XCVI) is formed as an intermediate in all three reactions:



The elimination of the anion X^- synchronously with the interaction of the $\Delta^{5,6}$ double-bond electrons and the C_3 cationic centre, necessary for the formation of the ion (XCVI), is in accord with the rigorous stereospecificity of the *i*-steroid rearrangement. Since entry of the $\Delta^{5,6}$ double-bond electrons into the octet of the C_3 atom is energetically most favoured from the side opposite to that of the leaving group, the *i*-steroid rearrangement proceeds readily when the OH group is equatorial; under similar conditions compounds with the axial 3α-hydroxy-group undergo normal dehydration to cholesta-3,5-diene[132–134].

Rearrangement with participation of the $\Delta^{5,6}$ double bond, exemplified by studies on cholesterol, has now been investigated in detail on a number of steroid[135–138] and terpenoid[139–144] compounds, and is known as homoallyl interaction[145–146].

II. INTRAMOLECULAR PYROLYTIC DEHYDRATION

Since Smith[147], and later Kraft[148], showed that olefines could be prepared by pyrolysing esters of the corresponding alcohols, this method has been widely used in organic chemistry. However, it was not until much later that a detailed investigation of the stereochemical features of the reaction was made. The pyrolytic cleavage of xanthates (the Chugaev reaction) has been examined in greatest detail, and we shall primarily be concerned with this.

Stereochemistry of the Chugaev reaction. In 1899 Chugaev[149] proposed a method for preparing olefines by pyrolysis of the corresponding xanthic esters:

$$RCH_2CH_2OH \xrightarrow{Na} RCH_2CH_2ONa \xrightarrow{CH_3I+CS_2} RCH_2CH_2O-\overset{\overset{S}{\|}}{C}-SCH_3$$
$$\downarrow 150°-200°$$
$$RCH_2=CH_2+COS+CH_3SH.$$

The direct dehydration under Chugaev[150] conditions proceeds at a comparatively low temperature (150°–200°) in the absence of acidic reagents; this minimises isomerisation of the olefines formed and permits alcohols that are sensitive even to traces of acid (pinacol[151], dimethylcyclobutylcarbinol[152]) to be smoothly dehydrated and also enables the reaction to be used for determining the structures of the initial and final compounds.

Extensive rearrangement of the carbon framework with an appreciable yield occurs under Chugaev conditions only in the pyrolysis of the xanthates of isoborneol, leading to camphene[153]. In the other cases examined (fenchol, camphanol), the products of this kind of isomerisation form less than 5% of the total yield. Epimerisation of the initial xanthate ester before pyrolysis[154], or conversion to more stable compounds[155,156], has been observed only in isolated cases.

Table 4 gives the most characteristic examples of the Chugaev reaction with alicyclic hydroxy-compounds, and clearly shows the stereospecificity of this reaction, which proceeds mainly with *cis*-elimination (in which the hydrogen atom at C_β participates, or if this is absent, as in fenchol, the hydrogen atom at C_γ) accompanied by the formation of a three-membered ring. Other conditions being similar, *cis*-elimination by the Chugaev reaction leads mainly to the most highly substituted olefine, in agreement with Zaitsev's rule[51].

To explain the rigid stereospecificity of the Chugaev reaction, Hückel[25] suggested that it proceeds through a

TABLE 4. Dehydration of cyclic alcohols under Chugaev conditions.

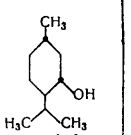
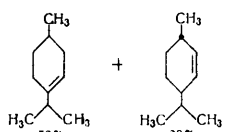
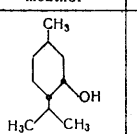
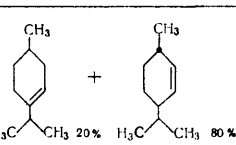
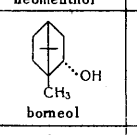
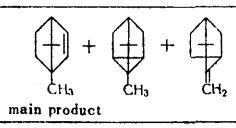
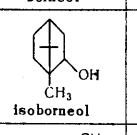
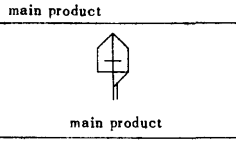
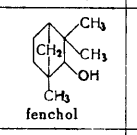
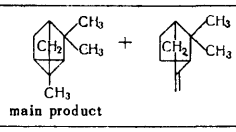
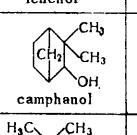
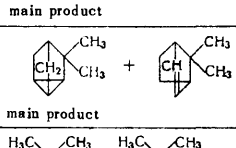
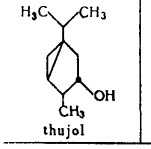
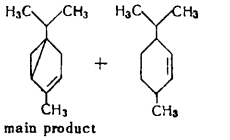
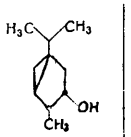
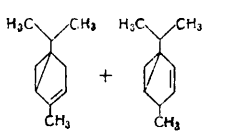
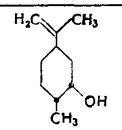
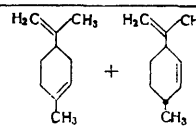
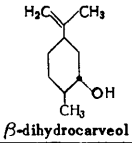
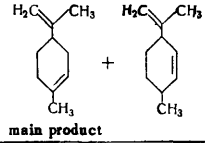
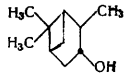
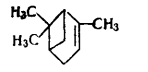
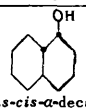
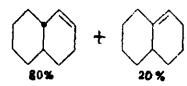
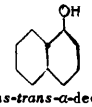
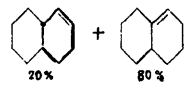
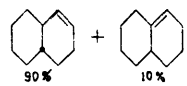
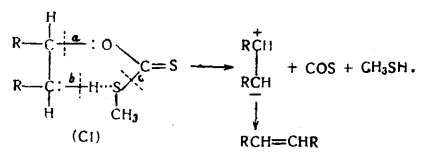
Initial alcohol	Reaction products and proportions	References
 menthol	 70% 30%	25, 157–159
 neomenthol	 20% 80%	25
 borneol	 main product	160–163
 isoborneol	 main product	153, 154
 fenchol	 main product	164–166
 camphanol	 main product	167
 thujol	 main product	168–172
 neothujol	 main product	173

TABLE 4. (contd.)

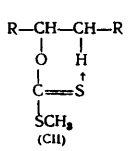
Initial alcohol	Reaction products and proportions	References
 α-dihydrocarveol	 main product	174–177
 β-dihydrocarveol	 main product	174–177
 pinocampheol	 main product	178
 *trans-cis*-α-decalol	 80% 20%	25, 179
 *trans-trans*-α-decalol	 20% 80%	25, 179
cis-cis-α-decalol	 90% 10%	25, 179

quasi-cyclic intermediate complex (CI), the C–O bond (*a*), the C–H bond (*b*) and the C–S bond (*c*) being ruptured simultaneously with the formation of the S–H bond.



This mechanism enabled Hückel to explain the possibility of elimination with participation of the hydrogen atom at C_γ: the xanthic acid residue is sufficiently long to form a seven-membered quasi-cyclic transition complex.

Later Stevens and Rechmond[180] ascribed a somewhat different structure (CII) to the intermediate complex in the Chugaev reaction:



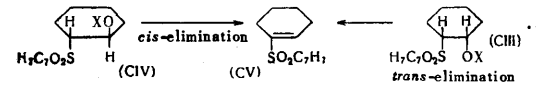
Unlike Hückel, who assumed that the complex (CI) is formed because of the electron-donating properties of the thiol sulphur atom, these workers assumed that the thione sulphur atom acts as an electron donor. Both these mechanisms, with slight modifications, have also been accepted by other workers[181–184], but a mechanism has also been considered in which the xanthates are first isomerised to dithiocarbonates[185].

An experimental test of the mechanism of the Chugaev reaction was made by O'Connor and Nace[184,186]; using cholesteryl xanthates having different substituents on the thiol S atom, they showed that pyrolysis of the xanthates is a homogeneous first-order reaction, unaffected by inhibitors of radical reactions. Moreover, the rate of decomposition of the xanthates increases with the electronegativity of the substituent on the S atom. It was also shown that the entropy of activation of the Chugaev reaction is negative, which indicates a highly ordered transition state.

The results are in good agreement with the idea of a quasi-cyclic transition state arising from a donor-acceptor bond. However, it was not clear whether a thiol or a thione sulphur atom acted as proton acceptor. This problem was solved by Salomaa[187], who compared the reactivities of the methyl carbonates, methyl thiolcarbonates, methyl thionecarbonates, and xanthates of menthol and fenchol; he showed conclusively that the thione sulphur atom acts as proton acceptor. Salomaa's results also show that the cleavage of xanthates does not include a stage in which dithiocarbonates are formed, since the esters containing an oxygen atom in the carbonyl group are much more resistant to pyrolytic cleavage than the corresponding thione esters.

Polar effect of the substituent and possibility of *trans*-elimination in the Chugaev reaction. The mechanism described satisfactorily explains preferential *cis*-elimination in the Chugaev reaction§. However, as was pointed out by Alexander and Mudrak[190,191], in some cases, in addition to the main *cis*-reaction in the pyrolysis of xanthates, there is also a *trans*-oriented side reaction. Examples include the formation of 20% of Δ^3-menthene from neomenthol[25], the mild cleavage of *cis*-2-methyltetralol to give 2-methyl-3,4-dihydronaphthalene, and the mild cleavage of *cis*-2-methylindanol to give 2-methylindene[190].

Since it is conceivable that the anomalous course of the Chugaev reaction is related to the activation of the hydrogen atom participating in it, Bordwell and Landis[192] studied the pyrolysis of the xanthates of *cis*- and *trans*-2-*p*-toluenesulphonylcyclohexanols (CIII) and (CIV) and showed that both isomeric products are converted to the αβ-unsaturated sulphone (CV) only:



Therefore, when the molecule contains a strong electron-acceptor group that increases the mobility of the adjacent hydrogen atom, the consequent participation of the activated hydrogen atom in the reaction controls the mode of hydrolysis, and the spatial arrangement of the eliminated groups plays a subordinate role; this also happens in some bimolecular dehydrations (see p. 24).

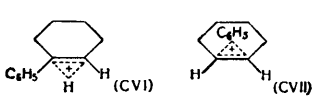
§ The composition of the pyrolysis product of other derivatives of xanthic acid is practically identical with the composition of the products of pyrolysis of its methyl esters[188,189].

Because *trans*-elimination in the Chugaev reaction is not in accord with the mechanism described above, Bordwell and Landis[193] suggested an alternative mechanism, according to which a bipolar ion is formed[193]. They have not, however, confirmed this mechanism experimentally.

Stereochemistry of pyrolysis of other esters. The development of organic synthesis in the field of polycyclic compounds has given rise to a demand for new convenient and reliable methods of introducing a double bond into a given position in the six-membered ring. For this purpose, detailed studies[194-199] have been undertaken on the pyrolysis of cyclic alcohols[194-199] and their esters, including acetates[183,185,195,200-217], benzoates[193,195,213-223], carbonates[187,193], sulphites[193,224-227], as well as other esters[228-231]. The results show that the thermal stability of esters is inversely proportional to the p*K* value of the corresponding acid[232]. This enabled convenient preparative methods to be developed for the elimination of one hydroxy-group in the presence of others. Thus, for example, the esters of anthraquinonecarboxylic acid are cleaved in pyrolysis more readily than the benzoates, and the benzoates more readily than the acetates[204,222,223].

Studies of ester hydrolysis kinetics with acetates[233,234], formates[233], and propionates[235] have shown that this is a homogeneous first-order reaction, which is not affected by the addition of radical-reaction accelerators[236]. Because the reaction rates and energies and entropies of activation are similar, O'Connor and Nace[184] suggested that the pyrolysis of cholesteryl acetate, cholesteryl ethyl carbonate, and cholesteryl xanthate proceed through the same mechanism, involving the quasi-cyclic transition complex (CII) (see p.30); this has been demonstrated experimentally by De Puy and King[217] using a tracer method. The stereochemistry of pyrolytic reactions undergone by both mono- and poly-cyclic compounds is in good agreement with this mechanism. Table 5 gives the relevant data illustrating the preference for *cis*-elimination in pyrolysis.

However, it cannot be concluded from the similarity in mechanism and stereochemistry that the pyrolysis of xanthates is identical with that of other esters. The pyrolysis of esters of organic acids proceeds at high temperatures (acetates, for example, pyrolyse above 400°), and the accumulation of considerable quantities of organic acid in the reaction facilitates the isomerisation of the olefine produced; this applies even more to the pyrolysis of esters of inorganic acids. This is exemplified by Berti's[225] comparison of the results of the pyrolysis of the methylsulphites and xanthates of the isomeric *cis*- and *trans*-2-phenylcyclohexanols (Table 6). The results obtained clearly showed the great steric selectivity of the Chugaev reaction, but Berti interpreted them as indicating that the mechanism for the sulphites differs fundamentally from the Chugaev mechanism; for the *cis*-isomer, the sulphite mechanism includes the non-classical ion (CVI), formed with participation of a hydrogen atom, as a transition state; for the *trans*-isomer the transition state is the "phenonium" ion (CVII):



However, a critical examination of these conclusions in their application to the pyrolysis of *cis*-2-*t*-butylcyclohexyl methylsulphate[193] showed that Berti's mechanism was not in accord with the experimental results. Actually, an ion of the type (CVI) should here lead to 1-phenylcyclohexene by *trans*-elimination, but in fact, 3-phenylcyclohexene was isolated from the pyrolysis products in 95% yield.

A parallel study of the pyrolysis of the xanthates and sulphites of cyclic alcohols by Bordwell and Landis showed

TABLE 5. Stereochemistry of pyrolysis of hydroxy-compounds and their esters.

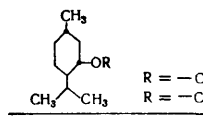
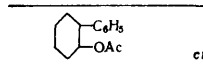
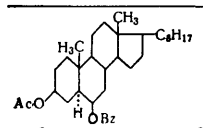
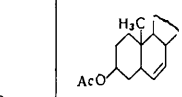
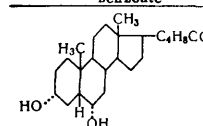
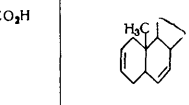
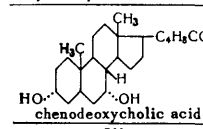
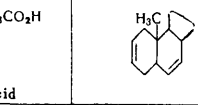
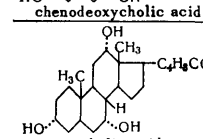
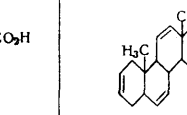
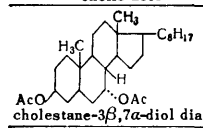
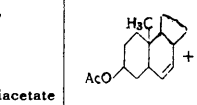
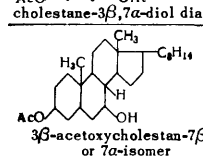
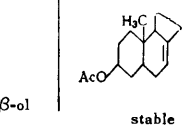
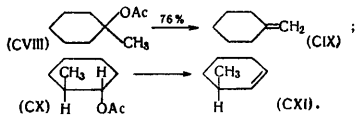
Initial compound	Olefines obtained and their proportions	References
 R = —COCH3 R = —COC6H5	Δ²-menthene + Δ³-menthene: 33% 66% / 33% 66%	206, 207 / 236
 cis trans	3-phenylcyclohexene + 1-phenylcyclohexene: 92.8% 7.2% / 13.5% 86.5%	183
 3β-acetoxycholestan-6β-ol-benzoate		237
 hyodeoxycholic acid		181
 chenodeoxycholic acid		181, 198
 cholic acid		181, 195
 cholestane-3β,7α-diol diacetate		223, 237
 3β-acetoxycholestan-7β-ol or 7α-isomer	 stable	198

TABLE 6.

Compound	Temp. of pyrolysis, °C	Yield of olefine	1-Phenylcyclohexene, % from sulphite	1-Phenylcyclohexene, % from xanthate
C6H5, OR — cis	200	93	22	96
trans	200	88	35	12

that in a large number of examples the primary products of these reactions are similar, clearly indicating a common mechanism. The actual difference in the final results of pyrolysis is due to isomerisation under conditions of sulphite cleavage.

The problem of the relative effects of polar and steric factors on the stereochemistry of pyrolysis of acetates is dealt with in the literature. Bailey *et al.*[210,216,238,239] conclude that pyrolysis of acetates is a specific method for the synthesis of thermodynamically less stable olefines (corresponding to Hofmann's rule). Thus, for example, pyrolysis of 1-methylcyclohexyl acetate (CVIII) gives methylenecyclohexane (CIX) in 76% yield, but pyrolysis of *trans*-2-methylcyclohexyl acetate (CX)[240] gives 3-methylcyclohexene (CXI) as the main product:



Thus, according to Bailey *et al.*, the mode of pyrolysis of acetates is determined not by the spatial orientation of the leaving groups but by the preferential elimination of hydrogen from the methylene group. Similar results have been published by Traynham and Pascual[241], and also by Siegel and Dunkel[211].

The obvious disagreement of these results with those obtained for the Chugaev reaction (see p. 29) compelled Royals[212], Benkeser and Hazdra[213], and also De Puy *et al.*[214,217] to reinvestigate the pyrolysis of acetates. From an analysis of the pyrolysis products by gas chromatography, these workers showed on a large number of examples that the experimental results of Bailey's school were erroneous¶. It was found that the pyrolysis of acetates leads to a complex mixture of reaction products, in which the compounds isolated by Bailey were not always the predominant ones. The results obtained were interpreted by De Puy *et al.*[214,217] as a proof of the lack of selectivity in the pyrolysis of acetates within the limits permitted by the *cis*-elimination principle. The mode of this reaction is therefore determined by the orientation of the leaving groups in the initial molecule. If several elimination routes are possible, the proportions of the reaction products will be determined entirely by statistical considerations. These views of De Puy[217] are in good agreement with the experimental findings.

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Two conclusions can be drawn from the published work on the stereochemistry of direct and indirect dehydration of six-membered alicyclic hydroxy-compounds. First, this reaction is stereospecific only when rupture of the old and formation of the new bonds are synchronous (bimolecular dehydration, rearrangements involving a non-classical transition ion in unimolecular dehydration, pyrolytic reactions); in reactions that proceed by a stepwise mechanism (monomolecular dehydration) steric selectivity is more weakly expressed and sometimes it is entirely lacking. Second, for stereospecific reactions the dehydration route is determined in the general case by the "reaction requirements", which are concerned with the orientation of the leaving groups corresponding to the given reaction mechanism (*trans*-orientation of the leaving groups in bimolecular dehydration and *cis*-orientation in pyrolysis). Compounds containing an activated hydrogen atom at C_β are exceptions; with these the preferred dehydration route is that which ensures participation of the mobile hydrogen atom; if this route does not correspond to the mechanism of the given reaction, then, as a rule, the mechanism undergoes substantial changes.

¶ In 1959, Bailey *et al.*[215] also reexamined their previous results, and their new results, obtained with the aid of gas chromatography, agree well with those of Royals, Benkeser and Hazdra, and De Puy.

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THE ANALYSIS OF COMPLEX ORGANIC MIXTURES BY GAS CHROMATOGRAPHY

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INTRODUCTION

Gas chromatography is now one of the most effective methods of analysing organic substances. The following represents a far from complete list of mixtures which can be studied by gas chromatography: petroleum and petroleum products boiling at up to 600°, organic fluorine- and chlorine-containing compounds, the combustion products from internal combustion engines, essential oils, resins, solvents for plastics and lacquers, fruit and vegetable components, tobacco smoke, the products of the Fischer–Tropsch synthesis, air, paraffin waxes, etc.

The present review is devoted to the problems of the analysis of complex mixtures by gas chromatography, with particular reference to methods for the analysis of the liquid hydrocarbons present in various natural products.

1. THE IDENTIFICATION OF CHROMATOGRAPHIC PEAKS

In the analysis of different mixtures by gas chromatography, an extremely important problem is the identification of the resulting chromatographic peaks. This is often made much more difficult by lack of the pure individual substances thought to be present in the mixtures being analysed. In this case it is necessary to use the various relationships between the elution characteristics of the components and their other properties.

Retention volume. A characteristic property of a component being analysed by gas chromatography is its retention volume, which corresponds to the quantity of carrier gas passing through the column before elution of the peak maximum. Extensive collections of data for the retention volumes of hydrocarbons and other organic substances for different sorbents and temperatures are now available[1-3]. In addition, extensive use is also made of the relationship between retention volume and other characteristics of the components.

From elementary theory[4] it is known that the retention volume (V) is proportional to the Henry coefficient (Γ), since

$$V = LS\Gamma \qquad (1)$$

where L is the length of the column and S its cross-section.

In addition,

$$\Gamma = Ae^{Q/RT}, \qquad (2)$$

where Q is the heat of sorption, T the absolute temperature of the system, R the universal gas constant, and A a constant.

Since the change in the heat of sorption when the number of carbon atoms in the molecule increases by one is a constant for a homologous series, the following relationships apply:

$$\log V = an_C + b \qquad (3)$$

for a homologous series at constant temperature, and

$$\log V = c\frac{1}{T} + d \qquad (4)$$

for any component. Here, n_C is the number of carbon atoms in the molecule and a, b, c, and d are constants.

The applicability of these relationships is confirmed by appropriate plots, obtained in experiments with a wide variety of substances.

James and Martin[5], who analysed normal and iso-acids on a column containing a mixture of silicone and stearic acid, were the first to obtain the relationship between the logarithm of the retention volume and the number of carbon atoms. The plots for normal and for iso-acids were found to be parallel and approximately straight lines (Fig. 1).

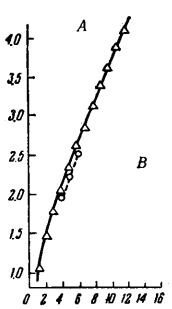

Fig. 1. Relationship between the logarithm of the retention volume (ordinate) and the number of carbon atoms (abscissa). Stationary phase: silicone and stearic acid. Temperature 137°: *A*) normal acids; *B*) iso-acids.

Analogous graphs were obtained by Hawke *et al.*[6] for esters of normal, branched, and unsaturated aliphatic acids, and by Ray[7] for normal paraffins, alcohols, ethers, and ketones (with dinonyl phthalate as stationary phase).

A method for calculating corrected retention volumes reduced to one gramme of stationary phase has been given by Littlewood *et al.*[8]

The retention time is a function of the nature of the substance, the nature of the stationary phase, and the column temperature, and also depends on the quantity of carrier gas used, the free volume between the point of admission of the specimen and the detector, the pressure drop, and the weight of stationary phase. The difference between the retention times of a given component and of hydrogen is multiplied by the quantity of carrier gas used and a coefficient which allows for the pressure drop[5,9]. If the flowmeter is calibrated at 0°, it is necessary to multiply by the quantity $T/273$, where T is the absolute temperature of the column. Division of the resulting product by the weight of stationary phase gives the retention volume reduced to one gramme.

In the work cited, Littlewood *et al.* give graphs of the relationship between the logarithm of the reduced retention volume and the number of carbon atoms for normal alcohols (column with Silicone 702) and of the relationship between the logarithm of the retention volume and the quantity $10^4/T$, for alcohols, acetates, and aromatic hydrocarbons. The last of these graphs is shown in Fig. 2.

Similar graphs have been constructed for organic compounds of boron by Seely *et al.*[10] and for light gases and normal paraffins by Janák (sorbents silica gel and zeolite)[11,12].

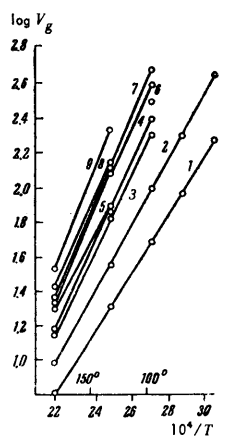

Fig. 2. Relationship between the logarithm of the reduced retention volume and the quantity $10^4/T$ for aromatic hydrocarbons on tritolyl phosphate: 1) benzene; 2) toluene; 3) *p*-xylene; 4) *o*-xylene; 5) isopropylbenzene; 6) mesitylene; 7) s-butylbenzene; 8) *p*-cymene; 9) t-pentylbenzene.

A recent paper[13] gives a generalised formula for calculating the retention volume reduced to one gramme of stationary phase:

$$V_g = \frac{z}{U} \cdot \frac{273}{T_m} \frac{p_0 - p_w}{760} \frac{F}{W} \cdot \frac{3}{2} \left[\frac{(p_i/p_0)^2 - 1}{(p_i/p_0)^3 - 1} \right], \quad (5)$$

where z is the distance between the peaks for air and the given component, U the velocity of the recorder chart, T_m the absolute temperature of the flowmeter, p_i the pressure at the column inlet, p_0 the pressure at the column outlet, p_w the vapour pressure of water at T_m, F the carrier-gas velocity, recorded by the flowmeter at the column outlet, and W the weight of stationary liquid.

At present, use is generally made of the relative retention volume, obtained by dividing the retention volume of the given component by the retention volume of a standard substance, which is often n-pentane. This characteristic is very convenient since it can be calculated without reduction to standard experimental conditions.

The Nomenclature Committee of the Symposium on Vapour-Phase Chromatography[14] recommended the following substances as standards: n-butane, isooctane, benzene, *p*-xylene, naphthalene, methyl ethyl ketone, and cyclohexanol.

Graphical interpretation of the relationship between the retention volume and the boiling point is often used. When the graphs are drawn on semi-logarithmic coordinates, various homologous series give almost straight lines. In the separation, for example, of hydrocarbons on a column with a polar phase, the straight lines corresponding to paraffins and alkylbenzenes will lie at a considerable distance from one another, but when a nonpolar liquid is used the straight lines will be extremely close together. Using these graphs it is possible to determine by two analyses the boiling point of an unknown substance and to find whether it belongs to a particular homologous series.

Graphical relationships for a wide range of organic compounds have been obtained by Tenney[15] — stationary phases: the unsaturated hydrocarbon oil "Convoil-20" †, squalane, di-(2-propionitrile) ether, the chlorinated oil "Convachlor-12" †, di(ethylhexyl) sebacate, the chlorotrifluorovinyl polymer "Fluorolube S" ‡, triethylene glycol, and a saturated solution of $AgNO_3$ in triethylene glycol — and by Bayer[16] — stationary phases: hexatriacontane, a mixture of polyethylene oxide and "Lubrol MO" §, di(ethylhexyl)sebacate, and dinonyl phthalate. Bayer used the graphs to determine the selectivity coefficients of the various liquid phases.

Lo Chang *et al.*[17] were able to identify 52 aromatic hydrocarbons in coal tar, by means of these graphs and infra-red spectrometry. Grant and Vaughan[18] constructed analogous graphs for paraffins and aromatic hydrocarbons in a study of the distribution of the latter in coal tar (stationary phases: dinonyl phthalate and tricresyl phosphate). Eggertsen and Knight[19] and McFadden[20] constructed curves for the direct graphical relationship between the retention time and the boiling point (stationary phases: glycol, squalane, and Silicone SF-96).

A number of authors have used the relationship between the logarithms of the retention volume and the vapour pressure. It is known[21] that the retention volumes v_1 and v_2 of the components being separated are inversely proportional to their vapour pressures p_1 and p_2 at the temperature of the experiment:

$$\frac{v_2}{v_1} = \frac{\gamma_1 p_1}{\gamma_2 p_2}, \quad (6)$$

where γ_1 and γ_2 are the activity coefficients. Within a homologous series the values of γ are close to one another (as is usual for non-polar substances in non-polar solvents), or vary linearly, so that the following relationship, given by Purnell[22], applies:

$$\log v = -a \cdot \log p + b, \quad (7)$$

where a is the ratio of the molar heat of solution at infinite dilution to the molar latent heat of volatilisation, and b is a constant. The graphs constructed on the basis of this equation were used by Purnell to discuss problems related to the choice of solvents. Jentzsch and Bergmann[23] studied the applicability of this relationship to aromatic hydrocarbons and used the graphs to identify the components. The relationship between the logarithms of the retention volume and of the vapour pressure has also been used in other work[24,25].

James *et al.*[26] proposed a graphical representation of the relationship between the retention volumes in different stationary phases (for example paraffin and benzylbiphenyl). The straight lines for the various homologous series intersect at a point. The existence of a relationship between the elution characteristics in polar and non-polar phases makes it possible to determine the chemical character of unknown substances. The diagram constructed by these authors is shown in Fig. 3.

Phillips[27] has given similar graphs for amines, alcohols, ketones, and hydrocarbons, with "Lubrol MO", liquid paraffin, zinc stearate, and Silicone 702 as stationary phases.

Construction of the relationship between the logarithms of the retention volumes gives almost parallel lines. Fig. 4 gives the graphs used by Desty and Whyman[28] to identify 81 hydrocarbons and 7 sulphur compounds by analysis on

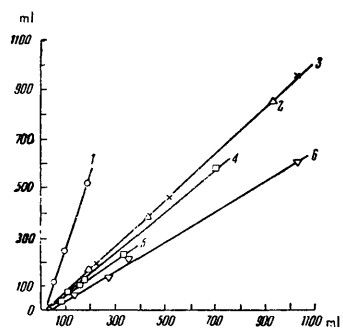

Fig. 3. Relationship between the retention volume in benzylbiphenyl (abscissa) and the retention volume in paraffin (ordinate):
1) normal aliphatic hydrocarbons; 2) aromatic hydrocarbons; 3) isoiodides; 4) normal iodides; 5) alcohols; 6) ketones.

† Made by Consolidated Electrodynamics Corp., USA (Ed. of Translation).

‡ Made by Hooker Chemical Corp., USA (Ed. of Translation).

§ An emulsifying agent made by Imperial Chemical Industries Ltd. (Ed. of Translation).

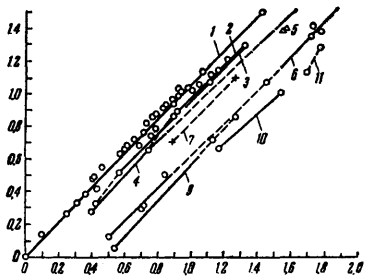

Fig.4. Relationship between the logarithms of the retention volumes (n-pentane = 1):
on ordinate axis: stationary phase n-hexatriacontane;
on abscissa stationary phase benzylbiphenyl:
1) paraffins; 2) alkenes; 3) cyclopentanes;
4) cyclohexanes; 5) bicyclic naphthenes; 6) aromatic hydrocarbons; 7) cyclic monoolefines; 8) cyclic diolefines; 9) sulphides; 10) thiophenes; 11) cyclic sulphides.

columns with n-hexatriacontane and benzylbiphenyl (in conjunction with mass-spectrometric data). The same authors gave the graphs of $\log v$ *vs.* n_C and $\log v$ *vs.* (boiling point) for these phases.

James[29] used graphical relationships to determine the degree of unsaturation of fatty acids. The graph which he constructed consists of a net: one family of straight lines correspond to the number of double bonds in the molecule and the family of straight lines intersecting these (dotted lines) correspond to the number of carbon atoms.

Hudy[30] constructed a graph showing the relationship between the logarithms of the retention volumes for the methyl esters of various acids (stationary phases: "Apiezon"¶ and succinate polyester), and Pierotti *et al.*[31] did the same for alkanes, alcohols, and ketones (in "Triol" and diisodecyl phthalate). [Triol, made by Union Carbide and Carbon Co., USA, is 2,4-dimethyl-2-(2-hydroxyethoxy)-pentane--1,5-diol (Ed. of Translation.)] Desty and Harborn[32] suggested the use of a detergent containing an alkyl aryl sulphonate as packing for chromatographic columns and gave a graph for the relationship between the retention volume and molecular weight for different hydrocarbons. Homologous series give straight lines on the graph. An analogous diagram was constructed from data obtained on a column with "Apiezon L".

Extensive work is at present being done on the determination of the retention volumes of various individual substances and their dependence on other physicochemical properties, to facilitate their identification in real mixtures. In this connection, the following have been proposed as standard stationary phases[14] (the temperature limits are given in brackets): n-hexadecane (20°–50°), dinonyl phthalate (20°–100°), squalane (20°–150°), dimethylformamide (-20° to +20°), benzylbiphenyl (80°–150°), and diglycerol (20°–100°). The use of a mixture of 20 parts by weight of liquid and 80 parts by weight of inert carrier — preferably "Celite 545"† — is recommended.

¶ Made by James G. Biddle Co., USA (Ed. of Translation).

† Highly porous filter aid made from diatomaceous earth by Johns-Manville Corp., USA (Ed. of Translation).

Determination of molecular weight. In the identification of various substances, a knowledge of their molecular weights is extremely important. In this connection, the development of methods capable of giving rapid, accurate, and reliable data is of considerable interest. The usual methods of determining molecular weights are time-consuming and require highly-trained personnel. A fairly large specimen is also required. Gas chromatography[33,34] makes possible a rapid and sufficiently accurate determination. An important advantage of this method is that it is possible to carry out the continuous identification of the components of a complex mixture being separated on a chromatographic column.

The determination is based on the addition, to the mixture of unknown composition, of a pure substance of known molecular weight to act as "internal standard". Two chromatographic analyses are then carried out on the same apparatus but with different carrier gases. The detector used is a Martin gas density balance which compares the densities of the gas streams leaving the separating and reference columns, the density difference being converted to an e.m.f. by means of a sensitive thermocouple.

Let us assume that an "internal standard" k with molecular weight M_k is added to an unknown component with molecular weight M_x and that the resulting mixture is eluted from a chromatographic column by a gas with molecular weight M_1. If another gas with molecular weight M_2 is used, the retention volumes will, of course, be analogous to those obtained in the first case, but even for identical velocities, the heights and areas of the peaks will be different, due not only to the difference in the size of the specimen being analysed, but also to the effect of the nature of the eluant.

The densities of the gas streams leaving the reference (d_1) and chromatographic (d_x) columns can be obtained from the Clapeyron equation:

$$d_1 = \frac{M_1 p}{RT};\quad d_x = \frac{(n_1 M_1 + n_x M_x)\,p}{RT}, \tag{8}$$

where n_1 and n_x are the mole fractions of the eluant and the substance being analysed. From this the density difference is

$$\Delta d_{x-1} = \frac{n_x (M_x - M_1) p}{RT}. \tag{9}$$

Similarly, for an eluant with molecular weight M_2

$$\Delta d_{x-1} = \frac{n_x (M_x - M_2) p}{RT}. \tag{10}$$

The quantity Q_x of the component being analysed may be written

$$Q_x = \int_0^\infty \frac{n_x M_x p}{RT}\, dv, \tag{11}$$

where v is the volume of gas mixture leaving the chromatographic column. Alternatively, substituting Eqn. (9):

$$Q_x = \frac{M_x}{M_x - M_1} \int_0^\infty \Delta d_{x-1} dv.$$

Similarly, the quantity q_k for the standard used during the same experiment is equal to

$$q_k = \frac{M_k}{M_k - M_1} \int_0^\infty \Delta d_{k-1} dv.$$

Here Δd_{k-1} is the difference between the densities of the gas streams at the moment when the standard passes through the detector. Similar relationships are obtained for the quantities Q'_x and q'_k obtained when a gas with molecular weight M_2 is used as eluant.

Since for sufficiently small specimens (several microlitres) the e.m.f. E of the detector thermocouple is proportional to the density difference, the relationship $\int_0^\infty \Delta d dv = k\int_0^\infty \Delta E dv$ applies; the value of this integral is, of course, proportional to the area of the corresponding peak on the chromatogram.

Since $\frac{Q_x}{q_k} = \frac{Q'_x}{q'_k}$, we obtain for the peak areas the relationship:

$$\frac{A_x}{a_k}\left(\frac{M_k - M_1}{M_x - M_1}\right) = \frac{A'_x}{a'_k}\left(\frac{M_k - M_2}{M_x - M_2}\right), \qquad (12)$$

where A_x, A'_x, a_k, and a'_k are the corresponding areas.

This last relationship is used to find the desired value of M_x. The accuracy of the determination is ~4%.

Determination of the elementary composition. There are two papers[35,36] devoted to the determination of the elementary composition of hydrocarbons by gas chromatography. This method has an accuracy comparable with that of Pregl's method and possesses a number of advantages over the latter; the time required for the analysis is small (< 10 min) and it is possible to work with very small amounts of specimen.

The specimen is ignited in a tubular furnace either in a current of dry oxygen or with cupric oxide and the resulting products are passed through a tube containing calcium carbide to convert the water into acetylene and then collected in a trap cooled with liquid nitrogen. The acetylene and carbon dioxide are then volatilised and passed in a current of argon or helium to a chromatographic column containing silica gel. A thermal-conductivity detector is placed after the column. Such an apparatus is illustrated in Fig. 5.

The areas of the resulting chromatographic peaks for acetylene and carbon dioxide are proportional to the percentage concentrations of hydrogen and carbon in the specimen being analysed. The elementary composition can be calculated by multiplying the peak areas by appropriate calibration coefficients.

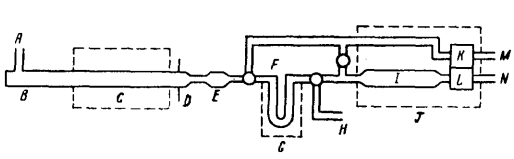

Fig. 5. Apparatus for the elementary analysis of hydrocarbons:
A) oxygen inlet; *B*) ignition tube; *C*) tubular furnace; *D*) aluminium shield; *E*) tube with calcium carbide; *F*) cold trap; *G*) Dewar vessel containing liquid nitrogen; *H*) vacuum connection; *I*) chromatographic column; *J*) insulating jacket; *K*) reference cell of detector; *L*) measuring cell of detector; *M*) helium inlet; *N*) outlet to gas meter.

The accuracy of the method is ~0.5% for carbon and 0.1–0.2% for hydrogen. Milligramme specimens are used and the quantities can be reduced considerably by using more sensitive detectors.

The use of molecular sieves. The molecular sieves normally used to separate light gases exhibit selective adsorption for certain homologous series; this is determined by the size and shape of the molecules. This has made it possible to use molecular sieves as an additional means of identifying the components being analysed[37,38]. It has been established that on passage through a column containing a molecular sieve, some components are not retained by the latter while others are irreversibly adsorbed. This property of molecular sieves can be used to remove certain groups of substances for identification "by difference". The assembly includes a column 50 cm long and 6.35 mm in diameter, filled with a 5 Å molecular sieve (pore diameter 5 Å) connected in series with an ordinary 2 metre column operating on the principle of gas-liquid partition chromatography.

When a mixture of normal paraffins, isoparaffins, cycloparaffins, and aromatic hydrocarbons was passed through the system, it was found that the C_3–C_{11} n-paraffins were irreversibly adsorbed by the molecular sieve, whereas the other classes of hydrocarbon gave appropriate peaks on the chromatogram. A number of other compounds were also found to be irreversibly adsorbed.

Table 1 gives components which pass readily through a column of 5 Å molecular sieve and Table 2 gives compounds which are irreversibly adsorbed.

It has been established that other types of molecular sieve do not behave in exactly the same way as the 5 Å sieves, due to their different pore diameters. Thus the

TABLE 1. Components passing through a column of 5 Å molecular sieve.

Group	Hydrocarbons studied
Isoparaffins	isobutane, isopentane, 2,3-dimethylbutane
Aromatic hydrocarbons	benzene, toluene, *m*-xylene
Cycloparaffins	cyclopentane, cyclohexane
Isoolefines	2-methylpropene, 2-methylbuta-1,3-diene
Esters	pentyl formate, ethyl acetate, ethyl propionate
Ketones	acetone, methyl ethyl ketone, mesityl oxide
Halogenated hydrocarbons	chloromethane, chloroform
Isoalcohols	isopropyl and isoamyl alcohols
Ethers	diethyl ether, diisopropyl ether
Other compounds	carbon monoxide, oxygen, nitrogen, the inert gases, methane, nitromethane, carbon disulphide, dimethyl sulphide, thiophen

TABLE 2. Components completely adsorbed by a column of 5 Å molecular sieve.

Group	Components studied
Normal paraffins (except methane)	propane, n-butane, n-hexane
Normal olefines	ethylene, propene, hex-2-ene
Normal alcohols	methanol, ethanol, n-butanol
Aldehydes	acetaldehyde, propionaldehyde, isovaleric aldehyde
Acids	formic acid, propionic acid

4 Å molecular sieve adsorbs only ethane from the normal paraffins and ethylene and propylene from the normal olefines. In the analysis of complex mixtures containing different homologous series, it is possible to simplify the identification of the components by using these properties of molecular sieves to remove one member of the series. Removal of a component from a system may also be useful when it is necessary to measure superimposed peaks.

Fig. 6 illustrates the removal of normal paraffins from mixtures. The upper chromatogram was obtained after passage of the specimen through a column filled with di-(2-propionitrile) ether deposited on "Chromosorb" ‡ and the lower one after passage through a system consisting of the same column and a column containing a molecular sieve.

Use of the chromatographic-detector characteristics. Components can be identified on the basis of measurement of the peak areas, using an ordinary katharometer. Quantitative determination of the composition of the mixture being analysed is carried out by normalisation of the peak areas, correcting for the thermal conductivity[39-43].

By carrying out a parallel analysis with chemical conversion of the chromatographic peaks before passage through the katharometer, it is possible to determine the carbon number of a component by combined calculations on the two chromatograms. There are now a number of methods involving conversion for the chromatographic analysis of mixtures. For instance, Norem[44] ignited the components to CO_2, removed the water formed, and determined the CO_2 by means of a katharometer. Green[45] passed the substances leaving the column through a layer of CuO to give CO_2 and H_2O, and then through iron powder to convert the water into hydrogen, which was passed to the katharometer cell. Zlatkis *et al.*[46,47], using hydrogen as carrier-gas, converted the components into methane and water over a nickel catalyst. The water was removed and the methane passed to the katharometer. In the analysis of hydrocarbons, of course, no water is formed.

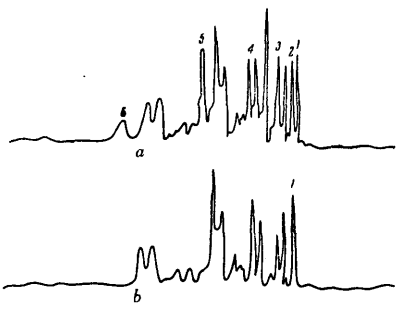

Fig. 6. Removal of normal paraffins by means of molecular sieves:
a) separation on a column of di-(2-propionitrile) ether; b) chromatogram of mixture after removal of normal paraffins by means of a molecular sieve: 1) isopentane; 2) n-pentane; 3) n-hexane; 4) n-heptane; 5) n-octane; 6) n-nonane.

The area of the peak obtained after conversion of the components is proportional not only to its concentration but also to the number of carbon (or hydrogen) atoms present, and it is possible to determine the latter by combined calculations on a given chromatogram and the chromatogram obtained without conversion. Instead of using the katharometer, it is possible to determine the CO_2 with an infra-red spectrometer[48-50], by titration with potassium methoxide[51], or coulometrically (carrier gas: oxygen; the CO_2 and O_2 are bubbled through $BaCl_2$ solution in a cell containing a platinum spiral which acts as an oxygen electrode)[52].

The components can also be identified by an ionisation detector[53,54] since the ionisation current is proportional to the "effective ionisation cross-section of the molecule" — a molecular characteristic[55].

It is also possible to use a flame detector[56,57] since the increase in the temperature of the thermocouple on combustion is proportional to the quantity of heat evolved, and hence for one carbon bond, *i.e.* to the peak area. The use of a micro-flame emission detector, which measures the luminescence of the flame[18,58] is also of interest, since in this case the response depends markedly on the nature of the substance. In particular, the response is much greater for aromatic substances than that for paraffins.

The use of infra-red and mass spectrometry. There are many examples of the identification of chromatographic peaks with the aid of infra-red or mass spectrometry. The simplest method used in these cases involves trapping the fractions leaving the gas chromatograph in cooled traps and then transferring, for example, to a cell for analysis by infra-red spectrometry.

The American firm of Beckman now produces a system consisting of a GC-2 gas chromatograph and IR-5 infra-red spectrometer[59]. The cell for the infra-red analysis has a very small volume, only 0.0002 cm^3, which ensures extremely accurate data in the determination of impurities in chromatographic bands. The same firm also produces a "Megachrom" gas chromatograph combined with an IR-4 infra-red spectrometer[60], which makes it possible to carry out the spectrographic analysis of the large fractions obtained in preparative work (the volume of the specimen separated by the "Megachrom" is ~20 ml). A serious disadvantage of these systems is the time required for the spectrographic analysis. Thus, for example, 16 min are required to record the spectrum of benzaldehyde on an IR-5 apparatus. When the chromatogram contains a large number of peaks, the time required for their identification naturally becomes very great.

Analogous schemes are used for the identification of peaks by mass spectrometry. In work by Desty and Whyman[28] and Bradford *et al.*[61], this method was used as an additional means of determining the composition of various light petroleum products. Whitham[62] identified the heavy $C_{10}-C_{14}$ hydrocarbons in kerosene fractions by freezing the chromatographic fractions with subsequent mass-spectrometric analysis.

The firm of Consolidated Electrodynamics (USA) produces a system consisting of a 26-201 A laboratory chromatograph and 21-620 mass spectrometer with mass range from 2 to 150 and a response of 1 sec.[63] This system is suitable for the comparatively rapid analysis of mixtures of hydrocarbons and other organic substances.

‡ Closely-graded calcined diatomite, made by Johns-Manville Corp., USA (Ed. of Translation).

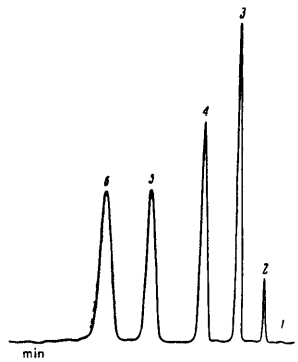

Fig.7. Chromatogram for the separation of a mixture of acetone, benzene, toluene, ethylbenzene, and styrene:
1) air; 2) acetone; 3) benzene; 4) toluene; 5) ethylbenzene; 6) styrene.

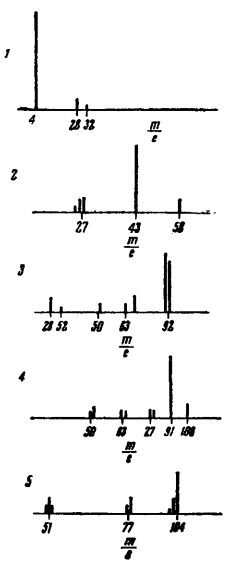

Fig.8. Mass spectra corresponding to the chromatographic peaks:
1) helium with a trace of air; 2) benzene; 3) toluene; 4) ethylbenzene; 5) styrene.

The use of a time-of-flight mass spectrometer for the direct observation of a chromatographic process is of considerable interest[64]. The mass spectrometer is connected to the chromatograph at a point between the column and the thermal conductivity detector and makes it possible to obtain on an oscillograph 2000 mass spectra per second (m/e from 1 to 6000), thus achieving continuous identification and determination of the degree of purity of the components corresponding to the chromatographic peaks.

Fig.7 shows the chromatogram for the separation of a mixture containing acetone, benzene, toluene, ethylbenzene, and styrene, and Fig.8 gives the mass spectra corresponding to the peaks obtained.

One possible method of combining mass spectrometry and chromatography is by carrying out parallel analyses on both instruments with subsequent combined calculation of the results. This method has been used, in particular, by Eggertsen and Knight[19] in the analysis of C_5-C_7 hydrocarbons. Howard and Ferguson[65] carried out the mass-spectrometric analysis of petrols without preliminary removal of pentanes and introduced into the mass spectra corrections based on the chromatographic analysis of hydrocarbons up to and including C_5.

2. SCHEME FOR THE SEPARATION OF COMPLEX ORGANIC MIXTURES

The complex mixtures of hydrocarbons and other organic compounds normally encountered in various real products can seldom be analysed in detail on an ordinary chromatographic apparatus consisting of one column, since various peaks are superimposed. This is due to the fact that the retention volumes of some isomers, or of substances of different type with different molecular weights, are equal. Thus in the analysis of the C_3-C_5 hydrocarbons on a column of diisodecyl phthalate, which is weakly polar, the components are separated according to their boiling points[66]. n-Butane, 2-methylpropene, and but-1-ene, however, appear as one peak, since their boiling points are very close. In addition, propane and propene, *cis*- and *trans*-but-2-ene, n-pentane and pent-1-ene, are not separated. When the more polar triethyleneglycol n-butyric ester[67] is used, the the olefines have retention volumes slightly higher than the corresponding paraffins, but in this case some of the C_4 olefines are superimposed on C_5 components. Analysis on a column of the strongly polar dimethylsulpholane§ [66] gave good separation of paraffins and olefines with the same number of carbon atoms, but the olefines were retained by the column to such an extent that they were superimposed on the peaks of paraffins with one more carbon atom in the molecule.

These features show the necessity for developing different schemes for the chromatographic analysis of complex mixtures, either by using several columns or by using supplementary techniques such as liquid chromatography, distillation, hydrogenation, sulphonation, infra-red, and mass spectrometry, etc.

The simplest version of multi-stage chromatography involves the use of two columns with different sorbents. All the components of the mixture being analysed are passed first through one and then through the other. With the correct combination of sorbents and column lengths, good separation of a large number of components can be achieved. Thus for the separation of hydrocarbons up to and including C_5, for example, Fredericks and Brooks[66] used columns of diisodecyl phthalate and dimethylsulpholane, and Zhukhovitskii *et al.*[68] used a column of alumina and a gas-liquid column with dibutyl phthalate. Single-stage columns with mixed stationary phases can also be used[20,69]. Of course, such schemes are of very limited application, since the degree of separation of any two components

§ 3,4-Dimethyltetrahydrothiophene-*S*-dioxide (Ed. of Translation).

achieved on the first sorbent may be reduced or eliminated completely on passage through the second sorbent.

A number of papers have been devoted to the problems of analysing the C_5-C_7 hydrocarbons. Thus a sorbent consisting of "Pelletex" furnace black¶, modified with 1.5% squalane[19,70], has been proposed for the separation of saturated hydrocarbons according to the number of carbon atoms. This packing, like solid adsorbents, has a slightly higher selectivity towards paraffins compared with naphthenes of similar boiling point, and this causes it to yield combined peaks according to carbon number. Modification by means of squalane eliminates tailing of the chromatographic peaks. A column of this sorbent has been used to separate the saturated C_5 and C_6 hydrocarbons.

For the analysis of the saturated C_5-C_7 hydrocarbons, Eggertsen and Groennings[71] suggested using three columns: one with 3% squalane on C-22 firebrick† (non-polar), one with 40% di-(2-propionitrile) ether on C-22 (polar), and one with 1.5% squalane on "Pelletex" (which separates according to the number of carbon atoms). Combination of the three chromatograms made it possible to determine all paraffinic and naphthenic C_5 and C_7 hydrocarbons except 3-ethylpentane. In the analysis of the raw material of catalytic reforming, containing C_8 hydrocarbons, whose peaks often overlap the C_7 peaks, these compounds can be removed beforehand on the third column of squalane on "Pelletex" and the C_5-C_7 fraction is analysed on the other two. Use can also be made of mass-spectrometric data.

Simmons and Snyder[72] analysed the products of platforming by means of a two-stage chromatographic column constructed in such a way that only the desired fractions passed from the first stage to the second for further separation. Thus the sections of the column can operate either in series or in parallel. Such a scheme, using squalane on "Pelletex" and silicone on firebrick as sorbents, is illustrated in Fig. 9; with this it was possible to separate paraffinic, naphthenic, and aromatic hydrocarbons containing up to 8 carbon atoms. An analogous scheme with silica gel and n-octadecane on "Celite 545" as sorbents was used by Amberg *et al.*[73] to analyse the products of the oxidation of ethylene.

Knight[74] has shown, by comparing the activity coefficients of hydrocarbons of different structure, that a column of 1.5% squalane on "Pelletex", which achieves greater retention of paraffins relative to naphthenes with similar boiling points, has the same effect on aliphatic olefines relative to cycloolefines, and it is therefore possible to separate unsaturated hydrocarbons according to the number of carbon atoms. On this basis a method has been developed for determining pentenes and hexenes in petrol from catalytic cracking. This involves liquid chromatography with fluorescent indicators to obtain an olefinic–aromatic fraction, distillation of the latter to obtain the pentene and hexene fractions, and analysis of the latter by gas chromatography. The pentene fraction was first analysed on a column of squalane on "Pelletex" to remove traces of hexenes and then on a dimethylsulpholane column; the hexene fraction was also analysed first on a column of squalane on "Pelletex" and then on di-(2-propionitrile) ether. In addition, the C_6 monoolefines were analysed on dimethylsulpholane, the C_6 cycloolefines on firebrick C-22 with 3% squalane, and the C_5 olefines on diisodecyl phthalate.

¶ Granulated carbon with an active surface of 21 $m^2\ g^{-1}$, made by Cabot Corp., USA (Ed. of Translation).

† Made by Johns-Manville Corp., USA (Ed. of Translation).

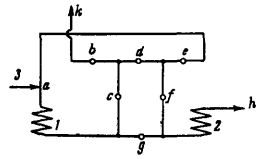

Fig. 9. Two-stage apparatus for analysis by gas chromatography:
1) column 1; 2) column 2; 3) carrier gas; *a*–*g*) valves; *h*, *k*) outlets to detector.

Combination of all these chromatograms makes it possible to determine 15 C_5 olefines (including cyclic olefines and dienes) and all 17 C_6 monoolefines (except 3- and 4-methylpent-1-enes) and also to obtain certain data on the cyclic olefines and C_6 dienes. The analytical scheme for the olefines is shown in Fig. 10 and the chromatograms for the separation on the various columns in Fig. 11. A serious disadvantage of this method is that it is cumbersome and time-consuming (the analysis of the C_5 compounds by gas chromatography requires 5 h, and that of the C_6 compounds 10–12 h).

A paper by Henschkel *et al.*[75] on the determination of traces of methylacetylene and allene in cracking gases is of interest. On a column of silicone oil, the peaks for these compounds come between the propane–propene and isobutane peaks. The polar phase diethylformamide holds back methylacetylene and propadiene to a greater extent than the saturated C_4 hydrocarbons. This has been used to carry out a two-stage analysis. The fraction containing the C_3 components and isobutane was taken from the first column and analysed on the polar column: this gave good separation of the peaks for the two trace substances being determined.

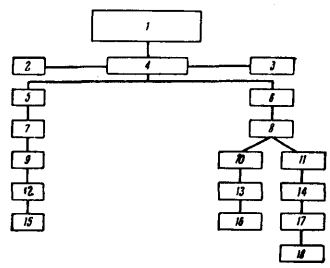

Fig. 10. Scheme for the analysis of C_5 and C_6 olefines by gas chromatography:
1) olefines; 2) hydrocarbons lighter than C_5; 3) hydrocarbons heavier than C_6; 4) 1.5% squalane on "Pelletex"; 5) C_5 hydrocarbons; 6) C_6 hydrocarbons; 7) 20% dimethylsulpholane on C-22; 8) 40% di-(2-propionitrile) ether on C-22; 9) some vapour undergoes further separation; 10) 13 out of 17 possible monoolefine peaks; 11) cycloolefines and dienes; 12) 10% diisodecyl phthalate on C-22; 13) 20% dimethylsulpholane on C-22; 14) 3% squalane on C-22; 15) all 14 possible components; 16) all components except the vapours of 3- and 4-methylpent-1-enes; 17) cycloolefines; 18) dienes.

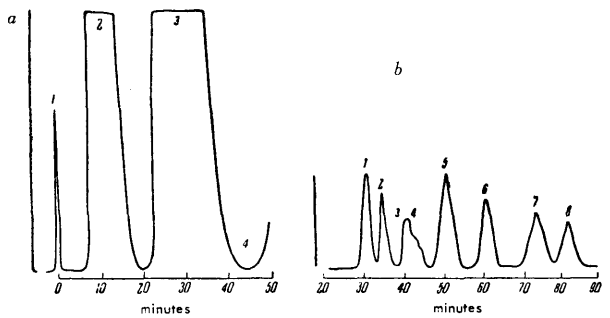

Fig. 11. Separation of olefines on various columns.
a) Separation on a column of squalene on "Pelletex":
1) air; 2) C_5 hydrocarbons; 3) C_6 hydrocarbons;
4) C_7 hydrocarbons.
b) Separation of the pentene mixture on a column of 10% diisodecyl phthalate on C-22 firebrick:
1) pent-1-ene; 2) 2-methylbut-1-ene; 3) and 4) ***cis***- and pent-***trans***-2-ene and 3,3-dimethylbut-1-ene;
5) 2-methylbut-2-ene and 3-methylbuta-1,3-diene;
6) 3-methylbuta-1,2-diene; 7) penta-1,2-diene;
8) cyclopentene.

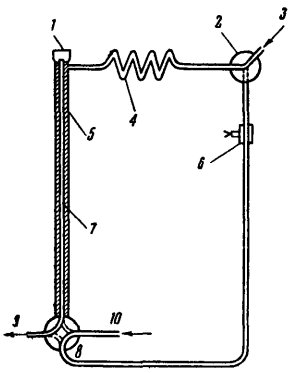

Fig. 12. System of preliminary fractionation for the analysis of the C_3-C_7 components present in petroleum:
1) silicone film; 2) three-way tap; 3) nitrogen;
4) nitrogen heater; 5) specimen inlet zone; 6) needle valve; 7) preliminary fractionation column; 8) four-way tap; 9) to analytical column; 10) nitrogen for blow-back.

The analysis of straight-run petrols by a combination of liquid chromatography (to separate the naphthene–paraffin fraction from the aromatic fraction) and gas chromatography with precise rectification, first used by Bradford *et al.*[61] and Lichtenfels *et al.*[76], was further developed by Kerenyi and Keszthelyi[77], who used a column of cetane on crushed 63 brick to analyse narrow naphthene–paraffin fractions of petrol, boiling up to 150°. This made it possible to carry out gas–liquid chromatography without using the pure components, since the fractions either had constant boiling point or were transitional. This method has been used for the analysis of petrols from eastern oils of the Soviet Union and has made it possible to determine the concentrations, in these materials, of a large number of hydrocarbons up to and including C_9.

Martin and Winters[78] used gas chromatography for the direct determination of the composition of petroleum up to and including the C_7 hydrocarbons, by means of a system of preliminary fractionation (Fig. 12).

A column containing "Apiezon" grease was used to separate the C_2-C_7 fraction, which was then passed to analytical columns containing isoquinoline and chloronaphthalene. The preliminary separation column was blown back to remove heavy components. Combined calculation on the two chromatograms makes it possible to determine 35 paraffinic, naphthenic, and aromatic hydrocarbons. This has been done for 20 Asiatic and American oils from different sources and has revealed a number of interesting features.

It is known that a large number of real hydrocarbon mixtures contain components of different classes, and this makes it difficult to develop methods for their chromatographic analysis. Methods have been proposed, based on the utilisation of the chemical reactions of given classes of substance. Thus Ray[79], in the analysis of non-olefinic trace impurities in ethylene, removed the latter beforehand on a column of carbon impregnated with bromine. Martin[80] used this "removal method" to analyse the C_3-C_6 hydrocarbons in cracking petrols. To absorb olefines he used an absorber containing sulphuric acid on silica gel. The analysis involved two runs on a column of isoquinoline, with and without the absorber connected in series. Combined calculations on the two chromatograms made it possible to determine 45 components in petrols from catalytic cracking and coking, and in commercial petrol (except for four groups of two to three components, which could not be separated). An analogous scheme is used with molecular sieves as separating agents, which irreversibly adsorb certain groups of substances, as mentioned above in connection with the problems associated with the identification of chromatographic peaks[37,38].

O'Connor and Norris[81] carried out a group analysis of petroleum distillates by a similar method, combining it with liquid chromatography on silica gel and with mass spectrometry. The analytical scheme is shown in Fig. 13. Hydrocarbons of normal structure, adsorbed by the molecular sieve, were extracted and analysed by gas chromatography.

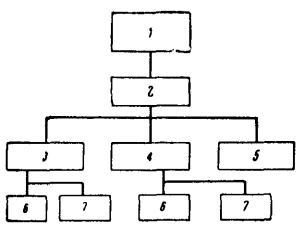

Fig. 13. Scheme for the analysis of petroleum distillates using molecular sieves and mass spectrometry:
1) specimen; 2) separation on silica gel;
3) saturated hydrocarbons; 4) olefines; 5) aromatic hydrocarbons; 6) 5 Å molecular sieves; 7) mass spectrometers.

Bayer *et al.*[24] analysed essential oils by successive separation of aldehydes and ketones (as the 2,4-dinitrophenylhydrazones), alcohols (as the dinitrobenzoates), and acids (as the alkali salts), with chromatographic separation of the residue on a column of silicone grease and $C_5H_{11}COOLi$ on brick.

Another method of using the chemical conversion of substances combined with gas chromatography has been proposed by Scharfe[82] for the analysis of hydrocarbon gases. According to this method, part of the specimen is hydrogenated in the presence of a platinum catalyst and then separated on a column containing 20% diisoheptene on kieselguhr. Another part of the specimen passes through a column of absorbent material (a solution of Ag_2SO_4 in H_2SO_4 on kieselguhr), which removes olefines, and is then subjected to chromatographic analysis. This method, which is applicable to the determination of the composition of C_1-C_5 hydrocarbons, can also be used for the analysis of hydrocarbons of higher molecular weight, if a knowledge of the individual composition of the olefines is not required and if it is possible to restrict the analysis to the determination of the concentration of groups with a given carbon skeleton.

When carrying out various chemical changes combined with gas chromatography, it is convenient to use the modified six-way tap proposed by Ettre and Brenner[83].

These examples illustrate the advantages of using multi-stage assemblies for the chromatographic analysis of complex mixtures.

Hurn *et al.*[84], in the analysis of waste gas consisting of hydrocarbons, the products of their partial oxidation, and other compounds, used a system of three different chromatographic columns connected in such a way that after passage through one column and detector, a fraction can be directed for further separation to either of the other two, and then, if necessary, to a third column. This scheme has been used to achieve good separation of components with 2–10 carbon atoms. In this case all components are passed through the first column (containing silicone oil), components up to and including heptane are passed through the second column (containing benzyl ether), and components up to hexane through the third (containing dibutyl maleate).

The American firm of Perkin–Elmer now produces a three-stage chromatograph[85] for the analysis of complex mixtures operating on the above principle. The apparatus is illustrated schematically in Fig. 14. In the analysis of petrols free from olefines, separation of saturated hydrocarbons from aromatic hydrocarbons and separation of the latter into individual components is achieved on the first column, packed with polyethyleneglycol on firebrick (Fig. 15*a*). The naphthene–paraffin fraction is then separated on a second column containing di-(2-propionitrile) ether as stationary phase (Fig. 15*b*). Finally, the light paraffins are separated on a column containing squalane (Fig. 15*c*). Cracking products cannot be analysed in this way, since they contain olefines.

Martin[86], in a study of the decomposition of α-cellulose, collected the products in a cold trap and separated these into two fractions. The first (light) fraction was then directed to a column of carbon or silica gel and the second to a gas–liquid column.

Madison[87] analysed light gases and C_1-C_4 hydrocarbons by means of columns of active carbon and dimethylsulpholane on firebrick, together with a cold trap containing

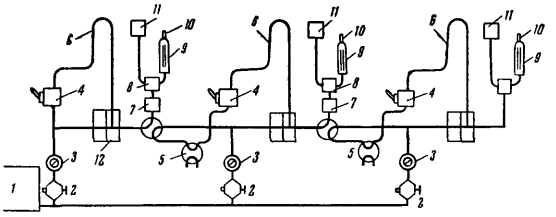

Fig. 14. The Perkin-Elmer Chromatograph, Model 188: 1) carrier-gas source; 2) pressure regulator; 3) manometer; 4) liquid specimen inlet; 5) tap for introducing gaseous specimen; 6) chromatographic column; 7) needle valve; 8) solenoid valve; 9) flowmeter; 10) outlet; 11) tap for removing specimen; 12) detector.

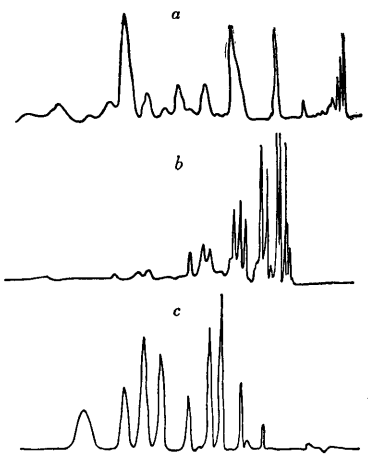

Fig. 15. Analysis of petrol on a Perkin–Elmer Chromatograph, Model 188: *a*) aromatic hydrocarbons, column of polyethylene glycol; *b*) paraffins, column of di-(2-propionitrile) ether; *c*) light paraffins, column of squalane.

carbon. An analysis was first carried out on the gas–liquid column, the light gases being retained in the trap, and the carrier gas (He) passed to the atmosphere *via* a bubbler (*D*). When the recording of the CH_4 was complete, the tap *B* was turned so that the hydrocarbons from C_2 upwards were removed from the system after analysis. The trap was then heated and taps *A*, *B*, *C*, and *D* were turned so that the light gases passed for analysis in a stream of helium from the trap containing carbon to the detector (see Fig. 16).

Cold traps can be used to concentrate trace impurities for analysis[88,89], and also to retain the components after separation for study by the other methods described in the discussion of the problems of component identification.

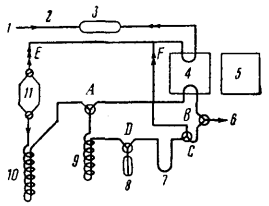

Fig. 16. Diagram of a two-stage chromatograph using a cold trap:
1) helium supply; 2) pressure regulator; 3) buffer vessel; 4) thermal-conductivity gauge; 5) recorder; 6) to gas-meter; 7) trap with active carbon; 8) bubbler; 9) 25 foot column with active carbon; 10) 25 foot column with dimethylsulpholane; 11) tube for specimen. *A*–*F*) Taps.

Other useful schemes for the determination of the composition of complex mixtures by chromatographic analysis include: a circulation chromatograph[90-92], which makes it possible to imitate any length of column without significant pressure drop; a rotating column[93] in the form of two concentric cylinders, which makes it possible to separate components according to the lag angle; and the use of various types of chromathermography[94], in particular the method proposed by Nerheim[95], in which a heater producing a temperature gradient passes repeatedly along the column with increasing heater temperature, so that the components or fractions with corresponding characteristic temperatures are eluted in succession as narrow peaks.

3. A REVIEW OF WORK ON THE ANALYSIS OF HYDROCARBONS

In this review particular attention is paid to the problems of analysing hydrocarbons from C_5 upwards. The problems of analysing lighter components are considered only when these components are present in mixtures with C_4 and C_5 hydrocarbons. Moreover, we shall not deal with certain papers considered in the preceding sections.

The analysis of C_5 and lighter hydrocarbons. Systems containing hydrocarbons up to and including C_5 play an important part in various branches of the petrochemical industry, and the development of rapid and accurate methods of analysis is of considerable interest, since these make it possible to achieve control of such processes as cracking, pyrolysis, gas-fractionation, etc. A number of authors have used various polar and non-polar stationary phases to solve these problems. Thus Keulemans and Kwantes[96] used dimethylformamide on brick for the analysis of the butane fraction of cracking products. All the components were separated, except propene and isobutane, which gave a single chromatographic peak. Bradford *et al.*[61] analysed hydrocarbons up to and including C_4 on columns of triisobutene, acetonylacetone, and a saturated solution of silver nitrate in glycol. Buta-1,3-diene, but-1-ene, and 2-methylprop-1-ene gave a common peak on triisobutene, and the last two a common peak on acetonylacetone. When silver nitrate solution was used, the saturated hydrocarbons gave a common peak, and ethylene and propene were not separated.

Armitage[97] used columns of silver nitrate solution and dimethylsulpholane to analyse the products of isoprene production.

Brodskii *et al.*[98,99] put forward a method for determining the individual composition of C_3-C_5 hydrocarbons, involving two parallel analyses on columns of acetonylacetone and diisoamyl phthalate; however, each analysis may take several hours. A chromatogram for the separation of a mixture of C_5 hydrocarbons on a column of diisoamyl phthalate is given in Fig. 17.

Taylor and Dunlop[100] have carried out parallel analyses on columns of dimethylformamide and dinonyl phthalate.

Turkel'taub *et al.*[69], selecting stationary phases for the analysis of C_2-C_5 hydrocarbons, found that complete separation of a mixture of C_2-C_4 and saturated C_5 hydrocarbons can be achieved with mixed solvents: 45% dimethylformamide + 1% liquid paraffin on brick or 45% dimethylformamide + 6.5% triisobutene on diatomite.

McKenna and Idleman[101] tested the efficiency of a number of liquids for the separation of C_4 hydrocarbons and found the best to be a 30:70 mixture of glutaronitrile and propylene carbonate. The chromatogram which they obtained showed complete separation of all components. For the same purpose Devyatykh *et al.*[102] used a composite 5 mm diameter column in which 1.5 m of carrier was impregnated with a solution of silver nitrate in glycol and 3 m with furfural.

McEwen[13] separated the C_2-C_7 hydrocarbons using the hexamethyltriamide of phosphoric acid as stationary phase. The 30 components of the mixture being analysed gave 22 chromatographic peaks. 2-Methylprop-1-ene and but-1-ene, n-pentane and buta-1,3-diene, *cis*-, and *trans*-pent-2-ene, and others were not separated.

Recently Dement'eva[67,103] proposed triethylene glycol n-butyrate as stationary phase for the analysis of C_3-C_5 hydrocarbons. This gives separation of almost all isomers (but-1-ene and 2-methylprop-1-ene give a common peak). Fig. 18 gives a chromatogram for the analysis of C_5 hydrocarbons and illustrates the high resolving power of this stationary phase.

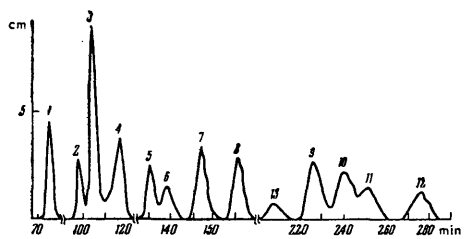

Fig. 17. Chromatogram for the separation of a mixture of C_5 hydrocarbons on a column of diisoamyl phthalate on crushed brick:
1) isopentane + 3-methylbut-1-ene; 2) n-pentane; 3) pent-1-ene; 4) 2-methylbut-1-ene; 5) pent-*trans*-2-ene; 6) pent-*cis*-2-ene; 7) 2-methylbut-2-ene; 8) isoprene; 9) *trans*-piperylene + cyclopentane; 10) cyclopentene; 11) *cis*-piperylene; 12) cyclopentadiene.

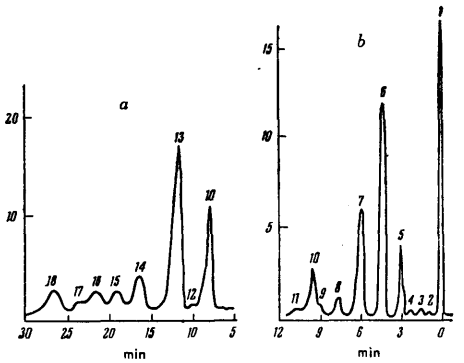

Fig. 18. Chromatograms for the separation of C_4 and C_5 hydrocarbons on a column of triethylene glycol n-butyrate: 1) air; 2) ethane; 3) propane; 4) propene; 5) isobutane; 6) n-butane; 7) isobutene + but-1-ene; 8) but-*trans*-2-ene; 9) but-*cis*-2-ene; 10) isopentane; 11) buta-1,3-diene; 12) 3-methylbut-1-ene; 13) n-pentane; 14) pent-1-ene; 15) 2-methylbut-1-ene; 16) pent-*trans*-2-ene; 17) pent-*cis*-2-ene; 18) 2-methylbut-2-ene.

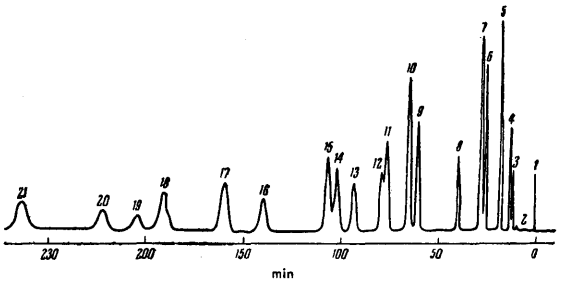

Fig. 19. Separation of a mixture of C_2-C_5 hydrocarbons on a column of dimethylsulpholane at 0°: 1) start of experiment; 2) air; 3) ethane; 4) ethylene; 5) propane; 6) propene; 7) isobutane; 8) n-butane; 9) but-1-ene; 10) 2-methylprop-1-ene; 11) isopentane; 12) but-*trans*-2-ene; 13) but-*cis*-2-ene; 14) n-pentane; 15) 3-methylbut-1-ene; 16) buta-1,3-diene; 17) pent-1-ene; 18) 2-methylbut-1-ene; 19) pent-*trans*-2-ene; 20) pent-*cis*-2-ene; 21) 2-methylbut-2-ene.

Complete separation of the C_2-C_5 hydrocarbons normally encountered has been achieved only by Fredericks and Brooks[66], who used a 15 m column of dimethylsulpholane at 0°. Analysis up to 2-methylbut-2-ene, however, required ~4.5 h. Isoprene comes out 390 min after insertion of the specimen. This is naturally a serious disadvantage of the method.

The C_3-C_5 hydrocarbons have also been separated by gas-adsorption chromatography on alumina. Scott's data[104] show that in this case 2-methylprop-1-ene comes off with but-*trans*-2-ene, and butadiene with isopentane. The last two hydrocarbons can be separated by treating the adsorbent with 2% silicone oil.

Greene *et al.*[105] have also obtained separate peaks for all unsaturated and monoolefinic C_1-C_4 hydrocarbons on alumina.

Zhukhovitskii *et al.*[68,106,107] analysed hydrocarbons up to and including C_5 by means of a universal chromathermographic apparatus including a column of alumina working on the chromatographic principle and a gas–liquid column of dibutyl phthalate on diatomite. The peaks for 3-methylbut-1-ene and isopentane coincide and to determine these compounds it is necessary to carry out a parallel analysis on a single column of alumina. *cis*- and *trans*-pent-2-ene are also obtained as a single peak.

In the VNIINP‡, a sorbent consisting of Zikeevskii tripoli treated with sodium carbonate and liquid paraffin has been proposed for the separation of C_3-C_5 hydrocarbons. This sorbent achieves separation of most components, but the peaks for butadiene and but-*cis*-2-ene, and for pent-*trans*-2-ene and 2-methylbut-1-ene coincide. A chromatogram obtained with this sorbent is shown in Fig. 20.

‡ Vsesoyuznyi Nauchno-Issledovatel'skii Institut po Pererabotke Nefti i Gazovi Polucheniyu Iskusstvennogo Zhidkogo Topliva (All-Union Scientific Research Institute for the Treatment of Petroleum and Gases and the Production of Synthetic Liquid Fuel) (Ed. of Translation).

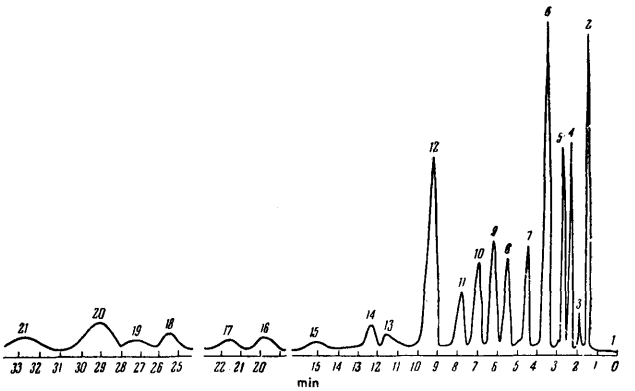

Fig. 20. Chromatogram for the separation of hydrocarbon gas on the VNIINP adsorbent: 1) specimen inserted; 2) methane; 3) ethane + ethylene; 4) propane; 5) propene; 6) 2-methylprop-1-ene; 7) n-butane; 8) but-1-ene; 9) 2-methylprop-1-ene; 10) but-*trans*-2-ene; 11) but-*cis*-2-ene; 12) isopentane; 13) 3-methylbut-1-ene; 14) n-pentane; 15) pent-1-ene; 16) pent-*trans*-2-ene + 2-methylbut-1-ene; 17) pent-*cis*-2-ene; 18) 2-methylbut-2-ene; 19) 2-methylpentane + + 2,2-dimethylbutane; 20) 3-methylpentane; 21) n-hexane.

Thus only one paper[66] reports the complete separation, in a single analysis, of the C_2-C_5 hydrocarbons normally encountered, up to 2-methylbut-2-ene, but in this case the time needed is a serious disadvantage. The method also requires that the column be cooled to 0°, and this is not always possible.

The analysis of saturated hydrocarbons. The development of methods for the analysis of saturated hydrocarbons is of considerable interest for the determination of the composition of light petroleum fractions, paraffins, and other products.

Although the choice of stationary phases for the analysis of normal paraffins is a fairly simple problem, considerable difficulty is introduced by marked difference in vapour pressures, since this makes analysis time-consuming under isothermal conditions. In this connection use is made of temperature programming [116,117] and chromathermography [95,110-113], which achieve separation fairly rapidly.

The analysis of mixtures containing both normal and isoparaffins as well as naphthenes is a more complex problem and cannot be achieved on a single column for hydrocarbons above C_6. Various natural mixtures of saturated hydrocarbons have been analysed by James and Martin [114], Lichtenfels *et al.* [76,120], and others, with substances such as phthalates, sebacates, high-boiling paraffinic hydrocarbons, polyethylene glycol, benzylbiphenyl, etc. as stationary phases. Table 3 gives some examples of the analysis of saturated hydrocarbons.

In the analysis of saturated and other hydrocarbons, use should be made of the extensive data given by Tenney [15], Bayer [16], Desty and Whyman [28], Desty and Harborn [32], and others, who have determined the elution characteristics of a large number of components on a wide variety of stationary phases.

TABLE 3. Analysis of saturated hydrocarbons.

Components being analysed	Stationary phase, temperature, °C	References
Normal paraffins C_3-C_7	diatomite, kaolin, natrolite* gradual heating to 100°–120° (chromathermography)	110–113
Normal paraffins C_2-C_7	sodium zeolite 20°–80°	12
Paraffins and naphthenes C_4-C_{10}	n-octadecane, 65°; solid paraffin, 78.6°; polyglycol, 78.6°; benzylbiphenyl, 78.6° (40% stationary phase on 100 g firebrick)	114
Paraffins and naphthenes C_5-C_7	1.5% squalane on "Pelletex", 40°, 75°; 3% squalane on firebrick, 25°; 40% β,β'-di-(2-propionitrile) ether on firebrick, 25°	70, 71
Paraffins and naphthenes C_5-C_7	13.4% isoquinoline on firebrick; 3.1% chloronaphthalene on firebrick	78
Paraffins and naphthenes C_5-C_6	40% heterocyclic amines on "Chromosorb"	115
Normal paraffins C_5-C_{36}	20–30% high-vacuum silicone grease on firebrick. Linear temperature programming up to 400°	116, 117
Normal paraffins $C_{20}-C_{27}$	asphaltenes on firebrick, 280°–320°	118
Normal paraffins C_5-C_6, isopentane	45% silicone oil on firebrick. Chromathermography with heater temperature rising to 217°	95
Hexane isomers	12% isoquinoline on firebrick	119
Paraffins and naphthenes C_5-C_6	dioctyl phthalate on "Celite", 65°; dioctyl sebacate on firebrick, 45°	76, 120
Paraffins and naphthenes C_5-C_9	paraffin, 78.5°	121

* The zeolite $Na_2O.Al_2O_3.3SiO_2.2H_2O$ (Ed. of Translation).

TABLE 4. Analysis of aromatic hydrocarbons.

Components being analysed	Stationary phase, temperature, °C	References
C_6-C_{11}	40% silicone 702 on firebrick, 132°	8, 61
Benzene, toluene, ethylbenzene, styrene	"Tide" detergent, 133°	64
Ethylbenzene, isopropylbenzene	liquid paraffin	122, 123
Xylenes	benzylbiphenyl, 78°, 100°; 7,8-benzoquinoline, 78.5°, 110.8°; phenanthrene, 110.8°; substituted montmorillonite, 80°; tetrahalogenophthalates; a mixture of ethylene carbonate and chloronaphthalene, 50°; dimethylsulpholane, 50°; chloronaphthalene, 40°, 50°	130, 131, 132, 133, 134, 135
Benzene, naphthalene, methylnaphthalene	silicone oil, dinonyl phthalate, 78.5°, 200°	136
Toluene, *p*- and *o*-xylenes, mesitylene, pseudocumene	silicone oil, 130°–220°	23
Benzene, ethylbenzene, xylenes, naphthalene, methylnaphthalene, biphenyl, dimethylnaphthalene	polyoxyalkylene adipate (Reoplex 400), 110°, 200°, etc.	125, 126, 137, 138
Cumene, n-propylbenzene, *p*-ethyltoluene, mesitylene, pseudocumene, etc.	dinonyl phthalate, tricresyl phosphate, 130°	18
High-boiling aromatic hydrocarbons	"Apiezon", high-vacuum silicone grease, polyethylene, asphaltenes, polyphenyl resins, 375°–445°	17, 124, 127
Impurities in commercial benzene, toluene, and xylene	squalane, tetrapentylsilane, *p*-nitroaniline picrate, fluorene picrate, picric acid with dibutyl phthalate, didecyl phthalate, β,β'-di-)2-propionitrile) ether, 2,4,7-trinitrofluoren-9-one	139, 140

The analysis of aromatic hydrocarbons. Aromatic hydrocarbons are of considerable importance as motor-fuel components and as raw material for various chemical processes. The aromatic hydrocarbons present in petrol can be analysed comparatively simply with various stationary phases [8,61]. The separation of *m*- and *p*-xylenes, whose boiling points are extremely close, is not always achieved, and a number of studies [124-129] have been devoted to the selection of conditions for their separation. This procedure is now relatively trivial.

A number of papers have been devoted to the determination of trace components in the commercial products: benzene, toluene, xylene, and cumene [122-125], which contain saturated hydrocarbons as well as aromatics.

As a result of the development of high-temperature chromatography, it has become possible to analyse the polynuclear aromatic hydrocarbons present in various natural products [17,126-129]. The temperature of the column may reach 475°.

Table 4 gives some typical examples of the analysis of aromatic hydrocarbons. These examples, with the work previously cited, give an idea of the possible uses of gas chromatography for determining the composition of hydrocarbons of this class, present in various products.

TABLE 5. Analysis of unsaturated hydrocarbons.

Components analysed	Stationary phase	References
C_5-C_6 olefines (mono-, di- and cyclo-)	1.5% squalane on "Pelletex"; 40% β,β'-di-(2-propionitrile) ether on firebrick, 10% diisodecyl phthalate on firebrick; 20% dimethylsulpholane on firebrick; 3% squalane on firebrick	74
Isomeric hexenes	phthalate esters	142
Cycloolefines	solution of $AgNO_3$ in glycol, on firebrick	143–145
Cyclopentadiene and methylcyclopentadiene	30% polyethylene glycol on firebrick	146
3- and 4-methylpent--1-ene	solution of $AgNO_3$ in glycol, on firebrick	141
Terpenes	tricresyl phosphate on crushed tile	150

The analysis of unsaturated hydrocarbons. Knight[74] has separated a mixture of C_5 and C_6 olefines of different structures. In particular, all 15 C_5 olefines and all 17 possible C_6 monoolefines except 3- and 4-methylpent-1-enes have been determined. Smith and Ohlson[141] studied the separation of this last pair of compounds, using a 17% solution of silver nitrate in glycol as stationary phase.

The analysis of the isomeric hexanes and hexenes has been studied by Sullivan *et al.*[142], who examined the possibility of using phthalate esters for this purpose.

Shabtai *et al.* have published a number of papers[143-145] on the problems of analysing alkylcyclopentanes, alkylcyclohexenes, and also cyclopentanes and cyclohexanes with unsaturated side chains. A solution of silver nitrate in glycol proved extremely effective for these and other purposes.

Since cyclopentadiene and its derivatives are present in a number of products, a method developed by Dahmen and van der Laarse[146] for the analysis of cyclopentadiene and methylcyclopentadiene is of considerable interest.

The analysis of the terpenes present in many natural products[147-149] is made difficult by the catalytic action of the solid carrier. To avoid this, Czechoslovak workers have used an unglazed brick ("porovin")[150] which is catalytically inert. This has made it possible to carry out the chromatographic process at high temperatures (136°); this is impossible when ordinary carriers are used[147].

Capillary chromatography. In the last few years, extensive development of capillary chromatography has taken place; this technique readily achieves certain separations which are extremely difficult when ordinary columns are used. Thus xylenes can be separated rapidly at various temperatures between room temperature and 80° on the weakly polar phases didecyl phthalate[151] and dinonyl phthalate[152].

Using a capillary column containing squalane, Zlatkis and Lovelock[153] separated a mixture of C_5-C_8 hydrocarbons containing 25 individual components, in 90 min.

Desty *et al.*[154] examined the problems of the theory and construction of apparatus for capillary chromatography and concluded that this method can be used for the analysis of petrols, lubricating oils, and other oil products.

Condon[155] used capillary columns 0.006–0.055 inch in diameter to separate a variety of hydrocarbon mixtures, including mixtures of C_6 isomers (40°, 150 ft column of diisodecyl phthalate), terpenes (125°, 175 ft column of polypropylene glycol), reforming products (115°, 150 ft column of diisodecyl phthalate), and a mixture of C_5-C_8 paraffins and naphthenes (33°, 175 ft column of polypropylene glycol).

A synthetic mixture of C_2-C_5 hydrocarbons has also been analysed at 33° on a composite column (200 ft of dimethylsulpholane and 100 ft of polypropylene glycol). In this case, however, but-1-ene and 2-methylprop-1-ene, and ethane and ethylene, gave common peaks.

Analytical distillation by gas chromatography. Eggertsen *et al.*[156] have achieved analytical distillation using a gas chromatograph instead of a fractionating column. The method makes it possible to separate petroleum products boiling in the range 40°–400°. A 6 inch long, $\frac{1}{4}$ inch internal diameter chromatographic column was filled with insulating brick impregnated with 20% silicone oil, and had an efficiency of 200 theoretical plates, which corresponds to 20 plates in a fractionating column. Programming of the column temperature from 2° to 280° makes it possible to distil a mixture boiling up to 400°, in 30 min. Fig. 21 gives graphs for the relationship between the temperature and times of leaving the column and the boiling points of paraffins, olefines, naphthenes, and aromatic hydrocarbons. These curves and the chromatograms obtained can be used to construct distillation curves.

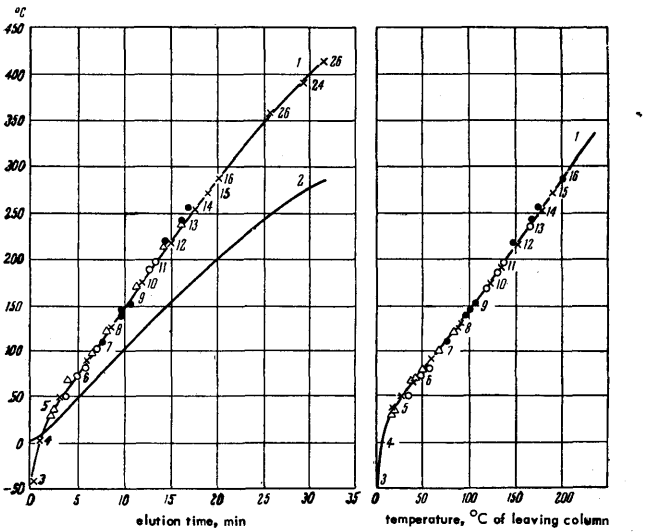

Fig. 21. Curves giving the relationship between the temperature and elution time and boiling point for hydrocarbons during analytical distillation by the gas-chromatography method:
1) boiling points of the substances; 2) column temperature.

Such curves have been obtained for the catalytic cracking products and have shown good agreement with distillation curves.

Analysis of mixtures of gaseous and liquid hydrocarbons. Some of the most complex hydrocarbon mixtures, containing a very large number of individual components, are the liquid raw material and products of pyrolysis. In a number of cases, in order to direct industrial plant conditions, it is necessary to know the individual components of the light fractions of the pyrolysis gas and the group composition of the heavier fractions. As shown above, these problems can be solved by means of an ordinary two-stage analytical scheme.

The method which we have developed for the analysis of the C_1-C_{10} hydrocarbons and hydrogen in pyrolysis gas makes it possible to determine the individual composition of the C_1-C_3 fraction, the concentration of C_4, C_5, and C_6 components, and the total concentration of heavier hydrocarbons[157]. The 3 m long, 4 mm internal diameter column of the first stage is filled with inzenskii brick impregnated with 20% liquid paraffin. This is placed in an air thermostat at 70°. The sorbent used makes it possible to separate the pyrolysis gas into a number of fractions, which are recorded by means of a thermal-conductivity detector and appropriate recording apparatus.

The first fraction containing hydrogen and the C_1-C_3 components is then directed to the column of the second stage for further separation. The fractions containing the C_4, C_5, and C_6 hydrocarbons are eluted directly to the atmosphere. After the components with six carbon atoms have been eluted, the carrier-gas (air) stream is blown back to elute the C_7 and heavier hydrocarbons. The consumption of carrier gas increases in this stage.

The 3 m long, 4 mm diameter column of the second stage is filled with KSK silica gel modified with 1–2% liquid paraffin and is placed in an air thermostat at 25°–40°. A detector responding to the heat of combustion is placed at the column outlet. This second column separates hydrogen, methane, ethane, ethylene, propane, acetylene, and propene with close degrees of separation between neighbouring peaks.

When necessary, the fractions eluted from the first column to the atmosphere can be analysed further in an additional section with suitably chosen sorbents, for example Zikeevskii tripoli or inzenskii brick impregnated with triethylene glycol n-butyrate. Pyrolysis tars have been analysed on columns of silicone elastomer and triethylene glycol, deposited on "Celite": The components were identified either by comparing the retention volumes of the components with those of standard substances or by using the "removal method" described above.

The petrols used as liquid raw material for pyrolysis are extremely complex mixtures and cannot be analysed on a single column due to superposition of the peaks. The petrols have therefore been separated by means of a chromatographic assembly including one column in the first stage, three columns in a second stage, and a system for redirecting the gas streams. After the first column, a small part of the stream is directed to a flame-ionisation detector. Flame-ionisation detectors and katharometers are also placed after the columns of the second stage. The device for redirecting the streams is constructed in such a way that if the eluate after the first stage is directed to one of the columns of the second stage, pure carrier gas passes to the other sections. By means of this system it is possible to carry out in the second stage a detailed separation of the narrow fractions produced in the first column.

The use of gas chromatography makes it possible to carry out a detailed analysis of complex mixtures, the study of whose composition previously seemed almost impossible.

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ISOTOPE EFFECT IN VAPOUR PRESSURE

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A. EXPERIMENTAL DATA

The vapour pressure of isotopic substances has attracted much attention from investigators mainly in connection with the use of fractional distillation as a method for separating isotopes. Keesom and van Dijk[1,2] were the first to achieve by this means a partial separation of the isotopes of neon. A year later Urey *et al.*[3] distilled hydrogen and increased its deuterium content by a factor of 25; this led to their discovery of deuterium. The same method was used[4] to prepare 50% deuterium (enrichment by a factor of 3200). The industrial production of deuterium by the low-temperature fractionation of hydrogen has now been achieved in the USSR[5] and in Western Germany[6] with the aim of preparing heavy water, for which purpose the fractionation of water itself is employed in the USA[7]. Highly efficient columns have been designed for this process, and it has been shown that, economically, it is especially suitable for the final concentration of the heavy water, starting from about 1% solutions[8].

Twenty years ago Brodskii *et al.*[9] and Huffman and Urey[10] were able to increase the content of heavy oxygen in water severalfold by fractionation. Recently Zhavoronkov and his coworkers have described the preparation by this means of water having $H_2{}^{18}O$ contents of 24.5%[11,12] and 60%,[13] while Dostrovsky and Raviv[14] have given an account of a column producing 99.8% $H_2{}^{18}O$ (490-fold enrichment).

Atmospheric helium contains only $(1.2-1.3)\times 10^{-4}$ at.% of ^3He, but Esel'son and Lazarev[15] fractionated ordinary helium until it contained 1.5% of the light isotope, and only three years later 99% ^3He was obtained in this way[16]. The same method has been used to separate the isotopes of argon[17].

Recently Tikhomirov and Tunitskii[18] have reported the enrichment of carbon monoxide by fractionation to a content of 37 at.% ^{13}C and 4.5% ^{18}O, while London[19] has described a column in which it is possible to obtain small quantities of CO containing 60–70 at.% of ^{13}C (~60-fold enrichment) and 5–6% of ^{18}O (~27-fold enrichment).

Zhavoronkov and his colleagues were the first to achieve a high concentration of the light isotope of boron, up to 57 at.% by the fractionation of BCl_3[12,20] and up to 86–96 at.% of ^{10}B by fractionating BF_3.[21]

Clusius and Schleich[22] have recently enriched nitric oxide with the ^{15}N isotope severalfold and have shown the advisability of the industrial production of heavy nitrogen by this method.

At the present time, research is being vigorously pursued in various countries to extend the use of fractionation for separating isotopes, and columns are being constructed for the industrial development of processes which have already been studied[14,21]. In the USSR investigations on these lines were started by Brodskii[9,23-25], and are being carried on by Zhavoronkov, Malkov, Tunitskii, and other scientists.

In order to settle the question of the usefulness of fractionation and to design columns, data are required on the relative volatility factor α, which is approximately equal to the ratio of the vapour pressures of the pure components at the given temperature, provided that the departure of the system from an ideal solution can be neglected. Because of this, and also in view of the theoretical interest attaching to the effect of isotopes on physicochemical properties, data have been obtained during the course of thirty years' investigation on the effect of isotopic composition on the vapour pressures of sixty substances of various chemical types.

When it was possible to work with concentrated isotopic compounds, the difference in their vapour pressures was measured directly, by means of differential manometers. When the content of one isotope was small, the mixtures were regarded as ideal and the ratio of the vapour pressures of the components was taken as α, which was determined directly from the composition of the equilibrium phases, by the Raleigh distillation method, or, in the last resort, from operating data for fractionating columns. These methods have been described in detail[25-27].

In the present review the vapour pressure of isotopic compounds is usually expressed in the form of empirical $\log P = f(T)$ equations, where P is the pressure in mm Hg. Values are also given for the ratio P_h/P_l, where the subscripts denote the heavy and the light forms of the molecules†. In the cases of helium and hydrogen, with which the isotopic effect is exceptionally large, numerical values of the vapour pressures are also given.

† The inverse ratio is often quoted in the literature. This originated in the fact that, with several substances which are liquid at comparatively low temperatures and which were investigated earlier than the others, $P_h < P_l$, while the ratio of these quantities was chosen to be such that it would exceed unity. However, the relationship $P_h > P_l$ is more general, as is shown in the account below, and for polyatomic isotopic compounds several workers[12] employ the quantity P_h/P_l. In order to compare the isotope effect in the vapour pressure of different classes of substances, this effect is always expressed in the same way in the present paper – by means of the ratio P_h/P_l. It is also preferable because with the vast majority of substances described – isotopic compounds of H, O, C, and N – the light variety is the usual form, and in expressing a new quantity in terms of one which is already known it is more logical to take the latter as unity.

1. VAPOUR PRESSURE OF MONATOMIC ISOTOPIC SUBSTANCES

The isotope effect proved particularly large in the vapour pressure of helium. For example, a 0.16% enrichment of ordinary helium with its light isotope at 1.5 °K produces an increase in vapour pressure of 6%.[28] The vapour pressure of pure ^{3}He formed by the decay of tritium has been studied[29-34]. The light helium isotope used by Abraham *et al.*[30] contained only 0.03% of ^{4}He. These results are evidently most accurate, and the corresponding data[35] for ^{4}He are given in Table 1, where the temperature has been measured on the 1955 T_E scale[35,36]. The exact variation of the vapour pressure of ^{3}He with temperature over the range 1.0°–3.3 °K is represented by the equation[30]:

$$\log P_{mm} = -\frac{0.97796}{T} + 2.5 \log T + 0.000302 T^3 + 1.91594, \qquad (1)$$

where T is measured on the 1948 scale[37] with Kistemacker's corrections[38].

The isotope effect decreases sharply with rise in temperature: at 1 °K the vapour pressure of ^{3}He exceeds the vapour pressure of ^{4}He by a factor of 72, but at 3.3 °K this factor has become only 3. Sydoriak and Roberts[39] were able to make very accurate measurements of the vapour pressure of ^{3}He below 1 °K (from 0.45° to 1.0°), their results being represented by the equation

$$\log P_{mm} = \frac{1.1037}{T} + 2.3214 \log T + 2.0936 - 0.08976 T + 0.03756 T^2 - 0.004 T^3, \qquad (2)$$

where the temperature is measured on the 1955 T_E scale.

The normal boiling point of ^{4}He exceeds that of ^{3}He (3.195 °K) by 1.021°. The data[30] in Table 2 on the heat of evaporation ΔH_e of ^{3}He have been calculated by means of the Clausius–Clapeyron equation, and are accurate to a few tenths of a calorie per mole.

Similar calculations have been carried also by Kerr[40] for the range 1.0°–3.3° and by Roberts and Sydoriak[41] between 0.54° and 1.25 °K. At 1.5 °K a calorimetric method[42] has given a value for ΔH_e (^{3}He) of 10.39 ± 0.02 cal mole^{-1}, which is quite close to the corresponding calculated value. The values given in Table 2 for ^{4}He are calorimetric, and are accurate to a few hundredths of a calorie per mole.

Interesting results have also been obtained[45-51] for the vapour pressure of solutions of ^{3}He in ^{4}He, Fig. 1 showing the corresponding diagrams for this system[47]. The curve of vapour pressure against liquid composition diverges markedly from the corresponding straight line representing Raoult's law‡.

The isotope effect is much smaller with liquid neon than with helium, but it is still considerable. As early as 1935 Keesom and Haantjes[57] measured the vapour pressure of a series of mixtures of neon isotopes having mean atomic weights between 20.04 and 21.16, and obtained by extrapolation the data for the pure isotopes given in Table 3§. It was found graphically that the temperature of the triple point for ^{22}Ne was 0.134° higher than that for ^{20}Ne (24.6 °K).

With argon the isotopic difference in vapour pressures is only a few tenths of 1%. The following results were obtained by Clusius and Meyer[17] for the isotopes having atomic weights of 40, 38, and 36 from data on the fractionation of natural argon (^{36}Ar 0.307, ^{38}Ar 0.060%) at temperatures near the triple point (83.8 °K):

$$0.995 > P_{40}/P_{36} > 0.993,$$
$$0.997 > P_{40}/P_{38} > 0.996.$$

TABLE 1. Vapour pressure of isotopes of helium on T_E temperature scale.

T, °K	P, mm Hg ^{4}He[35]	P, mm Hg ^{3}He[30]	$P_{^4He}/P_{^3He}$	T, °K	P, mm Hg ^{4}He[35]	P, mm Hg ^{3}He[30]	$P_{^4He}/P_{^3He}$
1.0	0.12170	8.564	0.0142	2.2	40.703	212.28	0.1917
1.1	0.29956	13.384	0.0224	2.3	51.266	248.52	0.2062
1.2	0.63253	19.765	0.0320	2.4	63.589	288.60	0.2203
1.3	1.2220	27.913	0.0433	2.5	77.793	332.71	0.2338
1.4	2.1776	38.03	0.0573	2.6	94.046	381.02	0.2468
1.5	3.6336	50.30	0.0722	2.7	112.438	433.73	0.2594
1.6	5.7414	64.91	0.9885	2.8	133.214	491.09	0.2713
1.7	8.663	82.06	0.1056	2.9	156.419	553.01	0.2829
1.8	12.565	101.93	0.1233	3.0	182.226	619.92	0.2940
1.9	17.607	124.69	0.1412	3.1	210.776	691.88	0.3046
2.0	23.930	150.55	0.1590	3.2	242.196	769.04	0.3149
2.1	31.625	179.68	0.1760	3.3	276.624	851.50	0.3249

TABLE 2. Heat of evaporation of isotopes of helium.

T, °K	ΔH_e, cal mole^{-1} ^{4}He[43,44]	ΔH_e, cal mole^{-1} ^{3}He	References for ^{3}He
1.0	18.8	9.1	30
1.5	21.40	10.6	
2.0	22.20	11.3	
2.5	22.05	10.8	
3.0	22.42	7.9	40
3.3	23.00	3.4	

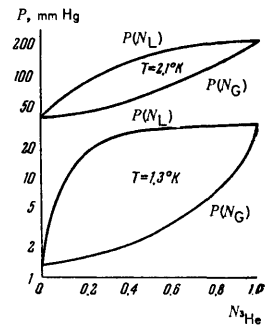

Fig. 1. Vapour pressure–composition diagrams for solutions of ^{3}He in ^{4}He. N = mole fraction; N_L = mole fraction of ^{3}He in liquid; N_G = mole fraction of ^{3}He in vapour.

‡ Melting-point curves for ^{3}He and ^{4}He up to 3500 kg cm^{-1} have been described by Mills and Grilly[52]. The method of measuring vapour pressure and additional data on the properties of ^{3}He and its solutions in ^{4}He have been given[53-55]. For the separation of the isotopes of helium see Kuznetsov[56].

§ Recently Roth and Bigeleisen[58] confirmed the data of Keesom and Haantjes using a specimen of neon containing 77.2% ^{22}Ne.

TABLE 3. Isotope effect in the vapour pressure of neon[57].

T, °K	$P_{^{22}Ne}/P_{^{20}Ne}$			T, °K	$P_{^{22}Ne}/P_{^{20}Ne}$		
	expt.	calc. from Eqns. (85)	calc. from Eqns. (92), (93)		expt.	calc. from Eqns. (85)	calc. from Eqns. (92), (93)
	Solid state				Liquid state		
20	0.924	0.935	0.925	25	0.957		
21	0.930	0.942		26	0.960		
22	0.935	0.946	0.936	27	0.962		
23	0.940	0.950					
24	0.944	0.954	0.945				

A differential manometer has been used[59] to measure differences in vapour pressure for two specimens of krypton differing in atomic weight by 1.74 units, and two specimens of xenon differing by 2.95 units. In the case of krypton the specimen enriched with the heavy isotope had a vapour pressure which was the smaller by 0.3% over the range 0–760 mm Hg¶; and with the isotopic mixtures of xenon the difference in vapour pressures over the same range already lies within the limits of error (0.02 mm Hg) of the measurements. Such a small isotope effect explains the absence of appreciable separation of isotopes in the experiments of Clusius[60] on the fractionation of xenon in a column equivalent to 25 theoretical plates at temperatures around the ternary point (161.36°K, 612.2 mm Hg)†. Another monatomic substance which has been investigated is mercury. Grigor'ev *et al.*[61] found by Rayleigh distillation and by other methods that ^{204}Hg has a lower vapour pressure than has ^{198}Hg, the difference not exceeding 0.2% at 253°K, and 0.08% at 453°K.

2. VAPOUR PRESSURE OF DIATOMIC ISOTOPIC SUBSTANCES

(a) Isotopes of Hydrogen

Only two years after the discovery of deuterium Scott *et al.*[62] made careful direct measurements of the vapour pressure of a specimen of this substances obtained from heavy water and containing only 0.1 at.% of the light isotope of hydrogen. Later such measurements were made by several investigators on deuterium of normal (n) ortho–para composition (high-temperature equilibrium mixture)[63-74], on the e composition (in equilibrium at 20.4°K)[69-71,74-76] and also hydrogen deuteride‡[69,73-75,77]. Data were obtained for the solid and liquid states of these substances right up to the critical temperature.

In 1942 only a rough calculation was possible[78] of the vapour pressure of tritiohydrogen HT from the radioactivity of the gaseous distillate of a 10^{-9} M solution of this substance in ordinary hydrogen. But Grilly[72] has subsequently made direct measurements on tritium containing only ~0.5% of light hydrogen.

More recent data on the vapour pressures of the isotopic modifications of hydrogen of identical ortho–para composition differ among themselves by only tenths of 1%, and these discrepancies are explained mainly by a difference in the temperature scales employed. The experimental results for isotopes of n composition can be represented by the following equations (in these and subsequent equations P = vapour pressure in mm Hg, and T = temperature in °K).

For the solids:

H_2 [74] $$\log P = 4.56488 - \frac{47.2059}{T} + 0.03939T, \quad (3)$$

HD [74] $$\log P = 4.70260 - \frac{56.7154}{T} + 0.04101T, \quad (4)$$

D_2 [72] $$\log P = 6.2100 - \frac{77.077}{T} + 28.8\times10^{-4}(T-16.5)^2, \quad (5)$$

T_2 [72] $$\log P = 6.4773 - 88.002/T. \quad (6)$$

For the liquids:

H_2 between 14° and 20°K [74]
H_2 between 19.5° and 24.5°K [72]
$$\log P = 3.66687 - \frac{44.9569}{T} + 0.020537T,$$
$$\log P = 5.5567 - \frac{54.650}{T} + 10.9\times10^{-4}(T-22)^2, \quad (3')$$

HD [74] $$\log P = 5.04964 - \frac{55.2495}{T} + 0.01479T, \quad (4')$$

D_2 [72] $$\log P = 5.8404 - \frac{70.044}{T} + 4.59\times10^{-4}(T-23)^2, \quad (5')$$

T_2 [72] $$\log P = 6.0334 - \frac{78.925}{T} + 2.0\times10^{-4}(T-25)^2. \quad (7)$$

The isotope effect is clear from Table 4. Both the results and the values obtained by calculation based on Eqns. (3)–(7) are accurate to within 0.01 mm Hg for pressures up to 10 mm, and to within 0.1 mm for higher pressures.

TABLE 4. Vapour pressure of isotopic variation of hydrogen*.

T, °K	P, mm Hg				$\frac{P(T_2)}{P(H_2)}$	$\frac{P(D_2)}{P(H_2)}$	$\frac{P(T_2)}{P(D_2)}$	$\frac{P(HD)}{P(H_2)}$
	n-T_2	n-D_2	HD	n-H_2				
				Solid state				
10		0.05	0.23	1.7		0.03		0.16
11		0.20	0.99	5.1		0.04		0.19
12	0.14	0.73	2.94	12.7	0.011	0.057	0.19	0.23
13	0.51	2.14	7.46	27.9	0.018	0.07	0.24	0.27
14	1.55	5.44	16.8				0.285	
15	4.08	12.3	34.4				0.332	
16	9.49	25.4	65.2				0.374	
17	20.0	48.6					0.412	
18	38.8	87.2					0.445	
19	70.1							
20	119.5							
				Liquid state				
19		145.1	264.2	490.8		0.296		0.538
20		219.9	382.0	675.7		0.325		0.565
21	170.1	322.2	534.9	906.4	0.188	0.355	0.528	0.590
22	252.5	458.5	728.5	1189.0	0.212	0.386	0.551	0.613
23	362.4	636.2	969.0	1529.6	0.237	0.416	0.570	0.633
24	505.1		1262.3					

* Data for T_2 calculated by means of Eqns. (6) and (7); published data were taken for H_2 and D_2,[74] and for HD.[75]

¶ According to Grigor'ev and Rudenko's data ["V Soveshchanie po Fizike Zhidkogo Sostoyaniya, Tezisy Dokladov" (Fifth Congress on the Physics of the Liquid State, Abstracts of Papers), Kiev University, 1961, p. 6], the vapour pressure of ^{86}Kr at the normal boiling point (120°K) is lower than that of ^{82}Kr by $(4.6 \pm 0.7) \times 10^{-2}$%.

† For argon see G. Boato, G. Scoles, and M. E. Vallauri, Nuovo Cim., 14, 735 (1959).

‡ n-H_2 contains 0.2500 para + 0.7500 ortho, and n-D_2 0.3333 para + 0.6667 ortho, modifications; e-H_2 consists of 0.979 para + + 0.021 ortho, and e-D_2 of 0.022 para + 0.978 ortho, modifications. Hydrogen deuteride is prepared by the reaction $LiAlH_4 + 4D_2O = LiOD + Al(OD)_3 + 4HD$.[79,80]

Above the boiling point the vapour pressure is about 3.5% lower with n-H_2 than with e-H_2, the corresponding difference for n-D_2 and e-D_2 being 0.5%. These percentage differences are somewhat greater below the boiling point[69,75].

Values of P_h/P_l for the different pairs of isotopic hydrogen molecules at the same temperature approach unity as the corresponding M_h/M_l approaches unity, where M is the molecular weight, and the subscripts h and l denote the heavy and the light varieties respectively, an increase in one of these ratios corresponding to a decrease in the other. However, the isotope effect is not a simple or direct function of the mass of the molecule. In particular, it is interesting that, in spite of the identical molecular weight of HT and D_2, the vapour pressure of the former is considerably greater than that of the latter: at 20.3°K, for example, the difference is ~45%§.[82] With the isotopic pairs T_2–D_2 and DH–H_2, which have the same value of M_h/M_l, however, the values of P_h/P_l at the same temperature differ by only 2%.

Tables 5 and 6 give the temperatures and the heats of the phase transformations of the hydrogen isotopes. Values of the latter calculated from the general form of the Clausius–Clapeyron equation agree with available calorimetric data to within a few calories per mole¶. No departure from Raoult's law was observed[81] for mixtures of hydrogen and deuterium. Hoge and Arnold[75], however, found from measurements of the dew points of such mixtures that their vapour pressures exceed by approximately 3% the values calculated on the assumption that such systems are ideal. In agreement with this, it has been shown[80] that the experimental plots of P and T against composition (N) for mixtures of H_2 and D_2 deviate by a few per cent from the plots based on Raoult's law.

(b) Diatomic Substances Differing in Isotopic Composition with Respect to Carbon, Nitrogen, Oxygen, Hydrogen, and Chlorine

Several investigations have been made[87-93] of the varieties of carbon monoxide $^{13}C^{16}O$ and $^{12}C^{16}O$. Johns[89,91] used a differential manometer to measure the difference in vapour pressure between a standard specimen of normal carbon monoxide (1.1 at.% of ^{13}C) and each of five specimens of the oxide containing between 14 and 73 mole % of $^{13}C^{16}O$. He found that, within the limits of experimental error, the vapour pressure of both liquid and solid phases varies linearly with the mole fraction of the heavy variety, and this enabled him to extrapolate the experimental results to the corresponding values for pure $^{13}C^{16}O$ and $^{12}C^{16}O$. Over the range investigated, 57°–81°K, the heavy oxide had the lower vapour pressure, the isotope effect decreasing with rise in temperature. The P_h/P_l ratio changes from 0.9795 to 0.9820 between 57.2° and 61.7°K, and from 0.9891 to 0.9930 over the range 68.3°–81.1°K. The following relation was found for the solid phase over the range 61.6°–68.1°K:

$$\log(P_h/P_l) = 0{,}16/T - 36/T^2; \quad (8)$$

while for the liquid phase between 68.2° and 81.2°K

$$\log(P_h/P_l) = 0.171/T - 33.9/T^2. \quad (8')$$

The error in the determination of $\log(P_h/P_l)$ was 1–2%.

It has been calculated that the melting point of $^{13}C^{16}O$ exceeds that of $^{12}C^{16}O$ by 0.061°. Results obtained by Groth *et al.*[90], who investigated only the liquid–vapour equilibrium, give values of $\log P_h/P_l$ which are 5% greater than those found by Johns. Although they also carried out[90] direct measurements of the differences in vapour pressures, they used an oxide containing only 10 at.% of ^{13}C, so that their extrapolation[90] might entail a greater error than that in the work of Johns[89,91].

Devyatykh *et al.*[92,93] employed Rayleigh distillation of ordinary carbon monoxide to investigate the vapour pressure of $^{13}C^{16}O$ relative to that of $^{12}C^{16}O$. The isotopes were analysed in a mass spectrograph. For temperatures between the normal melting and boiling points they obtained the equation

$$\log(P_h/P_l) = 0.0024 - 0.387/T. \quad (8'')$$

TABLE 5. Triple points and boiling points of isotopes of hydrogen.

Substance	Triple point T, °K	Triple point P, mm	B.p., °K (760 mm)	Ref.
n-H_2	13.96	54.0	20.39	72
e-H_2	13.81	52.8	20.28	75
HD	16.60	92.8	22.14	75
n-D_2	18.73	128.6	23.67	72
e-D_2	18.69	128.5	23.64	75
n-T_2	20.62	162.0	25.04	72

TABLE 6. Heats of phase transformations of hydrogen isotopes (from different published sources), in cal mole^{-1}.

Substance	ΔH_f at triple point: calorimetric	$\Delta H_{sublimation}$ at triple point: calc.	$\Delta H_{sublimation}$ at triple point: calorimetric	ΔH_e at b.p. (760 mm): calc.	ΔH_e at b.p. (760 mm): calorimetric
n-H_2	28[83]	247[72]	246[83]	219[86] 216[72]	219[84] 216[83]
p-H_2	28[84,85]				215[84]
HD	38[74]				257[74]
n-D_2	47[71]	346[72]	349[71]	293[72]	294[76]
e-D_2	47[76]			294[78]	
n-T_2		393[72]		333[72]	

§ According to Libby and Barter[78], HT and D_2 have identical vapour pressures. These results, however, obtained by Rayleigh distillation of a 10^{-9} M solution of HT in H_2, are evidently much less accurate than those of Bigeleisen and Kerr[82], which were calculated from the radioactivity of the phases in equilibrium with 10^{-8} M solutions. Pure HT cannot be investigated because of its thermodynamic instability.

¶ White *et al.*[232] report a calorimetric investigation of the heats of evaporation of ortho-deuterium and para-hydrogen from their boiling points up to the critical points.

It follows from Eqn. (8″) that P_h/P_l changes from 0.9876 at 68.3° to 0.9896 at 81.1°K, the vapour pressure of the heavy oxide thus being 1.24–1.04% lower than that of the light oxide, whereas according to Johns [89,91] the corresponding difference is 1.09–0.70%. This discrepancy is apparently due to the less accurate character of experiments involving Rayleigh distillation of a mixture having a low content of one of the isotopes, compared with the direct determination of the relative vapour pressure of a greatly enriched isotopic mixture.

Kirschenbaum [94] used a differential manometer to measure the difference in vapour pressure between ordinary nitrogen and its equilibrium isotopic mixture, the latter containing 12 at.% of $^{15}N_2$ and 45% of $^{15}N^{14}N$. By extrapolating his results on the basis of Raoult's law, Kirschenbaum and Urey [95] obtained the following relation for the pure liquid isotopes

$$\log [P(^{15}N_2)/P(^{14}N_2)] = 0.00582 - 0.7230/T. \quad (9)$$

Johns [96] compared the vapour pressures of natural nitrogen and of two mixtures, containing $^{15}N_2$ 81.6, $^{15}N^{14}N$ 16.9 at.%, and $^{15}N_2$ 35.1, $^{15}N^{14}N$ 47.9 at.%. The isotopic difference in pressure was proportional to the ^{15}N content, which confirms the applicability of Raoult's law to this case. It follows also from these results [96] that the law of the geometric mean is observed [97]

$$P^2(^{15}N^{14}N) = P(^{15}N_2) \times P(^{14}N_2), \quad (10)$$

or approximately

$$2[P(^{14}N_2) - P(^{15}N^{14}N)] = P(^{14}N_2) - P(^{15}N_2).$$

Clusius and Schleich [98] measured the vapour pressure of isotopically almost pure specimens of $^{15}N_2$ and $^{15}N^{14}N$ and obtained results close to those which follow from Eqns. (9) and (10), namely

$$\log [P(^{15}N_2)/P(^{14}N_2)] = 0.00691 - 0.7974/T, \quad (9')$$

$$\log [P(^{15}N^{14}N)/P(^{14}N)_2] = 0.00343 - 0.3985/T. \quad (11)$$

According to Eqn. (9′) the vapour pressure of heavy nitrogen is lower than that of ordinary nitrogen, by 1.3% at 63.3°K and by 0.8% at 77°K. In comparison with $^{14}N_2$, the $^{15}N_2$ variety has a higher melting point (63.19° compared with 63.14°K), boiling point (77.39° against 77.32°K), and heat of evaporation (1336.5 against 1333.0 cal mole^{-1}) [95,98].

An unexpectedly large isotope effect has been observed [98,99] with nitric oxide, and is represented by the equation

$$\log (P_h/P_l) = 0.01340 - 3.0230/T, \quad (12)$$

where the subscripts h and l refer to $^{15}N^{16}O$ and $^{14}N^{16}O$ respectively.

It follows from Eqn. (12) that in this case, too, the molecular species containing heavy nitrogen has the lower vapour pressure. However, the corresponding isotopic difference for $^{15}N^{16}O$ decreases from 3.1% at 111° to 2.7% at 120°K, whereas for $^{15}N^{14}N$ this difference is ~0.5% at pressures up to 1 atm. Yet the difference in mass between heavy and light molecules is approximately the same in the two cases. The relative volatility for $^{15}N^{16}O$ and $^{14}N^{16}O$ is according to Kuhn *et al.* [100,101] rather lower than would follow from Clusius and Schleich [98]. It must be assumed, however, that, since Clusius and Schleich carried out direct measurements of the vapour pressure of isotopically almost pure substances†, whereas Kuhn *et al.* employed the Rayleigh distillation of ordinary nitric oxide (0.36 at.% ^{15}N), the results obtained by the former investigators are the more accurate‡.

The relative vapour pressure of the isotopic varieties of molecular oxygen have been studied [87,91,102–107]. The most accurate results have apparently been obtained by Johns [91] by using oxygen which had been considerably enriched with heavy isotopes and by employing a method of direct differential measurements. Two specimens of oxygen containing 13.85 and 42.71 mole% $^{16}O^{18}O$ were compared with a standard specimen containing 0.45% of this isotopic variety (the $^{16}O^{17}O$ content was always calculated as $^{16}O^{18}O$). Extrapolation to 100% was based on the assumption that the isotopic difference in vapour pressure was proportional to the mole fraction of $^{16}O^{18}O$. The following relation was obtained for the range 65° – 89.2°K:

$$\log (P_h/P_l) = 0.124/T - 30/T^3, \quad (13)$$

where the subscripts h and l denote $^{16}O^{18}O$ and $^{16}O_2$ respectively. It follows from Eqn. (13) that at 73.8°K the vapour pressure of $^{16}O^{18}O$ is 0.90% lower than that of $^{16}O_2$, while at 90.1°K a slight extrapolation gives a difference of 0.54%. The corresponding values obtained by Kronberger [87] by Rayleigh distillation were 0.84% and 0.62%. Thode and Smith [105] found by the same method that at 90.1°K the difference between P_h and P_l is 0.65%. The data obtained by Johns also agree well with results [106] on the fractionation of oxygen, according to which the ratio P_h/P_l changes from 0.987 at 63.1° to 0.991 at 74.0°K, the heavy variety being, as above, $^{16}O^{18}O$.

Devyatykh and Zorin [107] used their data on the Rayleigh distillation of natural oxygen to calculate the relative vapour pressures of pure $^{18}O_2$. They postulated that the rule of the geometric mean [97] was applicable in this case, *i.e.* that

$$P(^{16}O^{18}O) = [P(^{16}O_2) \times P(^{18}O_2)]^{1/2}.$$

In this way the following relation was obtained from the experimental data for the range 66.07° – 99.13°K:

$$\log (P_h/P_l) = 0.00019 - 0.367/T, \quad (14)$$

where the subscripts h and l denote $^{18}O_2$ and $^{16}O_2$ respectively. Hence it follows that at 90°K the vapour pressure of $^{18}O_2$ is 0.89% lower than that of $^{16}O_2$, which is comparatively close to the corresponding value of 1.08% calculated from Johns' data. The difference between the results of Devyatykh and Zorin [107] and Johns [91] becomes somewhat larger at lower temperatures§.

Carbon monoxide containing heavy oxygen has been studied [91,107,108]. According to Devyatykh and Zorin's results [107], obtained by Rayleigh distillation of ordinary carbon monoxide, the ratio of the vapour pressures of $^{13}C^{18}O$

† The heavy nitric oxide contained $^{15}N^{16}O$ 98.00, $^{15}N^{18}O$ 0.20, $^{14}N^{16}O$ 1.80%.

‡ For the relative volatility factors for varieties of nitrous oxide containing different isotopes of nitrogen and oxygen, and also of nitrogen dioxide isotopic with respect to nitrogen, see section 3a.

§ Clusius *et al.* Helv. Chim. Acta., 44, 98 (1961), have measured the vapour pressure of 99.64% $^{18}O_2$ relative to that of ordinary oxygen. For pure $^{18}O_2$ and $^{16}O_2$ between 63.5° and 90°K they obtained $P_T/P_{\pi} = -(57.285/T^2) + (0.145/T) + 0.661 \times 10^{-3}$.

and $^{12}C^{16}O$ changes from 0.9848 to 0.9957 over the range 71.3° – 82.1°K, corresponding to the equation:

$$\log (P_h/P_l) = 0.0265 - 2.35/T. \quad (15)$$

According to Johns[91] the percentage difference in vapour pressures of these isotopic oxides is less by a factor of about 1.5–2.0 than would follow from Eqn. (15): between 69° and 77°K the ratio P_h/P_l changes from 0.9921 to 0.9941, and is represented by the equation

$$\log (P_h/P_l) = 0.132/T - 25.3/T^2. \quad (16)$$

Below the melting point we have for the β form of the solid phase

$$\log (P_h/P_l) = 0.13/T - 27/T^2. \quad (17)$$

The melting point of $^{12}C^{18}O$ is 0.047° higher than that of $^{12}C^{16}O$, while the α–β transition temperature is 0.11° higher. Direct differential measurements are reported[91], but only one specimen of the oxide, containing ~20 mole % of $^{12}C^{18}O$, was studied, and the results were extrapolated to 100% on the hypothesis that the isotopic difference in vapour pressure was proportional to the ^{18}O content.

It follows[96] from Johns' data that $^{12}C^{18}O$ occupies an intermediate position between $^{12}C^{16}O$ and $^{13}C^{16}O$ with respect to vapour pressure, although it has the largest molecular weight, so that the rule of the geometric mean[97] is not applicable here.

Clusius and Schleich[98] determined the vapour pressure of nitric oxide containing 100 at.% of heavy oxygen, their results being expressed as

$$\log (P_h/P_l) = 0.02103 - 4.4684/T, \quad (18)$$

where the subscripts h and l denote $^{14}N^{18}O$ and $^{14}N^{16}O$. It follows from Eqn. (18) that the isotope effect is somewhat greater for these varieties of the molecules than for the oxides described above, which were isotopic with respect to nitrogen. At about 111°K the vapour pressure of $^{14}N^{18}O$ is 4.3% lower than that of $^{14}N^{16}O$, and at 120°K 3.6% lower. Complete replacement of ordinary by heavy oxygen in nitric oxide produces increases of 0.14° in the melting point, 0.31° in the boiling point, and 20.5 cal mole^{-1} in the heat of evaporation.

The effect on the vapour pressures of hydrogen chloride, bromide, and iodide produced by replacing the hydrogen by deuterium is interesting. The following equations have been obtained[109] for DCl and HCl:

$$\log (P_h/P_l) = 0.075 - 15.4/T \quad (19)$$

for the liquid state, and

$$\log (P_h/P_l) = -0.387 + 57.7/T \quad (19')$$

for the solid state.

The vapour pressures of liquid DBr and HBr are represented[110] by equations of the type

$$\log P_{mm} = A - B/T, \quad (20)$$

values of the constants A and B being given in Table 7. The following equations have been obtained[111] for DI and HI:

$$\left.\begin{aligned} \log P_{mm}\ (HI) &= 26.119 - 0.002293T - 7.111 \log T - 1636/T; \\ \log P_{mm}\ (DI) &= 26.129 + 0.002293T - 7.111 \log T - 1636/T, \end{aligned}\right\} \text{ liquid state} \quad (21), (22)$$

$$\left.\begin{aligned} \log P_{mm}\ (HI) &= 10.493 - 0.003167T - 0.3771 \log T - 1406/T, \\ \log P_{mm}\ (DI) &= 10.505 - 0.003167T - 0.3771 \log T - 1406/T. \end{aligned}\right\} \text{ solid state} \quad (21'), (22')$$

Values of P_h/P_l for the liquid state calculated from Eqns. (19)–(22) are plotted against temperature in Fig. 2.

TABLE 7. Constants in Eqn. (20).

Substance	A	B	Substance	A	B
Liquid state			Solid state		
HBr	7.465	945.7	HBr	8.309	1103
DBr	7.517	956.5	DBr	8.306	1103

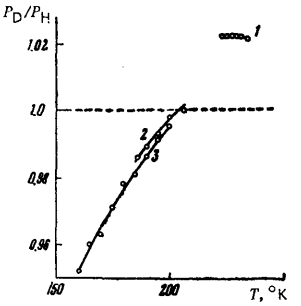

Fig. 2. Isotope effect in vapour pressure of liquid hydrogen halides:
1) DI/HI; 2) DBr HBr; 3) DCl/HCl.

TABLE 8. Phase transformations of isotopic hydrogen iodides[110].

Property	HI	DI
Triple point, °K	222.4	221.5
B.p., °K	237.05	237.00
ΔH_e at b.p., cal mole^{-1}	4725	4710

With hydrogen and deuterium chlorides P_h/P_l increases from 0.952 to 0.995 between 160° and 200°K, with HBr and DBr this ratio increases from 0.986 at 186° to 1.000 at 206°K, and in the case of HI and DI the ratio is 1.025 between 223° and 234°K. Comparison of the isotope effects for all three hydrogen halides in the liquid state shows that the ratio P_h/P_l, which is less than unity up to 200°K, increases with rise in temperature and becomes greater than unity¶.

The behaviour of solid hydrogen chloride is peculiar. With solid DBr and HBr the ratio P_h/P_l is 0.993 over the range 150° – 185°K, while for solid DI and HI it is 0.972–0.975 over the range 191° – 220°K, so that in both cases, as with the corresponding liquid phases, $P_h < P_l$. With solid DCl and HCl however, the value of P_h/P_l decreases[109] from 1.55 to 1.005 between 100° and 162°K. In the case of DCl the isotope effect in the vapour pressure of the solid phase is opposite in sign to the effect for the liquid phase, and a minimum is observed in the ratio at the melting point. As will be shown below, a similar phenomenon has been found to occur with heavy water.

Fractional distillation of hydrogen chloride on a column at 185°K has yielded[112] a value of 0.9992–0.9990 for the ratio P_h/P_l for $H^{37}Cl$ and $H^{35}Cl$. Zhavoronkov *et al.*[113]

¶ The vapour pressure of DF is discussed in section 4b.

established by the more accurate method of Rayleigh distillation that this ratio changes from 0.9978 to 0.9986 for these isotopic substances between 167° and 181°K.

Recently Matveev *et al.*[130] have carried out the Rayleigh distillation of molecular chlorine. Regarding the mixture of its isotopic varieties as ideal, they found that the ratio $P(^{37}Cl_2)/P(^{35}Cl_2)$ changes from 0.9827 to 0.9999 between the normal melting and boiling points (172° and 238.6°K). With both HCl and Cl_2 at vapour pressures of a few hundred mm Hg, the separation factor differs from unity by at most 0.2%. Consequently it is useless to employ fractionation of these substances to obtain pure isotopes of chlorine[113,114,130].

3. POLYATOMIC ISOTOPIC SUBSTANCES NOT ASSOCIATED BY HYDROGEN BONDS (COMPOUNDS ISOTOPIC WITH RESPECT TO HYDROGEN, BORON, CARBON, NITROGEN, SILICON, CHLORINE, AND GERMANIUM)

(a) Negative Isotope Effect

With all the monatomic and diatomic molecules described above, other than hydrogen iodide, the heavier isotopic variety has the lower vapour pressure. Several polyatomic molecules are also known with which a similar effect is observed, which will be termed a negative isotope effect in vapour pressure. Thus Kuhn *et al.*[101] found by Rayleigh distillation that with the isotopic pairs $^{15}N^{14}N^{16}O$–$^{14}N_2{}^{16}O$ and $^{15}N_2{}^{18}O$–$^{15}N_2{}^{16}O$ at about 184°K and $^{15}N^{16}O_2$–$^{14}N^{16}O_2$ at about 293°K the values of P_h/P_l are 0.9988, 0.9982, and 0.9973 respectively.

Several papers have shown that a decrease in vapour pressure takes place also when light carbon is replaced by heavy carbon in methane, ethylene, and ethane. Johns[91] measured directly the vapour pressure of three specimens of methane containing between 28 and 71 at.% $^{13}CH_4$, and extrapolated the results to a 100% content on the assumption that the isotopic difference in vapour pressure is proportional to the content of heavy carbon. He found that the ratio P_h/P_l changes from 0.9946 at 91.0° to 0.9965 at 104.8°K, corresponding to the equation

$$\log (P_h/P_l) = 0.191/T - 36.8/T^2. \quad (23)$$

The equation obtained for the solid phase was

$$\log (P_h/P_l) = 0.10/T - 30/T^2. \quad (23')$$

Groth *et al.*[90] made direct measurements of the difference in vapour pressure between natural methane and a specimen containing 10 at.% ^{13}C, over the range 90.7–96.0°K. Values of $\log P_h/P_l$ obtained by them are 5% smaller than the corresponding values derived from Eqn. (23). Clusius and Bühler[115] compared the vapour pressure of $^{13}CH_4$ containing only 0.2 mole % $^{12}CH_4$ with that of natural methane (1.1% $^{13}CH_4$) at the ternary point of the latter, obtaining a value of P_h/P_l = 0.996. Recently Clusius *et al.*[116] have made direct measurements on 99.05% $^{13}CH_4$ relative to ordinary methane between 91.17° and 110.44°K. Their results give a P_h/P_l ratio changing from 0.9945 to 0.9969 over this range, in good agreement with Johns' results †.[91]

† According to Clusius *et al.*[116] the melting and boiling points (at 760 mm Hg) are respectively 90.70° and 111.70°K for $^{13}CH_4$, and 90.67° and 111.66° for $^{12}CH_4$. The heat of evaporation is greater with $^{13}CH_4$ than with $^{12}CH_4$, by 3.20 cal mole^{-1} at the melting point and 2.52 cal mole^{-1} at 100°K.

Results obtained by the Rayleigh distillation of natural methane have shown[107] that the ratio P_h/P_l for $^{13}CH_4$ and $^{12}CH_4$ changes from 0.9893 to 0.9902 between 97.55° and 111.8°K, and also[117] that over the same temperature range this ratio increases from 0.9900 to 0.9932. Thus direct differential measurements between the normal melting and boiling points indicate that the difference in vapour pressure between $^{13}CH_4$ and $^{12}CH_4$ is ~0.5%, while investigations based on Rayleigh distillation of natural methane indicate the difference to be about twice as great.

Ordinary ethylene and ethane have also been subjected to Rayleigh distillation[117], the following relations having been obtained. For $^{13}C^{12}CH_4$ and $^{12}C_2H_4$ over the range 120.0–169.3°K:

$$\log (P_h/P_l) = 0.0945/T - 0.00136; \quad (24)$$

for $^{13}C^{12}CH_6$ and $^{12}C_2H_6$ over the range 130.0–184.5°K:

$$\log (P_h/P_l) = 0.00213 - 0.3958/T. \quad (25)$$

It follows from Eqns. (24) and (25) that $P_h < P_l$, but the difference between these quantities does not exceed 0.2%. With the ethanes the isotope effect diminishes rapidly with rise in temperature, and at the normal boiling point it has already reached zero within the limits of experimental error. It has been calculated that the heat of evaporation is greater with $^{13}CH_4$ than with $^{12}CH_4$, and greater with $^{13}C^{12}CH_6$ than with $^{12}C_2H_6$, by several calories per mole[118].

(b) Positive Isotope Effect and Mixed Cases

It was considered for a long time that a negative isotope effect in vapour pressure was a general phenomenon. However, a considerable majority of the polyatomic molecules, not associated by a hydrogen bond, which have been investigated exhibit a positive isotope effect — an increase in vapour pressure on replacement of a light by a heavy isotope — or else a negative effect at some temperatures and a positive effect at others. A positive isotope effect is observed also with compounds which show association by hydrogen bonds, provided that the hydrogen atom forming this bond is not substituted, or when the molecules remain associated in the gas phase.

Hydrocarbons and their derivatives. Let us begin with those cases in which the lighter molecules have the higher vapour pressure at comparatively low temperatures, while the opposite is true at elevated temperatures. The behaviour of the deuteromethanes is typical in this respect and has formed the subject of several papers[119–121], the most complete and accurate work being that of Armstrong *et al.*[121] They represented the isotope effect in vapour pressure by equations of the type

$$T \log (P_D/P_H) = A - B/T, \quad (26)$$

values of the constants A and B being given in Table 9 ("H" in this equation denotes CH_4).

The following equations are given for CH_4:

between 54° and 90.66°K (over the solid)

$$\log P_{mm} = 6.7838 - 477.46/T + 0.00469/T, \quad (27)$$

between 90.66° and 112°K (over the liquid)

$$\log P_{mm} = 7.55073 - 483.22/T - 0.0030686T.$$

Values of P_h/P_l for molecules with a successively increasing number of deuterium atoms approximately form a

TABLE 9. Constants in Eqn.(26).

Substance	A	B	Substance	A	B
	Solid state			Liquid state	
CH_3D	1.260	110.2	CH_3D	1.328	129.5
CH_2D_2	2.694	222.2	CH_2D_2	2.671	245.4
CHD_3	4.452	351.7	CHD_3	3.969	343.8
CD_4	5.529	410.5	CD_4	5.159	421.1

TABLE 10. Triple points of deuteromethanes[121].

Substance	P, mm Hg	T, °K
CH_4	87.5	90.66
CH_3D	84.5	90.41
CH_2D_2	82.0	90.17
CHD_3	80.2	89.96
CD_4	79.1	89.79

TABLE 11. Vapour pressure ratios for isotopic methanes.

T, °K	CH_3D/CH_4	CH_2D_2/CH_4	CHD_3/CH_4	CD_4/CH_4	T, °K	CH_3D/CH_4	CH_2D_2/CH_4	CHD_3/CH_4	CD_4/CH_4
		Solid state					Liquid state		
55	0.969	0.945	0.922	0.922	91	0.997	0.999	1.005	1.014
60	0.978	0.962	0.948	0.951	95	0.999	1.002	1.009	1.018
70	0.989	0.984	0.981	0.989	100	1.001	1.005	1.012	1.022
80		0.998	1.002	1.012	105	1.002	1.007	1.015	1.026
85	0.999	1.002	1.009	1.019	111	1.003	1.010	1.018	1.029

geometric progression. The departure of mixtures of the isotopic methanes from ideal behaviour is insignificant. Curves for the temperature dependence of P_D/P_H of all four deuterated methanes pass through the value unity (Fig.3), and the temperature at which this occurs is lower the greater the number of hydrogen atoms which have been replaced by deuterium. With tetradeuteromethane at 110°K the vapour pressure is already approximately 3% greater than with ordinary methane‡.

Similar behaviour to that of the deuteromethanes is observed when hydrogen in the silanes is replaced by deuterium. Stokland[123] determined the vapour pressures of monosilane, disilane, and their deutero-derivatives containing ~99 at.% of deuterium. The results were expressed in the form of equations of the type

$$\log P_{mm} = A/T + 1.75\log T + BT + C, \qquad (28)$$

values of the constants A, B, and C being given in Table 12.

It follows from Eqn.(28) that the vapour pressure *vs.* temperature curves for isotopic monosilanes intersect at 132.5°K: *i.e.* below this temperature replacement of

‡ Monodeuterotetramethylmethane (deuteroneopentane) boils at a lower temperature than ordinary neopentane[122], from which it follows that in this case, too, the deuterohydrocarbon has a greater vapour pressure than its hydrogen analogue near the normal boiling point (282.7°K).

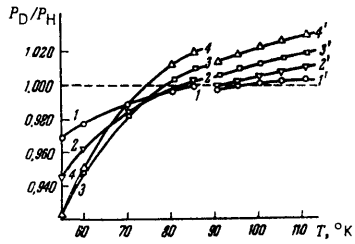

Fig.3. Isotope effect in vapour pressure of deuteromethanes, subscript H denotes CH_4; D: 1,1′) CH_3D; 2,2′) CH_2D_2; 3,3′) CHD_3; 4,4′) CD_4; 1–4) solid state; 1′–4′) liquid state.

TABLE 12. Constants in Eqns.(28) and boiling points of isotopic silanes.

Substance	−A	-10^7B	C	B.p., °K	Substance	−A	-10^7B	C	B.p., °K
SiH_4	740.0	79 701	4.87448	161.95	Si_2H_6	1380.2	69 309	5.78216	259.00
SiD_4	773.0	94 026	5.31421	161.80	Si_2D_6	1394.3	71 510	5.91428	257.80

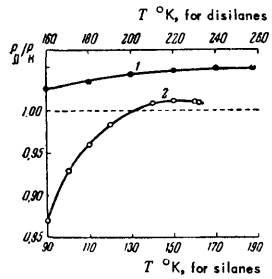

Fig.4. Isotope effect in vapour pressure of deuterosilanes:
1) Si_2D_6/Si_2H_6; 2) SiD_4/SiH_4.

hydrogen by deuterium in silane causes a decrease in vapour pressure, but above this temperature an increase is observed. In the case of disilane, replacement of hydrogen by deuterium causes an increase in vapour pressure over the whole temperature range between the normal melting and boiling points (Fig.4). In another paper[124] Stokland showed that liquid Si_3D_8 and Si_4D_{10} also have higher vapour pressures than their ordinary analogues Si_3H_8 and Si_4H_{10} respectively.

Zeltmann and Fitzgibbon[125] determined the vapour pressures of mono-, di-, and tri-germane in which 99.6% of the hydrogen had been replaced by deuterium, the results being expressed in the form of equations of the type

$$\log P_{mm} = -\frac{\Delta H_e}{4.575\,T} + B, \qquad (29)$$

applicable to vapour pressures between 10 and 800 mm Hg.

Values of ΔH_e and the constant B are given in Table 13, which includes also the melting points determined experimentally to within 0.2°, and the boiling points calculated from Eqn. (29). Unfortunately, the ordinary germanium hydrides were not studied at the same time as the deuterides in this work[125], and it is necessary to use the results of other work[126] for their vapour pressures, which diminishes the accuracy of the calculated isotope effect. The temperature variation of the ratios P_D/P_H calculated from the data given by Zeltmann and Fitzgibbon[125] and by Stull[126] is plotted in Fig. 5. With regard to the sign of the isotope effect, it is clear that the situation observed with the isotopic methanes and silanes is repeated.

The isotopic pentaboranes also show a greater vapour pressure with the heavy variety. According to Shapiro and Ditter[127] Eqns. (30) and (31) apply to these compounds between 250° and 320°K, the latter equation relating to 99.5 at.% of deuterium

$$\log P_{mm}(B_5H_9) = 9.49191 - 0.0028956T - 1881.29/T, \quad (30)$$

$$\log P_{mm}(B_5D_9) = 9.46916 - 0.0028783T - 1870/T. \quad (31)$$

The P_h/P_l ratios calculated from these equations are given in Table 14. The equations together with the Clausius–Clapeyron equation show that replacement of the hydrogen in pentaborane by deuterium depresses the boiling point by 1° (332.2° instead of 333.2°K) and decreases the heat of evaporation by 40 cal mole^{-1} (7390 instead of 7430).

A positive isotope effect on the vapour pressure is exhibited in the liquid phase, two cyclic hydrocarbons which have been studied in this connection being deuterobenzene C_6D_6 [128,129] and deuterocyclohexane C_6D_{12}.[129] The temperature dependence of the vapour pressure of these deuterated hydrocarbons and their hydrogen analogues is given by equations of the type

$$\log P_{mm} = A - B/(T-C); \quad (32)$$

values of the constants A, B, and C are given in Table 15, and the P_h/P_l ratios in Table 16.

The vapour pressure is increased, and the boiling point and the heat of evaporation are decreased, when hydrogen is replaced by deuterium in the methyl halides[132], chloroform[134], and chloropropyne[133], for which substances the following equations have been obtained

$$\log P_{mm}(CH_3Cl) = -1590.72/T - 3.97770\log T + 18.7955, \quad (33)$$

$$\log P_{mm}(CD_3Cl) = -1593.76/T - 4.06144\log T + 19.02286, \quad (34)$$

$$\log P_{mm}(CH_3Br) = -1696.01/T - 3.36805\log T + 17.23566,$$
$$\log P_{mm}(CD_3Br) = -1683.89/T - 3.28743\log T + 17.00870, \quad (35)$$

$$\log P_{mm}(CH_3I) = -1476.2/T + 7.5549, \quad (36)$$

$$\log P_{mm}(CD_3I) = -1471.9/T + 7.5613, \quad (37)$$

$$\log P_{mm}(CH_3C{\equiv}CCl) = -1480/T + 7.740, \quad (38)$$

$$\log P_{mm}(CD_3C{\equiv}CCl) = -1487/T + 7.782. \quad (39)$$

The isotope effect is indicated by the data in Table 17, which have been calculated by means of Eqns. (33)–(39).

It is interesting that the ratio P_h/P_l decreases for the methyl halides, but increases for chloropropyne, with rise in temperature over the same range in the two cases. It is seen from Figs. 3 and 4 that an increase in the ratio with rise in temperature occurs also with methane and the silanes. With other deuterohalogenohydrocarbons the vapour pressure has not been investigated, but typical data[134] are available on the effect of replacement of hydrogen by deuterium on the boiling point of dibromoethane (Table 19). Compared with the ordinary form of

TABLE 13. Temperatures of phase transformations and constants in Eqn. (29) for germanium deuterides[125].

Substance	M.p., °K	B.p., °K	ΔH_e, cal mole^{-1}	B
GeD_4	107.0	184.0	3744	7.327
Ge_2D_6	165.3	301.6	6483	7.579
Ge_3D_8	172.9	383.7	7876	7.367

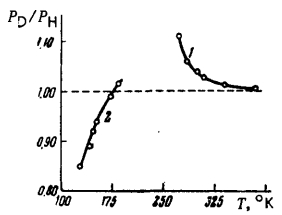

Fig. 5. Isotope effect in vapour pressure of deuterogermanes:
1) Ge_3D_8/Ge_3H_8; 2) GeD_4/GeH_4.

TABLE 14.

T, °K	$P_{B_5D_9}/P_{B_5H_9}$	T, °K	$P_{B_5D_9}/P_{B_5H_9}$
250	1.057	300	1.042
260	1.053	310	1.039
270	1.048	320	1.037
280	1.047	329	1.035
290	1.044		

TABLE 15. Constants in Eqn. (32), boiling points, and heats of evaporation of isotopic benzenes and cyclohexanes[129].

Substance	A	B	C	B.p., °K	ΔH_e at 353 °K, cal mole^{-1}
C_6H_6	6.9121	1214.64	51.96	353.26	7395
C_6D_6	6.8886	1196.38	53.96	352.47	7370
C_6H_{12}	6.8450	1203.53	50.30	353.90	7215
C_6D_{12}	6.8704	1203.29	48.72	351.58	7150

TABLE 16. Vapour pressure ratios for isotopic benzenes and cyclohexanes[129].

T, °K	$\frac{C_6D_6}{C_6H_6}$	$\frac{C_6D_{12}}{C_6H_{12}}$	T, °K	$\frac{C_6D_6}{C_6H_6}$	$\frac{C_6D_{12}}{C_6H_{12}}$
283	1.024	1.093	323	1.026	1.081
293	1.025	1.090	333	1.025	1.077
303	1.026	1.088	343	1.025	1.074
313	1.026	1.084	353	1.025	1.072

TABLE 17. Vapour pressure ratios for isotopic halogenated derivatives.

T, °K	$\frac{CD_3Cl}{CH_3Cl}$	T, °K	$\frac{CD_3Br}{CH_3Br}$	T, °K	$\frac{CD_3I}{CH_3I}$	T, °K	$\frac{CD_3C\equiv CCl}{CH_3C\equiv CCl}$
183	1.055	203	1.040	273	1.055	230	1.030
193	1.048	213	1.040	283	1.055	240	1.032
203	1.044	223	1.040	293	1.052	250	1.032
213	1.042	233	1.037	303	1.052	260	1.035
223	1.040	243	1.036	315	1.048	270	1.037
233	1.037	263	1.033			280	1.040
243	1.035	273	1.032			290	1.040
249	1.032	277	1.032				

TABLE 18. Heat of evaporation and boiling point of isotopic halogenated derivatives[131].

Substance	B.p., °K (760 mm Hg)	ΔH_e at b.p. of H cpd., cal mole^{-1}	Substance	B.p., °K (760 mm Hg)	ΔH_e at b.p. of H cpd., cal mole^{-1}
CH_3Cl	249.4	5310	CD_3Br	276.0	5900
CD_3Cl	248.6	5280	CH_3I	316.0	6750
CH_3Br	276.8	5910	CD_3I	314.6	6730

TABLE 19. Normal boiling points of dibromodeuteroethanes.

Substance	B.p., °C	Substance	B.p., °C
CH_2Br-CH_2Br	131.55	CH_2Br-CD_2Br	130.90
$CHDBr-CH_2Br$	131.25	$CHDBr-CD_2Br$	130.50
$CHDBr-CHDBr$	130.90	CD_2Br-CD_2Br	130.15

this substance, the deuterated derivatives boil at a lower temperature the greater the number of deuterium atoms in the molecule, the decrease per hydrogen atom replaced being 0.35°. The melting points of the deuterated compounds, however, lie above that of ordinary dibromoethane.

Compounds isotopic with respect to boron and silicon. Zhavoronkov and his coworkers[12,13,21,135] used Rayleigh distillation to determine the isotope effect in the vapour pressure of boron trichloride and trifluoride. With the $^{11}BCl_3-^{10}BCl_3$ system it was found that $P_h < P_l$ below 211.5°K, but the opposite is true above this temperature (Fig. 6). The isotope effect between 188° and 286°K is described by the equation

$$\log(P_h/P_l) = 0.00483 - 1.00757/T, \quad (40)$$

where h and l denote $^{11}BCl_3$ and $^{10}BCl_3$ respectively. At the normal boiling point (285.9°K) the value of P_h/P_l is 1.003. Earlier work[136] had given a value of 1.002 at the same temperature, but this value had been calculated from results for the fractionation of BCl_3, which would be less accurate than those obtained by Rayleigh distillation. The positive isotope effect in the vapour pressure of boron trifluoride is almost three times as great. The following equation has been given[21,137] for the $^{11}BF_3-^{10}BF_3$ system:

$$\log(P_h/P_l) = 0.01903 - 2.6796/T, \quad (41)$$

from which it follows that the ratio P_h/P_l increases with rise in temperature, as in the case of boron trichloride. At the normal boiling point (171.5°K) the ratio is 1.0075.

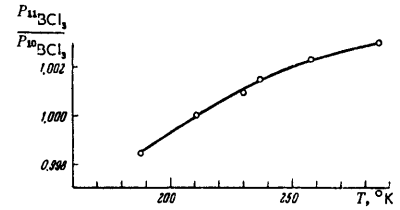

Fig. 6. Temperature dependence of vapour pressure ratio of isotopic boron trichlorides.

The same value was obtained by Nettley *et al.*[138], but values of 1.0082[139] and 1.0091[140] have also been obtained at the boiling point.

Zel'venskii *et al.*[141] have established that carbon disulphide $^{13}C^{32}S_2$ is more volatile than its isotopic analogue $^{12}C^{32}S_2$.

A positive effect on the vapour pressure has been established by Orlov and Zhavoronkov[142] also for the isotopes ^{30}Si, ^{29}Si, and ^{28}Si in silicon tetrachloride. Prolonged fractionation of the ordinary material resulted in a slight enrichment of the vapour with the heavy isotopes.

It is clear from the experimental results described above that the sign of the isotope effect in vapour pressure depends on the temperature range, the complexity of the molecule, and the relative difference in mass between its isotopic varieties. The nature of the isotopes themselves is also important in this connection[143]. When chloroform and carbon tetrachloride are distilled, heavy carbon (^{13}C) accumulates in the distillate, as in the case of benzene, but heavy chlorine (^{37}Cl) is concentrated in the residue. The distillation was carried out at 34.6° in columns having a large number of theoretical plates and with a very high reflux ratio. Analysis was carried out with a mass spectrograph. The relative difference in vapour pressure was calculated by means of Fenske's equation

$$(P_h - P_l)/P_l = (R_r/R_d)^{1/n} - 1, \quad (42)$$

where P_h and P_l are the vapour pressures of the pure heavy and light varieties, differing isotopically only with respect to a given atom, at the temperature of distillation; R_r and R_d are the concentration ratios of the light to the heavy isotope in the still pot and in the distillate respectively; and n is the number of theoretical plates. By approximate integration of the Clausius–Claypeyron equation on the assumption that the integration constants are identical for isotopic analogues and also by the use of Trouton's rule, an expression was obtained from Eqn. (42) for the isotopic difference in boiling points:

$$T_h - T_l = -(T^2/10.7 \times T_b n)\ln(R_r/R_d). \quad (43)$$

Here T_h and T_l are the absolute boiling points of the pure heavy and light varieties at the pressure at which the distillation was carried out, and T and T_b are the boiling points of the substance of normal isotopic composition at the same pressure and at 1 atm respectively. Results of the calculations are given in Table 20.

The results[143] represent two cases in which a given substance shows an isotope effect in the vapour pressure which is positive with respect to one element and negative with respect to another at the same temperature. It is noteworthy, however, that the percentage difference in vapour

TABLE 20. Data[143] for isotopic fractionation at 307.8°K.

System	P_h/P_l	$T_h - T_l$*
$^{13}CHCl_3 - {}^{12}CHCl_3$	1.0008	−0.02
$CH^{37}Cl^{35}Cl_2 - CH^{35}Cl_3$	0.9999	+0.003
$^{13}CCl_4 - {}^{12}CCl_4$	1.0013	−0.033
$C^{37}Cl^{35}Cl_3 - C^{35}Cl_4$	0.99997	+0.001
$^{13}C^{12}C_5H_6 - {}^{12}C_6H_6$	1.00025	−0.006

* T_h and T_l are the boiling points of the heavy and the light varieties at the pressure under which the given substance of normal isotopic composition boils at 307.8°K.

pressure is 10–40 times as great in substances which are isotopic with respect to carbon as in those which are isotopic with respect to chlorine, whereas the corresponding percentage differences in mass between the isotopic molecules or atoms are comparatively close to one another.

4. POLYATOMIC ISOTOPIC MOLECULES ASSOCIATED BY HYDROGEN BONDS

(a) Compounds Showing Little or No Association in the Gas Phase (Alcohols, Ammonia, Amines, Water, and Hydrogen Cyanide)

The work considered above[143] included also an investigation of the separation of the isotopes of carbon and oxygen by the fractionation of methanol, in which isotope effects of opposite sign were found. Heavy carbon accumulated in the distillate, as had been observed in the distillation of chloroform, carbon tetrachloride, and benzene, but heavy oxygen was concentrated in the residue (Table 21). However, whereas in the distillation of CCl_4 and $CHCl_3$ the percentage positive isotope effect due to ^{13}C exceeds the percentage negative effect due to ^{37}Cl by a factor of several tens, the percentage negative isotope effect due to ^{18}O in the distillation of methanol was nearly ten times as great as the positive effect due to ^{13}C.

Comparison of isotope effects in the vapour pressure of $^{12}CH_3{}^{18}OH$ and $^{14}CH_3{}^{16}OH$ is still more revealing, since these varieties of methanol show an almost identical relative increase in both the mass of the molecule and the mass of the isotopic atoms, compared with $^{12}CH_3{}^{16}OH$. Table 23 gives results obtained[141] in the fractionation of ordinary methanol to which $^{14}CH_3{}^{16}OH$ had been added. It was found, in agreement with Baertschi *et al.*[143], that heavy carbon accumulates in the distillate, and heavy oxygen in the residue. When the same isotope of oxygen is present, molecules containing ^{14}C are more volatile than those containing ^{13}C, which in turn are more volatile than molecules containing ^{12}C. The percentage accumulation of ^{18}O in the residue is about seven times as great as that of ^{14}C in the distillate. Enrichment of the residue with heavy oxygen when methanol is distilled has also been observed in other work[144,145]. It has also been established with methanol that deuterium accumulates to a considerable extent in the residue[141], and that this is due to a change in isotopic composition of the hydroxyl hydrogen[146]. Enrichment of the residue with deuterium has been observed during the fractionation of ethanol[147].

TABLE 21. Relative difference in vapour pressure and difference in boiling point for isotopic methanols*.

Heavy molecule (h)	P_h/P_l from ref. 143	P_h/P_l from ref. 141	T_h/T_l, deg, from ref. 143
$^{13}CH_3{}^{16}OH$	1.002	1.0043	$-5.5\cdot10^{-3}$
$^{14}CH_3{}^{16}OH$		1.001	
$^{12}CH_3{}^{18}OH$	0.997	0.9971	0.07

* Calculated from results of fractionation. The light molecule (l) is in all cases $^{12}CH_3{}^{16}OH$; T = b.p. at 200 mm Hg.

Beersmans and Jungers[148] prepared the isotopic methanols CD_3OH, CH_3OD, and CD_3OD, and measured the difference between the vapour pressure of each of these compounds and that of ordinary methanol (Fig. 7). Over the range 0°–60°C it was found that replacement of the three methyl hydrogen atoms by deuterium produced an increase in vapour pressure of about 0.7%. If only the hydroxyl hydrogen was substituted, a negative effect about seven times as great was produced, the diminution in vapour pressure being from 3% (at 60°) to 6% (0°). Replacement of all the hydrogen atoms in the methanol molecule by deuterium also causes a fall in the vapour pressure, but by a few tenths of 1% smaller than in the previous case, this being the resultant of the first two effects.

With respect to replacement of the methyl hydrogen by deuterium, methanol behaves like the hydrocarbons and halogenated derivatives, disilane, digermane, and pentaborane described above. For substitution of hydrogen in the hydroxyl group, however, a large negative isotope effect is observed, as with the monatomic and diatomic molecules at comparatively low temperatures. The vapour pressure of the isotopic varieties of methanol can be represented to within ~2 mm Hg by equations of the type

$$\log P_{mm} = A + B/T + C \log T. \qquad (44)$$

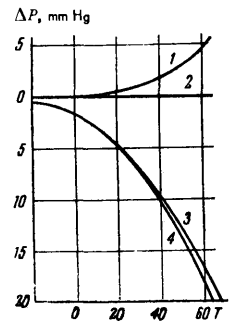

Fig. 7. Difference in vapour pressure P for isotopic methanols.
$\Delta P = P$ (D-alcohol) $- P$ (CH_3OH):
1) CD_3OH; 2) CH_3OH; 3) CD_3OD; 4) CH_3OD.

TABLE 22. Boiling points, heats of evaporation, and constants in Eqn. (44) for isotopic methanols.

Substance	D, at %	B.p., °K	ΔH_e at b.p., cal mole^{-1}	A	$-B$	$-C$	Ref.
CH_3OH	0	338.0	9010	16.36638	2348.68	2.58414	149
CD_3OH	98	337.8	9005	16.87022	2372.83	2.75386	148
CH_3OD	92	338.7	9105	17.20687	2408.54	2.85113	148
CD_3OD	98 in CD 97 in OD	338.6	9120	16.42088	2372.75	2.58178	148

TABLE 23. Constants in Eqn. (46) for ethanol and the propanols (over the range 20°–70°) and for the butanols (20°–80°).

Alcohol	A	$-B$	$-C$	Alcohol	A	$-B$	$-C$
C_2H_5OH	24.1146	2898.10	5.1000	$CH_3(CH_2)_3OH$	30.6838	3648.5	7.1166
C_2H_5OD	24.5030	2932.60	5.2209	$CH_3(CH_2)_3OD$	31.1884	3695.4	7.2691
$CH_3(CH_2)_2OH$	35.5791	3670.60	8.8750	$(CH_3)_2CHCH_2OH$	31.6340	3631.40	7.4415
$CH_3(CH_2)_2OD$	36.2509	3706.10	9.1110	$(CH_3)_2CHCH_2OD$	31.5004	3634.70	7.3871
$(CH_3)_2CHOH$	25.8692	3079.70	5.6153	$C_2H_5CHOHCH_3$	33.5817	3628.5	8.1468
$(CH_3)_2CHOD$	26.0250	3121.00	5.6348	$C_2H_5CHODCH_3$	34.3629	3488.7	8.8160

Values of the constants A, B, and C are given in Table 22. Differentiation of Eqn. (44) with respect to temperature and comparison with the Clausius–Clapeyron equation leads to the expression

$$\Delta H_e = -4.574B + 1.986CT. \qquad (45)$$

Heats of evaporation calculated from Eqn. (45) and the normal boiling points calculated from Eqn. (44) are also given in Table 22.

On the basis of calorimetric data[150] the heat of evaporation of CH_3OD at 273 °K is 9385 ± 20 cal mole^{-1}, compared with 9205 ± 20 cal mole^{-1} for CH_3OH, agreeing in the sign and the order of magnitude of the isotope effect with data given by Beersmans and Jungers[148]. In addition, CH_3OD has a lower heat of fusion and a lower melting point than CH_3OH, 726 ± 3 compared with 755 ± 3 cal mole^{-1}, and 173.5° as against 175.4 °K.[150]

Rabinovich *et al.*[151] investigated the effect of replacing the hydrogen by deuterium in the hydroxyl groups of methyl, ethyl, propyl, isopropyl, butyl, isobutyl, and s-butyl alcohols on their vapour pressures. The results for the isotopic methanols agree to within 1 mm Hg with those reported above[148]. The vapour pressures of other alcohols are represented by equations of the type of (46), the constants A, B, and C in which are given in Table 23

$$\log P_{mm} = A + B/T + C \log T. \qquad (46)$$

All the deuteroalcohols investigated (95–98% D in the hydroxyl) have a lower vapour pressure than their hydrogen analogues. The isotope effect amounts to several per cent. Its dependence on the composition and the structure of the alcohol and on the temperature can be seen from Fig. 8.

A decrease in vapour pressure when the hydrogen is replaced by deuterium in the –OH of pentanol and in the –SH of ethanethiol has been reported by Hobden *et al.*[153]. However, the numerical values which they give for P_D/P_H, 0.85 for the pentyl alcohols and 0.91 for the ethanethiols at

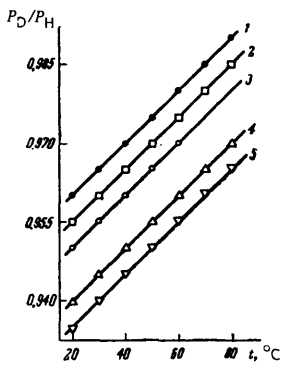

Fig. 8. Effect of replacement of hydroxyl hydrogen by deuterium on vapour pressure of alcohols (experimental values of P_D/P_H rounded off to 0.5%):
1) s-butanol; 2) isobutanol; 3) methanol; 4) ethanol and isopropanol; 5) propanol and n-butanol.

25°, are evidently much too low, since it is improbable that the percentage isotopic difference in vapour pressure in these cases would be several times larger than that for CH_3OD and almost the same as for D_2O (see Table 25).

A large reduction in the vapour pressure is produced by replacing the three hydrogen atoms in ammonia by deuterium[95,154]. According to the direct measurements made by Kirschenbaum and Urey[95] the data for ND_3 (subscript h) containing 98 at.% of D and ordinary NH_3 (l) are represented by

$$\begin{aligned} &\text{solid state } \log (P_h/P_l) = 0.1305 - 49.69/T, \\ &\text{liquid state } \log (P_h/P_l) = 0.14003 - 46.45/T. \end{aligned} \qquad (47)$$

The heat of evaporation of deuteroammonia is greater, and its boiling point higher, than for ordinary ammonia, by 212 cal mole^{-1} and 2.37° respectively. The corresponding differences in the heat of fusion and the temperature of the ternary point are 15 cal mole^{-1} and 3.11° in the same direction. Replacement of ^{14}N by ^{15}N in ammonia[155–157] also produces isotopic effects in the same direction as with deuterium. Thode[155] made direct measurements on liquid ammonia containing 70.6% $^{15}NH_3$ (h) compared with ordinary NH_3 containing 0.38% $^{15}NH_3$ (l), the following equation being obtained for the vapour pressure

$$\log (P_h/P_l) = 0.00325 - (0.9593/T). \qquad (48)$$

TABLE 24. Vapour pressure ratio for isotopic varieties of ammonia.

T, °K	ND_3/NH_3* solids[95]	T, °K	ND_3/NH_3* liquids[95]	T, °K	$^{15}NH_3/^{14}NH_3$** liquids[155]
180	0.715	202	0.815	198	0.994
185	0.728	210	0.831	209	0.996
190	0.740	220	0.851	228	0.997
195	0.751	230	0.869	240	0.998
		236	0.880		

* 98% deuterium.
** 100% heavy nitrogen – extrapolated.

It was calculated by extrapolation assuming additivity that complete replacement of ^{14}N by ^{15}N in ammonia would increase in the heat of evaporation, the boiling point, and the temperature of the triple point of 6.25 cal mole^{-1}, 0.055°, and 0.118° respectively.

Even before the work on deuteroammonia, it had been shown[158] that the vapour pressure is lowered on substitution of deuterium for hydrogen in methylamine. In this case the ratio P_D/P_H for 99 at.% D varies from 0.92 at 223° to 0.95 at 263°K. The melting point of ND_2CH_3 (184.0°) is 3.9° higher than that of NH_2CH_3.

Another amine which has been investigated is aniline. With this compound, too, replacement of the hydrogen in the amino-group by deuterium results in a lower vapour pressure[151]. In this case the isotope effect decreases comparatively rapidly with rise in temperature, being 3.5% for $C_6H_5ND_2$ at 50°, but only 0.5% at 80°. This is apparently explained by the comparatively rapid decrease in the degree of association of aniline with rise in temperature.

The isotope effect in vapour pressure has been subjected to particularly detailed investigation in the case of heavy water. Very accurate results have been obtained for deuterium oxide in several papers[159-167], mostly by direct measurement of the pressure. Table 25 gives values of P_h/P_l for liquid D_2O (99.7–99.8 at.%) and H_2O obtained by Kirschenbaum[162] by graphical averaging of experimental data[163-166], and also the corresponding results of the most recent precision measurements by Combs *et al.*[167] and Oliver and Grisard[161]. Two interesting facts are the comparatively large decrease in the vapour pressure of water over the range 0°–50° produced by substitution of deuterium for hydrogen, and the change in sign of the isotope effect in the vicinity of 225°. $P(D_2O) < P(H_2O)$ up to this temperature, but above it $P(D_2O) > P(H_2O)$, so that 225° is the point of intersection of the vapour pressure–temperature curves for heavy and ordinary water[165,166] (for brevity this point will be termed the "crossover temperature"). The following equation (in which the temperature is t°C) is accurate to ~0.5% over the range 20°–100°, and to within 0.1% between 100° and 370°

$$\log [P(D_2O)/P(H_2O)] = 0.0306605 - 9.14056/(75.753 + t)\ \S.$$

Combs and Smith[168] found that for ~0.1 M solutions of some electrolytes the value of $P(D_2O)/P(H_2O)$ is increased by several per cent and the crossover temperature lowered by tens of degrees (Table 26, Fig.9). Comparatively small ions such as Li^+ and F^- have a weaker effect than have large ions such as I^- and PO_4^{3-}. These workers[168] suggest that this effect can be used to enrich water with deuterium by extractive distillation above the crossover temperature, since with ~0.15 M LiI or ~0.10 M K_3PO_4 a separation factor can be achieved of

$$\alpha = [P(D_2O)/P(H_2O)]^{1/2} = 1.035\ ¶.$$

Unexpected results were obtained by Johannin-Gilles and Johannin[160] for the difference in vapour pressure between heavy and ordinary ice at 273°–240°K: as the temperature fell over this range, the ratio P_h/P_l increased, and at

TABLE 25. Vapour pressure ratios of isotopic varieties of water.

t, °C	$HT^{16}O/H_2^{16}O$ ref. 179	$D_2^{16}O/H_2^{16}O$ ref. 167	$D_2^{16}O/H_2^{16}O$ ref. 162	$HD^{16}O/H_2^{16}O$ ref. 162	$H_2^{18}O/H_2^{16}O$ ref. 26	$H_2^{17}O/H_2^{16}O$ ref. 170
0			0.79_7	0.89_3		
10		0.836	0.84_6	0.92_0		
20		0.854	0.86_7	0.93_1	0.9912	
30	0.80_0	0.871	0.88_9	0.93_9	0.9918	
40	0.85_5	0.885	0.89_1	0.94_4	0.9926	
50	0.97_5	0.899	0.903	0.051	0.9933	
60	0.88_5		0.914	0.956	0.9940	0.9970
70	0.89_5		0.926	0.962	0.9947	0.9975
80			0.934	0.966	0.9954	
90			0.943	0.971	0.9961	
100			0.951	0.975	0.9968	

t, °C	$D_2^{16}O/H_2^{16}O$ ref. 162	$HD^{16}O/H_2^{16}O$ ref. 162	t, °C	$D_2^{16}O/H_2^{16}O$ refs. 161, 162	$HD^{16}O/H_2^{16}O$ ref. 162	t, °C	$D_2^{16}O/H_2^{16}O$ ref. 161
110	0.957	0.978	180	0.989	0.995	260	1.007
120	0.963	0.981	190	0.992	0.996	280	1.010
130	0.969	0.984	200	0.995	0.997	300	1.012
140	0.974	0.987	210	0.997	0.998	320	1.014
150	0.978	0.989	220	0.999	1.000	340	1.017
160	0.982	0.991	230	1.001	1.000	360	1.019
170	0.986	0.993	240	1.004	1.002	370	1.021

TABLE 26. Effect of electrolytes on temperature of intersection of $P-T$ curves for D_2O and H_2O.[168]

Electrolyte	Concn., mole fraction	Depression of temp. of intersection, deg	Electrolyte	Concn., mole fraction	Depression of temp of intersection, deg
AgF	0.100	12	LiI	0.150	114
KF	0.100	30	LiI	0.100	50
KCl	0.110	74	LiI	0.0005	0
KBr	0.010	68	ZnI_2	0.100	46
KI	0.103	81	Na_2SO_4	0.100	0
NaI	0.092	67	K_3PO_4	0.100	137

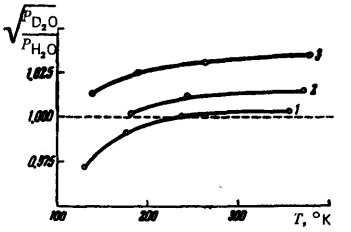

Fig.9. Temperature dependence of $\alpha = [P(D_2O)/P(H_2O)]^{1/2}$ for solutions of LiI at concentrations (in mole fractions) of: 1) 0.005; 2) 0.100; 3) 0.150.

§ C.B.Willingham *et al.*, J.Res.Nat.Bur.Stand., 35, 219 (1945); E.W.Walley, in "Proceedings of the Joint Conference on the Thermodynamic and Transport Properties of Fluids, 1957", Institution of Mechanical Engineers, London, 1958, p.15.

¶ It is assumed here that at low D contents $\alpha = P(HDO)/(H_2O)$ and that Eqn.(50) is valid.

about 249°K $P_h = P_l$. Hence there is a point of crossover at about 249°K of the vapour pressure–temperature curves for the solid state in addition to the above crossover point at about 498°K for liquid D_2O and H_2O. The vapour pressure of heavy ice over the range 240°–273°K is described[160] by the following equation

$$\log P_{mm} = -2886.9/T - 1.0327 \log T - 0.199156T + 0.000368T^2 + 40.5677 \quad (49)$$

the ice containing 99.5 at.% of D. Earlier data[171] for heavy ice between 273° and 275°K also agree with Eqn. (49). Fig. 10 shows the temperature dependence of P_D/P_H for heavy and ordinary water over the whole range studied, 240°–625°K.

The vapour pressure of HDO cannot be measured directly, since the following equilibrium is rapidly established

$$D_2O + H_2O \rightleftarrows 2HDO.$$

It follows from the equilibrium constant[25] of this reaction, for example, that with 50 at.% of deuterium at 25° the mixture contains ~48 mole % of HDO and 26% each of D_2O and H_2O. Some investigators, however, postulate[172,173] that the following relation holds

$$P(HDO) = [P(H_2O) \cdot P(D_2O)]^{1/2}, \quad (50)$$

i.e. that the rule of the geometric mean based on the masses of the molecules[97] is applicable in this case. Wahl and Urey[164] used Rayleigh distillation to determine the vapour pressure of HDO. They assumed that solutions of the isotopic varieties of water behave ideally, and hence that with a small deuterium content, when the concentration of D_2O is low, the separation factor α is approximately equal to the ratio of the vapour pressures of HDO and H_2O. Values of P(HDO) calculated from Eqn. (50) and from the experimental value of α were found to agree within the limits of error involved in determining the latter. Schutz[174], by carrying out a single distillation at 100° of water containing 1 at.% deuterium (1.98% HDO + 0.01% D_2O), determined α directly from experimental data on the composition of the phases in equilibrium It was found that $P(HDO)/P(H_2O)$ = = 0.971 at 100°, whereas the corresponding value calculated from Eqn. (50) is 0.975. According to Combs *et al.*[167], who used the same method, the difference between the values of α obtained experimentally and calculated from Eqn. (50) reaches 0.6% over the range 10°–50°, this being two or three times as great as the experimental error. The explanation is evidently that solutions of the isotopic varieties of water depart slightly from ideal behaviour.

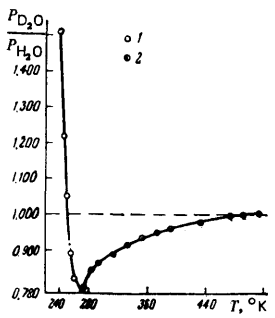

Fig. 10. Isotope effect in vapour pressure of heavy water: 1) solid, $P(D_2O)$ calculated from Eqn. (49). $P(H_2O)$;[233] 2) liquid[182].

Several papers have described investigations of the ratio $P(H_2{}^{18}O)/P(H_2{}^{16}O)$ using fractionating columns[170,172,175–177], Rayleigh distillation[28,164,165], and direct determination of the composition of the equilibrium phases[26]. The results of some of these investigations, however, do not agree sufficiently well. At about 80°, for example, values have been found of 0.9936,[176] 0.9951,[165] 0.9954,[26] and 0.996,[172]. The most detailed and apparently most accurate results are given by Zhavoronkov *et al.*[26] Water enriched to 1.1–1.4 mole % with $H_2{}^{18}O$ was used and, in addition to Rayleigh distillation, it was distilled in an apparatus equivalent to one theoretical plate, the composition of the equilibrium phases then being determined. Results obtained by the two methods agreed well. They can be represented by the following equation:

$$\log P(H_2{}^{18}O)/P(H_2{}^{16}O) = 0.00781 - 3.4492/T, \quad (51)$$

which also reproduces satisfactorily the data of Riesenfeld and Chang[165]. With heavy-oxygen water over the range investigated (10°–100°), as with heavy-hydrogen water, the vapour pressure is lower than that of ordinary water, and the corresponding relative difference diminishes with rise in temperature, the isotope effect for $H_2{}^{18}O$ being considerably less than that for D_2O (Table 25), as expected. Baertschi[178] found that the quantity $[1 - P(D_2{}^{18}O)/P(D_2{}^{16}O)]$ is about 20% smaller than $[1 - P(H_2{}^{18}O)/P(H_2{}^{16}O)]$†.

The ratio $P(H_2{}^{17}O)/P(H_2{}^{16}O)$ has been determined by means of a fractionating column[170] to be approximately 0.9969 at 58° and 0.9974 at 67°. The corresponding values of $P(H_2{}^{18}O)/P(H_2{}^{16}O)$ are 0.9939 and 0.9945. If allowance is made for the error of 0.0002 in the data of Thode *et al.*[170], it follows that the rule of the geometric mean with respect to molecular mass[97] holds approximately for the vapour pressures of $H_2{}^{18}O$, $H_2{}^{17}O$, and $H_2{}^{16}O$.

The vapour pressure of HTO has been investigated by Price[179], who used a standard sample of tritiated water to prepare solutions in H_2O having activities of 5–25 $\mu c\ ml^{-1}$, and measured the activities of their saturated vapours at a series of temperatures between 25° and 75°. He found that at a given temperature the ratio of the activities of the equilibrium phases is constant, from which it follows that Henry's law is applicable to this case. Since the solutions of HTO were very dilute, it is easy to show by the application of Raoult's and Dalton's laws that the ratio of the activity of the vapour to that of the liquid is approximately equal to the ratio $P(HTO)/P(H_2O)$. Values of this ratio determined in this way and averaged graphically are given in Table 25. Although the ratios of the molecular weights $M(HTO)/M(H_2O)$ and $M(D_2O)/M(H_2O)$ are very close to one another, the ratio $P(HTO)/P(H_2O)$ is about 9% smaller than the ratio $P(D_2O)/P(H_2O)$ over the range 25°–40°: *i.e.* the isotope effect is greater with HTO than with D_2O.

The most accurate value of the boiling point of D_2O is apparently 101.431° ± 0.003° obtained by Stokland[180]. The values given elsewhere[159,165] differ from this value by only 0.01° and 0.03° respectively. It has been established[181] that the elevation of boiling point of solutions of D_2O in H_2O relative to pure H_2O is proportional to the mole fraction of heavy water.

† For the $H_2{}^{16}O/H_2{}^{18}O$ and $D_2{}^{16}O/D_2{}^{18}O$ separation factors, see P. Baertschi and M. Thürkauf, Helv. Chim. Acta, 43, 80 (1960).

Determinations of the heat of evaporation of D_2O are described[61,165,166,182,183], and most of the results have been summarised[162]. At 3.82° ΔH_e (D_2O) = 11 109 ± 20 cal mole^{-1}, its value at 25° being 10 846 ± 20 cal mole^{-1}: *i.e.* at the two temperatures it is respectively 407 and 331 cal mole^{-1} greater than ΔH_e (H_2O). This isotopic difference in heat of evaporation decreases steadily as the temperature rises, being 208, 143, and 105 cal mole^{-1} at 100°, 160°, and 220° respectively. Golik *et al.*[184] give data for the heat of evaporation of solutions of D_2O in H_2O which show that such solutions depart from ideal behaviour.

The same temperature of 3.82° was obtained for the melting point of D_2O in several investigations[185-187,189]; other determinations have been made[159,180,188]. The pressure corresponding to the triple point is 5.06 mm Hg. The derivative dT/dP for D_2O, which measures the variation of its melting point with pressure, is about 93% of the corresponding value for H_2O.[185,187,190] The following formula is given by LaMer and Baker[191,192] for the freezing point of solutions of D_2O in H_2O.

$$t_s\,(°C) = 39.42\ \Delta\rho_{25}^{25} - 38.8\,(\Delta\rho_{25}^{25})^2, \qquad (52)$$

where $\Delta\rho_{25}^{25} = \rho_{25}^{25} - 1$, ρ_{25}^{25} being the density of the solution at 25° relative to H_2O at the same temperature.

According to Price[179], the mean values of ΔH_e over the range 25°–75° are 10 900, 10 600, and 10 300 cal mole^{-1} for HTO, D_2O, and H_2O respectively, the uncertainty being ±100 cal mole^{-1} in every case.

Libby and Cornog[193] concluded from their data on the vapour pressure of solutions of HTO in H_2O (numerical values of which are not given in the paper) that the normal boiling point of pure HTO is lower than that for H_2O. However, in view of the facts that (as shown by Price[179]) at about 70° the vapour pressure of HTO is 10% lower, and its heat of evaporation 600 cal mole^{-1} greater, than those of H_2O, and also in the light of the isotope effect and its temperature dependence in the vapour pressure of D_2O, the above conclusion[193] must evidently be regarded as erroneous.

It has been calculated[26] from the vapour pressure that, compared with $H_2{}^{16}O$, the boiling point of $H_2{}^{18}O$ is 0.09° higher and its mean heat of evaporation between 15° and 100° is 16 cal mole^{-1} greater; similar results have been obtained elsewhere[164,165]. From data on the separation of $H_2{}^{18}O$ and $H_2{}^{16}O$ by the fractional crystallisation of water, the melting point of the former is 0.05° ± 0.008°.[194]

Giguère[183] made calorimetric measurements of heats of evaporation over a wide range of concentrations in the systems heavy water–deuterium peroxide and ordinary water–hydrogen peroxide. Extrapolation of the curves to 100% peroxide showed that the heat of evaporation of D_2O_2 at 25° (12 510 ± 50 cal mole^{-1}) is greater than the corresponding quantity for H_2O_2 by 170 cal mole^{-1}.

The isotope effect in the vapour pressure of deuterium cyanide appears[195] to be somewhat unusual. The following equations were suggested[195] (P in mm Hg):

$$\log P\,(HCN_L) = 7.795 - 1467/T, \qquad (53)$$
$$\log P\,(HCN_S) = 9.372 - 1877/T.$$

$$\log P\,(DCN_L) = 7.695 - 1440/T - 175/T^2, \qquad (54)$$
$$\log P\,(DCN_S) = 9.476 - 1907/T.$$

It appears from Eqns. (53) and (54) that the ratio P_D/P_H for the solid state increases from 0.93 at 225°K to 0.97 at 258°K, but for the liquid state, on the other hand, the ratio decreases from 1.01 at 261°K to 0.93 at 298°K. Consequently there should be a maximum ratio at about the melting point, which according to Lewis and Schutz[195] is approximately 259°K for HCN and 261°K for DCN.

(b) Isotopic Compounds Which Are Strongly Associated in Both Liquid and Gaseous Phases (Hydrogen Fluoride, Carboxylic Acids)

It is clear from the above account that, in the case of liquids in which the association complexes decompose completely or almost completely on evaporation (water, alcohols, ammonia, etc.)‡, substitution of deuterium for hydrogen forming a hydrogen bond causes a decrease in the vapour pressure. At the same time, several papers have shown that the opposite isotope effect is observed when association persists in the gas phase. As early as 1934 Claussen and Hildebrand[196] represented the vapour pressure of the liquid isotopic hydrogen fluorides over the range 5–760 mm Hg by the equations:

$$\log P_{mm}\ (HF) = 7.3739 - 1316.79/T, \qquad (55)$$
$$\log P_{mm}\ (DF) = 7.2026 - 1261.16/T.$$

It follows from Eqn. (55) that the ratio $P(DF)/P(HF)$ is greater than unity and decreases steadily from 1.150 at 240° to 1.040 at 290°K, the boiling points being 293.07° for HF and 291.81°K for DF.

Lewis and Schutz[197] who were the first to study the vapour pressure of deuteroacetic acid CH_3COOD, found that at 50° it is 7.5%, and at 90° 3% greater than the vapour pressure of CH_3COOH§. The vapour pressure of CD_3COOH is 2–4% greater (at 35°–85°)[235] than that of CH_3COOH. Since this isotopic substitution has practically no influence on the association, the isotope effect observed has the same sign as in the replacement of hydrogen by deuterium in the methyl group of methanol or in unassociated compounds at moderate temperatures. The difference in vapour pressure between CD_3COOD and CH_3COOH should equal the sum of the positive isotope effects produced by substitution in the methyl and in the hydroxyl groups. Among experimental investigations of the effect of the complete deuteration of acetic acid on its vapour pressure[199-201], Wilson[200] described his data by the equation

$$\log P\,(CD_3COOD)/P\,(CH_3COOH) = 3.94/T + 0.0106, \qquad (56)$$

from which it follows that P_h/P_l decreases steadily from 1.06 at 20° to 1.05 at 100°. Halford and Anderson[201] show the isotope effect to be considerably lower, but Wilson's results[200] were confirmed within the limits of error of their measurements by Potter and Ritter[199], who give the following equations for the vapour pressure of the two isotopic acids:

$$\log P_{mm}\ (CH_3COOH) = 7.4275 - 1558.03/(T - 48.37), \qquad (57)$$

$$\log P_{mm}\ (CD_3COOD) = 7.4397 - 1556.17/(T - 48.34).$$

The most accurate value for the melting point of CD_3COOD is apparently 15.92°,[199] which is 0.68° below the melting point of CH_3COOH.

‡ In the vapours of alcohols, for example, only a few per cent of the molecules are associated[152].

§ No exchange was detected[197] between the hydrogen of the carboxyl and of the methyl groups in CH_3COOH. Such an exchange was shown later[198,199] to be possible, but it is very slow[199] even at 100°.

Rabinovich *et al.*[151] investigated how vapour pressure is affected by the substitution of deuterium for hydrogen in the carboxyl group of acetic, butyric, isobutyric, and isovaleric acids. Over the temperature ranges investigated (Fig.11) all four acids showed a positive isotope effect P_D/P_H, but an interesting feature was observed with acetic and butyric acids, for the curves showing the temperature dependence of the ratio passed through maxima. Since with the other two acids the ratio increases with rise in temperature over the ranges investigated, it can be supposed that at higher temperatures a maximum in the vapour pressure ratio will be observed in these cases too. The numerical values of the vapour pressures of the acids are represented by equations of the type

$$\log P_{mm} = A + B/T + C \log T, \qquad (58)$$

the constants in which are given in Table 27. According to our results the isotope effect amounts to a few per cent, and for CH_3COOD in particular it is about half the value found previously[197].

It is interesting that, as Dawber and Wyatt[202] have shown, the vapour pressure at 0° of deuteronitric acid DNO_3 (84.37% of N_2O_5 in D_2O) is 7% higher than that of HNO_3. Since this effect is opposite in sign to the isotope effects with D_2O, ND_3, and CH_3OD, but the same as that with CH_3COOD, these results[202] may perhaps mean that at about 0° nitric acid is associated to a considerable extent even in the gas phase.

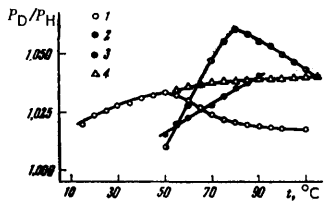

Fig.11. Effect of replacement of carboxyl hydrogen by deuterium on vapour pressure of: 1) acetic acids; 2) butyric acids; 3) isobutyric acids; 4) isovaleric acids.

TABLE 27. Constants of Eqns.(58) (H = ordinary acid; D = its analogue containing 99% D in the carboxyl).

Acid	A	$-B$	$-C$	Temp. range, °C
Acetic-H	15.5817	2480.4	2.4528	20—118
Acetic-D	16.9083	2542.0	2.9016	
Butyric-H	12.0505	2828.0	1.0168	50—115
Butyric-D	12.0505	2821.8	1.0154	
Isobutyric-H	8.8195	2532.7	0.0068	50—90
Isobutyric-D	9.9223	2615.0	0.3379	
Isovaleric-H	11.6256	2972.1	0.7826	50—110
Isovaleric-D	12.1938	2982.6	0.8621	

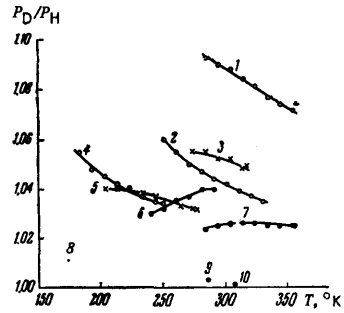

Fig.12. Positive isotope effect in vapour pressure of non-associated substances (hydrogen bonds absent): 1) C_6D_{12}/C_6H_{12}; 2) B_5D_9/B_5H_9; 3) CD_3I/CH_3I; 4) CD_3Cl/CH_3Cl; 5) CD_3Br/CH_3Br; 6) $CD_3C{\equiv}CCl/CH_3C{\equiv}CCl$; 7) C_6D_6/C_6H_6; 8) $^{11}BF_3/^{10}BF_3$; 9) $^{11}BCl_3/^{10}BCl_3$; 10) $^{13}CCl_4/^{12}CCl_4$.

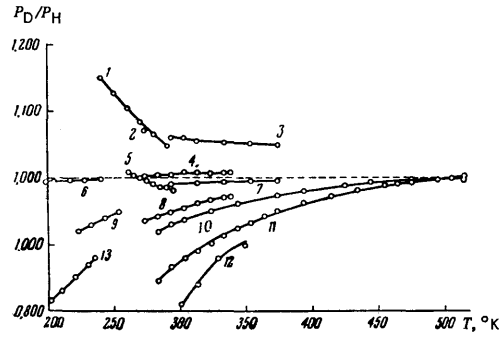

Fig.13. Isotope effect in vapour pressure of substances which are associated by hydrogen bonds: 1) DF/HF; 2) DNO_3/HNO_3; 3) CD_3COOD/CH_3COOH; 4) CD_3OH/CH_3OH; 5) DCN/HCN; 6) $^{15}NH_3/^{14}NH_3$; 7) $H_2{}^{18}O/H_2{}^{16}O$; 8) CH_3OD/CH_3OH; 9) ND_2CH_3/NH_2CH_3; 10) HDO/H_2O; 11) D_2O/H_2O; 12) HTO/H_2O; 13) ND_3/NH_3.

Fig.12 summarises the experimental data on the positive isotope effect in the vapour pressure of unassociated substances, and Fig.13 illustrates the effect on vapour pressure of replacing hydrogen by deuterium in various cases of association involving a hydrogen bond.

B. CALCULATIONS AND INTERPRETATION OF THE ISOTOPE EFFECT IN VAPOUR PRESSURE

1. INTRODUCTION

From the point of view of classical mechanics, the forces of interaction between isotopic atoms or molecules are identical. We therefore find that, to the degree of

approximation of classical statistics[203], the chemical potentials of isotopic substances should differ only by a constant multiplied by the temperature

$$\mu_h - \mu_l = -\frac{3}{2} kT \ln \frac{M_h}{M_l}, \quad (59)$$

where μ is the chemical potential for a single molecule, M is its mass, the subscripts h and l refer to the heavy and the light isotopic varieties respectively, and k is the Boltzmann constant. When the phases are in equilibrium we have

$$\mu_h^c(P_h, T_h) = \mu_h^g(P_h, T_h), \quad (60)$$

$$\mu_l^c(P_l, T_l) = \mu_l^g(P_l, T_l), \quad (61)$$

where the superscript c and g denote the condensed and gas phases respectively. Further, if the vapours obey the ideal gas laws, we also have

$$\mu_h^g(P_h\ T_h) = \mu_h^{g,0}(T_h) + kT \ln P_h, \quad (62)$$

$$\mu_l^g(P_l, T_l) = \mu_l^{g,0}(T_l) + kT \ln P_l, \quad (63)$$

where $\mu^{g,0}$ is the part of μ^g which depends only on the temperature. Since the chemical potential of the condensed phase is little affected by pressure, substitution of Eqns.(62) and (63) in (60) and (61), with $T_h = T_l = T$, yields

$$\ln \frac{P_h}{P_l} = \frac{(\mu_h^c - \mu_l^c) - (\mu_h^{g,0} - \mu_l^{g,0})}{kT}. \quad (64)$$

Since the difference (59) is the same for all phases of a given substance, and since for the gas phase this difference is represented by the difference between $\mu_h^{g,0}$ and $\mu_l^{g,0}$, it follows from Eqn.(64) that $P_h = P_l$. Thus within the limits of classical statistical mechanics, isotopic substances have the same vapour pressure. The incompatibility of this conclusion with the experimental data is a result of quantum-mechanical effects. Quantum statistics would lead to an isotopic difference in vapour pressure even if the intermolecular forces in the isotopic substances were equal. This difference cannot in general be calculated for any given substance, but approximate solutions are available for the simplest cases. Thus in the case of a monatomic substance we have according to Landau and Lifshits[203]

$$\mu^c = \mu^c_{\text{class}} + \frac{h^2}{24MkT} \overline{F^2}, \quad (65)$$

including terms of the order of h^2, where h is Planck's constant, and

$$\overline{F^2} = \overline{\left(\frac{\partial U}{\partial x}\right)^2} + \overline{\left(\frac{\partial U}{\partial y}\right)^2} + \overline{\left(\frac{\partial U}{\partial z}\right)^2} \quad (66)$$

is the mean square force in the condensed phase exerted on one atom by the remaining atoms, U is the potential energy, and x, y, z are coordinates. For a gas the chemical potential retains its classical value, since interaction between the particles can be neglected in this case. Substituting Eqn. (65) in (64), we therefore obtain

$$\ln \frac{P_h}{P_l} = \frac{h^2 \overline{F^2}}{24 (kT)^2} \cdot \left(\frac{1}{M_h} - \frac{1}{M_l}\right), \quad (67)$$

or in the case of a small difference in pressure ($\Delta P/P \ll 1$),

$$\Delta P_{\text{iso}} = P_h - P_l = P_{\text{class}} \frac{h^2 \overline{F^2}}{24 (kT)^2} \cdot \left(\frac{1}{M_h} - \frac{1}{M_l}\right), \quad (68)$$

where P_{class} is the common classical value of P_h and P_l. In order to calculate ΔP_{iso} from Eqn. (68) it is necessary to know how $\overline{F^2}$ depends on the temperature. However, this formula explains qualitatively the lower vapour pressure of the heavier isotope in the cases of monatomic substances described above.

Lifshits and Stepanova[204] have suggested an approximate formula for the isotopic difference in vapour pressure of monatomic solids which can be used for actual calculations. They started from Eqn. (64) and employed the quantum expressions for thermodynamic functions derived from the Debye theory of solids. Introduction of $\varphi = \mu_h - \mu_l$ converts Eqn. (64) into

$$\ln \frac{P_h}{P_l} = \frac{\varphi^c - \varphi^{g,0}}{kT}. \quad (69)$$

The quantity φ is expressed in terms of the classical relation (59), so that for a small difference in isotopic masses ($\Delta M/M \ll 1$) we have

$$\varphi^{g,0} = -\frac{3}{2} kT \frac{\Delta M}{M}. \quad (70)$$

The free energy of a solid whose atoms perform small oscillations about an equilibrium position is

$$F = NU_0 + \sum_a \left[\frac{h\nu_a}{2} + kT \ln (1 - e^{-h\nu_a/kT})\right], \quad (71)$$

where NU_0 is the interaction energy of all the atoms in the solid in the equilibrium position and ν_a is a characteristic frequency of their oscillations. If the isotopes are assumed to have the same value of U_0, the isotopic difference in free energy in the solid phase will then be

$$\Delta F = \Delta \sum_a \left[\frac{h\nu_a}{2} + kT \ln\left(1 - e^{-h\nu_a/kT}\right)\right] = -\frac{\Delta M}{2M} U, \quad (72)$$

where

$$U = \sum_a h\nu_a \left[\frac{1}{2} + \frac{1}{e^{h\nu_a/kT} - 1}\right], \quad (73)$$

and

$$-\frac{\Delta M}{2M} \simeq \ln \left(\frac{M_h}{M_l}\right)^{-1/2} = \ln \frac{\nu_{a,h}}{\nu_{a,l}} \simeq \frac{\Delta \nu_a}{\nu_a}. \quad (74)$$

The inverse proportionality between ν_a and $M^{1/2}$ arises from the assumption that the oscillations of the atoms in the lattice are harmonic. In Debye's approximation the energy U is represented by the formula

$$U = 3NkT\left[\frac{3}{8}\frac{\theta}{T} + U_D\left(\frac{\theta}{T}\right)\right], \quad (75)$$

where $\theta = h\nu_D/k$ is the characteristic temperature, ν_D the Debye (maximum) frequency of the atomic oscillations, and $U_D(\theta/T)$ is the Debye function

$$U_D(Z) = \frac{3}{Z^3} \int_0^Z \frac{t^3}{e^t - 1} dt. \quad (76)$$

From Eqns. (72) and (75) we have

$$\varphi^c = \left(\frac{\partial \Delta F}{\partial N}\right)_{p,u} = -\frac{3}{2}\frac{\Delta M}{M} kT\left[\frac{3}{8}\frac{\theta}{T} + U_D\left(\frac{\theta}{T}\right)\right]. \quad (77)$$

Hence, using Eqn. (70) we find that

$$\varphi^c - \varphi^{g,0} = -\frac{3}{2}\frac{\Delta M}{M} kT \varphi\left(\frac{\theta}{T}\right), \quad (78)$$

where

$$\varphi(Z) = \frac{3Z}{8} - 1 + U_D(Z). \quad (79)$$

Substituting Eqn. (78) in (69), we obtain for small isotopic differences in vapour pressure

$$\frac{\Delta P}{P} = -\frac{3}{2}\frac{\Delta M}{M}\varphi\left(\frac{\theta}{T}\right). \quad (80)$$

It is interesting that, with the monatomic substances discussed above, Eqn. (80) gives a qualitatively correct result for the liquid–gas equilibrium as well.

2. CALCULATIONS OF THE ISOTOPE EFFECT IN VAPOUR PRESSURE AT THE TRIPLE POINT BY LINDEMANN'S METHOD

(a) Monatomic Substances

By a different approach Lindemann[205] arrived at a relation fundamentally similar to Eqn. (80) as early as 1919, when he was examining the difference in vapour pressure of the isotopes of lead. Keesom and Haantjes[57] applied Lindemann's method to the isotopes of neon, and Clusius and Meyer[17] to argon. These workers also employ Debye's approximate theory of solids, but start from the Clausius–Clapeyron equation instead of the relations (60)–(64). The approximate form of this equation is used, in which the volume of the condensed phase is neglected, and the heat of evaporation ΔH_e is expressed, according to Kirchhoff's equation, in terms of its value at the absolute zero $\Delta H_{e,0}$ and the heat capacities of the vapour C_g and the solid C_s. Integration of the appropriate expressions for the isotopic substances yields

$$\ln\frac{P_h}{P_l} = -\frac{(\Delta H_{0,h} - \Delta H_{0,l})_e}{RT} - \frac{1}{R_0}\int_0^T\frac{dT}{T^2}\int_0^T(C_{s,h} - C_{s,l})\,dT + \\ + (i_h - i_l) + (a_h - a_l), \quad (81)$$

where i is the vapour pressure constant and a is a correction for the deviation of the vapour from ideal behaviour.

Further, the isotopic difference in heat of evaporation can be written

$$(\Delta H_{0,h} - \Delta H_{0,l})_e = -(U_{0,h} - U_{0,l}) - (E_{0,h} - E_{0,l}),$$

where U_0 is the potential energy of interaction between the atoms at $T = 0$, and E_0 is the zero-point (kinetic) energy of the atomic oscillations. It is also postulated that $U_{0,h} = U_{0,l}$. The zero-point energy is expressed, after Debye, in terms of the characteristic temperature: $E_0 = 9R\theta/8$, the term $(i_h - i_l)$ in Eqn. (81) is replaced by $1.5 \ln M_h/M_l$, and the difference $(a_h - a_l)$ is neglected. In addition, the heat capacity at constant pressure C_p is introduced into Eqn. (81). It is related to the heat capacity at constant volume C_v by the well-known formula

$$C_p = C_v + \frac{\alpha^2 TV}{\beta}, \quad (82)$$

where V is the atomic volume, α the (volume) coefficient of thermal expansion, and β the isothermal compressibility. On the hypothesis that the van der Waals forces are equal in isotopic substances, the latter are assumed to have identical values of V as well as of β, and very similar values of α. Under these conditions the isotopic difference in the second term on the right-hand side of Eqn. (82) can be neglected, so that we find that

$$C_{p,h} - C_{p,l} = C_{v,h} - C_{v,l}. \quad (83)$$

In view of this, we can introduce into Eqn. (81) the Debye function representing the free energy

$$\int_0^T\frac{dt}{T^2}\int_0^T C_s\,dT = -\frac{F_D}{T}. \quad (84)$$

Hence we finally obtain

$$\ln\frac{P_h}{P_l} = \frac{9}{8T}(\theta_h - \theta_l) + \frac{1}{RT}(F_{D,h} - F_{D,l}) + \frac{3}{2}\ln\frac{M_h}{M_l}. \quad (85)$$

The value of F_D/T for a given value of θ/T is found from tables of Debye functions[206]. Since it is accepted that characteristic temperatures are inversely proportional to the corresponding values of $M^{1/2}$, the value of θ for one of the isotopic varieties is sufficient to calculate the ratio P_h/P_l by means of Eqn. (85). It is easily shown that Eqns. (80) and (85) differ only in the presence in the latter of the additional term $9(\theta_h - \theta_l)/8T$, which represents the isotopic difference in zero-point energy of the atomic oscillations.

Table 3 gives a comparison of experimental results obtained by Keesom and Haantjes[57] on the isotopic effect in the vapour pressure of solid neon with values which they calculated by means of Eqn. (85) using the value of $\theta_l = 63.0°$ found by Clusius[207]. According to the experimental data, the vapour pressure of ^{22}Ne between 20° and 24°K is 7.5–5.5% less than that of ^{20}Ne, while the calculated difference is 6.5–4.5%. Thus, in spite of the number of approximations introduced into the calculation, the results in this case show satisfactory agreement with experiment.

For the argon isotopes ^{40}Ar and ^{36}Ar, Clusius and Meyer[17] obtained a value between 0.9916 and 0.9950 for P_{40}/P_{36} at the triple point using Eqn. (85), while their experimental results gave 0.993–0.995.

With xenon, however, calculation gives an incorrect result. As mentioned above, two isotopic mixtures of xenon differing in atomic weight by 3 units of mass have identical vapour pressures (to within 0.02 mm Hg)[57] at the triple point (161.4°K), whereas according to calculation they should differ by several tenths of a millimetre¶.

(b) Calculations for the Isotopes of Hydrogen

With the aim of obtaining a rough approximation, Urey *et al.*[3] used the Debye theory of specific heat to calculate the isotope effect in the vapour pressure of hydrogen. The solid–vapour equilibrium is considered at the temperature of the triple point of ordinary hydrogen (13.95°K), and the following postulates are made.

1) Hydrogen molecules are capable of free rotation in the crystal; the energy of this rotation and that of the atomic oscillations remain unchanged during evaporation, and are therefore disregarded.

¶ For calculations on the isotopes of Ne, Ar, Kr, and Xe, see G. Casanova, R. Fieschi, and N. Terri, Nuovo cim., 18, 837 (1960).

2) In the equation for the free energy of the vapour G_g:

$$G_g = U_g + PV_g - TS_g, \quad (86)$$

the internal energy U_g and the entropy S_g are represented by the corresponding expressions for an ideal monatomic gas.

3) The free energy of isotopic substances in a real solid is calculated on the basis of the Debye theory. The following expression is used for the free energy G_S:

$$G_s = E_0 + T(F_D/T) + PV_s, \quad (87)$$

where, as above, E_0 is the zero-point energy, and F_D/T is the Debye function for the free energy. Further, since a phase equilibrium is being considered, the right-hand sides of Eqns. (86) and (87) are equal. The term PV_S is neglected, since it is small compared with PV_g, and the latter is replaced by RT. Hence we obtain for the vapour pressure

$$\ln P = \frac{9\theta}{8T} + \frac{F_D}{RT} + \frac{3}{2}\ln M + \frac{5}{2}\ln T - \frac{\Delta H_0'}{RT} + \text{const.} \quad (88)$$

Here $\Delta H_0'$ is the heat of evaporation at $T = 0$ when the translational energy of the molecules in the vapour and the zero-point energy of their vibrations in the solid are ignored. Under these conditions the heat of evaporation is a measure of the van der Waals interaction energy, which is regarded as identical for isotopic substances. The constant in Eqn. (88) is independent of the molecular mass. Hence it follows from Eqn. (88) that, with the approximations made by Urey *et al.*[3], Eqn. (85) can be applied to the isotopes of hydrogen at the temperature of the triple point. With $\theta_1 = 91°$,[83] calculation based on Eqn. (85) for HD and H_2 at 13.95 °K indicates that $P_h/P_l = 0.45$, the corresponding experimental value[74,75] being ~0.30.

Several refinements were introduced into the above calculation by Scott *et al.*[62], but make no fundamental difference to the calculations, which remain, as before, in the nature of an extremely rough approximation. Thus the value of P_h/P_l calculated by these authors for D_2 and H_2 at 13.95 °K is 0.30, whereas the corresponding experimental value is ~0.09†.

(c) Calculations for Some Complicated Substances

The above principles for calculating the isotope effect in vapour pressure at the triple point have also been applied as approximations to some more complicated substances, it being assumed that various rotational terms should be introduced in addition to the terms for vibrational motion. In calculating the P_h/P_l ratios for $^{13}C^{16}O$–$^{12}C^{16}O$, $^{12}C^{18}O$–$^{12}C^{16}O$, and $^{13}CH_4$–$^{12}CH_4$, therefore, Johns[91] introduced the following additional postulates: (1) the heat capacity is the sum of the corresponding Debye and Einstein terms; and (2) the frequencies of rotation, and consequently also the Einstein characteristic temperature, are inversely proportional to the square root of the moment of inertia of the molecule. On this basis the following equation was obtained[91]:

$$\ln\frac{P_h}{P_l} = -\frac{E_{g,h} - E_{g,l}}{RT} + \frac{1}{T^2}\left[\frac{3}{40}\theta^2_{D,l}\left(\frac{M_l}{M_h} - 1\right) + \sum\frac{n_E}{24}\theta^2_{E,l}\left(\frac{I_l}{I_h} - 1\right)\right], \quad (89)$$

† It has been shown[74] that experimental data on the heat capacity C_v for H_2 and D_2 give values of $\theta_l = 105°$ and $\theta_h = 97°$. Hence it follows that the postulated proportionality between θ and $M^{-1/2}$ is incorrect for the isotopes of hydrogen.

where E_g is the energy of mutual attraction of the molecules, θ_D the Debye characteristic temperature, n_E the number of possible rotational and torsional degrees of freedom, θ_E the corresponding Einstein characteristic temperatures, M and I are the masses and moments of inertia of the molecules, and the subscripts h and l denote the heavy and the light isotopic substances. Although the isotopic difference in the van der Waals energy is shown here, in actual calculations the corresponding term in Eqn. (89) is omitted, since no data are available for estimating this difference. For $^{13}C^{16}O$–$^{12}C^{16}O$ the calculated numerical values of $(P_h - P_l)/P_l$ are about 20% smaller than the corresponding experimental values obtained by the same investigator[91]; with $^{12}C^{18}O$–$^{12}C^{16}O$, on the other hand, the calculated values are 35% greater than the experimental; while in the case of $^{13}CH_4$–$^{12}CH_4$ the calculated are about double the experimental results.

Kirschenbaum[208] calculated the vapour pressures of $^{15}N_2$ and $^{14}N_2$ for several possible models of solid nitrogen. The best approximation to the experimental data was obtained with a model in which the molecules undergo oscillations corresponding to restricted rotations.

Devyatykh[209] employed the principle of Lindemann's method to calculate the isotope effect in the vapour pressure of $^{13}C^{16}O$, $^{12}C^{18}O$, $^{13}CH_4$, $^{12}CD_4$, $H_2{}^{18}O$, and $D_2{}^{16}O$ at the temperature of the triple point; together with Shavarin[210] he made a similar calculation for ND_3 and NT_3. This work was based on the chemical potential of a given isotopic variety being the same in the solid and gas phases at equilibrium, the potential being expressed in terms of components due to the different forms of motion. Introduction of the approximations characteristic of the method and also of several other assumptions resulted in the equation

$$\ln\frac{P_h}{P_l} = \frac{3}{2}\ln\frac{M_h}{M_l} + \frac{1}{2}\ln\frac{(ABC)_h}{(ABC)_l} - \frac{h}{2kT}\sum_i(\Delta\nu_{i,h} - \Delta\nu_{i,l}) + \frac{9}{8}\frac{\theta_{k,h} - \theta_{k,l}}{T} + \frac{1}{RT}(F_{k,h} - F_{k,l}) + \frac{9}{8}\frac{\theta_{B,h} - \theta_{B,l}}{T} + \frac{1}{RT}(F_{B,h} - F_{B,l}), \quad (90)$$

where A, B, and C are the principal moments of inertia of the molecule, $\Delta\nu_i$ is the change in the ith frequency when a molecule passes from the vapour into the crystalline phase, θ_k and F_k are the characteristic temperature and the free-energy function describing the lattice vibrations

TABLE 28. Comparison of calculated and experimental values of P_h/P_l at the temperature of the triple point.

Isotope molecules	Temp. of triple point of light variety, °K	$-100(P_h - P_l)/P_l$			
		calc.	ref.	expt.	ref.
$^{13}CH_4$–$^{12}CH_4$	90.7	0.7	209	0.5	91
				1.1	107
$^{13}C^{16}O$–$^{12}C^{16}O$	68.1	1.2		1.1	91
				1.2	93
$^{12}C^{18}O$–$^{12}C^{16}O$	68.1	1.6		1.3	91
				1.9	107
$H_2{}^{18}O$–$H_2{}^{16}O$	273.2	1.2		1.1	26
$^{12}CD_4$–$^{12}CH_4$	90.5	−0.4		−1.3	121
$^{14}ND_3$–$^{14}NH_3$	195.4	21.1	210	24.8	95
$^{14}NT_3$–$^{14}NH_3$	195.4	25.6		*	
$D_2{}^{16}O$–$H_2{}^{16}O$	273.2	15.3	209	20.3	162

* No experimental data. It follows from the relation $P(ND_3) = [P(NT_3) \times P(NH_3)]^{1/2}$ that $P(NT_3)/P(NH_3) = 0.566$.

of the molecules, and θ_B and F_B are the corresponding quantities for the librations of the molecules in the lattice.

The most representative quantity for judging the agreement between calculated and experimental results is evidently $(P_h - P_l)/P_l$, the values of which based on calculations[209,210] differ, in most cases in Table 28, by 10–30% from the corresponding experimental values. With tetradeuteromethane, which shows a positive isotope effect, the calculated value of this ratio is less than one-third of the experimental value.

3. CALCULATION BASED ON EVALUATION OF THE PARTITION FUNCTION BY HENKEL'S METHOD

Johns[211] has obtained good results in calculating the isotope effect in the vapour pressure of solid neon by using Henkel's method[212] for calculating the partition function Q of a solid. This method is a variant of the Einstein treatment of the crystal lattice in which allowance is made for the anharmonic character of the atomic vibrations. Henkel assumed that the potential energy of an atom with respect to another, identical atom at a distance r is of the form

$$U = \frac{A}{r^n} - \frac{B}{r^6}, \qquad (91)$$

and he expressed the partition function Q as a function of r, n, A, and B. Agreement between calculated and experimental values is governed by suitable choice of values for the last three quantities. For neon Johns took the values: $n = 14$, $A = 0.373 \times 10^{-119}$ erg cm^{14}, and $B = 0.90 \times 10^{-59}$ erg cm^6, which are close to values used earlier[213]. The procedure for calculating the partition function has been set out in detail[211,212], and will be omitted here. The free energy at constant volume A of a solid is calculated from this function by means of the well-known formula

$$A = -RT \ln Q. \qquad (92)$$

The solid–vapour equilibrium was then considered by Johns[211], the isotopic difference in free energy at constant pressure for the solid phases being put equal to the corresponding difference for the vapours. It was then postulated that the deviation of the vapours from ideal gas behaviour can be neglected, and that the difference in free energy at constant pressure for the solids can be replaced by the corresponding difference in free energy at constant volume. The isotope effect in the vapour pressure is then calculated from the equation

$$\ln \frac{P_h}{P_l} = \frac{F_h - F_l}{RT} + \frac{3}{2} \ln \frac{M_h}{M_l}. \qquad (93)$$

It is seen from Table 3 that results obtained in this way for the isotopes of neon agree far better with the experimental data than do values calculated by Lindemann's method. However, the Henkel–Johns method is applicable only to monatomic solids, and moreover its application is very restricted owing to the absence of data on the quantities n, A, and B in the Lennard-Jones expression, Eqn.(91), for the potential.

4. DE BOER'S METHOD

Another interesting, semi-empirical method of calculation has been developed by de Boer on the basis of his quantum theory of corresponding states[214-216], and used by him to predict the vapour pressure of the light isotope of helium. According to this theory, the field of two molecules is described by a somewhat modified Lennard-Jones potential[217]

$$\varphi(r) = 4\varepsilon \left[\left(\frac{\sigma}{r}\right)^{12} - \left(\frac{\sigma}{r}\right)^{6}\right], \qquad (94)$$

where r is the distance between the molecular centres, ϵ the absolute interaction energy at the minimum on the potential-energy curve, and σ the intermolecular distance when $\varphi = 0$. The quantities ϵ and σ are used to express the thermodynamic variables in "molecular units": temperature in the form ϵ/k, pressure as ϵ/σ^3, and molar volume as $N\sigma^3$, where N is the Avogadro number and k the Boltzmann constant. Dimensionless reduced values of the temperature, pressure, and volume are then introduced, these being the ratios of the ordinary values to the corresponding values in molecular units

$$T^* = T/(\varepsilon/k), \quad P^* = P/(\varepsilon/\sigma^3), \quad V^* = V/(\sigma^3 N). \qquad (95)$$

An additional dimensionless quantity is introduced to take care of quantum effects — the reduced de Broglie wavelength

$$\lambda^* = \lambda/\sigma = h/(\varepsilon M)^{1/2},$$

where M is the molecular mass. The reduced equation of state is of the form

$$f(P^*, V^*, T^*, \lambda^*) = 0. \qquad (96)$$

This function is assumed to apply to all substances having the same intermolecular force law. Since, however, its form is unknown, theoretical calculation of vapour pressure by means of Eqn. (96) is impossible, and a semi-empirical method is therefore used. Values of P^* are plotted against λ^* at constant V^* and T^* for a number of substances with known vapour pressures having the same intermolecular force law as the test material. The value of P^* for the test material is then found graphically from the known value of λ^*, and finally P is determined from P^*. In this way de Boer was able, by using plots of P^* against λ^* for the inert gases, to calculate the vapour-pressure curve and the boiling point of ^{3}He a year before the first work on its liquefaction. The experimental vapour pressures obtained later[29] lay on the theoretical curve within the limits of error of the measurements.

Hammel[218] used the same method to predict the vapour pressure of tritium, but in this case the calculated and subsequent experimental[72] values differed by 25%. Maslan[219] and also Devyatykh[209] attempted to employ de Boer's method to calculate the isotope effect in the vapour pressure of oxygen, nitrogen, methane, carbon monoxide, and several other substances, but obtained poor results. Evidently this method can be used satisfactorily only in the simplest case of the inert gases.

Friedman *et al.*[220] remark that de Boer's method cannot be applied to the isotopes of hydrogen, since their molecules are not spherical, and hence cannot be compared in thermodynamic properties with the inert gases. A still more specialised empirical method was employed[220] to calculate the vapour pressures of HD and HT, based on the hypothesis that the phase transformation temperatures for all the isotopic varieties of hydrogen are inversely proportional to the square roots of the molecular weights. Appropriate graphs plotted from experimental data for H_2, D_2, and T_2 were used to determine the melting and boiling points of HD and HT, and equations of the type $\log P = A + B/T$ were set up based on these values. Since the molecular weights of HT and D_2 are identical, identical values were

obtained for the corresponding phase transformation temperatures and vapour pressures. As, however, subsequent experimental results [82] showed that at ~20°K the vapour pressure of HT is about 45% greater than that of D_2, the method of calculation employed by Friedman *et al.*[220] is evidently unsound.

According to Babloyantz[221] the difference in thermodynamic properties between HT and D_2 is due to the fact that, while the total mass is identical, its distribution between the two atoms is different. Quantum-mechanical calculation shows that the energy of the ground state is greater for ensembles of heteronuclear molecules than for those of homonuclear molecules, so that the corresponding equations of state are different.

5. INTERPRETATION OF THE NATURE OF THE ISOTOPE EFFECT

The calculations of the isotope effect in vapour pressure by Lindemann's method discussed above also make clear the corresponding interpretation of the nature of this effect with monatomic solids. Since $M_h > M_l$ and $\theta_h/\theta_l = (M_l/M_h)^{1/2}$, the term in Eqn. (85) representing the isotopic difference in zero-point energies is negative, while the integral involving the difference in heat capacities and the logarithmic term in the equation are positive. Hence according to Eqn. (85) a lower vapour pressure of the heavy compared with the light substance is due to the effect of the isotopic difference in zero-point energy and heat capacity on the ratio P_h/P_l predominating over the direct effect of the difference in mass. In other words, a negative isotope effect in the vapour pressure of a monatomic solid is explained by a lower zero-point energy and a greater heat capacity, and thus a greater heat of evaporation of the heavy substance, the zero-point energy being the principal factor at low temperatures.

As mentioned above, calculations by Lindemann's method gave to a first approximation a correct result for the vapour pressure of the isotopes of neon. Corresponding principles and approximations proved to be applicable also to some complicated substances in the solid state, such as varieties of methane and carbon monoxide isotopic with respect to carbon and oxygen. With deuterium and hydrogen at the temperature of the triple point of the latter, however, calculation led to a value of P_h/P_l which was about three times as great as the experimental value. Calculation also proved unsatisfactory for methane and tetradeuteromethane (Table 28), an example of a positive isotope effect. It is therefore clear that some important factors have been ignored in the above explanation of the difference in vapour pressure between isotopic substances.

An original interpretation of a positive isotope effect has been suggested by Bradley[222]. He starts from the dependence of vapour pressure on the entropy and the heat of evaporation, and considers only the translational entropy S_{tr} of the molecules in the vapour. The quantity $(S_h - S_l)$ is then positive, since $M_h > M_l$. The difference in heats of evaporation $(\Delta H_h - \Delta H_l)_e$ is also positive, since it is equated to the corresponding difference in zero-point energies of the quasi-oscillations in the liquid state with the opposite sign $[-(E_{0,h} - E_{0,l})]$. Hence it follows from the equation

$$\ln(P_h/P_l) = (\Delta S^0_h - \Delta S^0_l)_e /R - (\Delta H_h - \Delta H_l)_e /RT, \qquad (97)$$

where S^0 is the entropy when $P = 1$, that P_h can be either greater than or less than P_l depending on the ratio of the absolute magnitudes of the entropy and enthalpy terms.

Bradley further assumes that the zero-point energy considered here can be represented as a sum of zero-point energies of the quasi-oscillations corresponding to interaction between different pairs of atoms in two neighbouring molecules. He also introduces the idea that, with complicated molecules having a central atom, such as CCl_4, $CHCl_3$, and CH_3OH, the intermolecular interaction is governed mainly by the outer atoms, since the central atom is screened by them. Therefore replacement of the central atom by a heavy analogue, *e.g.* substitution of ^{13}C for ^{12}C in the above substances, produces an increase in entropy of the vapour, but does not affect the intermolecular interaction. In such a case the isotopic difference in zero-point energies of the quasi-vibrations should, in Bradley's opinion, be disregarded, so that the difference in heat of evaporation between heavy and light varieties will be zero, with the result that $P_h > P_l$.

In cases of the substitution of a peripheral atom by its heavy analogue, for example, in the replacement of ^{36}Cl by ^{37}Cl in $CHCl_3$ or CCl_4, however, the enthalpy term in Eqn. (97) will, according to Bradley, be numerically greater than the entropy term, so that $P_h < P_l$. The relative difference between these quantities is greater the lighter the peripheral atom which is replaced and the stronger the intermolecular interaction. An explanation on these lines has been given[222] for the experiments of Baertschi *et al.*[143] on the fractionation of CCl_4, $CHCl_3$, C_6H_6, and CH_3OH reported above, in which a positive isotope effect was observed with respect to carbon, but a negative effect with respect to chlorine and oxygen.

However, Bradley's treatment evidently cannot be regarded as satisfactory. Firstly, it does not agree with the experimental results for a number of substances. Thus the postulated decrease in vapour pressure when peripheral atoms are replaced by their heavy analogues contradicts the facts of an increase in vapour pressure when hydrogen is replaced by deuterium in methane, silanes, germanes, halogenated hydrocarbons, and the methyl group of methanol; the assumed increase in vapour pressure when the central atom is replaced by its heavy isotope does not agree with the decrease in vapour pressure accompanying replacement of ^{12}C by ^{13}C in methane, ethylene, and ethane, nor with the similar effect of substituting ^{15}N for ^{14}N in ammonia. Moreover, in the case of substitution of the central atom, when according to the above treatment $(\Delta H_h - \Delta H_l)_e = 0$, it follows from Eqn. (97) that the sign of the isotope effect is independent of the temperature. According, however, to published results[135], the vapour pressure of $^{11}BCl_3$ is lower than that of $^{10}BCl_3$ below 211.5°K, whereas above this temperature the opposite effect is observed.

Secondly, neglect of the isotopic difference in entropy of the liquid, and also of the isotopic difference in zero-point energies of the quasi-oscillations on substitution of the central atom, has no theoretical basis. Finally, as will be shown below, the difference in heats of evaporation of heavy and light varieties of molecules cannot be reduced solely to a difference in the zero-point energies of the quasi-oscillations.

Since the electron shells of isotopes are identical, it is usually considered that the molecular interaction between isotopic molecules is identical. In particular, this assumption has been made in Lindemann's method of calculating

the isotope effect in vapour pressure described above. However, as has been shown[114,223-228], the isotopic difference in the energy of intermolecular dispersion forces is substantial. Baertschi and Kuhn[114] consider that the dispersion energy should be smaller for heavy than for light molecules, since the former show lower infra-red frequencies for the intramolecular vibrations involving isotopic atoms.

According to London[230] the energy of dispersion interaction E_d between two molecules of different type is given by the formula

$$E_d = -\frac{3}{2}\frac{h}{r^6}\sum_{i,k}\alpha_{1,i}\alpha_{2,k}\frac{\nu_{1,i}\ \nu_{2,k}}{\nu_{1,i}+\nu_{2,k}}, \qquad (98)$$

where $\nu_{1,i}$ and $\nu_{2,k}$ are the frequencies of the absorption bands, and $\alpha_{1,i}$ and $\alpha_{2,k}$ the corresponding polarisability components, for molecules 1 and 2. Only absorption bands in the visible and ultra-violet regions are usually considered, since the contribution of other frequencies to the interaction energy is much smaller. We therefore use the simpler formula

$$E_d = -\frac{3}{2}\frac{\alpha_{1,0}\alpha_{2,0}}{r^6}h\frac{\nu_{1,0}\ \nu_{2,0}}{\nu_{1,0}+\nu_{2,0}}, \qquad (99)$$

where $\nu_{1,0}$ and $\nu_{2,0}$ are the mean sums of the optical frequencies, the products $h\nu_0$ being roughly equal to the ionisation potentials of the given molecules, and $\alpha_{1,0}$ and $\alpha_{2,0}$ are the sums of the static polarisabilities associated with the optical frequencies.

Baertschi and Kuhn[114] assume that both these frequencies and the corresponding electron polarisabilities have very similar values in heavy and light varieties of molecules, and can be regarded as identical. It is, however, necessary to take into account the difference in infra-red frequencies if isotopic atoms take part in the corresponding vibrations. When such an infra-red frequency $\nu_{2,R}$ is present in one of the interacting molecules, corresponding to a polarisability $\alpha_{2,R}$, Eqn. (99) is replaced by

$$E_d = -\frac{3}{2}\left[\frac{\alpha_{1,0}\alpha_{2,0}}{r^6}h\frac{\nu_{1,0}\ \nu_{2,0}}{\nu_{1,0}+\nu_{2,0}} + \frac{\alpha_{1,0}\ \alpha_{2R}h}{r^6}\frac{\nu_{1,0}\ \nu_{2,R}}{\nu_{1,0}+\nu_{2,R}}\right]. \qquad (100)$$

Since $\nu_{2,R} \ll \nu_{1,0}$ the second term on the right-hand side of Eqn. (100) is proportional to $\nu_{2,R}$. When the two interacting molecules are identical and have an infra-red absorption which is identical in frequency and intensity, we obtain to a first approximation:

$$E_{h,d} = -\frac{3h}{4}\frac{\alpha_{1,0}^2}{r^6}\left[1+4\frac{\nu_{h,R}\ \alpha_{1,R}}{\nu_{1,0}\ \alpha_{1,0}}\right] \qquad (101)$$

Here $E_{h,d}$ is the energy of dispersion interaction between two heavy molecules, and $\nu_{h,R}$ is their infra-red vibration frequency in question; the corresponding polarisability $\alpha_{h,R}$ for the heavy molecule is regarded as equal to the value $\alpha_{1,R}$ for the light molecule. For two light molecules having an interaction energy of $E_{1,d}$ the quantity $\nu_{h,R}$ in Eqn. (101) is replaced by $\nu_{1,R}$. It is further assumed that the difference in the forces of attraction of heavy and light molecules affects the equilibrium intermolecular distance, and that this causes a difference in the energy of repulsion. The isotopic difference in the quantity E_d is equated, with suitable correction, to the isotopic difference in absolute magnitude of the heats of evaporation, yielding after some rearrangement

$$(\Delta H_h - \Delta H_l)_e = 8(\Delta H_l)_e \cdot \alpha_{1,R}(\nu_{h,R} - \nu_{1,R})/\nu_{1,0}\ \alpha_{1,0}. \qquad (102)$$

It is then assumed[114] that at temperatures well above the Debye characteristic temperature ($\theta = h\nu_D/k$) the effects on the value of P_h/P_l of all factors other than the isotopic difference in dispersion energy cancel out, and this ratio is evaluated from the formula:

$$\ln(P_h/P_l)_R = -(\Delta H_h - \Delta H_l)_e/RT. \qquad (103)$$

Calculated and experimental values of $(P_h - P_l)/P_l$ differ by a factor of 1.5–2. This discrepancy must be explained by the crude approximations made in the calculations, in particular the neglect of the isotopic difference in zero-point energy of the molecular oscillations in the liquid lattice. However, the fact that calculated and experimental results agree in sign and order of magnitude is evidently an important justification for the view that the main reason for the higher vapour pressure of the heavy compared with the light varieties of molecules is the smaller energy of dispersion interaction with the former (Table 29).

It is assumed[114] that above the Debye characteristic temperature a negative isotope effect caused by the difference in zero-point energy of the molecular vibrations decreases as T^{-2}, whereas a positive effect, caused by a difference in van der Waals interaction, decreases as T^{-1} at temperatures below $h\nu_{1,R}/k$. Thus over the range $\theta < T < h\nu_{1,R}/k$ the positive effect decreases with rise in temperature more slowly than does the negative effect, which explains several cases of a change in sign of the isotopic difference in vapour pressure.

According to the treatment of Baertschi and Kuhn[114], the polarisabilities of isotopic substances are identical, which applies to both atom and electron polarisabilities. However, this does not agree with experiment. A difference between α_h and α_l in gases was observed long ago by Larsen[231], and a similar effect has been established for liquids by Rabinovich and Volokhova[224].

The idea of a difference in the dispersion interaction of heavy and light molecules has been developed by us[223-228] using a different theoretical approach to the problem from that of Baertschi and Kuhn[114], and we have been the first to provide a broad experimental basis for this isotopic effect. In particular, we have established that the decrease in dispersion interaction when hydrogen is replaced by deuterium is responsible for the accompanying decrease in electron polarisability[224] and the critical temperature[225] and the increase in compressibility[227].

TABLE 29. Results of calculations based on Eqns. (102) and (103).

Isotope substances	$100(P_h - P_l)/P_l$ at normal b.p.		
	calc. from ref. 114	expt.	ref.
$^{13}CCl_4/^{12}CCl_4$	0.28	0.13	143
$^{13}CS_2/^{12}CS_2$	0.16	0.1	114
$^{11}BCl_3/^{10}BCl_3$	0.6	0.3	135
$^{11}BF_3/^{10}BF_3$	1.2	0.8	13
C_6D_6/C_6H_6	3.5	2.5	129

The present reviewer has suggested the following interpretation of the isotope effect in the vapour pressure of liquids, which, although qualitative, does explain a number of fundamental characteristics of this phenomenon.

It follows from the fact that the free energies of the liquid (L) and the vapour (G) are equal that:

$$\log(P_h/P_l) = -\frac{1}{RT}(\Delta H_h - \Delta H_l)_e + \frac{1}{R}[(S_h^0 - S_l^0)_G - (S_h^0 - S_l^0)_L], \quad (104)$$

where the difference in enthalpy between the equilibrium phases has been replaced by the heat of evaporation ΔH_e, and S^0 is the entropy at $P = 1$. The heat of evaporation can be regarded as the sum of the work of expansion and the energy of intermolecular interaction (in absolute magnitude) less the zero-point energy of the quasi-oscillations of the molecules in the liquid phase $E_{0,q}$. However, the work of expansion is approximately RT for both substances, and is eliminated from Eqn. (104). The interaction energy, in its turn, is the sum of the dispersion, orientation, and polarisation energies and in some cases also the energy of association by means of a hydrogen bond (U_{ass}). As a result, Eqn. (104) becomes

$$\ln(P_h/P_l) = \frac{1}{RT}[\underset{(1)}{(E_{0,h} - E_{0,l})_q} \underset{(2)}{- K'(\alpha_h^{3/2} r_h^{-6} - \alpha_l^{3/2} r_l^{-6})} \underset{(3)}{- K''(r_h^{-6} - r_l^{-6})} - \underset{(4)}{K'''(\alpha_h r_h^{-6} - \alpha_l r_l^{-6})} \underset{(5)}{- (U_h - U_l)_{ass}}] + \frac{1}{R}[\underset{(6)}{(S_h^0 - S_l^0)_G - (S_h^0 - S_l^0)_L}]. \quad (105)$$

Here the dispersion energy (*2*) is expressed by the Slater–Kirkwood formula[229], with $K' = (3eh/8\pi)(n/m)^{1/2}$, h being Planck's constant, e and m the charge and the mass of the electron, n the total number of valency electrons belonging to all the atoms in the molecule, α the static electron polarisability, and r the distance between the molecules. Isotopic differences in the orientation (*3*) and polarisation (*4*) energies are expressed by means of the appropriate well-known formulae of Keesom and of Debye and Falkenhagen: $K'' = -2d_l^4/3kT$ and $K''' = -2d_l^2$, where d is the dipole moment, it being assumed that to a first approximation $d_h = d_l$‡. The individual terms in Eqn. (105) have the following effects on the ratio P_h/P_l.

(a) The Quantity $(E_{0,h} - E_{0,l})_q$

This quantity is always negative, which depresses P_h relative to P_l. The effect of the van der Waals interaction energy — terms (*2*)-(*4*) in Eqn. (105) — depends on the isotopic difference in polarisability and the intermolecular distance.

(b) Isotopic Difference in Polarisability[224]

Since replacement of a light by a heavy isotope involves a decrease in the zero-point energy of the atomic vibrations E_0, whereas the electronic potential energy curve and the force constants of the bonds (f) remain practically unchanged[25,237], the polarisability is diminished. Thus in the simplest case of a diatomic molecule it is found by making certain approximations that the lowering of the vibrational levels in the electronic spectra causes an increase in energy of the electronic transitions (E^e) from the ground (0) to an excited (i) level. By neglecting the difference in electronic energy between light and heavy compounds at the same i levels, and also disregarding the difference in rotational energy, since its absolute magnitude is small compared with the difference in vibrational energy, we obtain

$$\Delta E^e = (E_h^e)_{0,i} - (E_l^e)_{0,i} = (E_{0,l} - E_{0,h})_0 - (E_{0,l} - E_{0,h})_i. \quad (106)$$

For the isotopic difference in E_0 we have approximately, omitting terms of higher order[25,237]:

$$E_{0,l} - E_{0,h} = {}^1/_2 h\nu_{0,l}(1-\zeta) - {}^1/_4 h\nu_{0,l} x_0(1-\zeta^2) = \frac{h}{4\pi}\mu_l^{-1/2} f^{1/2}[(1-\zeta) - \frac{x_0}{2}(1-\zeta^2)], \quad (107)$$

where μ is the reduced mass, x_0 the anharmonicity constant, and $\zeta = (\mu_l/\mu_h)$. Hence it follows from Eqn. (106) that:

$$\Delta E^e = \frac{h}{4\pi}\mu^{-1/2}(f_0^{1/2} - f_i^{1/2}) \cdot [(1-\zeta) - \frac{x_0}{2}(1-\zeta^2)]. \quad (108)$$

Since $f_0 > f_i$, $(1-\zeta)$ and $(1-\zeta^2)$ are positive and of the same order of magnitude, and x_0 is of the order 0.01,[25,237] we have from Eqn. (108):

$$\Delta E^e > 0 \text{ or } \nu_{i,h}^e > \nu_{i,l}^e, \quad (109)$$

where ν_i^e is the frequency of the electronic transition. The relations (109) are probably valid also for a polyatomic molecule. This opinion was apparently held by Ingold *et al.*[128], since they used fundamentally the same arguments as given above for a diatomic molecule, but in a cruder form, to explain the decrease in the polarisability of benzene observed when hydrogen is replaced by deuterium. Urey and Teal[238] explained the smaller polarisability of heavy water compared with ordinary water also by the inequality $\nu_{i,h}^e > \nu_{i,l}^e$. This relation is supported also by spectroscopic data[239-243]. The electron polarisability is given by the formula[244]

$$\alpha = \frac{2}{h}\sum \frac{\nu_i^e P_i^2}{(\nu_i^e)^2 - \nu^2}, \quad (110)$$

where P_i^2 are the probabilities of electron transitions, and ν is the frequency of the incident light. Since the electron shells of isotopic molecules are identical, $P_{i,h}^2 \simeq P_{i,l}^2$. From Eqn. (110) we obtain for the polarisability α_i at level i:

$$\frac{\alpha_{i,h}}{d_{i,l}} = \frac{\nu_{i,l}^e - \nu^2/\nu_{i,l}^e}{\nu_{i,h}^e - \nu^2/\nu_{i,h}^e}. \quad (111)$$

Since $\nu_{i,l}^e < \nu_{i,h}^e$, and for colourless substances $\nu_i^e > \nu$, it follows from Eqn. (111) that $\alpha_{i,h} < \alpha_{i,l}$. In view of this, it is probable that in general

$$\alpha_h < \alpha_l. \quad (112)$$

This has been confirmed experimentally: it has been shown that replacement of hydrogen by deuterium in hydrocarbons and their nitro- and halogeno-derivatives, water, alcohols, and acids, produces a decrease in the electron polarisability of a few tenths of 1%, depending on the number of atoms substituted[224].

(c) and (d) Isotopic Difference in Intermolecular Distances[226]

The decrease in the zero-point energy of the molecular vibrations on replacement of a light isotope by a heavy iso-

‡ The isotopic difference in the energy of repulsion of the molecules is neglected.

tope causes a decrease in molar volume, *i.e.* in the intermolecular distance r. This has been proved rigorously by London[245] for monatomic and diatomic substances in the solid phase, and also by Schäfer[246] for solid hydrogen in particular. The effect has been observed experimentally with the pairs H_2–D_2,[74] ^{6}Li–^{7}Li,[247] ^{6}LiF–^{7}LiF,[248] NaH–NaD, KH–KD, and LiH–LiD.[249] An increase in mass of the particles should cause a decrease in molar volume in the liquid phase as well, since here, too, vibrations play the main part in molecular motion. The isotopic change in r should be especially large for substances of low molecular weight at low temperatures, *e.g.* for helium and hydrogen, with which the zero-point energy of the quasi-oscillations and also its isotopic difference form a large fraction of the total energy of these vibrations§. According to the experimental data, the molar volume of ^{4}He at 2°K is 29% less than that of ^{3}He, and with D_2 at 20°K the molar volume is 17% lower than with H_2.[250] On the other hand, since intermolecular dispersion forces depend on the electron polarisability, it may be supposed from Eqn. (112) that these forces will become weaker when a light isotope is replaced by a heavy one, and this will increase the distance between the molecules. However, the isotopic increase in r evidently predominates over its decrease only at elevated temperatures, when the influence of the zero-point energy of the quasi-vibrations of the molecules is insignificant. Thus at about 300°K the molar volumes (V) of C_6D_6 and C_6D_{12} are still 0.2–0.3% smaller than those of C_6H_6 and C_6H_{12} respectively[251].

With substances which are associated by hydrogen bonds an additional factor enters into the isotopic change in r. As pointed out by Samoilov[253,254], even in solids, when the closeness of packing of the atoms is low it can be increased by introducing some disorder into their arrangement. Such a phenomenon is especially probable with molecular liquids. In them, formation of a lattice or other ordered arrangement is evidently associated with increasing deviations from the closest packing of the molecules, and consequently with some expansion. Water represents a clear example of such behaviour. Because of this, an increased degree of association when the hydrogen forming the hydrogen bond is replaced by deuterium can cause some increase in the mean intermolecular distance. This is supported by the experimental results: such substitution produces an increase in molar volume in water[162], hydrogen peroxide[255], methanol[256], and other alcohols[226] even in the vicinity of 300°K, far below the corresponding critical temperatures.

(e) Isotopic Difference in Energy of Association[236]

Substitution of deuterium for hydrogen forming a hydrogen bond produces a decrease in the zero-point energy of the vibrations corresponding to this bond. With a characteristic frequency of 175 cm^{-1}, for the OH ... O bond[257], for example, an approximate calculation shows that $\Delta E_0 = E_{0,H} - E_{0,D} = 3 \times 10^{-16}$ erg per molecule. Further, very roughly:

$$\bar{n}_D/\bar{n}_H = e^{(U_H - U_D)/kT} = e^{-\Delta E_0/kT}, \qquad (113)$$

where n is the number of molecules remaining unassociated and U the energy of the bond. According to data of Oster and Kirkwood[258], the mean number of hydrogen bonds linking a molecule in a chain is about 1.4 for monohydric alcohols from methanol to pentanol; in the three-dimensional network of water at about 300°K each molecule has on the average ~2 hydrogen bonds[259,260]. Assuming that the number of "unruptured" bonds exceeds the number of "ruptured" bonds by a factor of at most a few units¶, we find that replacement of hydrogen by deuterium produces an increase in the energy of association of a few tens of calories per mole. On the basis of Swain and Bader's work[252] it can be supposed that in several cases a considerably greater difference in the intermolecular energy of isotopic associated substances can be caused by a difference in the rotational frequencies of their molecules. Statistical calculation[252] has shown that the difference in libration frequencies of the molecules H_2O (three frequencies each of 667 cm^{-1}) and D_2O (483 cm^{-1}) corresponds to a difference in enthalpy between these substances of several hundred calories per mole. This is confirmed by the fact that the heat of evaporation is about 100 cal mole^{-1} greater with monohydric deuteroalcohols than with their hydrogen analogues[148,150,151] and it is 330 cal mole^{-1} greater with heavy water than with ordinary water (at 25°)[162]. An increase in the degree of association of alcohols on replacement of the hydroxyl hydrogen by deuterium has been shown also by cryoscopic measurements[263], by data on the isotope effect in viscosity[236], and by spectroscopic data[262].

(f) Entropy Component

The component entropies due to the various forms of motion in the vapour and the liquid are increased when a light isotope is replaced by a heavy isotope, since both the masses and the moments of inertia of the molecule are increased, and the frequencies of the atomic and molecular vibrations are decreased. However, entropy terms relating to atomic vibrations can, to a first approximation, be eliminated from Eqn. (105) if the difference in frequencies between identical atoms in the vapour and in the liquid is neglected. In view of this, it can be supposed that the isotopic difference in entropy of motion of the molecules in the liquid has been subtracted from the corresponding difference for the vapour phase in term (6) of Eqn. (105). It is possible that, to a first approximation, these differences have similar values, and practically balance one another, as has been assumed[114]. However, it is also probable that the isotopic difference in entropy is appreciably greater for the vapour than for the liquid, and this, according to Eqn. (105), will cause some increase in P_h relative to P_l.

The joint influence of the above factors (a)–(f), with their varying dependence on the temperature, the nature of the substance, the mass of the molecule, and the number and mass of the isotopic atoms, results in the isotope effect in vapour pressure manifesting itself in a variety of ways. With substances of low molecular (atomic) weight at low temperatures, when r_h is considerably smaller than r_l, the decrease in intermolecular distance on substitution of a light by a heavy isotope affects the dispersion energy

§ The zero-point energy of liquid ^{4}He is about 50–70 cal mole^{-1}, while its actual thermal energy at the critical temperature (5.2°K) is only ~10 cal mole^{-1}. The rather lower value of r_h compared with r_l is probably due to the fact that the vibrations are less anharmonic with the heavy than with the light molecules.

¶ In water, for example, 10–15% of the hydrogen bonds have already been ruptured on melting[254,261], and the number of ruptured bonds increases with rise in temperature.

to a greater extent than does the decrease in polarisability†. Therefore the terms (2)–(4) in Eqn. (105) are positive and, like term (1), cause a decrease in P_h relative to P_l.

If the entropy term in Eqn. (105) is assumed to be small compared with the enthalpy terms, a comparatively large negative isotope effect in the vapour pressure ($P_h < P_l$) should be observed with a low molecular weight at low temperatures. This is confirmed experimentally in the cases of hydrogen and helium (Tables 1 and 4). This also explains the negative isotope effect with other non-associated substances at comparatively low or reduced temperatures.

Since at an absolute temperature of a few hundred degrees $r_h \simeq r_l$ or $r_h > r_l$,[226] it follows from Eqn. (112) that the terms (2) and (4) in Eqn. (105) are negative, while term (3) is negative or close to zero. Hence the terms (2)–(4) and perhaps also (6) in Eqn. (105) cause an increase in P_h relative to P_l, whereas term (1), as before, affects the vapour pressure in the opposite direction. Consequently, at such temperatures the sign of the isotope effect in the vapour pressure of non-associated substances depends on the relative absolute magnitudes of terms (2)–(4) and (1) in Eqn. (105), and both $P_h > P_l$ and $P_h < P_l$ are possible. Since the role of vibrations in the thermal motion of molecules in a liquid diminishes rapidly with rise in temperature‡, the relation $P_h < P_l$ should be observed at lower temperatures than $P_h > P_l$, with respect to the same isotopes in the same substance. Every substance should have a temperature above which $P_h > P_l$, provided that this transition does not lie above the critical point. As has been shown in section A of the present review, all this has been established experimentally for a number of substances.

The above treatment of the isotopic difference in vapour pressure can be used to give a qualitative explanation of the occurrence of opposite effects for different isotopic substitutions in the same substance, such as the cases of chloroform and carbon tetrachloride described above, in which $P_h > P_l$ with respect to ^{12}C–^{13}C but $P_h < P_l$ with respect to ^{35}Cl–^{37}Cl (Table 20). With these substances, isotopic substitution of a chlorine atom produces a change in the zero-point energy of one atomic vibration, but substitution of carbon affects four such vibrations, each of them being associated with a greater change in E_0 than in the case of the chlorine isotopes. In view of Eqns. (106)–(111) it can be assumed that replacement of ^{12}C produces a greater decrease in electron polarisability, and hence a greater reduction in the intermolecular dispersion energy, a factor which tends to raise the vapour pressure. On the other hand, the decrease in zero-point energy of the quasi-oscillations of the molecules, a factor tending to lower the vapour pressure, is greater on isotopic replacement of ^{35}Cl than when ^{12}C is replaced.

In another case, that of isotopic substitutions in liquid methane, the experimental results relate to temperatures of 90°–110°K, which are considerably lower than in the cases of CCl_4 and $CHCl_3$. Therefore the decrease in the zero-point energy of the quasi-oscillations of the molecules plays a greater part with methane, and replacement of ^{12}C by ^{13}C still produces a decrease in vapour pressure, but this effect diminishes with rise in temperature. When, however, a hydrogen atom is replaced by deuterium, the decrease in zero-point energy of the corresponding atomic vibration is much greater, while the decrease in zero-point energy of the quasi-oscillations of the molecules is the same as for the isotopic replacement of carbon, and $P_h < P_l$ up to about 97°K, whereas above this temperature $P_h > P_l$. When all four hydrogen atoms are replaced by deuterium, the relation $P_h > P_l$ is already observed above 75°, up to the melting point (Table 11 and Fig. 3).

It has been shown above that the energy of association, term (5) in Eqn. (105), is increased by substitution of deuterium for the hydrogen forming a hydrogen bond by which a substance is associated in the liquid phase, while its vapour is monomeric, and the heat of evaporation is thereby increased by tens of calories per mole. This effect is opposite in sign to the isotopic change in van der Waals interaction energy, and can be shown to be several times greater than the latter in absolute magnitude. In this way term (5) affects the vapour pressure in the same direction as term (1) and, taking into account the above remarks on the role of the entropy term in Eqn. (105), we find that $P_h < P_l$ over the temperature range within which association persists in the liquid phase. This explains the decrease in vapour pressure when hydrogen is replaced by deuterium in water, ammonia, the hydroxyl groups of alcohols, the amino-group of aniline, and in other similar cases (Fig. 13). This interpretation is confirmed by the fact that substitution of deuterium for the methyl hydrogen in methyl alcohol produces the opposite effect — an increase in vapour pressure[148].

With rise in temperature the degree of association decreases and consequently the influence of association on the isotope effect should also diminish. This will explain the fact that with heavy and ordinary water $P_h < P_l$ only up to 225°, whereas the opposite relation is observed above this temperature. It is evident that above 225° water is hardly, if at all, associated. Similar temperatures at which $P_h > P_l$ as with non-associated substances, can probably be found for alcohols and amines in which the hydrogen forming a hydrogen bond is replaced by deuterium. Bernal and Fowler[265] have shown that in a number of cases the dissolution of electrolytes in water has a similar effect on its structure to that of a rise in temperature. It is now clear[254] that such electrolytes produce a decrease in the activation energy for the passage of molecules from one equilibrium position to another, which is equivalent to an increase in the number of hydrogen bonds ruptured. Solutions of these substances in ordinary and heavy water should therefore have a lower temperature of intersection of the vapour pressure curves than have the pure solvents. In other words, dissolution of appropriate electrolytes should lower the temperature above which the relation $P_h > P_l$, characteristic of non-associated substances at moderate and elevated temperatures, is observed for D_2O and H_2O. Phenomena which confirm this experimentally[168] have been described in section A of the present review. In cases in which hydrogen forming a hydrogen bond is replaced by deuterium in compounds which show considerable association in the gas phase as well, consideration

† As Schäfer[246] has shown, owing to the greater distance between H_2 molecules compared with D_2 molecules, the interaction energy at $T = 0$ is −460 cal mole^{-1} for H_2, whereas it is −520 cal mole^{-1} for D_2 (its value at the potential-energy minimum is −560 cal mole^{-1}). If the zero-point energy of $9R\theta_D/8$, ~ 235 cal mole^{-1} for H_2 and ~ 215 cal mole^{-1} for D_2, is added to the above energy, almost correct values are obtained for the heats of sublimation at $T = 0$; 225 and 305 cal mole^{-1} for H_2 and D_2 respectively.

‡ According to Frenkel'[264], $\tau = \tau_0 U/kT$, where τ is the duration of the vibrations of the molecule between two transitions from one position of equilibrium to another, τ_0 is the period of the vibrations, and U the activation energy of the transition.

must be given to the combined effects of two factors: (1) an increase in the energy of rupture of the hydrogen bond, and (2) a decrease in the proportion of associated complexes which decompose on evaporation. The first of these factors, by increasing the heat of evaporation, produces a decrease in vapour pressure; whereas the second factor, which is a consequence of the first, by decreasing the heat of evaporation produces an increase in vapour pressure. Since the proportion of aggregates decomposed depends exponentially on the bonding energy, the effect of the second factor should predominate. This is confirmed by experiment: with carboxylic acids containing deuterium in the carboxyl and with hydrogen fluoride it is found that $P_h > P_l$ at all the temperatures investigated. The fact that the curve showing the variation with temperature of the ratio P_h/P_l for acids passes through a maximum (Fig. 11) can be explained by the temperature dependence of the degree of association in the vapour§.

Such a treatment of the isotope effect in carboxylic acids is also supported by the fact that, as Potter *et al.*[268] have calculated from experimental data on the temperature dependence of vapour density, the heat of dimerisation of CD_3COOD is about 300 cal mole^{-1} greater than that of CH_3COOH, while the dimerisation constant in the vapour at 120° is 1.17 times greater in the former than in the latter compound.

§ The strengthening of a hydrogen bond when the hydrogen is replaced by deuterium, and also the reason for the accompanying change in vapour pressure of alcohols and acids, were first pointed out by Lewis and his coworkers[266,267].

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NEW METHODS FOR SYNTHESIS OF THERMALLY STABLE POLYMERS HAVING RINGS IN THE CHAIN

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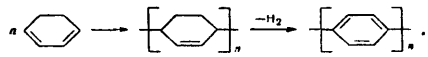
Various thermally stable polymers are required for wide application in modern technology. Most of the known polymeric materials have a low thermal stability. Research on the synthesis of polymers stable to high temperatures is therefore being expanded and new methods are being discovered. One of the possible ways of making heat-resistant polymers which are also thermally stable is to synthesise polymers containing homocyclic (carbon) and heterocyclic rings in the main chain[1,2]. Progress in the last two years on the synthesis of new heat-resistant and thermally stable polymers, having rings in the main chain, is reviewed here.

I. POLYMERS HAVING BENZENE RINGS IN THE MAIN CHAIN

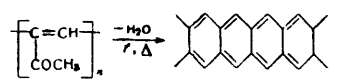
Recent work has shown conclusively that polymers constructed only of benzene rings have very high thermal stability. Such polymers, obtained by polycondensation and polymerisation are, as a rule, of low molecular weight. Marvel and Hartzell[3] attempted to obtain high-molecular-weight polyphenylene, starting from polycyclohexadiene. With a Ziegler catalyst 1,3-cyclohexadiene gave a linear polycyclohexadiene soluble in benzene and with molecular weight ~10 000. This polymer was converted, by dehydrogenation with chloranil, to polyphenylene, which does not melt up to 530° in a nitrogen atmosphere:



The polymer was heated in air at 230°–240° for 72 h without noticeable change.

Replacement of all the hydrogen atoms in polyphenylene by fluorine gives polyperfluorophenylene[4] which has even greater thermal stability.

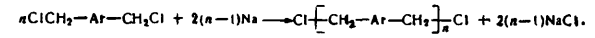
Nesmeyanov *et al.*[5] observed an interesting polycondensation of 1-chlorobut-1-ene-3-one to a polymer, which on further heating *in vacuo* underwent cyclopolymerisation (with loss of water) to form a polymer of the acene series, which had high thermal stability and interesting magnetic and electrical properties:



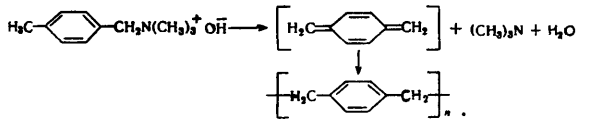
Polymers constructed entirely of benzene rings have high thermal stability but are brittle, so that their practical use is hindered. New methods have appeared, in recent years, for the synthesis of polymers having flexible elastic links (CH_2, S, O, etc.) in the main chain as well as benzene rings. There are, for example, the reactions of perarylation[6], polyrecombination[7], migration polymerisation of aromatic hydrocarbons with two isopropenyl groups[8], cyclic polymerisation[9,10], and reactions in macromolecular chains[11].

Poly-*p*-xylylene, which has high thermal stability and satisfactory mechanical properties, attracted attention long ago, but until recently there were no good reproducible methods for its synthesis or that of its analogues. Vansheidt *et al.*[12] used the Wurtz reaction for this purpose; the reaction of sodium metal with bischloromethyl derivatives of

aromatic hydrocarbons in dioxan at 25° yielded polycondensation products as white powders with various degrees of crystallinity:

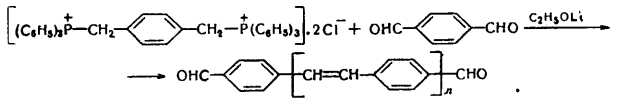


Young showed[13] that macromolecular poly-*p*-xylylene can be obtained in good yield (80%) from the reaction of 50% aqueous solutions of *p*-methylbenzyltrimethylammonium bromide (or chloride) with sodium hydroxide:

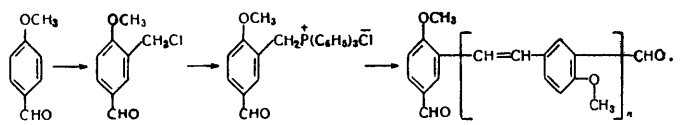


The poly-*p*-xylylene so obtained dissolves readily in chlorinated paraffins or benzyl benzoate, forming, at 300°, solutions with intrinsic viscosity $[\eta] = 1.0-2.0$.

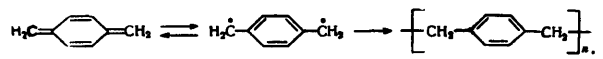
McDonald and Campbell[14] used the Wittig reaction for the synthesis of poly-*p*-xylylidene and its analogues. The reaction of *p*-xylylenebis(triphenylphosphonium) chloride with terephthalic aldehyde in the presence of lithium ethoxide gives poly-*p*-xylylidene, which is yellow and melts above 400°:



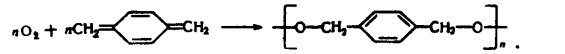
Similarly, starting from anisaldehyde, a poly-*p*-xylylidene with m.p. about 180° and intrinsic viscosity $[\eta] = 0.31$ was obtained:



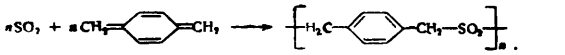
Errede *et al.*[15] developed an original method for obtaining solutions of *p*-xylylene in hexane. Pyrolysis of *p*-xylene at 1000° *in vacuo* gives the *p*-xylylene pseudoradical which is introduced into the solvent at -78°. Under these conditions the *p*-xylylene does not lose its reactivity for a long time. At -78° its half-life is 22 h, but at -36° it exists for only 12 min. When a solution of *p*-xylylene is kept for a very long time at -78°, polymerisation takes place to form poly-*p*-xylylene with molecular weight 200 000 and more:



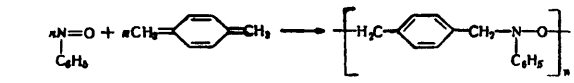
In hexane solution at -78° *p*-xylylene is very active and forms copolymers[16]. With oxygen it gives a polymeric peroxide which decomposes explosively at 100°:



Copolymerisation of *p*-xylylene and SO_2 takes place easily to form an insoluble copolymer, which can be melted at 200° under 500 atm pressure giving transparent flakes:

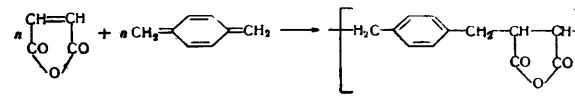


p-Xylylene forms copolymers with various nitroso--compounds (*e.g.* nitrosobenzene, *p*-nitroso-*NN*-dimethylaniline, α-nitroso-β-naphthol) which have interesting compositions and properties:



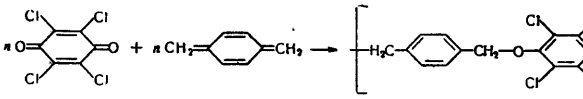
These are soluble in organic solvents and melt or soften at 200°.

p-Xylylene also gives copolymers with maleic anhydride, diethyl maleate, diethyl fumarate, acrylonitrile, n-butyl acrylate, and styrene:

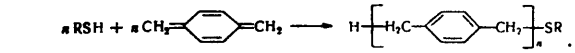


All of them are thermoplastic.

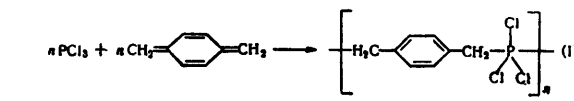
An interesting copolymer is that of *p*-xylylene and chloranil, with softening point 195°–200°:



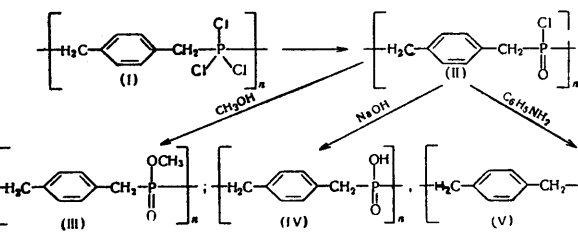
With mercaptans, macromolecular telomers are formed:



The copolymerisation of *p*-xylylene and PCl_3 is unusual, polymers having phosphorus atoms in the principal chain being produced[17]:



Under the influence of moisture, polymer (I) easily loses two chlorine atoms to form polymer (II); when treated with methanol this forms the polymeric ester (III), softening point 150°, which can be compressed to transparent films. When polymer (II) is treated with alkali, a salt is obtained, and hence the corresponding polymeric acid (IV), which can be used as an ion-exchange resin. Polymeric amides (V) are obtained by treating polymer (II) with aniline or hexamethylene diamine:

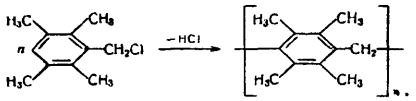


Similar reactions take place easily between *p*-xylylene and the compounds PBr_3, PI_3, $C_6H_5PCl_2$, and $(C_6H_5)_2PCl$, but not $POCl_3$ and $(C_6H_5)_3P$.

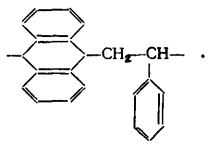
Preparation of poly-*p*-xylylene from *p*-chloromethyltoluene has been proposed[18], by passing the latter, at 102°

and reduced pressure, through a gypsum tube heated to 750°; the polymer is deposited in a receiver, in 65% yield.

A highly branched polybenzyl was obtained by polycondensation of benzyl chloride. Polycondensation of chloromethyldurene in the presence of a ferric oxide catalyst at 100° gives[19] a polymer with m.p. 260°–280°:

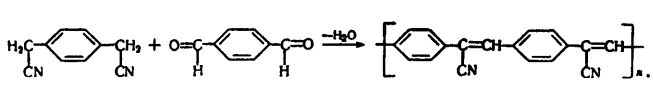


Imoto[20] states that the copolymer of anthracene and styrene had high thermal stability:

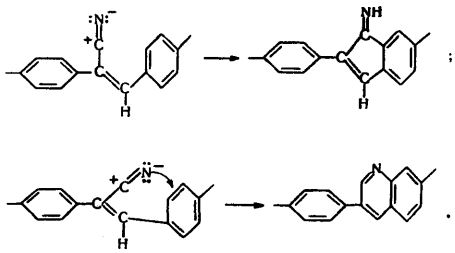


On heating to 305° for 4 h, the loss in weight amounted to 5.5–13.1%.

The polymer of acenaphthylene (M = 200 000), obtained in the presence of the boron trifluoride ether complex, undergoes no change on heating to 280°. Lentz and Handlovits[21] have developed a method of preparing polycyanoterephthalidene by the condensation polymerisation of α,α'-dicyano-p-xylene and terephthalic aldehyde:

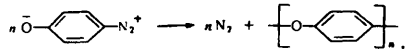


Polycyanoterephthalidene is insoluble, infusible, and has exceptional thermal stability. On heating to 450° for 3000 sec, the polymer loses ~15% of its weight, and ~25% on heating to 500° for 6000 sec. The infra-red spectra of the polymers heated at 450° and 500° differ from those of the original polymers. Possibly cyclisation occurs to form an iminoindene structure or a quinoline residue in the chain:

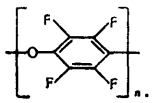


The thermal stability of the polymer increases after heating at 550°; when heated again at this temperature for 30 min, it loses not more than 2% in weight.

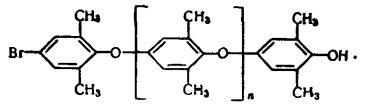
Polymers are known which contain an etheric oxygen atom, –O–, in the chain as well as rings. An interesting method for their preparation is the decomposition of derivatives of benzene-1,4-diazooxide:



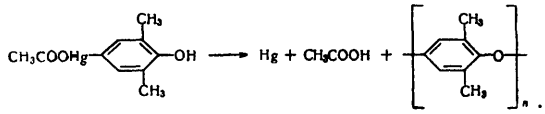
Dewar and James[22] showed that, in the thermal decomposition of 3,5-dibromobenzene-1.4-diazooxide in chlorobenzene solution at 70°, nitrogen is liberated and a polymer with softening point 200°–220° is formed. Decomposition of tetrafluorobenzene-1,4-diazooxide gives, similarly, the elastomer[23]



Staffin and Price[24] used 2,6-disubstituted phenols to obtain macromolecular 2,6-disubstituted p-phenylene ethers. A benzene solution of 2,6-dimethyl-p-bromophenol was shaken at room temperature with alkali in the presence of lead dioxide as oxidising agent to give the polymer

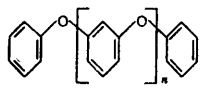


This polymer is soluble in organic solvents, its intrinsic viscosity [η] is 0.43 and softening point 260°. It has a rigid chain structure and possesses great thermal stability. According to Madorskii's data[24], the loss in weight on heating at 320° for 30 min amounted to 1%, 13% at 370°, and 69% at 420°. Attempts were made to obtain the same polymer by decomposing 4-(acetoxymercury)-2,6-dimethylphenol at 200°:



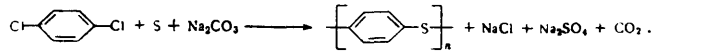
Only 12% of soluble polymer was obtained, the major part having a cross-linked structure.

Phenoxypoly(m-phenoxylene)benzenes with great thermal and radiation stability were obtained by Ullman's method[25]:

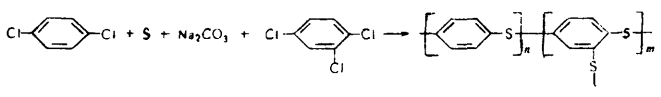


The polymers with a low degree of polymerisation (n = = 2 to 5) are high-boiling liquids (b.p. 463°–650°), useful as lubricating oils.

Polymers are also known with sulphur atoms, –S–, in the main chain as well as rings. Lentz and coworkers[26] described a new method of producing thioether polymers by the high-temperature (250°–350°) condensation of polyhalogenoaromatic compounds with alkali or alkaline-earth sulphides:



Linear crystalline poly(phenylene sulphide) had m.p. 285°. Linear, soluble or cross-linked, insoluble polymers with great thermal stability at 400°–500° and resistance to chemical reagents are obtained similarly:



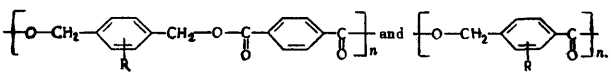
Organoarsenic polymers have also been synthesised[27]; they are prepared by the reaction of dilithium aromatic

derivatives with aromatic chloroarsines. Most of these polymers are soluble in alcohol and ether. The polymers synthesised and their properties are listed in the Table.

Korshak and Vinogradova[28] and Conix[29] described the preparation of various polyesters from dibasic aromatic acids and bisphenols. Aromatic polyesters have very great thermal stability (up to 500°), high solubility, and are capable of forming films.

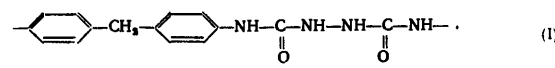
Another group of polymers with high thermal stability and fibre-forming properties are aromatic polyanhydrides[30]. Those of terephthalic acid are especially stable, decomposing above 400°. They are resistant to concentrated acids and *aqua regia*.

Mitin *et al.*[31] carried out polymerisation of aromatic dialdehydes by the Cannizzaro–Tishchenko reaction in non-aqueous medium. In the presence of aluminium ethoxide as catalyst terephthalic aldehyde in the melt forms a transparent amorphous linear polymer, soluble in chloroform, with molecular weight 100 000 to 120 000 (determined by light scattering):



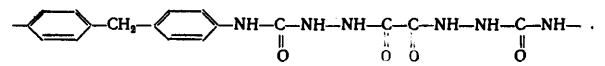
The m.p. of the polymers of some aromatic dialdehydes are: terephthalic aldehyde 120°, isophthalic aldehyde 80°, 2,5-dimethylterephthalic aldehyde 140°, and 4,4′-diformylbiphenyl 250°.

Starting from diisocyanates and dihydrazides or hydrazine, Campbell and coworkers[32] obtained new polymers containing benzene rings in the chain. The reaction of methylenebis-*p*-phenylene diisocyanate with hydrazine hydrate in dimethylformamide solution gives a transparent viscous solution of polymer (I) with the structure:

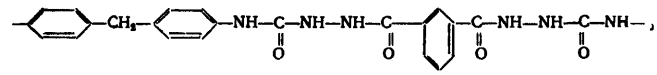


(I)

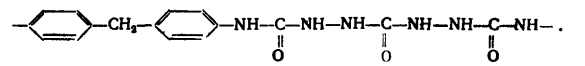
The polymer forms tough flexible films and fibres stable up to 300°. It is stable to the action of light: after 200 h exposure, the film remains tough and flexible. When (I) reacts with oxalyl dihydrazide in dimethyl sulphoxide solution, a polymer with an unusual link structure is obtained:



From a solution of such a polymer, tough films showing 200% elongation at 200° and stable up to 270° can be obtained. Isophthalyl dihydrazide condenses easily with (I) in dimethyl sulphoxide solution to form the polymer

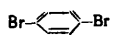
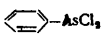
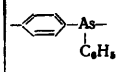
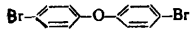
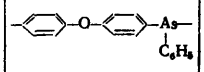
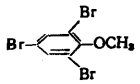
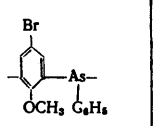
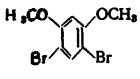
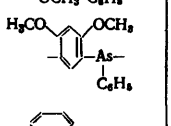
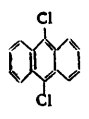
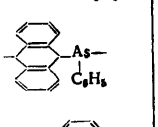
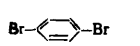
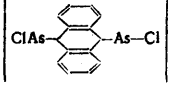
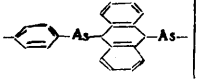


which has an intrinsic viscosity, $[\eta]$, of 1.7 and gives tough films with 31% elongation at rupture, and melting at 250°. Carbonyl hydrazide $NH_2NHCONHNH_2$ reacts easily with (I) forming a polymer with the structure



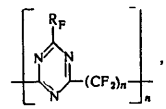
Its intrinsic viscosity, $[\eta]$, is 0.33 and it melts with decomposition at 260°. A polymer with greater thermal stability and a higher degree of polymerisation is obtained in the reaction of carbonyl hydrazide with 3,3′-dimethyl-4,4′-biphenylene diisocyanate; it has an intrinsic viscosity. $[\eta]$, of 1.46, and m.p. 280°.

TABLE. Synthesis and properties of arsenic-containing polymers.

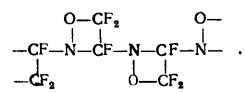
Aromatic halogen compound	Chloroarsine	Polymer	M.p. of polymer, °C	Mol. wt. of polymer
			40	6000
	»		140	2000
	»		300	2000
	»		220	1900
	»		270	2000
			250	13 300

II. POLYMERS HAVING HETEROCYCLIC RINGS IN THE MAIN CHAIN

Polymers containing no hydrogen, which possess great chemical and thermal stability, are very interesting. By the condensation of perfluoroamidines and perfluorodiamidines, Brown[33] obtained elastomers with triazine rings and CF_2 groups in the main chain:



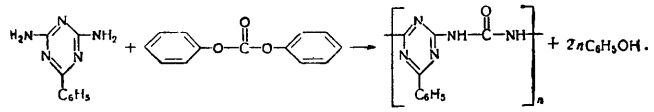
where R_F is perfluoroalkyl. The elastomer is stable at 350°–410° and loses weight (30–50%) only when kept at 470° for 30 min. It possesses exceptional chemical stability: its main properties did not change after it had been boiled with fuming nitric acid for 24 h. In the polymerisation of trifluoronitrosoethylene $CF_2=CF-N=O$, Griffin and Haszeldine[34] observed the formation of poly(perfluoro-1,2-isooxazetidin-2,3-ylidene) with the unusual chain structure



When heated for 2 h at 400°, the elastomer changed into a solid yellow polymer with liberation of carbonyl fluoride:

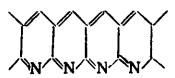
$$=CF-N=CF-N=CF-N= \cdot$$

A polymer with very high thermal stability is obtained[35] by polycondensation of diaminophenyltriazine with diphenyl carbonate:



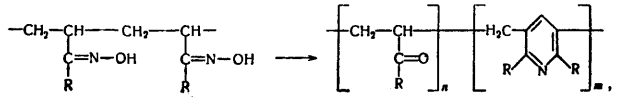
It is soluble in sulphuric acid and melts at 350°.

By a special heat treatment of polyacrylonitrile, Topchiev and coworkers[36] obtained a cyclic polymer with the structure



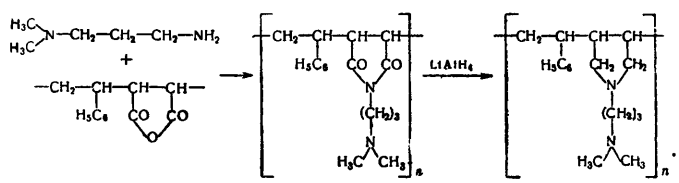
Polymers of this type have exceptional thermal stability; they do not burn when introduced into a flame, and they possess interesting semiconductor properties.

Under the action of an alcoholic solution of hydrogen chloride, ketoximes of poly(methyl vinyl ketone) and poly(phenyl vinyl ketone) form[37] a copolymer which has pyridine, as well as ketone, residues in the main chain:

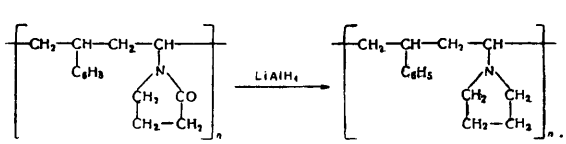


where R is methyl or phenyl. The copolymers are soluble in chloroform, with intrinsic viscosity $[\eta] = 0.11-0.14$. They are thermally stable, losing ~3% in weight when heated at 225° for 12 h.

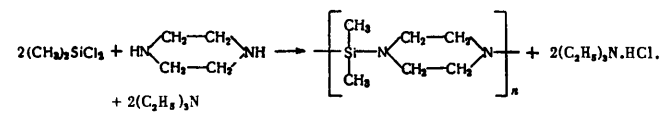
Reduction of some copolymers with lithium aluminium hydride produces new copolymers containing pyrrolidine residues in the main chain[38]. The copolymer formed by the reaction of γ-dimethylaminopropylamine and the copolymer of styrene with maleic anhydride, when reduced with lithium aluminium hydride, gives a copolymer of a substituted pyrrolidine:



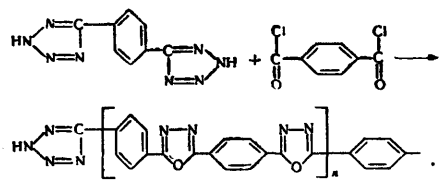
The copolymer of styrene and vinylpyrrolidone is also easily reduced to a copolymer of styrene and vinylpyrrolidine:



The reaction of dimethyldichlorosilane with piperazine in ether, in the presence of triethylamine as catalyst, gives a polymer with silicon atoms and piperazine rings in the main chain[39]:

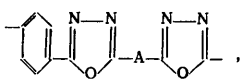


Marvel and coworkers[40] synthesised polymers containing oxadiazole, thiazole, triazole, and benzoimidazole rings in the chain. Those containing oxadiazole are formed when bis(tetrazolyl)benzenes are boiled in pyridine with diacyl chlorides. *p*-Bis(tetrazolyl)benzene and terephthaloyl chloride give a polymer soluble only in concentrated sulphuric acid:



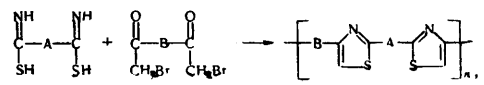
where n is 17–50. This polymer has high thermal stability; the loss of weight when it is heated for 12 h at 350° does not exceed 10%.

Polymers having repeated oxadiazole rings interlinked by aliphatic or aromatic groups (A) are thermally very stable. For example, the polymer

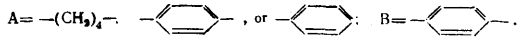


with A = $(CH_2)_7$ is soluble and its formic acid solution yields brittle films. It is thermally stable and softens at about 270°.

Polymers containing the oxazole ring were obtained from bis(tetrazolyl)benzene and pyridine-2,6-dicarboxylic acid; they are black, soluble in formic acid and phenol, and their solutions yield brittle films. The weight loss of the polymer on heating in the air for 12 h at 350° was ~28%. Introduction of triazole rings into the polymer chain raises the solubility of the polymers[41]. The polymers, obtained by the reaction of bis(tetrazolyl)benzene with *NN'*-diphenylisophthaloyliminochloride, are black and soften at 235°–300°. Marvel introduced the thiazole ring into the polymer chain by condensation of the corresponding dithioamides with bis(α-bromoketones):



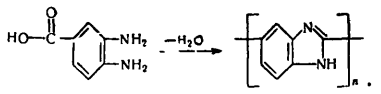
where



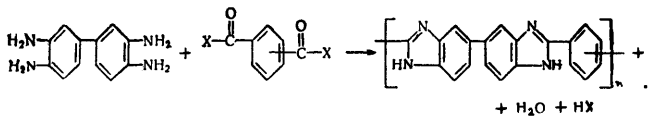
These polymers are thermally very stable up to 300°.

Polymers having benzoimidazole rings in the main chain possess exceptionally high thermal stability; this is apparently connected with the aromatic nature of the benzoimidazole rings. Marvel and coworkers[43] developed methods for the preparation of polybenzoimidazoles and a

series of model compounds. Condensation of 3,4-diaminobenzoic acid in boiling sulphuric acid produces green poly-2,5(6)-benzoimidazole, soluble only in concentrated sulphuric acid and unstable when heated to 350°:

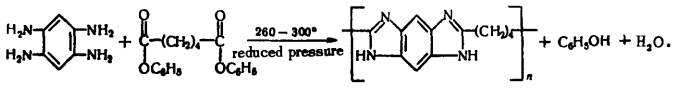


Polybibenzoimidazoles have recently been obtained by the reaction of *oo'*-diaminobenzidine with diphenyl esters of dicarboxylic acids:



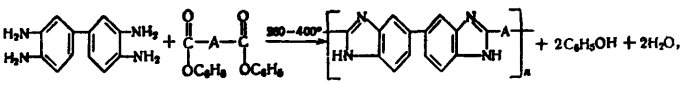
where X = OC_6H_5. Solutions of the poly[2,2'-(*p*-phenylene)--5,5'-bibenzoimidazole] so obtained, a yellow powder soluble in formic acid and concentrated sulphuric acid, yield brittle films. It has great thermal stability, losing 2% in weight when heated for 7 h at 350° in a nitrogen atmosphere. Poly[2,2'-(*m*-phenylene)-5,5'-bibenzoimidazole], yellow and more flexible than the *p*-isomer, also has high thermal stability.

Among other polymers with heterocyclic rings in the main chain, the polydiimidazobenzenes are of interest. The general method for their synthesis can be demonstrated by the example of poly(2,6-tetramethylenediimidazobenzene):



They are bluish grey and their solutions in formic acid yield transparent films.

Interesting properties are possessed by poly[2,2'-(3,3'--pyridylene)-5,5'-bibenzoimidazole] and poly[2,2'-(2,2'--furylene)-5,5'-bibenzoimidazole], prepared by the general method.



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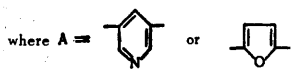
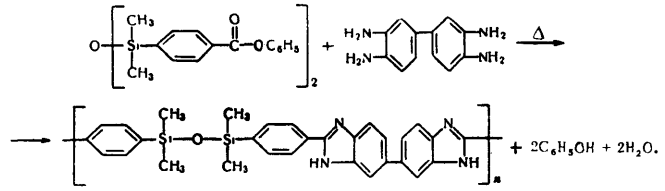


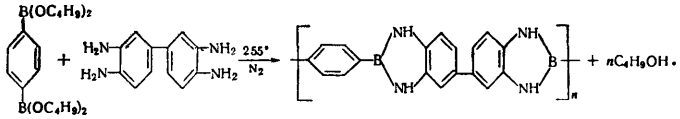
Poly[2,2'-(3,3'-pyridylene)-5,5'-bibenzoimidazole] has very great thermal stability; weight is lost only on heating to above 500°. In contrast to other *m*-phenylene polymers, it displays some crystallinity. Poly[2,2'-(2,2'-furylene)-5,5'--bibenzoimidazole] is orange and softens at 480° with a little decomposition.

Siloxane derivatives of benzoimidazole polymers were obtained[42] in the reaction of *oo'*-diaminobenzidine with a diphenyl ester of a disiloxane:



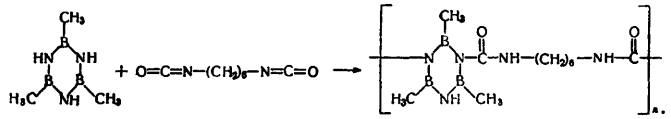
The polymer is soluble in formic and concentrated sulphuric acids, has high thermal stability, and melts above 420°–450°.

The borimidazoline polymer[42], obtained in the reaction of tetrabutyl benzene-1,4-diboronate with *oo'*-diaminobenzidine, has very interesting properties:

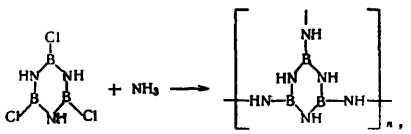


It is soluble in sulphuric acid and dimethyl sulphoxide, and has exceptionally high thermal stability. When heated to 800° in a nitrogen atmosphere (rate of heating 150 deg h^{-1}), the polymer lost ~25% in weight, but above 600° the weight loss was less than 10%.

Interesting properties are also possessed by polymers which have borazole rings in the main chain. Korshak and coworkers[44] obtained a glassy copolymer in the reaction of trimethylborazole with hexamethylene diisocyanate:

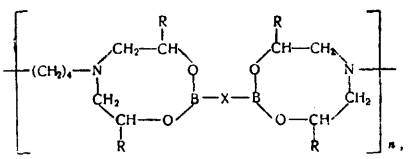


Polycondensation of trichloroborazole with ammonia[45] gave a white amorphous powder:



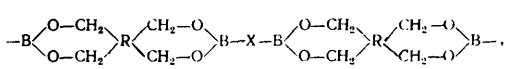
which does not change on heating to 300°.

The reaction of alkylenediboronic [benzenediboronic? (Ed. of Translation)] acids with tetra(hydroxyalkyl)polymethylene diamines resulted in interesting polyesters[46] with the structure

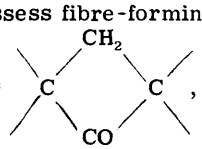


where R = CH_3, X = $-C_6H_4-$. These polymers withstand boiling in water for 4 h and are thermally stable up to 300°.

The products of the polycondensation of the diboronic acids and tetrols [pentaerythritol and tetra(hydroxymethyl)-cyclopentane], with the structure

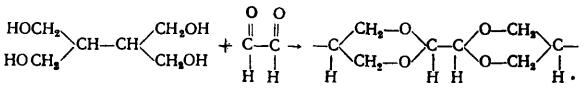


possess fibre-forming properties. When X = $-C_6H_4-$ and



, the softening point of the polymer is 240°.

Recently[47] a new class of linear polycycloacetals was reported. The reaction of dialdehydes with tetrahydric alcohols, which contain two 1,2- or 1,3-diol groupings, easily produces linear polycycloacetals, in which each unit contains a ring:



In this reaction the dialdehydes and tetrols can be considered as bifunctional compounds. The reaction of more stable acetals of aliphatic aldehydes of the general formula $(C_2H_5O)_2CH(CH_2)_nCH(OC_2H_5)_2$ with various tetrols, such as pentaerythritol or $(HOCH_2)_2CH(CH_2)_mCH(CH_2OH)_2$, where $m = n = 6-10$, gives yellow or white solid polymers, m.p. 146°–205°, which are soluble in chlorinated hydrocarbons and have film- or fibre-forming properties. The dielectric constant of these polymers is 2.1–2.4, the dielectric loss 0.03, and the resistivity $10^{16}-10^{17}$ ohm cm.

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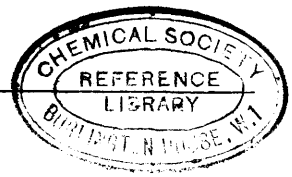

THE SATURATED CYCLIC SULPHIDES OF PETROLEUM AND THEIR SYNTHESIS

Yu. K. Yur'ev and E. G. Rozantsev

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INTRODUCTION

A high sulphur content is typical of many petroleum deposits. Thus Californian petroleum (Santa Maria Valley deposit) contains 4.5% total sulphur, Venezuelan (Boscan) 4.8%,[1] and Iraq up to 7.8%.[2] In Russian petroleums, a high sulphur content is found in the deposits of the Bashkir and Tartar Autonomous Soviet Socialist Republics, the Kuibyshev region, and particularly South Uzbekistan, where, for example, Uch-Kizyl petroleum contains 6.3% total sulphur[3]. This sulphur occurs mainly as organosulphur compounds, particularly cyclic and aliphatic sulphides.

Since Mabery first separated saturated cyclic sulphides of the general formula $C_nH_{2n}S$ from North American petroleum[4,5], these sulphides have been detected in all sulphur-containing petroleums: for instance, thiophan has been found in petroleums from Iran[6,7], Turkey[8], USA[9], Mexico[10-13], and USSR[3,14,15]. Many homologues of thiophan and tetrahydrothiopyran can now be separated from petroleum and identified, by using mercury salts[16,17,18], sulphur dioxide, alumina[19], silica gel[20-22], or hydrofluoric acid[23], together with spectrometry, thermal diffusion, and accurate rectification methods.

Hartough[24] has given the physical properties of all cyclic organosulphur compounds detected in petroleum up to 1951. It was remarked that it was very difficult to establish the structure of the saturated cyclic sulphides, because of the absence of synthetic model compounds[25].

Thiophan, 2- and 3-methylthiophan, 2-ethylthiophan, 2,3- and 2,4-dimethylthiophan, 2,3,4- and 2,3,5-trimethylthiophan, tetrahydrothiopyran, 2-, 3-, and 4-methyltetrahydrothiopyran[7,26], and thiaadamantane[27] have been separated from Iranian petroleum and identified, and tetrahydrothiopyran and 3-butyltetrahydrothiopyran[28] from Kuwait petroleum. The structures of the following nine saturated cyclic sulphides from American petroleum (Wasson deposit) have been accurately established: thiophan, 2- and 3-methylthiophan, tetrahydrothiopyran, *cis*- and *trans*-2,5-dimethylthiophan, and 2-, 3-, and 4-methyltetrahydrothiopyran[9]. In the USSR, 2-methylthiophan has been isolated from South Uzbekistan petroleum[3], 2,5-dimethylthiophan from the Ishimbaev deposit[29], and 3-butylthiophan from the Tuimazinsk deposit[30].

Saturated cyclic sulphides are thus components of all sulphur-containing petroleums. Since by 1955 more than half of the petroleum worked in the USSR was of the sulphur-containing type from the Urals–Volga oil-bearing region[31], organosulphur compounds of this type merit as deep a study as the hydrocarbons themselves. Studies in this field would form the basis of a more rational and efficient utilisation of the ready-made organosulphur compounds presented to us by nature, in the national economy and industry[32-37].

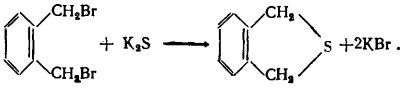
I. SYNTHESIS OF SATURATED CYCLIC SULPHIDES

The term "thiophan" has been most widely used to designate tetrahydrothiophen in Soviet and foreign literature, and we shall use it here.

The following are the most general of the existing methods for the synthesis of saturated cyclic sulphides.

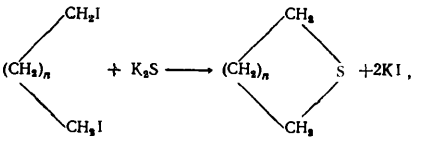
1. Action of Alkali Metal Sulphides on δ- and ε-Dihalides

In 1884 Leser[38] and somewhat later Hjelt[39] obtained 3,4-benzothiophan by the action of potassium sulphide on *o*-xylylene dibromide:



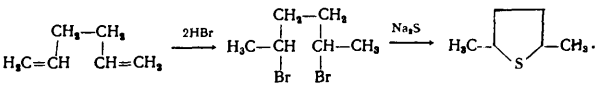
The same compound was prepared by von Braun, Bayer, and Kaiser[40] using sodium sulphide.

Thiophan itself and tetrahydrothiopyran were first prepared in 1910 by von Braun and Trümpler[41] by the action of potassium sulphide on alcoholic solutions of 1,4-diiodobutane and 1,5-diiodopentane respectively; high yields were obtained:



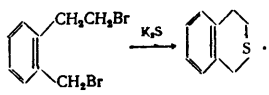
where $n = 2$ or 3. 2-Methylthiophan was prepared analogously[42].

In 1916 Grishkevich-Trokhimovskii made a detailed study of the reaction of α,ω-dihalides with sodium sulphide in aqueous-alcoholic solution, and used this method to prepare a large number of saturated cyclic sulphides, including several homologues of thiophan and tetrahydrothiopyran[43]. 2,5-Dimethylthiophan was prepared from *meso*-2,5-dibromohexane, itself obtained by addition of hydrogen bromide to diallyl[44]:

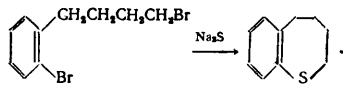


In this preparation of 2,5-dibromohexane, in addition to the crystalline dibromide a liquid isomer was obtained; in 1901 Wislicenus showed that the solid dibromide is the *meso*-form, and the liquid the racemic form[45].

von Braun and Zobel prepared 3,4-benzotetrahydrothiopyran by the action of potassium sulphide on the corresponding dibromide[46]:



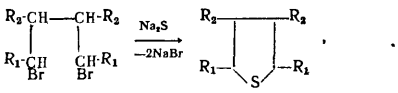
von Braun, Bayer, and Kaiser[40] obtained 2,3-benzohexamethylene sulphide (homothiochroman) in 40% yield by an analogous method from 2-(4-bromobutyl)bromobenzene:



1930 saw the start of an intensive investigation of possibilities for purifying petroleum fractions from sulphides, thiophans, and tetrahydrothiopyran[20]. To this period belong the studies of Bost and Conn on the properties of organic sulphides, including thiophan and tetrahydrothiopyran, and these compounds were used in developing methods for the preparation of sulphones, double compounds with mercuric chloride and iodide, and methyltetra- and methylpenta-methylenesulphonium halides; the synthesis of the cyclic sulphides themselves was considerably improved[47-49].

In 1938 Müller and his coworkers used the reaction of α,ω-dihalides with sodium sulphide to prepare a series of macrocyclic sulphides of the general formula $C_nH_{2n}S$ (n = = 12–14)[50,51], and later, hexa-, octa-, and nona-methylenesulphides[51].

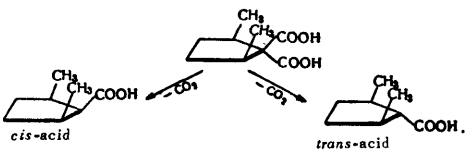
In preparing new cyclic sulphones, Marvel and Williams synthesised 3,4- and 2,5-dipropylthiophan by a complex route in yields of 77.5 and 77% respectively[52]:



where R_1 = H, R_2 = C_3H_7; R_1 = C_3H_7, R_2 = H.

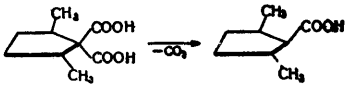
In 1951 Whitehead, Dean, and Fidler published an interesting study on the synthesis of homologues of thiophan and tetrahydrothiopyran by the action of sodium sulphide on 1,4- and 1,5-dibromides. In addition to the known thiophan, 2- and 3-methylthiophan, tetrahydrothiopyran and 2-methyltetrahydrothiopyran, the compounds 3- and 4-methyltetrahydrothiopyran, and *cis*- and *trans*-2,5-dimethylthiophan were obtained for the first time[53].

It was mentioned above that the solid 2,5-dibromohexane is the *meso*-form, and the liquid is the racemic form[45]. Condensation of *meso*-2,5-dibromohexane with disodio-malonic ester and saponification of the reaction product produces *cis*-2,5-dimethylcyclopentane-1,1-dicarboxylic acid; on decarboxylation this acid gives two acids of different melting point, thus proving the *cis*-configuration of the starting acid:

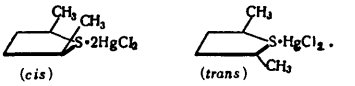


cis-acid *trans*-acid

Condensation of racemic 2,5-dibromohexane with disodio-malonic ester gives *trans*-2,5-dimethylcyclopentane-1,1-dicarboxylic acid, from which only one acid, *trans*-2,5-dimethylcyclopentane carboxylic acid, is obtained by decarboxylation:



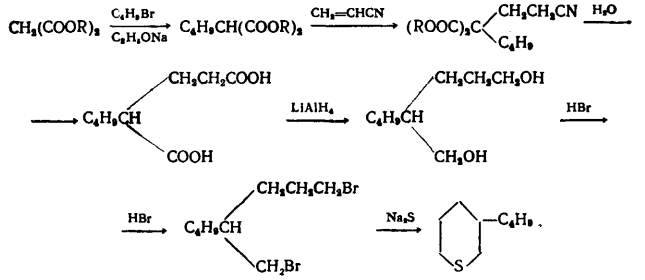
We may conclude from these data that the 2,5-dimethylthiophan obtained by the action of sodium sulphide on *meso*-2,5-dibromohexane is the *cis*-form, while the isomer obtained from racemic 2,5-dibromohexane has the *trans*-configuration. The former gives a complex with two molecules of mercuric chloride (m.p. 180°), and the latter a complex with one molecule of mercuric chloride (m.p. 110°–111°):



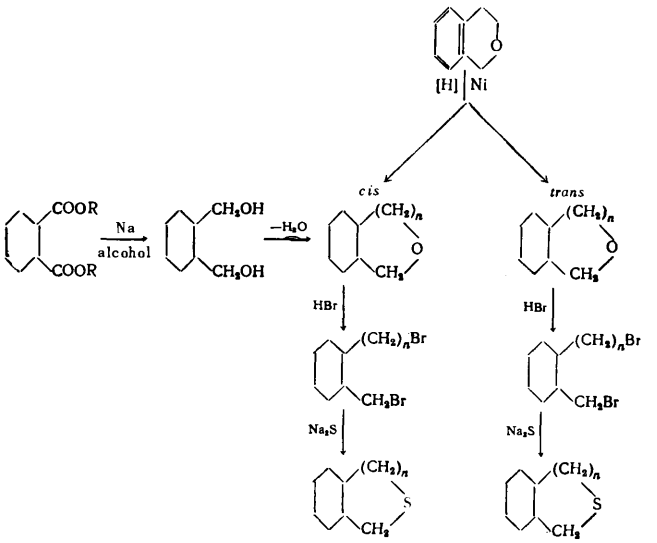
(*cis*) (*trans*)

In this connection, the mercuric chloride complex of 2,5-dimethylthiophan (m.p. 109°–110°) prepared by Grishkevich-Trokhimovskii from *meso*-2,5-dibromohexane[43] corresponds, from the melting point, not to *cis*-2,5-dimethylthiophan, but to the *trans*-form. Apparently the composition and so the melting point of the mercuric chloride complexes depends on their method of preparation. Obolentsev and Dronov[54] obtained *cis*- and *trans*-2,5-dipropylthiophan[52] analogously from 4,7-dibromodecane and sodium sulphide.

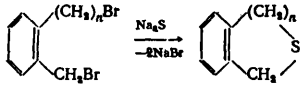
Emmott[28] prepared 3-butyltetrahydrothiopyran in 22% yield by the following series of reactions:



In 1954 several papers appeared on the synthesis of various bicyclic sulphides similar in type to those found in petroleum. Thus Birch, Dean, and Whitehead[55] prepared *cis*- and *trans*-2-thiahydrindanes and *cis*- and *trans*-2-thiadecalins as follows:



The stereoisomeric cyclic oxides were separated by rectification. The configuration of the resulting dibromides was established by Wislicenus's method[45]. High yields of the bicyclic sulphides were obtained: *cis*- and *trans*-2--thiahydrindane 75% and 91% respectively, and *cis*- and *trans*-thiadecalin 83.5% and 86.5% respectively. These workers also prepared 2-thiaindane and 2-thiatetralin in yields of 67% and 59% respectively[56]:



where n = 1 or 2.

In 1955 the American Petroleum Institute, the United States National Bureau of Stan ards and the United States Bureau of Mines prepared, in accordance with plan 48A†, 25 sulphur compounds in a high state of purity, including thietan, thiophan, and tetrahydrothiopyran. In the same year, in accordance with a decision of the Seventh Italian National Chemical Congress, work was begun on the synthesis of various cyclic sulphides so that they could be thoroughly investigated; Onesta and Ferretti[57] prepared a series of 2-alkylthiophans by the action of sodium sulphide on the corresponding dibromides (alkyl = C_3H_7, C_4H_9, iso-C_4H_9, iso-C_5H_{11}).

It is interesting that the melting points of the mercuric chloride complexes given by the Italian workers differ from those given by Yur'ev and Gragerov[58] (Table 1).

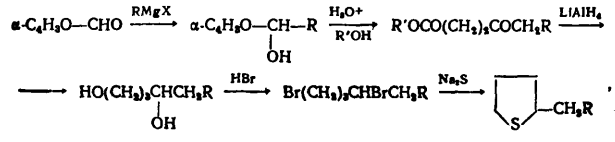
The unsatisfactory nature of the explanations for the different melting points of the mercuric chloride complexes[59] led to the appearance of a special study, which showed that the composition of the monoalkylthiophan–mercuric chloride double compounds, and therefore their melting points, depends on the method of their preparation[60]. We have already referred to a similar discrepancy in the melting points of mercuric chloride complexes, in discussing the work of Whitehead and coworkers[53].

TABLE 1.

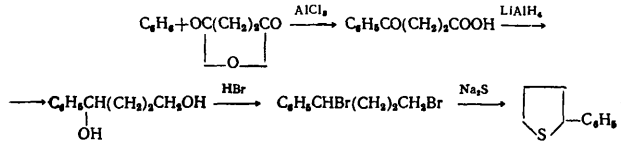
Mercuric chloride complex of	M.p., °C	References
2-Propylthiophan	132—133	57
2-Propylthiophan	51—52	58
2-Butylthiophan	111—113	57
2-Butylthiophan	39.5—41	58

In 1958 Obolentsev and his coworkers[61] prepared a number of sulphides, including the saturated cyclic sulphides 2-pentylthiophan, tetrahydrothiopyran, and thiacycloheptane, by the action of sodium sulphide on the corresponding dihalides.

Later, Obolentsev and Bukharov[62] reported the synthesis of ten 2-alkyl- and 2-aralkyl-thiophans starting from furfural:



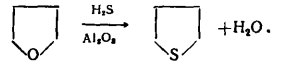
where R = CH_3, C_2H_5, C_3H_7, iso-C_3H_7, iso-C_4H_9, t-C_4H_9, iso-C_5H_{11}, iso-C_8H_{17}, $C_6H_5CH_2$, or $C_6H_5CH_2CH_2$. These workers also prepared 2-phenylthiophan by a slightly different route:



Onesta and Ferretti's data on the boiling point of 2-butylthiophan[57,63] have not been confirmed; the boiling point given by Obolentsev and Bukharov coincides with that given earlier by Yur'ev and Gragerov[58] and is the true figure.

2. Catalytic Conversion of γ- and δ-Oxides into Saturated Cyclic Sulphides

In 1937 Yur'ev and Prokina[64] obtained thiophan in a high yield by passing tetrahydrofuran in a current of hydrogen sulphide through a tube containing alumina and heated to 400°:



Yur'ev and Tronova passed tetrahydrofuran over pyrites (FeS_2) and the easily hydrolysed aluminium sulphide, but no sulphur-containing heterocyclic compounds were formed in the temperature range 350°–600°; when, however, a mixture of tetrahydrofuran and water was passed over aluminium sulphide at 300° or 350°, thiophan was obtained in yields of 32.5% and 30.5% respectively[65].

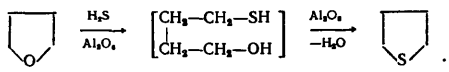
This new reaction provided the possibility of systematic synthesis and detailed study of this important group of saturated cyclic sulphides. The reaction linked the saturated oxygen-containing heterocyclic compounds with the corresponding sulphur compounds, showed their genetic relationship, and provided an approach towards the elucidation of the complex natural processes producing the sulphur-containing heterocyclic compounds in petroleum‡.

† In 1948 the American Petroleum Institute put forward two projects of study, named 48A and 48B, connected with the presence in petroleum of various organosulphur compounds and the great increase in the working of high-sulphur petroleum. Work on project 48A (the synthesis, purification and properties of the sulphur compounds in petroleum) was carried out at two Bureau of Mines stations – the Petroleum and Shale Experimental Station at Laramie (Wyoming) [Laramie Petroleum Research Center (Ed. of Translation)], and the Petroleum Experiment Station at Bartlesville (Oklahoma). The group at Laramie is concerned with the preparation, purification and study of the properties of such compounds, including the preparation of 1.5 litres of highly pure (99.9 mole %) compound in each case, and the determination of their physical and thermodynamic properties and their spectroscopic characteristics.

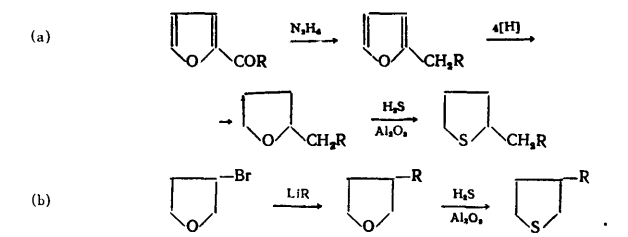
‡ Postovskii, Bednyagina, and Mikhailova[66] and Birch[7] consider that under conditions pertaining in nature, oxygen- and nitrogen-containing heterocyclic compounds can be converted into cyclic sulphides by the Yur'ev reaction.

By this method Yur'ev prepared 2-methylthiophan from 2-methyltetrahydrofuran in 69% yield[67].

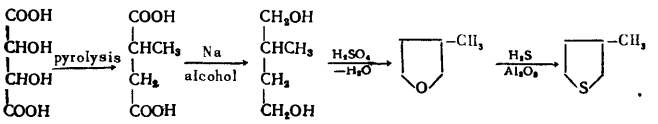
Yur'ev, Minachev, and Samurskaya have shown[68] that, at elevated temperature in the presence of alumina, 4-mercaptobutanol produces thiophan almost quantitatively§. This reaction confirmed the mechanism put forward by Yur'ev for the catalytic conversion of tetrahydrofuran into thiophan in the presence of hydrogen sulphide[64,68,70], which includes the intermediate formation of a 1-mercapto-4--hydroxy compound (4-mercaptobutanol) by ring-opening of the tetrahydrofuran at a carbon–oxygen bond and addition of the elements of hydrogen sulphide:



This reaction was later applied to other tetrahydrofuran homologues[58,71-73]; thus in 1949 Yur'ev and Gragerov prepared a number of 2- and 3-alkylthiophans as follows[58,73]:

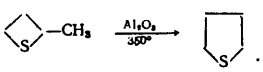


2-Ethyl-, 2-propyl-, 2-butyl-, 3-methyl-, 3-propyl-, and 3-butyl-thiophan were obtained in this way. 3-Methylthiophan was prepared by the following series of reactions:



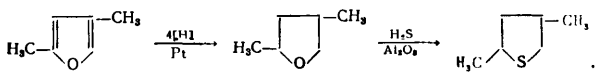
In the study of the catalytic interconversions of tetrahydrofuran, thiophan, and pyrrolidine, Yur'ev and Bugorkova obtained thiophan in 33.5% yield by the action of hydrogen sulphide on pyrrolidine[74].

Yur'ev, Dyatlovitskaya, and Levi[75] achieved an interesting synthesis of thiophan by the contact isomerisation of 2-methylthietan at 350° in the presence of alumina:



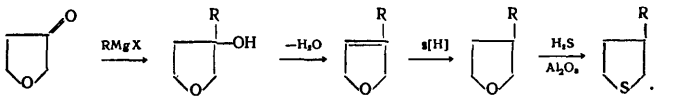
When 3-oxotetrahydrofuran was passed over alumina at 350° in a current of hydrogen sulphide, thiophan was obtained, in place of the expected 3-oxothiophan[76].

Yur'ev, Kondrat'eva and Kartashevskii have described the catalytic conversion of 2,4-dimethyltetrahydrofuran into 2,4-dimethylthiophan in 58% yield[77]:



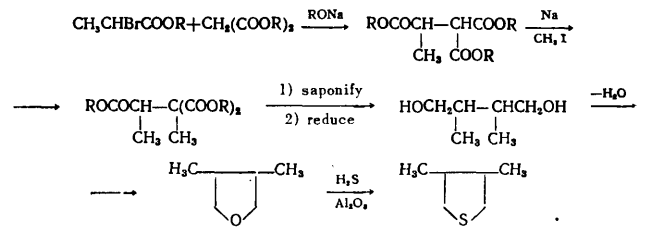
Although 3,3-dimethylthiophan was obtained in 73% yield by Yur'ev, Kondrat'eva, and Sadovaya[78], 2,2-dimethylthiophan was obtained in only 27% yield by Yur'ev, Kondrat'eva, and Akishin[79]; Yur'ev and his coworkers also obtained 2,5-diethylthiophan in a yield of only 12%.[80] These effects are due to an increased steric effect around the hetero--atom because of the introduction of the alkyl groups into the tetrahydrofuran ring (see Figure).

In 1954 Yur'ev, Lukina, and their coworkers developed a general method for the preparation of 3-alkyl- and 3-aryl-thiophans from 3-oxotetrahydrofuran by the following series of reactions:

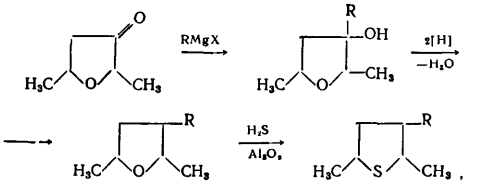


This method was used to prepare 3-pentyl- and 3-phenyl--thiophan in 64% and 58% yields respectively[81], and, later, 3-isopentyl-, 3-hexyl-, and 3-*p*-tolyl-thiophan in yields of 60%, 57%, and 51%.[82]

Yur'ev and Kondrat'eva prepared 3,4-dimethylthiophan as follows, with a 71% yield on the last step[83]:



Later Yur'ev, Rozantsev, and Godovikova put forward a new general method for the preparation of the difficultly attainable 2,3,5-substituted thiophans[84], by the action of hydrogen sulphide on the 2,3,5-substituted tetrahydrofurans[85]:



where R = CH_3, C_2H_5, or C_3H_7. Yur'ev, Rozantsev, and Gribov have also described the preparation of 3-butyl-, 3-isobutyl-, 3-pentyl-, and 3-isopentyl-2,5-dimethylthiophans by the same method[86].

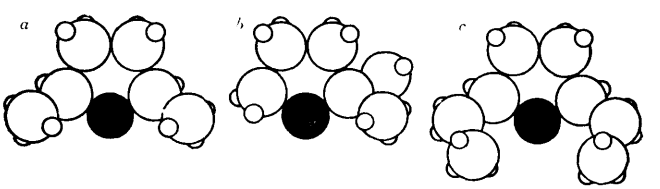
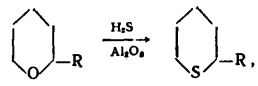


Figure. *a*) 2,5-dimethylthiophan (68% yield); *b*) 2,2-dimethylthiophan (27% yield); *c*) diethylthiophan (12% yield).

§ Under these conditions thiophans are also formed from 1,4-diols[69] and 4-chlorobutanol in the presence of hydrogen sulphide.

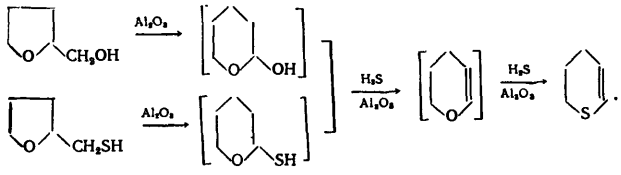
The six-membered tetrahydrothiopyran and its homologues were prepared by this method in 1939 by Yur'ev, Pervova, and Sazonova [87] and later by Yur'ev and Revenko [88]:



where R = H, CH_3, C_2H_5, C_3H_7, iso-C_3H_7, C_4H_9, or iso-C_4H_9.

The preparation of unsaturated cyclic sulphides with the double bond in a definite position presented great difficulties. Δ^2-Dihydrothiopyran was first obtained by Yur'ev, Dubrovina, and Tregubov [89] by the action of hydrogen sulphide on Δ^2-dihydropyran at 300° in the presence of alumina.

Yur'ev and Vendel'shtein prepared Δ^2-dihydrothiopyran by the catalytic conversion of tetrahydrofurfuryl alcohol with hydrogen sulphide at 300 (yield 27%) and by passing 2-(tetrahydrofuryl)methanethiol over alumina at 300° (yield 22%) [90]:



When tetrahydrofurfuryl alcohol is reacted as above at 450°, in addition to Δ^2-dihydrothiopyran a mixture of thiopyran and tetrahydrothiopyran is obtained [91].

3. Reduction and Catalytic Hydrogenation of Thiophens

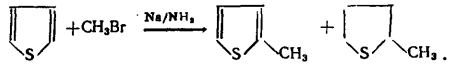
Attempts have been made to hydrogenate the comparatively easily available thiophen homologues into the corresponding thiophans, but the early experiments had little success [92-95].

In 1925 Fricke and Spilker showed [96,97] that benzothiophen is reduced by sodium in boiling alcohol to give 2,3-benzothiophan in 17% yield. Mozingo and his coworkers were able to hydrogenate thiophen and some of its derivatives under moderate hydrogen pressure in the presence of palladium catalysts; the yields reached 71%. [98,99]

Later Wender, Levine, and Orchin [100,101] hydrogenated some thiophen homologues at 185° at elevated hydrogen pressure in the presence of cobalt carbonyl, and obtained thiophan, 2-methylthiophan, 2-ethylthiophan, and 2,5-dimethylthiophan, in yields of 66, 77, 82, and 22% respectively.

Birch and McAllan [102] attempted the reduction of 3-methyl- and 2,5-dimethyl-thiophen with nascent hydrogen (sodium in liquid ammonia), and obtained mixtures of the dihydro- and tetrahydro-thiophen homologues.

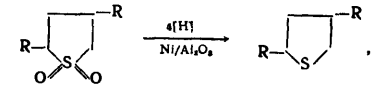
Zimmerschied and Arnold [103] reported the reduction of the thiophen ring as a side reaction in the alkylation of thiophen in liquid ammonia: on reacting the metallised thiophen with methyl bromide in liquid ammonia, 2-methylthiophan was obtained in 29% yield, in addition to the 2-methylthiophen:



Hydrogenation of thiophen, 2-isobutylthiophen, and 2-isooctylthiophen with sulphide catalysts — nickel, molybdenum, and tungsten sulphides — produced thiophan, 2-isobutylthiophan, and 2-isooctylthiophan in yields of 59, 22.2, and 35% respectively [104]. Bateman and Shipley [105] have successfully hydrogenated homologues of dihydrothiophen and dihydrothiopyran with palladium on carbon and palladium on barium sulphate catalysts.

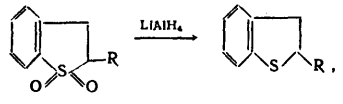
4. Reduction of Sulphones

In 1949 Moore and Trimble [106] catalytically reduced thiophan and 2,4-dimethylthiophan *S*-dioxides in the presence of nickel on alumina to thiophan and 2,4-dimethylthiophan respectively:



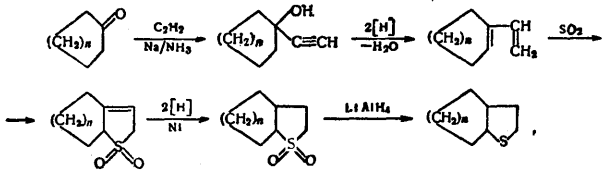
where R = H or CH_3.

Bordwell and McKellin [107] obtained benzothiophan and 2-methylbenzothiophan by reducing the corresponding *S*-dioxides [108] with lithium aluminium hydride:



where R = H or CH_3.

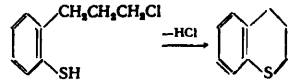
Later Birch *et al.* [109] described the preparation of *cis*-2-thiabicyclo[3,3,0]octane and *cis*- and *trans*-7-thiabicyclo[4,3,0]nonane by the following method:



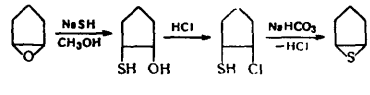
where *n* = 1 or 2, and they also prepared *cis*- and *trans*-3-thiabicyclo[3,3,0]octane. An attempt to prepare *trans*-2-thiabicyclo[3,3,0]octane [110] *via* isomerising the *cis*-sulphone intermediate [111] was unsuccessful, although this method has been successfully used for obtaining *trans*-7-thiabicyclo[4,3,0]nonane.

5. Intramolecular Cyclisation

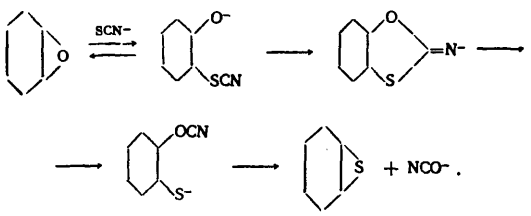
In 1910 von Braun obtained 2,3-benzotetrahydrothiopyran by the intramolecular condensation of 2-(3-chloropropyl)thiophenol [42]:



and by an analogous method van Tamelen [112] prepared cyclohexene sulphide and cyclopentene sulphide in yields of 73 and 75% respectively, starting from the corresponding oxides:

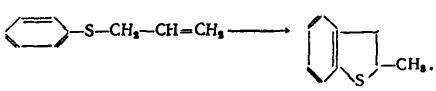


Culvenor, Davies, and Pausacker[113] obtained cyclohexene sulphide in 60% yield by the action of potassium or ammonium thiocyanate on cyclohexene oxide in an alkaline medium; Snyder, Stewart, and Ziegler[114] used this method for the preparation of several ethylene sulphide homologues, including cyclohexene sulphide, and suggested the following mechanism for this reaction:

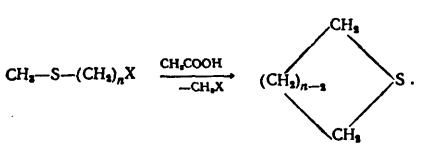


Many ethylene sulphide homologues are known[115-120], but up to the present have not been found in petroleum. However, they may be of interest in the study of, for instance, the spectrographic features of cyclic sulphides, or in the calculation of various physicochemical and thermodynamic values, and this is also true of trimethylene sulphide and its homologues[121,122].

Hurd and Greengard[123] have reported the isolation of 2-methylbenzothiophan from the pyrolysis products of phenyl allyl sulphide:

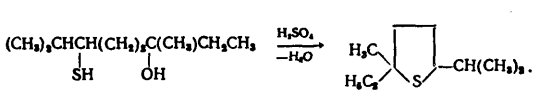


Bennett and Gudgeon suggested that macrocyclic sulphides could be obtained by eliminating methyl halide from ω-halogenoalkyl methyl sulphides, *e.g.* by heating with acetic acid or sodium iodide, and used this method to prepare cyclic sulphides with 14, 16, and 18 methylene groups[124]:

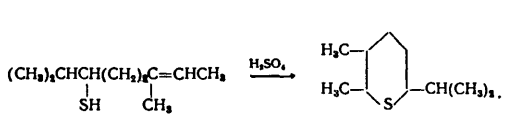


In 1951 a group of American workers reported the formation of sulphides by adding hydrogen sulphide to olefines in the presence of aluminium bromide or sulphuric acid, with subsequent addition of the resulting thiol to a second olefine molecule[59].

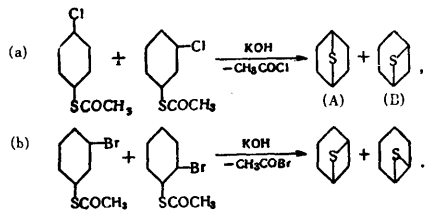
Bateman and Glazebrook used this reaction for the preparation of many thiacycloalkenes, using the corresponding mercaptoketones as starting compounds[125,126]. Glazebrook and Saville[127] then applied the method to 4-mercaptoalcohols, and so obtained 2-methyl-2-ethyl-5-isopropylthiophan:



Bateman, Glazebrook, and Moore showed that the intramolecular addition of a thiol group to a double bond also produces saturated cyclic sulphides, and obtained 2,3-dimethyl-6-isopropyltetrahydrothiopyran by this method[128]:

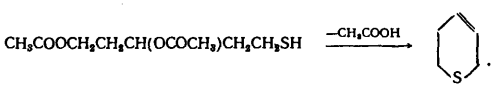


Intramolecular condensation was used in 1958 by Birch, Dean, and Hunter for the preparation of 7-thiabicyclo-[2,2,1]heptane (A) and 6-thiabicyclo[3,1,1]heptane (B):



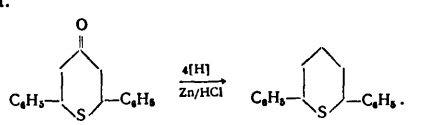
The resulting mixtures of bicyclic sulphides were separated by azeotropic distillation and chromatography; the by-product of cyclohexene sulphide — reaction (b) — was identified spectroscopically[129].

Olsen and Rutland suggested a method for the preparation of Δ^3-dihydrothiopyrans by the intramolecular condensation of 3,5-diacetoxypentan-1-thiol, with the elimination of acetic acid: Δ^3-dihydrothiopyran was obtained in 37% yield[130]:

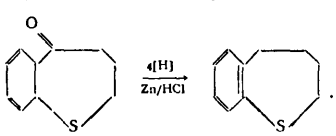


6. Reduction of Carbonyl Derivatives of Cyclic Sulphides

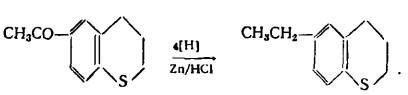
The possibility of obtaining cyclic sulphides from thiabenz-4-one and tetrahydrothiabenz-4-one has long attracted the attention of chemists[131-136]. Arndt and Schauder[135] obtained 2,6-diphenyltetrahydrothiabenz-4-one in 40% yield by reducing 2,6-diphenyltetrahydrothiabenz-4-one in hydrochloric acid:



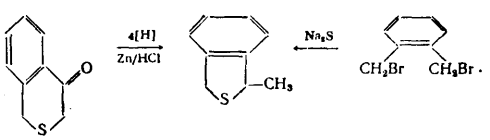
Cagniant and Deluzarche[137] and then Truce and Milionis[108] prepared 2,3-benzothiacycloheptane (homothiochroman) by the reduction of 2,3-benzo-4-thiacycloheptanone:



Krollpfeiffer *et al.* prepared 1-thiatetralin (thiochroman) and then 6-methyl- and 6,8-dimethyl-1-thiatetralin[138,139]. Cagniant and Deluzarche obtained 6-ethyl-1-thiatetralin by Clemmensen reduction of 6-acetyl-1-thiatetralin[140]:

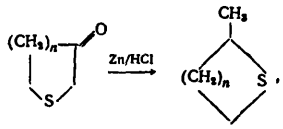


In an attempt to reduce 1,2,3,4-tetrahydro-2-thianaphthalen-4-one by the Clemmensen method, von Braun and Weissbach[141] obtained 2-methyl-3,4-benzothiophan, the structure of which was established by synthesis:



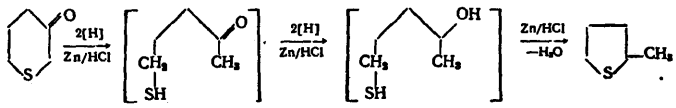
The reduction of 1,2-dihydro-2-thianaphthalen-5-ol under the same conditions produced 1,2-dihydro-2-thianaphthalene, described earlier by von Braun and Zobel[46].

The same anomalous reaction was observed later by Leonard and Figueras[142] in the reduction of 1-thiacyclohexan-3-one and 1-thiacycloheptan-3-one to 2-methylthiophan and 2-methylthiacyclohexane respectively:

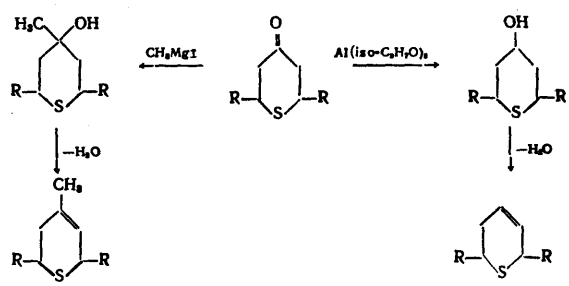


where n = 2 or 3.

This reaction apparently passes through the intermediate formation of the methyl ω-mercaptoalkyl ketone, which is then reduced to the corresponding mercapto-alcohol, which by the elimination of water gives the cyclic sulphide with one methylene group less in the ring[143,144]:



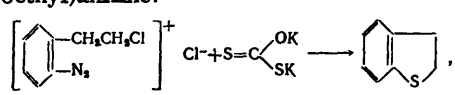
Naylor[91] prepared Δ^3-dihydrothiapyran and its homologues from tetrahydrothiabenz-4-one and its homologues:



where R = H or CH_3. 2,2,6,6-Tetramethyl- and 2,2,4,6,6-pentamethyl-Δ^3-dihydrothiapyrans were prepared similarly.

7. Other Methods

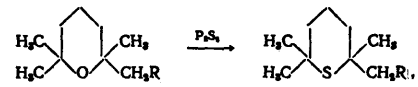
von Braun, Bayer, and Kaiser[40] and Challenger and Clapham[145] have described the preparation of 2,3-benzothiophan by the action of potassium xanthate on diazotised 2-(2-chloroethyl)aniline:



and Bennett and Hafez[146] described its analogous preparation from diazotised 2-(2-hydroxyethyl)aniline.

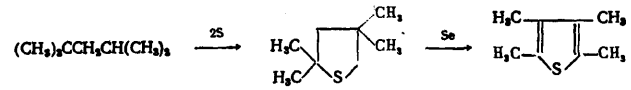
In 1947 Farmer and Shipley observed the formation of 2,2-dimethyl-5-isobutylthiophan, 2,3-dimethyl-5-isobutylthiophan, 2,2,6,6-tetramethylthiacyclohexane, 2,2,6-trimethyl-6-ethylthiacyclohexane, and 2,3-dimethyl-6-isopropylthiacyclohexane when dienoid hydrocarbons were heated at 140° with elementary sulphur; unsaturated cyclic sulphides were also formed. The cyclic sulphides were said to be formed by the addition of hydrogen sulphide across the double bonds of the dienes[147]. The structures of the compounds were established by comparing their infra-red absorption spectra with those of synthetic models[148]. The difficulties of identification were made worse because some of the products contained a tertiary carbon atom attached to sulphur, so that the solid mercuric chloride derivatives could not be obtained[149].

In the same year Naylor added hydrogen sulphide to geraniolene, dihydromyrcene, and 2,6-dimethylocta-2,6-diene[150] to obtain 2,2,6,6-tetramethyl-, 2,2,6-trimethyl-6-ethyl-, and 2,3-dimethyl-6-isopropyl-thiacyclohexane. He also prepared the two former compounds by the action of phosphorus pentasulphide on the corresponding tetrahydropyran derivative[151]:

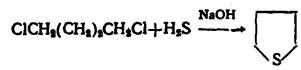


where R = H or CH_3.

Friedmann[152] reported an interesting synthesis of 2,2,4,4-tetramethylthiophane by boiling 2,2,4-trimethylpentane with sulphur; when the reaction product was dehydrogenated with selenium, isomerisation occurred to form 2,3,4,5-tetramethylthiophen:



A convenient method from the preparative point of view is the preparation of thiophan from 1,4-dichlorobutane and hydrogen sulphide in alcoholic alkali (yield 70%)[153]:



Birch and Dean obtained *cis*-3-thiabicyclo[3,2,1]octane in 77% yield from sodium sulphide and, instead of the α,ω-dihalide, cyclopentane-1,3-dimethoxy di-*p*-toluenesulphonate[154]:

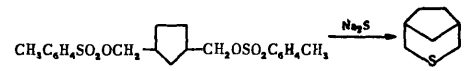


TABLE 2. Physical properties and yields of saturated cyclic sulphides of the thiophan and tetrahydrothiopyran series*.

No.	Compound	B.p., °C (mm Hg)	n_D^{20}	d_4^{20}	Yield, %	Reference
1.	Thiophan	121.1 (760)	1.5047	0.9998	91	18, 21, 41—43, 47, 48, 53, 64, 65, 68, 69, 74—76, 92—95, 98—101, 104, 106, 153, 202, 208, 209, 210—217
		120—120.5 (767)	1.5054	0.9961	90.5	
2.	2-Methylthiophan	132.4 (760)	1.4909	0.9552	90	42, 43, 53, 67, 77, 95, 101, 103, 142, 151, 189, 200, 218,
		131.2—131.9 (747)	1.4927	0.9553	69	
3.	3-Methylthiophan	138.2 (760)	1.4924	0.9634	82	43, 53, 58, 73, 200
		136.9—137.3 (747)	1.4932	0.9630	81	
4.	2,2-Dimethylthiophan	138—138.8 (750)	1.4807	0.9220	27	79
5.	2,4-Dimethylthiophan	147—148 (742)	1.4818	0.9265	58	77, 106
6.	2,5-Dimethylthiophan	140.2—140.8 (758)	1.4822	0.9220	68	71, 199, 204
7.	*cis*-2,5-Dimethylthiophan	60 (45)	1.4799	0.9222	73	43, 53
8.	*trans*-2,5-Dimethylthiophan	58 (44)	1.4776	0.9188	—	53
9.	3,3-Dimethylthiophan	144—145 (755)	1.4861	0.9374	73	78
10.	2-Ethylthiophan	156.8—156.4 (745)	1.4900	0.9433	71	58, 72, 73, 101, 205
11.	3-Ethylthiophan	164.5—165.4 (750)	1.4911	0.9497	80	58, 73, 205

* Literature references printed in heavy type are those containing constants and yields of the cyclic sulphides.

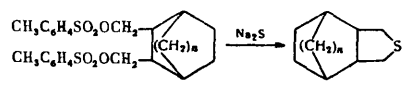
TABLE 2 (contd.)

No.	Compound	B.p., °C (mm Hg)	n_D^{20}	d_4^{20}	Yield, %	Reference
12.	2-Propylthiophan	180.4 (766)	1.4859	0.9259	62	57, 58, 63, 73
		179.3—179.8 (743)	1.4862	0.9308	63	
13.	3-Propylthiophan	187.1—187.6 (733)	1.4886	0.9375	72	58, 73
14.	2,3,5-Trimethylthiophan	162—163 (751)	1.4786	0.9104	56	84
15.	2-Butylthiophan	201.5—202 (753)	1.4862	0.9221	60	57, 58, 63, 73
16.	2-Isobutylthiophan	192.5 (766)	1.4800	0.9114	58	57, 63
17.	2-t-Butylthiophan	186—187 (760)	1.4850	—	60	104
18.	2,5-Diethylthiophan	183.5—184.5 (760)	1.4825	0.9104	12	80
19.	2,2,4,4-Tetramethylthiophan	m.p. 158—161°	—	—	—	152
20.	2,5-Dimethyl-3-ethylthiophan	172—173 (744)	1.4782	0.9094	56.5	84
21.	3-Butylthiophan	209.5—209.9 (733)	1.4868	0.9271	79	58, 73
22.	2-Isopentylthiophan	218.4 (764)	1.4821	0.9193	56	57, 63
23.	2,5-Dimethyl-3-propylthiophan	197—198 (747)	1.4770	0.8989	52	84
24.	3-Pentylthiophan	92—93 (10)	1.4870	0.9151	64	81
25.	3-Isopentylthiophan	87—88 (10)	1.4868	0.9196	60	82
26.	3-Phenylthiophan	112—113 (5)	1.6000	1.1009	58	81
27.	2,5-Dipropylthiophan	74—75 (1)	1.4795	0.8955	77	52
28.	*cis*-2,5-Dipropylthiophan	78.5—79.5 (4)	1.4786	0.8979	—	54
29.	*trans*-2,5-Dipropylthiophan	78.5—79.5 (4)	1.4770	0.8944	—	54
30.	2-Methyl-2-ethyl-5-isopropylthiophan	87 (10)	1.4765	—	77	127
31.	2,5-Dimethyl-3-butylthiophan	210—211 (748)	1.4557	0.8930	26	86
32.	2,5-Dimethyl-3-isobutylthiophan	208—209 (752)	1.4740	0.8922	36	86
33.	3-Hexylthiophan	121—122 (16)	1.4870	0.9170	57	82
34.	3,4-Dipropylthiophan	65—66 (1)	1.4830	0.9129	77.5	52
35.	3-*p*-Tolylthiophan	127,5—128 (4)	1.5847	1.0645	51	82
36.	2,5-Dimethyl-3-pentylthiophan	237—238 (765)	1.4734	0.8868	22	86
37.	2,5-Dimethyl-3-isopentylthiophan	233—234 (752)	1.4736	0.8862	19	86
38.	2-Isooctylthiophan	252—253 (760)	1.4801	—	—	104
39.	7-Thiabicyclo[2,2,1]heptane	164 (765)	1.517 (in dibutyl sulphide)	—	low	129
40.	*cis*-2-Thiabicyclo[3,3,0]octane	87.7—88 (25)	1.52424	1.0419	63	109
41.	*cis*-3-Thiabicyclo[3,3,0]octane	88.3—88.5 (25)	1.52328	1.0427	79	109, 160
42.	*trans*-3-Thiabicyclo[3,3,0]-octane	95.5—96 (28)	1.52099	1.0294 (30°)	76	109, 160
43.	2,3-Benzothiophan	235.68 (760)	—	1.1398	26	40, 58, 107 145, 146
44.	3,4-Benzothiophan	241.5 (760)	—	1.1446 (25°)	67	38—40, 56
45.	*cis*-7-Thiabicyclo[4,3,0]nonane	102—102.5 (20)	1.52716	1.0383	54	109
46.	*trans*-7-Thiabicyclo[4,3,0]-nonane	102.7—103.7 (21)	1.52115	1.0209	55	109
47.	*cis*-8-Thiabicyclo[4,3,0]nonane	108.5 (21)	1.53215	1.0430	75	55
48.	*trans*-8-Thiabicyclo[4,3,0]-nonane	104.6—105.6 (20)	1.52481	1.0203	91	55
49.	5-Methyl-2,3-benzothiophan	m.p. 114—115°	—	—	49	206
50.	4-Methyl-2,3-benzothiophan	96.5—97 (6)	1.5969	1.0980	67	206, 207
51.	2-Methyl-3,4-benzothiophan	m.p. 115—116°	—	—	70	141
52.	*cis*-4-Thiatricyclo[5,2,1,$0^{2,6}$]-decane	m.p. 123.5—125°	—	—	18	155
53.	*cis*-4-Thiatricyclo[5,2,2,$0^{2,6}$]-undecane	m.p. 56—58°	—	—	47	155
54.	Tetrahydrothiapyran	141.6 (760)	1.5067	0.9855	80	21, 28, 41—43, 47, 48, 51, 53, 61, 87, 142, 151 167, 202, 203
55.	2-Methyl-tetrahydrothiopyran	151—151.5 (750)	1.4906	0.9427	55.5	13, 48, 53, 88, 142
56.	3-Methyl-tetrahydrothiopyran	157.9 (760)	1.4922	0.9473	82	53
57.	4-Methyl-tetrahydrothiopyran	54 (22)	1.4923	0.9471	80	53
58.	2-Ethyl-tetrahydrothiopyran	107.5—108.5 (45)	1.4874	0.9427	50	88
59.	2-Propyl-tetrahydrothiopyran	89—89.5	1.4860	0.9164	48	88
60.	2-Isopropyl-tetrahydrothiopyran	80—81 (18)	1.4849	0.9141	50	88
61.	2-Butyl-tetrahydrothiopyran	85.5—86 (10)	1.4838	0.9086	30	88
62.	2-Isobutyl-tetrahydrothiopyran	79—80 (10)	1.4828	0.9063	31	88
63.	3-Butyl-tetrahydrothiopyran	218 (760)	1.4884	—	22	28
64.	2,2,6,6-Tetramethyl-tetrahydrothiopyran	65 (12)	1.4763	—	low	150, 151
65.	2,6,6-Trimethyl-2-ethyl-tetrahydrothiopyran	87 (13)	1.4849	—	26	127, 150, 151

TABLE 2 (contd.)

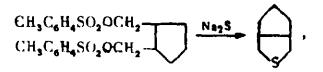
No.	Compound	B.p., °C (mm Hg)	n_D^{20}	d_4^{20}	Yield, %	Reference
66.	2,3-Dimethyl-6-isopropyl-tetrahydrothiopyran	86—89 (8)	1.4805	—	—	150
67.	2,6-Diphenyl-tetrahydrothiopyran	m.p. 98°	—	—	40	135
68.	6-Thiabicyclo[3,1,1]heptane	175 (775)	1.519 (in dibutyl sulphide)	—	low	129
69.	6-Thiabicyclo[3,2,1]octane	m.p. 174—175°	—	—	77	154
70.	1-Thiatetralin	m.p. 128—130°	—	—	85	42, 56, 139
71.	2-Thiatetralin	164.7 (760)	—	1.1328	59	46, 56
72.	*trans*-1-Thiadecalin	80—82 (2)	1.5210	—	—	7
73.	*cis*-2-Thiadecalin	122.5—123.25 (20)	1.53346	1.0350	83.5	55
74.	*trans*-2-Thiadecalin	115.5—116.5 (20)	1.52173	1.0058	86.5	55
75.	6-Methyl-1-thiatetralin	137 (12)	1.600	1.086	—	139
76.	6-Ethyl-1-thiatetralin	163—164 (23)	1.5845 (23°)	—	—	137
77.	6,8-Dimethyl-1-thiatetralin	146—147 (12)	1.594	1.075	—	139

Birch, Hunter, and McAllan prepared *cis*-4-thiatricyclo-[5,2,1,$0^{2,6}$]decane (yield 18%) and *cis*-4-thiatricyclo-[5,2,2,$0^{2,6}$]undecane (yield 47%) by the same method[155]:

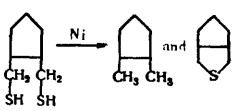


where n = 1 or 2.

Owen and Peto prepared the stereoisomeric 3-thiabicyclo[3,3,0]octanes¶ by the action of sodium sulphide on the *p*-toluenesulphonic acid esters of *cis*- and *trans*-1,2-di-(hydroxymethyl)cyclopentane:



and also showed that with Raney nickel *trans*-1,2-di(mercaptomethyl)cyclopentane produces 1,2-dimethylcyclopentane and *trans*-3-thiabicyclo[3,3,0]octane[160]:



Thus of the existing methods for the preparation of saturated cyclic sulphides the two most important are: reaction of α,ω-dihalides with potassium or sodium sulphide, and the catalytic conversion of tetrahydrofuran and tetrahydropyran homologues or α,ω-diols into the corresponding saturated cyclic sulphides by the action of hydrogen sulphide at elevated temperature.

Table 2 gives the physical properties and yields of the saturated cyclic sulphides of the thiophan and tetrahydrothiopyran series prepared up to 1960.

¶ It is interesting that cyclic sulphides of this type do not obey the Auwers-Skita rule[156—159].

II. SPECTRA OF SULPHIDES OF THE THIOPHAN AND THIACYCLOHEXANE SERIES

1. Ultra-Violet Spectra

Unlike ordinary alcohols and ethers, which are almost transparent in the spectral region attainable with quartz spectrographs and are therefore used as solvents, dialkyl sulphides have absorption bands in the long-wave region[161-164].

Fehnel and Carmack[165] studied a large number of ultra-violet spectra of dialkyl sulphides, and showed that they give a narrow absorption band near 2100 Å ($\log\epsilon \sim 3$); the intensity of absorption increases with branching of the alkyl radicals attached to the sulphur, and the maximum shifts towards the long-wave region (Table 3).

Up until 1954 no more than 20 ultra-violet spectra of alkyl sulphides had been recorded[166], including those of thiophan[18] and tetrahydrothiopyran[17]. Only very limited use can be made of electron absorption spectra for the identification of organic sulphur compounds in petroleum products. Thus according to Obolentsev and Lyubopytova's data[168,169] the ultra-violet spectra of 2-alkylthiophans (where alkyl = = C_3H_7, iso-C_4H_9, C_5H_{11}, iso-C_5H_{11}, or iso-C_6H_{13}) are almost identical with the spectra of the corresponding dialkyl sulphides; they differ only in having an inflection at 230–235 mμ, and have such similar intensities that the spectra practically coincide (Table 4).

The ultra-violet spectra of 2-phenylalkylthiophans differ from those of the 2-alkylthiophans. The absorption band of 2-phenylthiophan begins at about 310 mμ. The fine structure characteristic of aromatic hydrocarbons is not observed, and the intensity of the absorption is somewhat greater than in the alkylthiophans. The ultra-violet spectra of 2-phenylethyl- and 2-phenylpropyl-thiophan are practically identical.

TABLE 3. Ultra-violet spectra of alkyl sulphides (in ethanol).

Compound	Absorption band, mμ		Inflection, mμ	
	λ_{max}	ϵ_{max}	λ	ϵ
Dimethyl sulphide	210	1020	229	140
Diethyl sulphide	210	1800	229	140
Dibutyl sulphide	210	1200	229	145
Di-isopropyl sulphide	211	2100	—	—
Di-t-butyl sulphide	213	2600	—	—
Thiophan	210	1100	239	55
Tetrahydrothiopyran	210	1800	229	180

TABLE 4. Comparison of the extinction in the ultra-violet absorption spectra of thiophans.

Compound	Logarithm of the molecular extinction coefficient			
	225 mμ	230 mμ	235 mμ	245 mμ
Thiophan	2.56	2.12	1.87	1.60
2-Propylthiophan	2.47	2.02	1.96	1.63
2-Isobutylthiophan	2.54	2.05	1.79	1.58
2-(3-Methylbutyl)thiophan	2.51	2.03	1.81	1.61

It has been shown that the indirect determination of aliphatic sulphides in petroleum products from the absorption spectra of their iodine complexes[170-172] is better than potentiometric titration for determining sulphide sulphur[173,174].

2. Raman Spectra

Yur'ev, Tatevskii, and Gragerov have published data on the Raman spectra of thiophan and eight 2- and 3-alkylthiophans[175].

The characteristic frequency 690 cm^{-1} was found in all the spectra studied, and it was assigned to fully symmetrical vibrations of the thiophan ring. However, the Raman spectra of sulphides with an open chain of carbon atoms were also found to have intense frequencies in the region 600–700 cm^{-1},[176-179] assigned to valency vibrations of the C–S bond. This assignment was confirmed by a theoretical calculation of the frequencies of methyl mercaptan[180], and then of the simpler organic sulphides and disulphides[181-184].

A group of workers has shown that the frequency 690 cm^{-1} and a number of other frequencies in the region 600–740 cm^{-1} in the Raman spectra of cyclic sulphides must be related to the characteristic stretching vibrations of the C–S bonds[185-189].

A decisive interpretation of the frequencies in the Raman spectra of cyclic sulphides of the thiophan and tetrahydrothiopyran series became possible as a result of a detailed study of the cyclopentane molecule, which was chosen as a structural model of the thiophan molecule[190]; it was found that the cyclopentane ring is distorted and exists in several forms of almost the same energy, *i.e.* the distortion of the cyclopentane ring is indefinite in character[190].

On passing from cyclopentane to thiophan, *i.e.* exchanging a methylene group for a sulphur atom, the symmetry of the molecule should be largely destroyed. Since there is a large difference in mass between the sulphur atom and the methylene group, and the harmonic vibrations of the C–S bond are small compared with the vibrations of the C–C bond, the interaction of the C–S bond with the other bonds should decrease, and conditions should be such that a characteristic frequency appears for the C–S bond. At the same time, the vibrations of the ring in the thiophan molecule are apparently highly distorted, and their effect is so reduced that they are practically indiscernible in the spectra. Some workers consider that the Raman spectra cannot be used to identify such an important structural fragment as the thiophan ring[191].

The stretching vibrations of the C–S bonds in the Raman spectra of thiophans are in the region 600–700 cm^{-1}; for example, the spectra of 2,5-dimethylthiophan[189] and 2,3,5-trimethylthiophan[84] show three lines in this region. The 1450 cm^{-1} region apparently contains the deformation vibrations of the methylene and methyl groups of the thiophans; thus the frequency 1448 cm^{-1} in the spectrum of 2,5-dimethylthiophan corresponds to the frequency 1451 cm^{-1} in the spectrum of 2,3,5-trimethylthiophan.

The C–H stretching vibrations of the methylene and methyl groups appear at 2870–3174 cm^{-1}. The spectra of 2,5-dimethyl- and 2,3,5-trimethyl-thiophan, for example, show a splitting of the frequencies in this region, because of the effects of rotational isomerism and Fermi resonance[192,193].

It is difficult to utilise the results obtained in the study of the Raman spectra of saturated cyclic sulphides for

analytical purposes, because on passing from one homologue to another, many of the spectral lines change their frequency, and in most cases the spectra themselves are accompanied by a considerable background.

3. Infra-Red Spectra

Since Raman spectra are unsuitable for the identification of the ring of saturated cyclic sulphides, attempts have been made to use infra-red absorption spectra for this purpose. The C–S bonds of organic sulphides are very difficult to identify in the infra-red spectra, since the corresponding absorption bands are of very low intensity, and their position varies considerably[194].

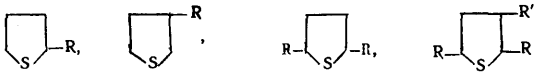
Many workers have considered the assignment of the C–S bands; for example, Thompson gives the frequency range 600–700 cm^{-1} for this group[195], while Colthup considers it absorbs in the range 675—760 cm^{-1}.[196] Sheppard[187] subdivides the region 600–700 cm^{-1} as follows:

	CH_3-S	685–705 cm^{-1};
Primary	RCH_2-S	630–660 cm^{-1};
Secondary	$RR'CH-S$	600–630 cm^{-1};
Tertiary	$RR'R''C-S$	570–600 cm^{-1}.

This division of the frequency interval is correct only for saturated open-chain sulphides.

The infra-red spectra of thiophan[18,51,190,197] and tetrahydrothiopyran[51,142,167,198] have been much studied. Thus Leonard and Figueras[142] have published the infra-red spectra of 2-methylthiophan, 2-methyltetrahydrothiopyran, and thiacycloheptane. Glazebrook and Saville[127] used the infra-red spectra of thiophan and tetrahydrothiopyran homologues for the analysis of mixtures of sulphides. The infra-red spectra of 2-propyl-, 2-butyl-, 2-isobutyl-, and 2-isopentyl-thiophan have also been recorded[63].

In investigating possible characteristic properties for analytical use in the spectra of thiophan homologues of the types:



Yur'ev, Rozantsev, and Egorov studied the infra-red spectra of the 2-alkylthiophans (R = C_2H_5, C_3H_7, C_4H_9), the 3-alkylthiophans (R = C_2H_5, C_3H_7, C_4H_9, C_5H_{11}, iso-C_5H_{11}, C_6H_{13}), 2,5-dimethylthiophan and the 2,5-dimethyl-3-alkylthiophans (R = CH_3, R′= CH_3, C_2H_5, C_3H_7, C_4H_9, iso-C_4H_9, C_5H_{11}, iso-C_5H_{11}). For these compounds, the frequencies of the C–S bond vibrations are lower in the 2-alkylthiophans (715–730 cm^{-1}) than in the 3-alkylthiophans (730–750 cm^{-1}). The characteristic band corresponding to vibrations of the carbon skeleton of the thiophan molecule has a frequency of about 1260 cm^{-1} in the monoalkylthiophans and about 1250 cm^{-1} in the trialkylthiophans[199].

Yur'ev, Rozantsev, and Egorov have described the infra-red spectra of 2-methyl-, 3-methyl-, 3-phenyl-, 3-tolyl-, 2,5-dimethyl-3-phenyl-, and 2,5-dimethyl-3-benzyl-thiophans[200]. The infra-red spectra of various bicyclic and tricyclic sulphides have been published by Birch and his coworkers[26,55,56,109,129,155]. A comparative study of the infra-red spectra of various 2-alkyltetrahydrothiopyrans (where alkyl = CH_3, C_2H_5, C_3H_7, iso-C_3H_7, C_4H_9, iso-C_4H_9)[201] has shown the existence of a series of typical bands.

The infra-red spectra which have been obtained for a large number of thiophan and tetrahydrothiopyran homologues and derivatives can be used for the successful solution of specific problems of group analysis and identification of individual organic sulphur compounds present in petroleum.

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THE CHEMISTRY OF MAGNESYLAMINES†

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COMPOUNDS

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INTRODUCTION

Magnesylamines are derivatives of nitrogenous compounds in which the nitrogen is joined to magnesium subhalide (MgX). They were first prepared by Meunier[1] in 1903 by the reaction of primary and secondary amines with Grignard reagents:

$$RNH_2+R'MgX \longrightarrow RNHMgX+R'H,$$
$$R_2NH+R'MgX \longrightarrow R_2NMgX+R'H.$$

In primary amines magnesium subhalide may substitute both hydrogen atoms with the formation of dimagnesylamines[2]:

$$RNH_2+2R'MgX \longrightarrow RN(MgX)_2+2R'H$$

Unsubstituted magnesylamine may be prepared by the reaction of Grignard reagents with ammonia, ammonium chloride[3], and chloramine[4,5]:

$$RMgX+NH_3 \longrightarrow RH+H_2NMgX,$$
$$2RMgX+NH_4Cl \longrightarrow 2RH+MgClX+H_2NMgX,$$
$$RMgX+NH_2Cl \longrightarrow RCl+H_2NMgX.$$

† Aminomagnesium halides (Ed. of Translation).

In the last case primary amines can also be formed:

$$RMgX+NH_2Cl \longrightarrow RNH_2+MgXCl.$$

The reaction depends to a large extent on the nature of the halogen in RMgX: chlorides favour the formation of amines and iodides that of the magnesylamine.

Apart from the mixed magnesylamines, symmetrical diaminomagnesium compounds, obtained by the reaction of amine with activated magnesium[6,7],

$$2RNH_2+Mg \longrightarrow H_2+(RNH)_2Mg,$$

are also known. However, they have not found wide applications.

Present developments in the chemistry of magnesylamines are concerned with increasing their application in organic synthesis and with studies on new nitrogenous compounds. About 100 different magnesylamines are now known and their number is increasing continuously. They resemble Grignard reagents in their reactivity and like them find wide application in organic syntheses.

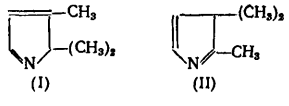
Since they are more nucleophilic than amines, they react under milder conditions and can yield compounds which cannot be prepared from free amines.

They are particularly important in the chemistry of certain heterocycles (pyrrole, indole), where they can be used for the synthesis of alkyl-derivatives, aldehydes, ketones, acids, and esters. They have been used to synthesise certain 3-, 4-, 5-, and 6-membered heterocyclic systems, alkaloids, vitamin A, and anaesthetics. They have proved to be excellent catalysts for the ketol condensation of ketones.

The time is now ripe for a general review of the chemistry of these compounds.

1. REACTIONS WITH HALOGENO-DERIVATIVES

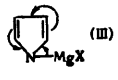
Reactions between magnesylamines and halogeno-derivatives yield products with various degrees of substitution. Thus when methyl iodide reacts with pyrrolylmagnesium bromide 2, 2, 3-trimethyl-2*H*-pyrrole (I) and 2, 3, 3-trimethyl-3*H*-pyrrole (II) are obtained[8]:



(I) (II)

A mixture of monoethyl- and dimethyl-pyrroles is formed in the reaction between pyrrolylmagnesium bromide and ethyl halide[9,10]. As a rule, pyrrolylmagnesium halide yields *C*-derivatives and only in certain cases can *N*-derivatives be obtained: the structure of these compounds was the subject of a lively discussion[9,11-14].

It can now be regarded as established that pyrrolylmagnesium halide has an Mg–N bond. This is confirmed by experiments on the determination of the active hydrogen atom in pyrrole[15] and by the inability of *N*-methylpyrrole to form a true Grignard reagent[16]. According to Nesmeyanov[17] pyrrolylmagnesium halide possesses two types of reactivity and its structure may be represented by formula (III):

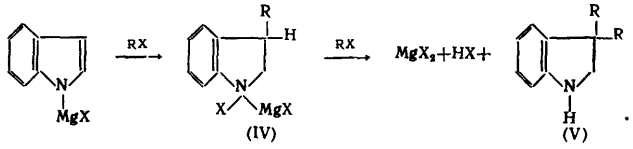


(III)

Reaction of imidazolylmagnesium bromide with methyl and ethyl iodides yields 1, 2-dimethyl- and 1, 2-diethyl-imidazoles[18].

Reaction with indolylmagnesium halide results in the formation of 3-alkyl-derivatives of indole[19].

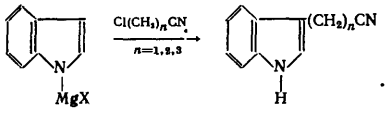
Majima and Hoshino[20] at first proposed a radical mechanism for their reaction, but later Hoshino[21] adopted a mechanism involving 1, 3-addition of alkyl halide to the pyrrole nucleus of indole:



(IV) (V)

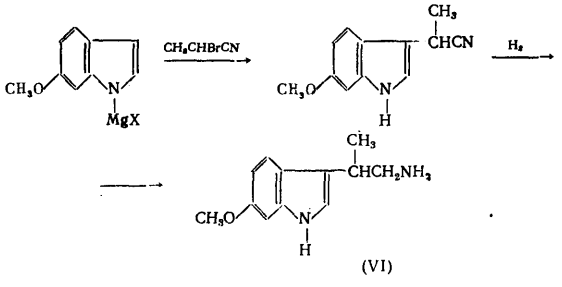
Apart from 3, 3-dialkylindoline (V), 3-alkyl-derivatives of indole can be obtained, through hydrolysis of compound(IV).

Reaction between halogeno-nitriles and indolylmagnesium halide has assumed considerable importance for the synthesis of biologically active compounds[22-25]:



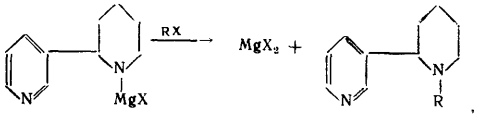
On hydrolysis of the resulting nitriles β-indolylcarboxylic acids — plant growth hormones — are obtained.

According to a patent[26], 2-(6′-methoxyindol-3′-yl)-1-propylamine (VI), which is an intermediate in the synthesis of physiologically active reserpine-like compounds, is obtained in the following way:



(VI)

Orekhov and Norkina[27] successfully employed the reaction between anabasylmagnesium iodide and alkyl halides for the synthesis of *N*-alkyl derivatives of anabasine (yield 50–60%):



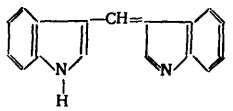
where R = CH_3, C_2H_5, $CH_2=CH-CH_2$, $C_6H_5CH_2$.

Methods based on magnesylamines have been developed for the synthesis of trimethylhydrazine (yield 25%)[28] and azino-derivatives of ketones (yield 57%)[29]:

$$CH_3NH-N(MgI)CH_3+CH_3I \longrightarrow MgI_2+CH_3NH-N(CH_3)_2,$$

$$2(C_6H_5)_2C=NMgBr+I_2 \longrightarrow 2MgBrI + (C_6H_5)_2C=N-N=C(C_6H_5)_2.$$

A complex reaction between indolylmagnesium bromide and carbon tetrachloride results in the formation of indol-3-yl(2*H*-indolyl-3-yl)methane[30]:



2. REACTIONS WITH NITRILES

Reaction between magnesylamines and nitriles results in the formation of amidines (yield 24–58%)[31]:

$$RCN \xrightarrow{R'NHMgX} RC(=NMgX)NHR' \xrightarrow{H_2O} Mg(OH)X + RC(=NH)NHR',$$

where R = n-C_4H_9, C_6H_5, *p*-$CH_3OC_6H_4$; R′ = H, CH_3, C_6H_5, $C_6H_5CH_2$.

Diphenylaminomagnesium bromide does not react with benzonitrile, probably because of steric hindrance, and benzyl cyanide yields α-cyano-β-imino-α, γ-diphenylpropane in 81% yield instead of the corresponding amide:

$$C_6H_5{-}CH_2CN \xrightarrow{R_2NMgX} C_6H_5CH{=}C{=}NMgX \xrightarrow{C_6H_5CH_2CN}$$

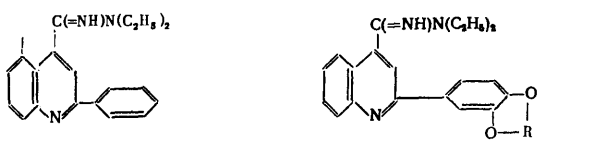
$$\longrightarrow C_6H_5{-}CH_2{-}\underset{\underset{NMgX}{\|}}{C}{-}CH(CN)C_6H_5 \xrightarrow{H_2O} C_6H_5CH_2\underset{\underset{NH}{\|}}{C}{-}CH(CN)C_6H_5.$$

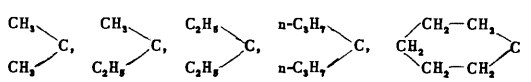
Under the same condition diethylcyanamide yields a guanidine derivative in 58% yield:

$$(C_2H_5)_2NCN \xrightarrow{(C_2H_5)_2NMgX} (C_2H_5)_2NC(=NMgX)N(C_2H_5)_2 \xrightarrow{H_2O}$$

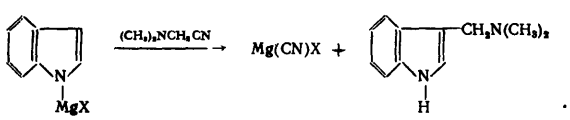
$$\longrightarrow (C_2H_5)_2NC(=NH)N(C_2H_5)_2 + Mg(OH)X.$$

Lusinhi *et al.*[32] employed the reaction between diethylaminomagnesium bromide and nitriles of substituted 2-phenylquinoline-4-carboxylic acids for the synthesis of pharmacologically active *NN*-diethylamidines of 2-(3′, 4′-dialkylmethylenedioxyphenyl)quinoline-4-carboxylic acids (yields 52–97%):

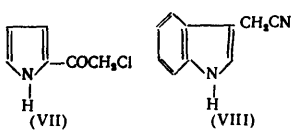


where R = 

Like alkyl halides, certain nitriles enter into exchange reactions. Thus when indolylmagnesium halide was allowed to react with dimethylaminoacetonitrile, the alkaloid harmine was obtained in 40% yield[33]:



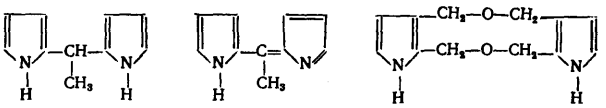
It is interesting that chloroacetonitrile behaves differently with pyrrolylmagnesium and indolylmagnesium halides, yielding 2-chloroacetylpyrrole (VII) with the first[34], and (3-indolyl)acetonitrile (VIII) with the second[23]:



(VII) (VIII)

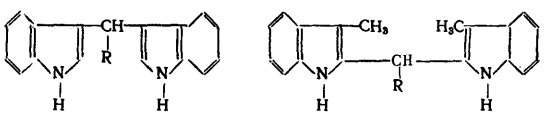
3. REACTIONS WITH ALDEHYDES, KETONES, AND QUINONES

The reaction of aldehydes and ketones with heterocyclic magnesium halide derivatives was mainly studied. It was established that pyrrolylmagnesium halide yields two products with acetaldehyde: 2, 2′-ethylidenedipyrrole (IX) and 2-[1-(2-pyrrolyl)ethylidene]-2*H*pyrrole (X)[35,36]; with formaldehyde the cyclic diether (XI) derived from 2, 3-di(hydroxymethyl)-pyrrole is formed[37]:



(IX) (X) (XI)

The ability to replace the aldehyde oxygen with two indolyl radicals is more clearly shown in reactions with indolylmagnesium halide. As a result 3,3′-alkylidene- or 3, 3′-arylidenediindoles (XII) are formed (yield up to 60%)[38–40]; when the β-position is occupied, the product is 2,2′-arylidenebis(3-methylindole) (XIII)[38–40]:



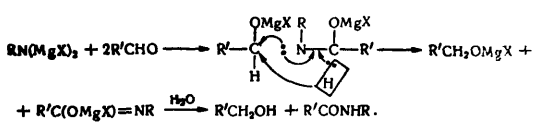
(XII) (XIII)

With benzaldehyde, aminomagnesium halide (NH_2MgX) yields hydrobenzamide and ammonium benzoate[3] and hydrazobenzene-*NN*′-dimagnesium iodide yields dibenzoylhydrazobenzene[41].

Reaction between the magnesium derivative of phenylurethane and benzaldehyde results in the formation of phenyl-α-hydroxybenzylurethane[42]:

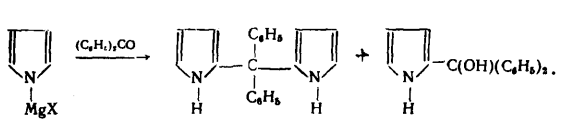
$$C_6H_5N(MgBr)COOC_2H_5 \xrightarrow{C_6H_5CHO} C_6H_5CHOHN(C_6H_5)COOC_2H_5.$$

Unlike the monomagnesylamines, dimagnesylamines react in 1:2 ratio with aromatic aldehydes with the formation of aromatic amides and alcohols[43]. The highest yields (50–90%) are obtained when the reaction is carried out in pyridine or dioxane[44]. The reaction is of the oxidation–reduction type and apparently proceeds as follows[45]:



The importance of steric hindrance in this reaction has been investigated[46].

Chelintsev *et al.*[47] showed that in ketones the carbonyl oxygen can be either replaced by two radicals with the formation of hydrocarbons (XIV) or can add on one molecule of magnesylamine halide, the corresponding substituted methanol (XV) being then formed:

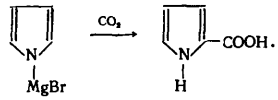


(XIV) (XV)

Reactions of magnesylamines with various ketones[39,47–49] and with anthraquinone and phenanthroquinone[50,51] have been described.

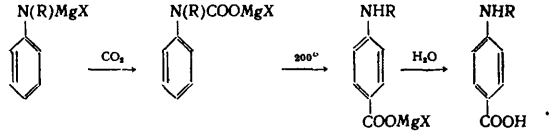
4. CARBOXYLATION

Reaction between a magnesylamine and carbon dioxide results in the formation of carboxylic acids, an important reaction for syntheses in the heterocyclic series. Thus pyrrolylmagnesium bromide and its derivatives with at least one free α-position yield α-pyrrolecarboxylic acids[52-55]:

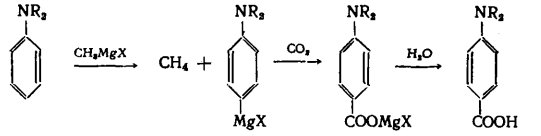


The carboxyl group enters at the β-position when both α-positions are occupied[56,57] or when the reaction is carried out at 250°–270°.[39] Indolylmagnesium halide gives 3-indolecarboxylic acid[39,53], and when the β-position is occupied, 1- and 2-indolecarboxylic acids[53].

Houben and his coworkers[58-60] proposed a method for the preparation of aromatic amino-acids (yield 50%):



p-Dialkylaminobenzoic acids are synthesised as follows[59]:



Primary aromatic amines do not give acids, since instead of rearrangement the carbamate undergoes conversion to diarylurea[58]:

$$2C_6H_5NHCOOMgX \longrightarrow C_6H_5NHCONHC_6H_5 + MgCO_3 + MgX_2.$$

Carboxylation of diphenylaminomagnesium iodide[61], hydrazobenzene-*NN'*-dimagnesium halide[41], and magnesium derivatives of aromatic amines[6,7] has been described.

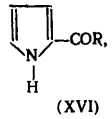
5. REACTIONS WITH ACID CHLORIDES AND ANHYDRIDES, ESTERS, AND LACTONES

Magnesylamines react in equimolar proportions with acid chlorides with the formation of amides:

$$RNHMgX + R'COX \longrightarrow MgX_2 + RNHCOR'.$$

With benzoylchloride aminomagnesium iodide gives benzamide[3], anilino-*NN*-dimagnesium halide gives dibenzoylaniline[2], hydrazobenzene-*N,N'*-dimagnesium halide gives *NN'*-dibenzoylhydrazobenzene[41], and ethoxycarbonylaminomagnesium bromide gives benzoylurethane[62].

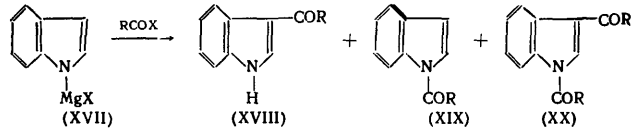
Reaction between magnesylamines, obtained from heterocycles with a secondary nitrogen atom in the ring, and acid halides yields ketones or *N*-acyl derivatives. This reaction constitutes the principal method for the synthesis of the ketones of certain heterocycles (pyrrole, indole). Thus when pyrrolylmagnesium halide reacts with acid chlorides, α-alkyl(aryl)pyrrole ketones (XVI) are formed in yields up to 80%[63-68]:



(XVI)

where R = CH_3, $CHCl_2$, CCl_3, C_2H_5, CH_3CHCl, n-C_3H_7, C_6H_5, $C_6H_5CH_2$, , , and . In the reaction of homologues of pyrrolylmagnesium halide the acyl group enters at an α-position, and when these are occupied, at a β-position[69,70].

Indolylmagnesium halide (XVII) yields 3-acyl derivatives (XVIII) and very small quantities of *N*-acyl (XIX) and 1, 3-diacyl derivatives (XX)[71]:



The quantity of (XIX) increases when the temperature is lowered. If a substituent is present at the β-position of (XVII), the acyl group enters at the α-position[72].

Pyrrolylmagnesium and indolylmagnesium halides react with dicarboxylic acid halides to form diketones[73-75]; with the acid chlorides of the corresponding ethyl half-esters, esters of keto-acids are formed[70,76-80].

Reaction between imidazolylmagnesium halide and acid halides yields alkyl-2-imidazolylketones[81], *N*-acyl derivatives being formed in the reaction between acid halides and magnesylamines derived from pyrazole[78,82,83], benzoimidazole[84], carbazole[61,85], and phenothiazine[86].

In the reaction between acid halides and magnesium halide derivatives of ketimines (intermediates in the reaction between nitrile and alkylmagnesium compounds) *N*-acyl derivatives of the ketimines were isolated[87]:

$$C_6H_5CN \xrightarrow{RMgX} C_6H_5RC{=}NMgX \xrightarrow{R'COX} C_6H_5RC{=}NCOR',$$

where R = C_2H_5, iso-C_4H_9; R' = CH_3, n-C_3H_7, iso-C_4H_9, and C_6H_5.

Acid anhydrides react similarly to the halides[88,89].

The reaction between magnesylamines and esters was first studied by Bodroux[90,91]. Its mechanism can be represented as follows:

$$2RNHMgX + R'COOR'' \longrightarrow (RNH)_2CR'OMgX + Mg(OR'')X,$$
$$(RNH)_2CR'OMgX \xrightarrow{H_2O} RNH_2 + Mg(OH)X + RNHCOR'.$$

It is evident that only half of the amine employed is converted to the amide, the second half not reacting. According to Bassett and Thomas[92], the reaction proceeds in equimolar proportions with the formation of the complex (XXI):

$$RCOOR' + R''NHMgX \longrightarrow \underset{(XXI)}{RC(NHR'')(OR')OMgX}.$$

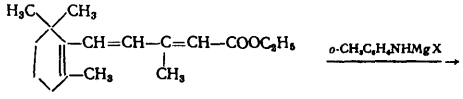
The role of the second molecule of the magnesylamine is to decompose the complex (XXI) and thus ensure the maximum yield of the reaction product. Later the Bodroux reaction was extended to esters of aromatic acids[95], halogeno-[93,94], and hydroxy-acids[86], and dicarboxylic acids[91].

Esters of chloroformic acid yield the corresponding carbamates[61]:

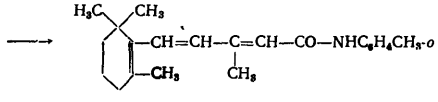
$$R_2NMgX + ClCOOC_2H_5 \longrightarrow MgXCl + R_2NCOOC_2H_5.$$

The reaction is exceptionally important in the chemistry of heterocyclic compounds since it gives the esters of the corresponding carboxylic acids in 70–80% yields. Numerous examples of this reaction are quoted in Fisher and Orth's monograph[97]. The esters of carbamic acid are also obtained when magnesylamines react with carbonic acid esters[13].

The Bodroux reaction has acquired considerable importance for the synthesis of natural polyenes (vitamin A). Kuhn and Morris[98] used it to convert the ester of β-ionylideneacetic acid (XXII) to the corresponding toluidide (XXIII), from which β-ionylideneacetaldehyde, the starting material for the synthesis of vitamin A, was obtained by the method of Braun and Rudolph[99]:



(XXII)



(XXIII).

Good results were also obtained in the synthesis of certain local anaesthetics[100,101].

Dimagnesylamines react in equimolar proportions with esters, which ensures the most complete utilisation of the amine, the yield of the aromatic amides increasing twofold[2]:

$$RCOOR' + R''N(MgX)_2 \longrightarrow Mg(OR')X + RC(OMgX)=NR'' \xrightarrow{H_2O} Mg(OH)X + RCONHR''.$$

Later this reaction was employed for the synthesis of aromatic amides of 9-hydroxyfluorene-9-carboxylic[102], mandelic[103], anthranilic[104], and *N*-substituted anthranilic acids[105].

Berdinskii and Mityanin[106] developed a method for the preparation of unsymmetrical diphenylhydrazides of carboxylic acids by allowing esters to react with diphenylhydrazo-*NN*-dimagnesium bromide (yield 70–94%):

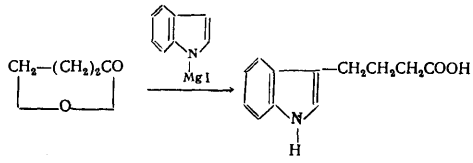
$$(C_6H_5)_2N{-}N(MgX)_2 + RCOOR' \longrightarrow Mg(OR')X +$$

$$+ RC(OMgX)=N{-}N(C_6H_5)_2 \xrightarrow{H_2O} Mg(OH)X + RCONHN(C_6H_5)_2,$$

where R = CH_3, n-C_3H_7, C_6H_5, $C_6H_5CH=CH$, *o*-HOC_6H_4.

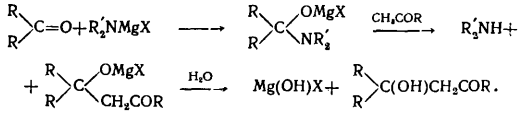
The reaction of magnesylamines with esters of heterocyclic compounds was first studied by Chelintsev and Terent'ev[12]. They established that the reaction proceeds in equimolar proportions with the formation of aldehydes and ketones: aldehydes are formed in the reaction with formic acid ester (yield 28%)[107] and ketones with esters of other acids (yield 50–60%)[108]. *N*-Acyl derivatives can also be obtained, their formation being favoured by low reaction temperature. Putokhin[109] studied in detail the effect of temperature on the reaction between indolylmagnesium halide and esters, and examined the mechanism of this reaction.

Among the lactones, only the reaction of butyrolactone, which with indolylmagnesium halide yields γ-(3-indolyl) butyric acid, was studied[110]:



6. CONDENSATION REACTIONS

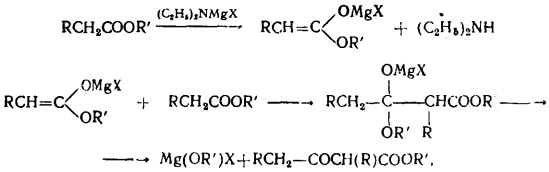
(a). Ketol condensation. Magnesylamines have proved to be excellent condensing agents for this reaction of ketones. They have made it possible to condense pinacolones and also aromatic and acyclic ketones, which enter into this reaction either with considerable difficulty or even not at all[111-113]. The condensing agents may be magnesylamines derived from primary and secondary aromatic amines. Aliphatic amines, however, are less suitable since in their presence yields are reduced from 70–80 to 10%[114]. The reaction proceeds as follows:



It has been employed for the condensation of the same and two different ketones[111-117].

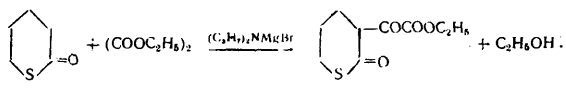
Chelintsev and Pataraya[117] established that, depending on the ease of removal of the hydroxyl group, unsaturated ketones may be obtained together with the ketols.

(b). Ester condensation. Hauser and Walker[118] found that magnesylamines can catalyse ester condensation. The reaction proceeds rapidly and with high yield of β-keto-acid esters (up to 75%). Diethylaminomagnesium bromide proved to be the best reagent for this purpose. The authors proposed the following reaction scheme:



where R = H, CH_3, CH_3CH_2, C_6H_5; R' = C_2H_5, $C_6H_5CH_2$. Good results were also obtained in mixed ester condensation.

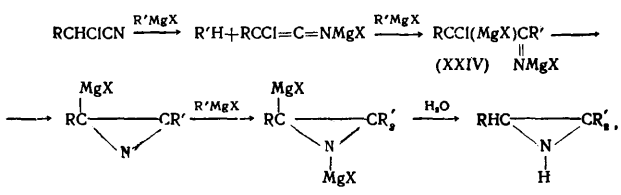
A disadvantage of the method is the fact that apart from ester condensation a competing amide-forming reaction may also occur. For example, in the case of isobutyric and isovaleric acid esters the amides of the initial acids were obtained instead of the β-keto-acid esters. Korte and Buchel[119] successfully employed diisopropylaminomagnesium bromide in the condensation of δ-thiovalerolactone with oxalic acid ester; α-ethoxyoxalyl-δ-thiovalerolactone was obtained in 74% yield:



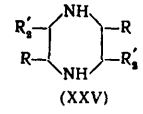
Thus magnesylamines have proved to be extremely active condensing agents.

7. USE OF MAGNESYLAMINES FOR THE SYNTHESIS OF HETEROCYCLES

Magnesylamines have found application in the synthesis of heterocyclic compounds. Thus ethyleneimine derivatives are obtained when Grignard reagents react with α-chloro-nitriles[120,121]:

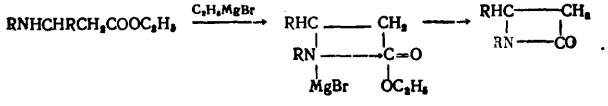


where R and R′ = C_2H_5; R = C_3H_7, R′ = C_2H_5; R = iso-C_4H_9, R′ = C_2H_5. The ethyleneimine ring closes when magnesium halide is split out from the ketimine derivative (XXIV). Together with the ethyleneimine derivative, a dimeric product, a piperazine derivative (XXV), is also formed:



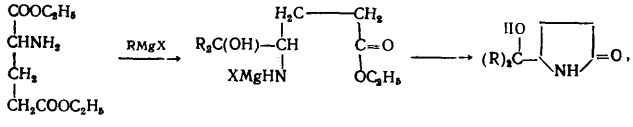
(XXV)

A method for the preparation of β-lactams, based on the cyclisation of β-amino-acid esters, has been developed[122,123]. The reaction proceeds *via* a stage in which an *N*-magnesium bromide derivative of the ester is formed, which increases the electron density at the nitrogen atom and facilitates the closure of the β-lactam ring:



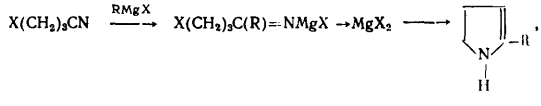
This method was developed further in studies on the synthesis of penicillin and was used for the preparation of a number of azetidines which are structurally related to penicillin[124]. A disadvantage of the method is the intermolecular formation of open-chain amides together with β-lactam cyclisation. This occurs particularly in experiments with unsubstituted esters of β-amino-acids. Thus unsubstituted 2-azetidinone was obtained in only 0.76% yield[125].

Under the action of Grignard reagents ethyl glutamate cyclises to yield pyrrolidone derivatives[126]:



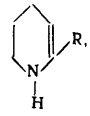
where R = CH_3, C_2H_5, n-C_4H_9, C_6H_5, $C_6H_5CH_2$.

γ-Halogeno-nitriles were employed for the synthesis of pyrroline derivatives (yield 41–69%)[127-132]:



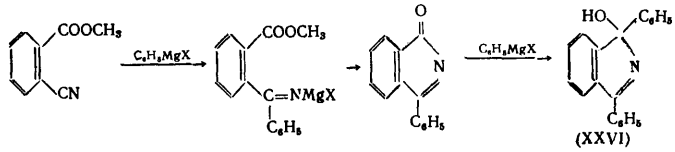
where R = C_2H_5, C_6H_{11}, C_6H_5, $C_6H_5CH_2$, *o*(*m*,*p*)-$CH_3C_6H_4$. Pyrrolines are also obtained in a small yield (11%) when Grignard reagents act upon γ-phenoxybutyronitrile[131].

Similarly δ-chlorovaleronitrile readily yields α-substituted tetrahydropyridine derivatives (yield 22–66%)[133]:

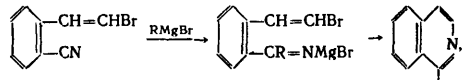


where R = n-C_4H_9, C_6H_{11}, C_6H_5, *p*-ClC_6H_4, *p*-$CH_3C_6H_4$.

All these reactions proceed *via* a stage in which magnesylamines are formed. Magnesylamines function as intermediates in the conversion of methyl *o*-cyanobenzoate to 1-hydroxy-1, 3-diphenylisoindole (XXVI) (yield 90%)[134] and of *o*-cyano-ω-bromostyrene to isoquinoline derivatives (XXVII) (yield 4–15.5%)[135]:



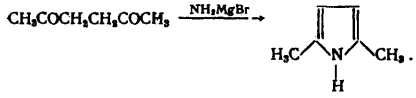
(XXVI)



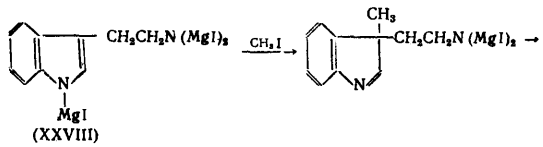
(XXVII)

where R = CH_3, C_6H_5, $C_6H_5CH_2$.

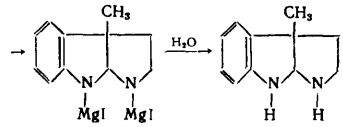
Oddo and Calderaro[3] found that reaction between aminomagnesium halide and acetonylacetone yields dimethylpyrrole:



Magnesylamines have been used for the preparation of tricyclic systems from indole derivatives. Hoshino and Tamura[23] prepared dinordeoxyeseroline (XXIX) from a trimagnesyl derivative of tryptamine (XXVIII) and methyl iodide:

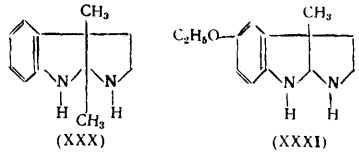


(XXVIII)



(XXIX)

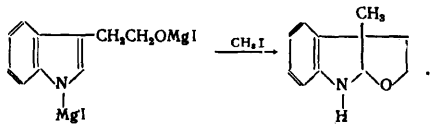
Similarly the methyl derivative of dinordeoxyeseroline (XXX)[23] was prepared from 2-methyltryptamine, and dinoreseretol (XXXI) from 5-ethoxytryptamine[136]:



(XXX) (XXXI)

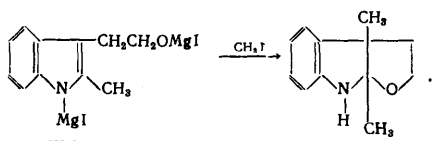
These investigations were of considerable importance for the synthesis of the fundamental cyclic structure of the alkaloid physostigmine.

Hoshino[137] also converted tryptophol (XXXII) to the furanoindoline (XXXIII):



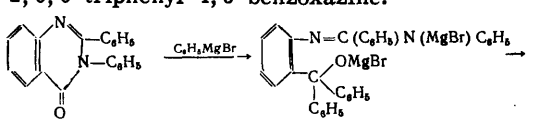
(XXXII) (XXXIII)

Very recently this reaction was employed[138] for the closure of the furan ring in 2-methyltryptophol (XXXIV):

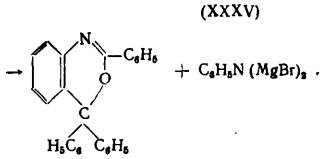


(XXXIV)

Mustafa and his coworkers[139] found that reaction of phenylmagnesium bromide with 2,3-diphenyl-4-quinazolone yields 2, 6, 6-triphenyl-4, 5-benzoxazine:



(XXXV)

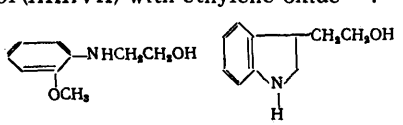


This reaction also goes *via* a stage in which a magnesylamine complex (XXXV) is formed.

8. OTHER REACTIONS

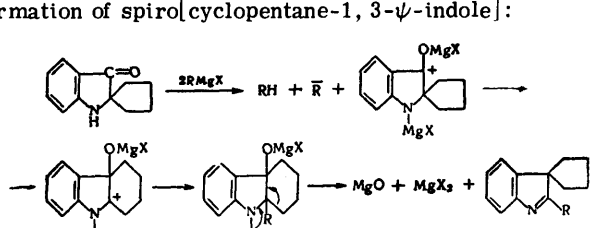
Reactions of magnesylamines with sulphur dioxide[140], hydrogen peroxide[141], ferric chloride[142], halides[9], phosphorous trichloride[143], and amides[144] have been described.

Dithiocarboxylic acids[54,140] were isolated in reactions of pyrrolyl- and indolyl-magnesium halides with carbon disulphide, the reactions with sulphonyl chloride yielding sulphones[140]. Alkene oxides react with ring opening to yield the corresponding alcohols. Thus *o*-methoxyanilinomagnesium bromide gave *o*-methoxyphenylaminoethanol (XXXVI)[145] and indolylmagnesium halide gave 2-(3′-indolyl)ethanol (XXXVII) with ethylene oxide[137]:



(XXXVI) (XXXVII)

Witkop and Patrick[146] showed that under the action of alkylmagnesium halide spiro[cyclopentane-1, 2′-ψ-indoxyl] undergoes the Wagner–Meerwein rearrangement with the formation of spiro[cyclopentane-1, 3-ψ-indole]:



It is thus evident that the rearrangement proceeds *via* a stage in which a magnesylamine is formed.

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Perm Pharmaceutical Institute

THE CHEMISTRY OF THE POLYMYXINS AND RELATED ANTIBIOTICS

Z. T. Sinitsyna and S. M. Mamiofe

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INTRODUCTION

The polymyxins are the most powerful and most specific antibiotics against gram-negative bacteria. The polymyxins are very effective in the treatment of several diseases (dysentery, gastroenteritis, meningitis, etc.) due to gram-negative microorganisms. A very valuable property of the polymyxins is their ability to suppress the growth of *Pseudomonas aeruginosa*, which is almost unaffected by other antibiotics and frequently produces suppurating and intestinal infections. The polymyxins comprise a group of antibiotics, very closely related both chemically and biologically, produced by various strains of *Bacillus polymyxa* and related species[1].

The polymyxins were discovered at the same time in 1947 by three independent groups of research workers in America and Great Britain[2-6]. The polymyxins A and D, which were first isolated, although highly active therapeutically, were also nephrotoxic. The polymyxins B, E, and C, prepared later, had a similar therapeutic activity but the first two were not nephrotoxic[7-10]. The related antibiotics, denoted A, B, C, D, and E, were combined in one polymyxin group[6,10,11].

In 1946 a strain of *Bacillus polymyxa*, which produced a new type of polymyxin termed polymyxin M, [12,13] was isolated from Moscow soil. Further studies showed that polymyxin B consists of two closely related antibiotics, polymyxin B_1 and polymyxin B_2. [14,15] In addition to the polymyxins, the related antibiotics circulins A and B, [16,17] the colistins (colimycins) A, B, and C, [18-20] and the polypeptins[21] may be assigned to this group.

As all types of polymyxins show great similarities in structure and properties, and they have always been studied in parallel, it is useful to examine them together, dealing with other representatives of this antibiotic group in separate paragraphs.

1. THE POLYMYXINS

General characteristics. The polymyxins are readily formed during the growth of *Bacillus polymyxa* on a medium containing various nutrients. The antibiotic may be isolated from the fermentation broth by methods based on precipitation, extraction, or sorption[22-28].

The similarity in physicochemical properties is due to the closely related chemical structures of this group of antibiotics. All the polymyxins are basic polypeptides that form a series of salts with acids[3,13,14,22,26-34], some of which have been obtained crystalline. They all give characteristic biuret and ninhydrin reactions, and negative Mollisch, Sakaguchi, Pauli, and Hopkins–Cole reactions[3,32-35]. All the polymyxins are optically active: $[\alpha]_D^{25}$ for polymyxin B_1 = -85.1° (C = 2.33 in 75% ethanol)[15], and for polymyxin M $[\alpha]_D^{25}$ = -48.1° (C = 2.505 in water)[13]. The most extensively studied amorphous salts, the sulphates and the hydrochlorides, are readily soluble in water and in methanol. Polymyxin M sulphate is insoluble in methanol†[26]; the hydrochlorides and sulphate are sparingly soluble in ethanol and other organic solvents[3,14,26,34,36,37]. The picrates are insoluble in water, readily soluble in methanol, ethanol, and acetone[34]. A compound of polymyxin B with formalin and $NaHSO_3$ is considerably less toxic than the sulphate or hydrochloride; similar compounds have also been obtained with other aldehydes[3,38-40].

Dry polymyxin salts retain their activity for several years. Aqueous polymyxin solutions are also fairly stable and retain their activity at room temperature for long periods at pH 3–5. Alkaline solutions are much less stable than acid solutions[3,33,36]. Silaev[41] found that a solution of polymyxin M in 0.1 N ammonia at 37°–38° lost nearly all its biological activity in three days; his report includes a preliminary discussion of the mechanism of inactivation of polymyxin M.[41] A report[42] has also appeared on the thermal decomposition of polymyxin B.

As has been pointed out above, all the antibiotics of this group are similar, both biologically and chemically. A more detailed study has revealed some differences in their composition and properties. All the antibiotics of the group are basic polypeptides, the basicity being due to the presence of considerable amounts of $\alpha\gamma$-diaminobutyric acid ($\alpha\gamma$-DABA); they all contain threonine and a fatty acid, identified, with rare exceptions, as 6-methyloctanoic acid (MOA). The absence of free carboxyl and α-amino-groups indicates that they have a cyclic structure; this has been demonstrated for most of the polymyxins B (B_1 and B_2)[14,15,43-46], and D[30] and M[13] that have been investigated. Polymyxin A, previously known as aerosporin‡, has been studied less[30,33,49-53], and there are only a few published references to the polymyxins C and E.[10,11,29,54,55]

In this review, work done in recent years on the structure of the polymyxins B and M and on circulin A will be examined in detail and data on the other antibiotics of this group will be referred to briefly.

The polymyxins differ from one another both quantitatively and qualitatively in their amino-acid composition (Table 1), infra-red absorption spectra[60], mobility on paper chromatograms, as well as in several other properties[11,13,61-63]. Because of differences in basicity, the polymyxins B and E are precipitated from aqueous solutions of their salts, when these are made alkaline,

† A commercial sample of polymyxin B sulphate (7757 units mg^{-1}) behaved in the same way: there is therefore some doubt about the data of Buckwalter[36] on the solubility of polymyxin sulphate in methanol.

‡ "Aerosporin" is now a trade mark [of Burroughs Wellcome and Co. (Ed. of Translation)] for polymyxin B[47,48].

TABLE. Comparative amino-acid composition of different types of polymyxin and related antibiotics.

Antibiotic	Amino-acid composition: leucine	L-isoleucine	L-Threonine	D-serine	phenylalanine	α, γ-diaminobutyric acid	Aliphatic acid	References
Polymysin								25, 30, 33
A	+D	—	+	—	—	L+D, L	MOA	49, 52, 56
B_1	1L	—	2	—	1D	6(1D+5L)	MOA	15, 25, 56
B_2	1L	—	2	—	1	6	isooctanoic	
C	—	—	+	—	+L	+	+	10, 25, 56
D	1D	—	3	1	—	5L	MOA	25, 30, 56
E	+D	—	+	—	—	+L	+	20, 25, 56
M	1D	—	3	—	—	6	1	13, 57
Circulin A	1D	1	2	—	—	6L	MOA	17, 58
Colistin	2(L+D)	—	1	—	—	5	MOA	20, 59
Polypeptin*	2L	1	1	—	1D	3L	hydroxyheptanoic acid	21, 25, 56

* In addition to the acids indicated, polypeptin contains one molecule of D-valine.

Note: 1. The figures in the columns denote the number of residues of the amino-acids in the antibiotics.
2. The symbol + indicates the presence of the given amino-acid or an unknown aliphatic acid when the number of residues has not been established.
3. The symbol - indicates the absence of amino-acid residues or of an unknown aliphatic acid.

whereas the polymyxins A, C, D, and M remain in solution under similar conditions§.

The properties and chemical composition of this group of compounds have been studied by countercurrent distribution, spectroscopic analysis, different kinds of chromatography, etc. The special part played by chromatographic methods should be emphasised; these have been widely used in detecting both the separate amino-acid components of the polymyxin molecule and the larger low-molecular peptide fragments formed by partial hydrolysis. Compounds of similar composition behaved completely differently in paper chromatography with certain solvent systems, and this has enabled polymyxins A and D, for example, to be separated[30]. Polymyxins A, B, C, D, and E showed different rates of movement in the 1-butanol–15% acetic acid (1:1) system[64]. Polymyxins B and M differed in their mobilities in the butanol–acetic acid–water (2:1:1) system[13,57], etc.

Molecular weight. The molecular weights of the fairly large polymyxin molecules have been determined in different ways; the mean molecular weight is about 1200. Using osmotic pressure measurements, British workers found the molecular weight of polymyxin A to be 1293, and that of polymyxin D 1115.[30] From a study of monomolecular films of the four polymyxins, A, B, D, and E on the surface of an air–water interface, Few and Schulman[65] concluded that the molecular weights of the members of the polymyxin group differ little from one another, the average being 1250. Hausmann and Craig[15] used the method of partial dinitrophenylation, which had previously been used in the study of polypeptin and other peptides[66,67]. Partial dinitrophenylation with subsequent separation of the reaction products by paper electrophoresis has been used[68] to determine the molecular weight (1185 ± 25) of polymyxin M. Other workers[69] obtained similar results by determining the equivalent weight of polymyxin M by ion-exchange sorption. It has been shown that this antibiotic behaves here as a tetravalent ion and the equivalent weight is 280.

Amino-acid composition. The amino-acid composition of the polymyxins was studied using acid hydrolysates from which the fatty acid had first been thoroughly removed. With polymyxin B (B_1 + B_2),[15] the residue after evaporation under diminished pressure was subjected to countercurrent distribution in the system 1-butanol–2-butanol–5% HCl (1:1:2). The fractions containing phenylalanine and leucine were analysed spectrophotometrically (λ = 259 mμ). The mixture of these amino-acids was separated by further countercurrent extraction; $\alpha\gamma$-DABA and threonine, which moved together in the distribution, were also completely separated on redistribution. All four amino-acids were recrystallised and obtained analytically pure. This established that polymyxin B_1 contains $\alpha\gamma$-DABA, threonine, leucine, phenylalanine, and an aliphatic acid, identified as 6-methyloctanoic. Whether the amino-acids belonged to the L or D series was determined by means of acid D-amino-acid oxidase, which selectively destroys D-amino-acids. After the hydrolysate had been treated with the enzyme, phenylalanine was not found on the chromatogram, and the relative amount of $\alpha\gamma$-DABA decreased considerably (from 6 to 5 residues). This showed that all the component amino-acids in the polymyxin B molecule belong to the L series, with the exception of phenylalanine and one $\alpha\gamma$-DABA residue, which have the D-configuration[46]. The configuration of the leucine residue in polymyxin A was established in the same way[33,51].

A study of the amino-acid composition of polymyxin M by qualitative and quantitative paper chromatography, with subsequent isolation and identification of the amino-acids produced by hydrolysis, showed that the molecule contains one D-leucine, 3 L-threonine, and 6 $\alpha\gamma$-DABA residues[13,57]. This was confirmed by countercurrent distribution of the dinitrophenylation products of the hydrolysates of polymyxin M.[13] Polymyxin M therefore differs in its amino-acid composition from all known types of polymyxin and from related antibiotics, with the exception of polymyxins E and A. Polymyxin M differs markedly from polymyxin A in not being nephrotoxic, and from polymyxin E in that it is not precipitated at alkaline pH values[13].

Nature of the free groups. The nature of the free (end) groups in the molecule of polymyxin and related antibiotics was investigated by the methods generally used in examining peptides. Ordinary and formol titration showed[30] that the polymyxin D molecule contains no free carboxyl groups. An attempt to find carboxyl groups in the polymyxin B molecule by the thiohydantoin method[46], or by the action of diazomethane[43] on polymyxin B_1, led to the same results. The electrophoretic behaviour of polymyxin M and its dinitrophenyl derivative also indicates that the molecule contains no free carboxyl groups. This was confirmed[13,57] by the reaction of polymyxin M with hydrazine. All tests showed that a free carboxyl group was definitely absent. The nature of the free amino-groups in the polymyxins was investigated by converting them

§ In earlier papers it was stated that polymyxins A and D can also be precipitated as bases[22,30].

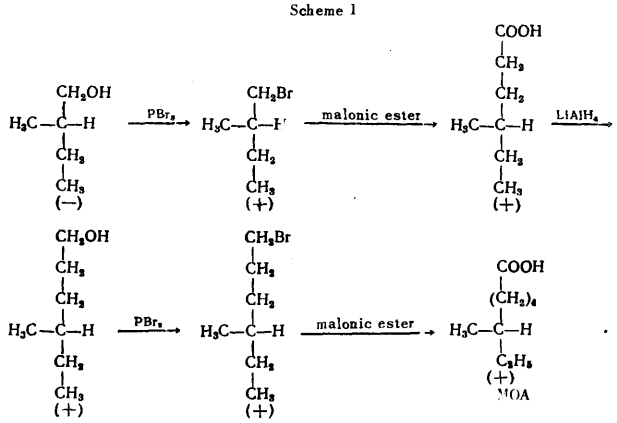
to dinitrophenyl derivatives, which were then hydrolysed [13,30,43,57,70]. γ-(2,4-Dinitrophenyl) (γ-DNP) derivatives of $\alpha\gamma$-DABA were isolated from the hydrolysates and identified by comparison with the dinitrophenyl derivatives of a synthetic specimen of $\alpha\gamma$-DABA. The absence of any other dinitrophenyl amino-acid in the hydrolysates of the dinitrophenyl derivatives of the polymyxins indicates that the free amino-groups in the polymyxin molecule are the γ-amino-groups of $\alpha\gamma$-DABA. However, Bell *et al.* [30] discovered a small amount of unsubstituted L-$\alpha\gamma$-DABA, together with the dinitrophenyl derivatives, in the total hydrolysate of polymyxin D, and since 4 moles of γ-DNP-$\alpha\gamma$-DABA were obtained on quantitative chromatographic analysis of the hydrolysate, it was concluded that the γ-amino-group of this acid was acylated with 6-methyloctanoic acid.

In the same way, it was shown that the hydrolysate of the dinitrophenyl derivative of polymyxin M also contains one molecule of unsubstituted $\alpha\gamma$-DABA, which forms amide links involving its γ- as well as α-amino-group. Polymyxin M [57] may have a branched peptide chain involving one $\alpha\gamma$-DABA amino-group, similar to that in polymyxin B. [43]

Aliphatic acid. As mentioned above, all the polymyxins have an aliphatic acid component; this was extracted from the acid hydrolysate with ether and purified [13,15,30,32] by distillation under reduced pressure, or through its bromothiuronate salt. A comparison of the infra-red spectra and also the analytical results on the amides and silver salts of this acid with those of a synthetic sample, showed that all the known types of polymyxin and related antibiotics contain L(+)-6-methyloctanoic (isopelargonic) acid in the molecule, except for polymyxin B_2 which contains isooctanoic acid [15], identical with the acid previously discovered in the fat isolated from wool [14,30,31,33,52,71-75].

Several methods have been published for the synthesis of racemic and optically active methyloctanoic acid. Syntheses [71,76] from L(-)-2-methylbutan-1-ol, which confirm that it has the L-configuration, deserve attention. A synthesis [75] published in 1960 differs from previous syntheses in being much simpler (Scheme 1).

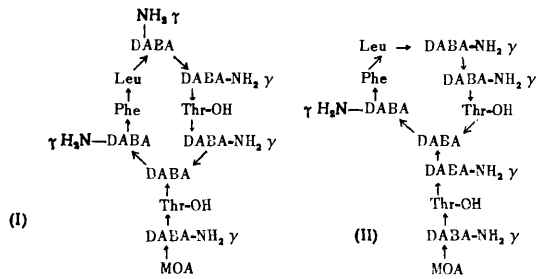
Scheme 1



Amino-acid sequence in the polymyxin B (B_1 and B_2) molecule. Two groups of workers have been independently engaged in studying the sequence of the amino-acid residues in the polymyxin B molecule. Hausmann [43] has given a detailed account of these investigations, which may be summarised as follows. Fully substituted dinitrophenylpolymyxin B_1 was partially hydrolysed with acid, and the resulting mixture of peptides was fractionated by numerous dialyses and countercurrent distributions in different solvent systems; fourteen DNP-substituted peptides were isolated pure. Subsequent detailed examination of these peptides and their dinitrophenyl derivatives, before and after hydrolysis, by means of countercurrent distribution, electrophoresis, and paper chromatography revealed the positions of all the amino-acids. On the basis of these results, the author suggests an empirical formula and two possible structural formulae for polymyxin B_1 (Scheme 2).

Scheme 2

Proposed structure of polymyxin B_1 ($C_{56}H_{98}O_{14}N_{16}$) [43]
(the arrow indicates the direction from CO to the NH group)



Symbols: DABA-$NH_2\gamma$ = $\alpha\gamma$-diaminobutyric acid residue, Leu = leucine residue, Phe = phenylalanine residue, Thr = threonine residue, MOA = 6-methyloctanoic acid residue.

Structure I in Scheme 2 is a large ring consisting of 8 amino-acids with a peptide side-chain terminating in a 6-methyloctanoic acid residue. The only difference in Structure II is that one DABA residue is in the side-chain instead of in the ring, which now contains seven amino-acids. To decide on one of the two proposed structures, it would be necessary to isolate the peptide MOA → DABA → → Thr → DABA → DABA → Phe. However, the peptide bond with the threonine amino-group is unstable to acids, which makes it impossible to separate a peptide without an *N*-terminal threonine.

French workers [46,76-78] used the strongly acidic cation exchanger Dowex-50 to separate the products of partial hydrolysis of polymyxin B. Seven different buffers were used for fractional elution. The peptides separated were determined qualitatively and quantitatively by one- and two-dimensional paper chromatography. The peptides containing phenylalanine were isolated from the acid hydrolysate by chromatography on specially treated activated charcoal. The fractions eluted from the charcoal with distilled water saturated with ethyl acetate and carbon disulphide were examined by paper electrophoresis. Having determined the structure of the peptides isolated, most of which were identical with those isolated and studied by Hausmann, and having established the absence of free α-amino- and carboxyl groups, the authors also arrived at 8- or 7-amino-acid structures with the same sequence of amino-acid residues as had been proposed by the American workers.

The main difficulty in making a choice between the structures is the lack of an enzyme [13,46] that would selectively cleave the peptide at the required link. It was also not clear at which of the two amino-groups (α or γ) of diaminobutyric acid the chain branches.

Several workers attempted to synthesise polymyxin B to confirm the porposed structure. In 1959, a synthesis[75,79,80] of polymyxin B_1 was published. For this purpose several low-molecular peptides were prepared including the pentapeptides I and II:

$$\text{For} \rightarrow \text{L-Leu} \rightarrow \text{L-DABA} \rightarrow \text{L-DABA} \rightarrow \text{L-Thr} \rightarrow \text{L-DABA-OH}; \quad \text{(I)}$$

$$\begin{array}{l} \qquad\qquad\quad \text{H} \rightarrow \text{L-DABA} \rightarrow \text{L-DABA} \rightarrow \text{D-Phe} - \text{OCH}_3. \\ \qquad\qquad\quad\ \uparrow \qquad\qquad\quad\ \uparrow \\ \text{MOA} - \text{D-DABA} \rightarrow \text{L-Thr} \qquad \gamma\text{-Tos} \\ \qquad\ \downarrow \\ \qquad \text{CBO} \end{array} \quad \text{(II)}$$

Some of the peptides had been previously known and described, but some were prepared and characterised as new compounds for the first time. Cyclicpeptides giving a negative ninhydrin reaction and containing all the component amino-acids were obtained from the polypeptides I and II by the carbodiimide method, the amino-groups being protected by various residues, such as the formyl (For), the carbobenzyloxy(CBO) and the *p*-toluenesulphonyl(Tos). The free decapeptide was obtained by removing the protecting groups with sodium in liquid ammonia. The structure of the polypeptide fully agreed with the proposed structure I (Scheme 2). Comparative chromatography on paper, and also comparison of the biological activity of synthetic and natural specimens of polymyxin B sulphate showed that their mobilities on paper were close, but the synthetic was less active biologically. According to the authors, further purification of the synthetic preparation and a comparison with polymyxin B_1 are required.

2. CIRCULIN

We shall now describe polypeptide antibiotics closely related to polymyxin, the most extensively studied being circulin, first described in 1948.[16,81-86]

Like the polymyxins, circulin is a basic polypeptide that forms salts with acids. It acts selectively on gram-negative microorganisms, but differs in its amino-acid composition (Table) and also in its behaviour with lipase and with alkali[81,82,85,86], in the presence of which it is completely inactivated; this does not occur with the polymyxins[87,88].

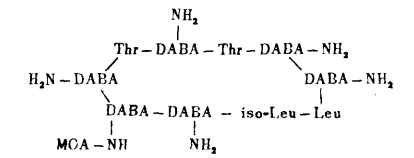
Several papers[82,83,86] have been published on the chemical composition and structure of circulin. However, they are not entirely reliable, as the investigations were made on samples that were not sufficiently homogeneous. It was later shown[17] by paper chromatography that circulin consists of two closely related antibiotics, circulin A and circulin B.

Finally, the amino-acid composition and structure of circulin A were established by Koffler and his coworkers; the results of this work were reported in 1958 at the Fourth Biochemical Congress in Vienna[58]. Five of the six γ-amino-groups of $\alpha\gamma$-DABA were found to be free. It was shown conclusively that the aliphatic acid residue is linked to the cyclicpeptide not through the threonine hydroxy group, as had been previously suggested[86,87], but through the *N*-acyl link with the γ-amino-group of DABA.[89] This agrees well with the following facts: (1) no hydroxamic acid was obtained when circulin A hydrochloride was treated with hydroxylamine; (2) on hydrolysis, in addition to dinitrophenyl-substituted amino-acids and an aliphatic acid, the dinitrophenyl derivative of circulin A gives one molecule of unsubstituted $\alpha\gamma$-DABA; this was not found after hydrolysis of the dinitrophenyl-substituted cyclicpeptide without the aliphatic acid residue; (3) the fragment isolated on partial hydrolysis of circulin A hydrochloride contained DABA and MOA in the ratio 3:1; α-amino-γ-(2,4-dinitroanilino)butyric acid and DABA were isolated from the DNP derivative of this peptide in the ratio 2:1.

To elucidate the amino-acid sequence in the molecule, circulin was partially hydrolysed in the same way as polymyxin B_1, and the structures of the low-molecular peptides were determined by dinitrophenylation and with the enzyme carboxypeptidase. The following structure was proposed for circulin A (Scheme 3):

Scheme 3

Structural formula of circulin



It was shown by the same workers that circulin is a lipopeptide antibiotic, which destroys the microorganisms that are sensitive to it by acting on the cell envelopes or on the cytoplasmic membranes. To elucidate the relation between its bactericidal action and molecular structure, circulin was subjected to partial changes, and the individual fragments were tested for antibacterial activity in parallel with the intact circulin. It was shown that the cyclicpeptide without the aliphatic acid was several times less active than the intact antibiotic[90]; this also applied to other fragments of the molecule.

3. COLISTIN (COLIMYCIN)

The antibiotic colistin was described by Japanese workers[18,20] in 1950, and it was extensively studied in Japan, Italy, and France under the names colistin and colimycin. Salts of colistin with various acids have been described and also its derivative with formaldehyde and sodium bisulphite, termed sodium colistinmethanesulphonate[20,91-95]. The antibiotic is characterised by thermal stability and very high stability towards acids, pepsin, and pancreatin[96].

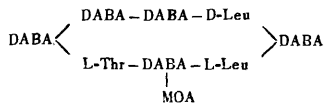
Using paper chromatography, the Japanese workers[19] established the presence of three components, colistins A, B, and C; these were characterised by different R_f values. Examination of the acid hydrolysate by paper chromatography established the qualitative amino-acid composition of colistin and the nature of the aliphatic acid[94,97]. Further studies by a variety of modern methods enabled the quantitative amino-acid composition to be established. Colistin contains L-$\alpha\gamma$-DABA, L-threonine, D-leucine, L-leucine, and methyloctanoic acid(MOA) in the ratios 5:1:1:1:1 (Table). Four free amino-groups and one hydroxy-group were found to be present. The molecule does not contain terminal carboxyl or amino-groups, and it has a cyclicpeptide structure, like other members of this antibiotic group.

Seven peptides were isolated[59,91] from the partial-hydrolysis products and characterised by ion-exchange chromatography, paper electrophoresis, and other

methods. The amino-acid sequence was established[63] and the following structural formula was proposed (Scheme 4)[20]:

Scheme 4

Proposed structure of colistin



4. POLYPEPTIN

Polypeptin is an antibiotic of this group that should be considered somewhat separately; in addition to the components common to all members of the group, it contains D-valine[66], a unique component. By countercurrent distribution, the antibiotic was separated into two polypeptides closely related in amino-acid composition[67]. One of these was studied in greater detail, and its molecular weight and amino-acid composition have been established (Table). Polypeptin differs from the antibiotics of the group considered here, not only in its amino-acid composition, but also in the aliphatic acid residue, which, according to Craig[25,26], is probably hydroxyheptanoic acid.

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THE INTERMOLECULAR TRANSFER OF ENERGY DURING THE RADIOLYSIS OF SOLUTIONS OF ORGANIC SUBSTANCES

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1. TRANSFER OF ENERGY DURING THE RADIOLYSIS OF LIQUID MIXTURES

In the chemical action of ionising radiation on a substance the absorption of the energy of the radiation leads to the formation of ions and excited molecules capable of further chemical changes. The decomposition of, or any other change in the ions and excited molecules, taking place with the rupture or formation of a new chemical bond, is called the "primary" radiochemical process, and the resulting products (for example ions, free radicals, or molecules) are called primary radiolysis products. The primary radiolysis products may react with one another or with other molecules to give secondary products.

Unlike light, ionising radiation is not absorbed selectively by substances, since the absorbing power of the latter with respect to radiation is determined by their electron density, *i.e.* by the number of electrons in unit volume. It is therefore usually assumed that when ionising radiation acts on a multicomponent system, the radiation energy absorbed by each component is proportional to its electronic fraction in the mixture. The electronic fraction of a given component (ε_i) is defined by the expression

$$\varepsilon_i = \frac{n_i e_i}{\sum_i n_i e_i}, \qquad (1)$$

where n_i is the mole fraction of the i-th component in the mixture and e_i the number of electrons in the molecule of this component.

Accordingly, we can formulate an additivity (averaging) rule, for the radiolysis of multicomponent mixtures, according to which the yield of the primary products of the radiochemical change for each component of the mixture should be proportional to the electronic fraction of the component.

The additivity rule has been confirmed in the study of the radiolysis of binary mixtures of certain organic liquids (benzene–toluene[1], methyl methacrylate–ethyl acetate[2], methyl methacrylate–styrene[3], cyclopentane–cyclohexane[4], etc.).

Muccini and Schuler[4] studied the radiolysis of cyclopentane–cyclohexane mixtures and showed that in the presence of iodine, which reacts with the cyclopentyl and cyclohexyl radicals formed during the radiolysis, the yields of cyclopentyl iodide and cyclohexyl iodide are proportional to the electronic fractions of the corresponding hydrocarbons. At a high dose rate ($\sim 2 \times 10^5$ r sec^{-1}) the yields of cyclopentylcyclopentane, cyclohexylcyclopentane,

and cyclohexylcyclohexane correspond to the additivity rule if it is assumed that at this dose rate the recombination of the radicals formed initially is more rapid than their reaction with hydrocarbon molecules.

However, it has been shown that the additivity rule is not obeyed during the radiolysis of many binary mixtures. Thus Manion and Burton[1], who studied the dependence of the radiation yield† of hydrogen $G(H_2)$ on the composition of a cyclohexane–benzene mixture, found that $G(H_2)$ decreases sharply with increase in the proportion of benzene in the solution. If it is assumed that the hydrogen evolved during the radiolysis of a cyclohexane–benzene mixture is formed either by the primary decomposition of excited molecules, for example

$$C_6H_{12}^* \rightarrow C_6H_{10} + H_2, \qquad (2)$$

or by the reaction of the atomic hydrogen, formed during the primary decomposition, with hydrocarbon molecules, then the yield of hydrogen is equal to the yield of excited hydrocarbon molecules decomposing with the formation of H_2 and H. Thus according to the additivity rule it would be expected that $G(H_2)$ would decrease linearly with increase in the electronic fraction of the component most stable to radiation, *i.e.* benzene. The more rapid decrease in $G(H_2)$ than expected from the additive scheme was attributed by the authors to the fact that radiation energy, absorbed initially by the cyclohexane, is later transferred to the benzene, whose molecules have a higher probability of deactivation.

Generally speaking, the transfer of energy from a component less stable to radiation to a more stable component usually leads to an increase in the stability to radiation of the whole system, the so-called "sponge type protection", and the dependence of the yield of primary radiolysis products on the composition of the mixture should then be described by a curve of type *II* in Fig.1. Curve *III* corresponds to the transfer of energy from a component more stable to radiation to a less stable component A. Sometimes, in addition to sensitisation of the decomposition of A, a decrease in the decomposition yield of B takes place – "sacrificial protection"[1].

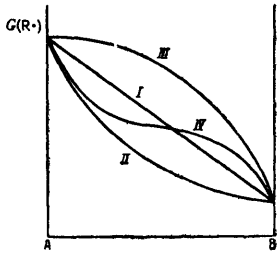


Fig.1. Typical curves for the dependence of the yield of primary radiolysis products on the composition of binary mixtures.

† The radiation yield is the number of molecules of substance formed, or decomposed for the absorption of 100 eV of energy by the starting material.

Since radiolysis yields ions and excited molecules, the transfer of energy may take place either by transfer of charge or by transfer of the energy of electronic excitation from the molecules of one component to the molecules of another according to the scheme

$$A^+ + B \rightarrow A + B^+,$$
$$A^* + B \rightarrow A + B^*. \qquad (3)$$

It is usually assumed that a necessary condition for the transfer of energy is that $E_A \geq E_B$, where E_A and E_B are the lowest electronic excitation levels of the molecules of the energy donor and acceptor. Transfer of charge can take place only when the corresponding relationship holds for the ionisation potentials.

Since the yield of hydrogen formed during the radiolysis of cyclohexane–benzene mixtures may be influenced by various secondary reactions, in particular by the reaction

$$H^\cdot + C_6H_6 \rightarrow C_6H_7^\cdot, \qquad (4)$$

the data obtained are to some extent ambiguous. To elucidate the role of secondary chemical processes in the decrease in the yield of hydrogen, Burton and Patrick[6,7] studied the radiolysis of cyclohexane–[D_6]-benzene mixtures. It was shown that even if allowance is made for reaction (4), the dependence of $G(H_2)$ on the composition of the cyclohexane–benzene mixture does not change significantly.

Freeman[8] determined the yields of cyclohexene, bicyclohexyl, cyclohexylcyclohexadiene, and other products of the radiolysis of the cyclohexane–benzene mixture in addition to the yield of hydrogen. The yields of all the products determined, with the exception of cyclohexylcyclohexadiene, decreased with increase in the electronic fraction of the benzene much more rapidly than expected from the linear law. In an examination of the possible reactions involved in the formation of these products from the primary radiolysis products Freeman also concluded that the excited molecules of cyclohexane may be deactivated by transfer of energy to the benzene. Some of the excited cyclohexane molecules, which decompose to radicals with the subsequent formation of cyclohexylcyclohexadiene, however, are apparently not deactivated by benzene, since in the case of this product a linear dependence on the composition of the mixture is observed. The author concludes that two types of excited cyclohexane molecule exist. This suggestion appears to be confirmed by the data of Gäumann[9], who found that, when the electronic fraction of benzene in the mixture is increased from 0.1 to 1, the yield of phenylcyclohexane decreases linearly from 0.2 to 0.

In other mixtures the additivity rule is again observed for some products and not for others: in a toluene–benzene mixture[1] the yield is linearly dependent on the composition for H_2 and CH_4, whereas the additivity rule is not observed for acetylene and ethylene. Manion and Burton, who studied this mixture, attributed this result to the fact that the first two substances are formed by the decomposition of excited molecules and the second two by the decomposition of ionised molecules. During the radiolysis transfer of charge apparently takes place from the benzene to the toluene, but there is no transfer of excitation energy.

Analogous results were obtained at the same time for the cyclohexane–benzene system. In propionaldehyde–[D_6]-benzene[6] mixtures, a linear relationship is observed for products such as CH_4 and C_2H_4 but not for C_2H_6.

Schuler *et al.*[10] determined the yields of primary free radicals from a cyclohexane–benzene mixture. Iodine was used as the radical acceptor. The yield of radicals was determined from the consumption of iodine, which reacts with radicals according to the scheme $R\cdot + I_2 \rightarrow RI + I\cdot$. They obtained for the free radicals a curve of type *II*, in accordance with Burton's data.

It is interesting to estimate the efficiency of the transfer of energy from cyclohexane to benzene. Let us consider the following kinetic scheme for the formation of radicals or other primary products during the radiolysis of a two-component mixture‡:

$$\begin{array}{ccc} A \underset{k_A}{\overset{k_{A^*}}{\rightleftarrows}} A^* \xrightarrow{k_{\dot{A}}} 2R\cdot & & \\ \Big\downarrow k_{AB} & & (5) \\ B \underset{k_B}{\overset{k_{B^*}}{\rightleftarrows}} B^* \xrightarrow{k_{\dot{B}}} 2R\cdot . & & \end{array}$$

From the steady-state condition for radiolysis, we can write

$$\begin{aligned} I k_{A^*} e_A &= k_A[A^*] + k_{\dot{A}}[A^*] + k_{AB}[A^*][B], \\ I k_{B^*} e_B &= k_B[B^*] + k_{\dot{B}}[B^*] - k_{AB}[A^*][B]. \end{aligned} \qquad (6)$$

The left-hand sides of Eqns.(6) give the rates of formation of excited molecules A* and B* (in mole litre^{-1} sec^{-1}) by the direct action of radiation at a dose rate of I eV litre^{-1} × × sec^{-1}. The rates of the elementary reactions in which these excited molecules take part are summed on the right-hand sides of the equations.

From this, we readily obtain

$$\frac{G_a(A)}{G_a(A) + G_a(B) - G(R\cdot)} = \frac{1}{1-\nu}\left(1 + \frac{k_A + k_{\dot{A}}}{k_{AB}}\,\frac{1}{[B]}\right), \qquad (7)$$

where $G_a(A) = \dfrac{100 k_{A^*} k_{\dot{A}} e_A N}{k_A + k_{\dot{A}}}$ and $G_a(B) = \dfrac{100 k_{\dot{B}^*} e_B N}{k_B + k_{\dot{B}}}$

are the radiation yields of radicals during the radiolytic decomposition of the components A and B, calculated from the additivity rule (N is Avogadro's number); $G(\dot{R})$ is the yield of radicals determined experimentally, and

$$\nu = \frac{k_{\dot{B}}}{k_{\dot{B}} + k_B} \Big/ \frac{k_{\dot{A}}}{k_{\dot{A}} + k_A}$$

is the ratio of the probability of decomposition of the excited molecules of B to the corresponding quantity for the excited molecules of A. The quantity defined by the left-hand side of Eqn.(7) should be linearly dependent on 1/[B].

Fig.2 shows the corresponding linear relationships, constructed on the basis of the yield of free radicals[10] and the yield of hydrogen[6] from a benzene–cyclohexane mixture. The ratios $k_{AB}/(k_{\dot{A}} + k_A)$ and ν, which can be determined graphically, characterise the efficiency of the transfer of energy from the excited molecules of cyclohexane to benzene and the relative probability of the decomposition of excited molecules of benzene compared with cyclohexane.

‡ A number of assumptions have been made to simplify the proposed scheme. In particular, it is assumed that the excited molecules formed by energy transfer from A to B are kinetically identical to those formed by the direct action of radiation. Analogous considerations are applicable to processes involving charge transfer.

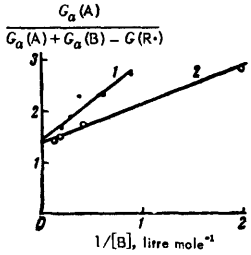


Fig.2. Variation of the radiochemical yields with the reciprocal of the benzene concentration in benzene–cyclohexane mixtures.

It follows from the data of Schuler *et al.* that $k_{AB}/(k_{\dot{A}} + k_A) = 1$ litre mole^{-1} and $\nu = 0.3$; from Burton and Patrick's data $(k_{AB}/(k_{\dot{A}} + k_A) = 2$ litre mole^{-1} and $\nu = 0.3$. Freeman[8] obtained $k_{AB}/(k_{\dot{A}} + k_A) = 0.78$. It is important to note that part of the hydrogen evolved during the radiolysis of cyclohexane is formed independently of the radical stage, for example by reaction (2)[11,12]. On the other hand, the decomposition of excited molecules at the C–C bond to form radicals does not as a rule lead to the subsequent formation of hydrogen. The fact that the values of ν and $k_{AB}/(k_{\dot{A}} + k_A)$ determined by two different methods (from the yield of radicals and from the yield of H_2) are similar probably indicates that cyclohexane molecules in the same excited state can decompose either with the formation of radicals or by a non-radical method.

Despite the fact that the cyclohexane–benzene mixture has been studied in most detail and is the "classical" example of a system in which sponge-type protection takes place, it is not even clear if the additivity rule applies to this system. Recently Lamborn and Swallow[13] suggested that the absorption of the energy of the fast electrons and δ electrons formed as a result of the Compton scattering of γ-rays depends on the structure of the hydrocarbons. They consider that the excitation cross-section of the π electrons of the benzene is about 10 times greater than that of the δ electrons in benzene and cyclohexane. Thus the protective action of benzene is attributed to the greater probability of primary absorption of radiation energy by the benzene molecules.

Determination of the radiation yield of the primary free radicals appears to be one of the most convenient and unambiguous methods of studying energy transfer during the radiolysis of liquid mixtures. The yields of radicals during the radiolysis of liquids are usually determined from the consumption of solutes which react with free radicals[14].

Free-radical acceptors which have been used include iodine, αα-diphenyl-β-picrylhydrazine (DPPH)[15,16], ferric chloride[17,18], benzoquinone[18,19], and other substances[20,21] which react effectively with free radicals. The concentration of these acceptors should be high enough to ensure that all the radicals formed during the radiolysis of the liquid are able to react with the acceptor before recombination with one another. This concentration should remain fairly low (usually less than 0.1 M), however, so that the direct action of radiation on the acceptor can be neglected[16].

This method (with DPPH as the radical acceptor) has been used to study a number of binary mixtures[2,22,23], particularly systems in which one or both components are chlorinated hydrocarbons[22,23]. The yields of primary free radicals of all the mixtures studied, containing halogenated hydrocarbons, showed deviation from the additive values (Table 1)§.

As a rule, the addition of even small quantities of alkyl chlorides to hydrocarbons and esters leads to a considerable positive deviation from the additivity rule (curve of type *III* in Fig. 1), but in some cases, at higher alkyl chloride concentrations, the $G(R^{\cdot})$–composition curves show an inflection (curve *IV* in Fig. 1). Table 1 shows that this S-shaped curve is characteristic of mixtures of alkyl halides with aromatic hydrocarbons. It may be that when the alkyl chloride content of the mixture is high, processes involving energy transfer from the alkyl chloride to the aromatic hydrocarbon predominate and that at low alkyl chloride concentrations the energy transfer takes place in the opposite direction. An interesting features is that chlorobenzene shows a protective action with respect to chloroform (curve of type *II*) but gives a relationship of type *III* in mixtures with benzene.

The efficiency of the energy transfer $k_{AB}/(k_A + k_A)$ during the radiolysis of mixtures containing alkyl halides, calculated from formula (7), lies in the range 1–5 litre × × mole^{-1}.

TABLE 1. Nature of the dependence of the yield of primary radiolysis products on the composition for different binary mixtures.

Linear relation	Positive deviation from linear relation	Negative deviation from linear relation	S-shaped curve
Cyclohexene – benzene		cyclohexane – cyclohexene[1,26]	
Benzene – toluene[1]	methyl acetate – benzene[22]	cyclohexane – benzene[1,6–8]	CCl_4 – benzene[24,25]
Propionaldehyde – [D_6] benzene[6]	vinyl acetate – benzene[2]		
Methyl methacrylate – ethyl acetate[2]	CCl_4 – methyl acrylate[24,25]	$CHCl_3$ – chlorobenzene[23]	CCl_4 – styrene[2]
Methyl methacrylate – styrene[3]	CCl_4 – methyl methacrylate[2]	methyl methacrylate – benzene[29]	$CHCl_3$ – benzene[22]
	$CHCl_3$ – methyl acetate[22]	octane – benzene[27] $CHCl_3$ – CCl_4[28]	
	CCl_4 – vinyl acetate[24]		
	chlorobenzene – benzene[23]		

§ Analysis of the products of the radiolysis of dilute solutions of DPPH in CCl_4 and $CHCl_3$ by Chapiro *et al.*[29] showed that these products are extremely varied and of complex composition. DPPH apparently reacts not only with the primary products but also with secondary intermediate products. Nevertheless, the authors consider that the consumption of DPPH during radiolysis gives unambiguous information on the yield of free radicals. Dainton *et al.*[30], on the basis of a study of the kinetics of the decoloration of solutions of DPPH in CCl_4 and $CHCl_3$ under the influence of γ-rays, suggested that DPPH reacts not only with free radicals but also with excited molecules.

When one of the components of the mixture is a monomer capable of undergoing radical polymerisation, the yield of radicals during radiolysis of the mixture can be determined from the kinetics of the polymerisation of the monomer[31]. This method has been used by Chapiro[32], and later by Nikitina and Bagdasar'yan[33], who studied the radiolysis of CCl_4–styrene and CCl_4–methyl methacrylate mixtures. The relationships for the yield of radicals initiating polymerisation are described by an S-shaped curve for the first mixture and by a curve of type *III* for the second. (The yield of radicals from pure CCl_4 or at very low concentrations of monomer cannot be determined by the polymerisation method.) Nikitina and Bagdasar'yan were the first to explain the sensitising action of CCl_4 on the basis of a theory of redistribution of the initially absorbed energy between the components of the mixture and they put forward a phenomenological theory to describe quantitatively the experimental data[2,23]. They suggest that the rate of energy transfer is much greater than the rates of deactivation and decomposition of the excited molecules, from which

$$\frac{[B^*]}{[A^*]} = \alpha \frac{[B]}{[A]}, \qquad (8)$$

where α is a coefficient characterising the redistribution of the absorbed energy.

If $\alpha > 1$, then for equal concentrations of A and B the energy is transferred from A to B; when $\alpha < 1$ energy transfer occurs in the opposite direction.

Using Eqn. (8), and remembering that the sum $[A^*] + [B^*]$ is proportional to the dose rate (I_{abs}) and that the rate of initiation is

$$V_R = [A^*]\frac{k_{\dot{A}}}{k_A + k_{\dot{A}}} + [B^*]\frac{k_{\dot{B}}}{k_B + k_{\dot{B}}}, \qquad (9)$$

we obtain

$$G(R\cdot) = \frac{kV_R}{I_{abs}} = k\frac{k_{\dot{A}}}{k_A + k_{\dot{A}}}\frac{1 + \alpha\,[B]/[A]\,\nu}{1 + \alpha\,[B]/[A]}. \qquad (10)$$

Table 2 gives the values of α and ν for the mixtures studied by Nikitina and Bagdasar'yan[2]. Table 3 gives the values of $G(R\cdot)$ calculated by Nikitina and Bagdasar'yan on the assumption that $\nu = G_B(R\cdot)/G_A(R\cdot)$ and that $G(R\cdot)$ for benzene is equal to 0.7. Table 3 also gives for comparison the values of $G(R\cdot)$ for the same liquids, determined by means of DPPH. The two methods give similar results.

Of particular interest is the idea of using protective action of the sponge type to retard the radiolytic decomposition of substances which can be used as organic heat-carriers and retarding agents in nuclear reactors. Colichman and Fish[35] studied the radiolysis of terphenyls at 400°–450°. The stability of the isomers to radiation

TABLE 2. Values of α and ν for some two-component systems (A = monomer).

System	α	ν
Methyl methacrylate – ethyl acetate	1.0	1.0
Methyl methacrylate – benzene	1.5	9.1
Methyl methacrylate – CCl_4	45.0	0.42
Styrene – CCl_4	30.0	0.053

TABLE 3. Yields of radicals for some liquids.

Substance	From polymerisation[2]	By means of DPPH
Benzene	0.7	0.7[34]
Styrene	0.8	0.6[3]
Methyl methacrylate	6.3	5; 6.7[3,24]
Ethyl acetate	6.3	7[34]
Carbon tetrachloride	15.4	19; 18; 3[24,25]

was compared from the yield of polymers. *p*-Terphenyl had the highest stability. The decrease in the yield of polymer by 30% when 4.5% of *p*-terphenyl was added to *m*-terphenyl was attributed by the authors to the redistribution of the absorbed energy between the components of the mixture.

There is no direct experimental indication of the mechanism of the transfer of energy from one component to another. According to Burton *et al.*[36-38], the transfer of charge from one component to another in mixtures of liquid hydrocarbons is unlikely, since the probability of formation of negative ions as a result of the attachment of a thermal electron to a neutral molecule is small in this case, and the neutralisation of the initially formed positive ions by thermal electrons takes place in $< 10^{-13}$ sec. It may be assumed that, in mixtures of the benzene–cyclohexane type, the energy of electronic excitation is transferred from cyclohexane to benzene. Freeman[39] has recently cast doubts on this suggestion.

In mixtures containing halogenated hydrocarbons the capture of thermal electrons by the molecules of the latter is possible, due to the high electron affinity of these substances. The resulting negative ions may decompose, leading to an increase in the yield of radicals in these mixtures, for example

$$C_nH_{2n+2} \rightsquigarrow C_nH_{2n+2}^{+} + e\,,$$
$$e + RCl \rightarrow RCl^{-} \rightarrow R + Cl^{-}. \qquad (11)$$

This process involves essentially the transfer of charge from the hydrocarbons to the halogen derivatives. Since the latter are less stable to radiolysis, the total yield of radicals in such mixtures is higher than expected from the additivity rule.

The S-shaped curves obtained for mixtures of alkyl halides and aromatic hydrocarbons can be explained if it is assumed that the excited molecules of the alkyl halides can transfer electronic excitation energy to the aromatic hydrocarbons and at the same time act as electron acceptors for the transfer of charge from the aromatic hydrocarbons. In this case, at low concentrations of the aromatic hydrocarbons, the processes of excitation-energy transfer predominate and the total yield of radicals is smaller than the averaged value. On the other hand, the addition of alkyl halides to aromatic hydrocarbons leads to a sharp increase in the yield of radicals, as a result of the transfer of charge to the molecules of the additive, which are less stable to radiation.

This scheme cannot, however, explain the fact that the addition of CCl_4 to styrene leads to a sharp increase in the rate of initiation of polymerisation, not only under the influence of ionising radiation, but also under the influence of ultra-violet light, which is absorbed chiefly by the monomer[35]. No ionisation takes place during photo-initiation, so that the transfer of charge according to scheme (11) should not take place.

Chapiro *et al.*[23] attribute the S-shaped curves to the fact that the processes of energy transfer involve excited molecules of the halogen derivatives in two different electronic levels, for example singlet and triplet. Here the energy transfer takes place in the direction: alkyl halide (singlet level) → aromatic hydrocarbon → alkyl halide (triplet level).

A more general explanation, covering the behaviour of mixtures containing halogenated hydrocarbons under the influence of ionising radiation and light, is the suggestion that intermediate complexes of excited molecules (which are electron donors) with the molecules of acceptors are formed, with subsequent decomposition to positive and negative ions or radicals:

$$A^{*} + B \rightarrow (A^{-}B^{+})^{*} \rightarrow A^{-} + B^{+}. \qquad (12)$$

This mechanism of charge transfer was considered by Weiss[41,42] to explain the quenching of the fluorescence of dyes by oxygen, Fe^{3+}, I^{-}, Br^{-}, etc. The quenching of fluorescence by these substances is attributed to redox reactions of type (12), leading to the non-radiative deactivation of the excited molecules A*. Reaction (12) can take place if

$$E_A + h\nu \geqslant E_B + X, \qquad (13)$$

where E_A and E_B represent the electron affinities of the molecules of A and B, $h\nu$ the energy of electronic excitation of A, and X the change in the potential energy of the components in the process of electron transfer, *i.e.* the rate of energy transfer is higher, the greater the electron affinity of the luminescent material and the lower that of the quenching agent. It is obvious that in the case of the reaction

$$A^{*} + B \rightarrow (A^{+}B^{-}) \rightarrow A^{+} + B^{-}, \qquad (14)$$

E_A and E_B should appear in Eqn.(13) with opposite signs.

An even more general explanation of the deviation of binary mixtures from the additivity rule was given by Bagdasar'yan[43], who considers that it is always necessary to make allowance for the reaction of the excited molecules with the surrounding molecules of liquid, irrespective of whether the latter are individual liquids or mixtures. Formally this interaction can be regarded as the formation of binary complexes as a result of exchange and donor–acceptor forces. In a pure liquid complexes of the type (AA)* are formed, and in mixtures also complexes (AB)*. If the energy of the excited states of A and B differ considerably, the exchange interaction is small. The formation of a complex can be expected only if the conditions favour donor–acceptor bonds $(A^{-}B^{+})^{*}$ or $(A^{+}B^{-})^{*}$ (see for example Eqn.(13)].

Thus the radiolysis of a two-component mixture involves formation, deactivation, and decomposition of excited complexes to radiolysis products:

$$A^{*} + A \xrightarrow{k_{AA}} (AA)^{*} \nearrow^{A+A}_{\searrow 2R\cdot \text{ (or } 2R\cdot + A),}$$
$$A^{*} + B \xrightarrow{k_{AB}} (AB)^{*} \nearrow^{A+B}_{\searrow 2R \text{ (or } 2R\cdot + A, \text{ or } 2R + B).} \qquad (15)$$

Analogous processes take place during the interaction of B* with A and with B. If the probability of decomposition of (AB)* with the formation of radicals or other products is greater than that for (AA)*, the addition of B to A leads to

a positive deviation from additivity, and if the probability is smaller it leads to a negative deviation. From this viewpoint, when the additivity rule is observed, we have a particular case, where $k_{AB}/k_{AA} = 0$ and $k_{BA}/k_{BB} = 0$, *i.e.* the probabilities of decomposition of the complexes (AB)*, (AA)*, and (BA)* and (BB)* are respectively equal. The scheme suggested by Bagdasar'yan explains from a single viewpoint the different cases where the additivity rule is not observed during the radiolysis of binary mixtures.

The lifetime (τ) of the excited molecules of the energy donor can be estimated from Smolukhovskii's formula for calculating the number of collisions (Z) between these molecules and acceptor molecules[44]

$$Z = 4\pi DRN, \qquad (16)$$

where D is the diffusion coefficient, R the radius of interaction, and N Avogadro's number.

Assuming that the probability of energy transfer when the molecules approach to the interaction distances is equal to 1, *i.e.* $k_{AB} = 4\pi DRN$, and making allowance for the fact that $1/(k_A^* + k_A) = \tau$, we have

$$\frac{k_{AB}}{k_A^* + k_A} = 4\pi DRN\tau. \qquad (17)$$

Since the transfer of energy by the above mechanism requires the overlap of the electronic orbitals of the interacting molecules, *i.e.* it requires their approach to a distance not exceeding the kinetic radii of the molecules, $R = 2-5$ Å. For liquids such as cyclohexane, benzene, and CCl_4, $D \simeq 10^{-5}$ cm^2 sec^{-1}. Since $k_{AB}/(k_A^* + k_A) = 1$, we obtain from Eqn.(17) $\tau = 5 \times 10^{-10}$ sec.

2. TRANSFER OF ENERGY DURING THE RADIOLYSIS OF DILUTE SOLUTIONS

a. Liquid phase. In the radiolysis of some solutions containing small quantities of acceptors (< 0.1 M), the deviation of the yields of radiolysis products from the values corresponding to the additivity rule are often found to be greater than those at high acceptor concentrations.

Krongauz and Bagdasar'yan[45] found that in the radiolysis of solutions of benzoyl peroxide in benzene the yield for the decomposition of benzoyl peroxide at concentrations < 0.01 M is greater by at least one and a half powers of ten than the yield corresponding to the direct action of radiation on the solute.

Study of the radiolysis of such solutions in the presence of DPPH showed that the high decomposition yield is not related either to reaction with the radicals formed from the solvent or to chain decomposition of the peroxide. It was suggested that decomposition of the peroxide in dilute solutions is due to the transfer of excitation energy from the solvent to the solute.

Later, studies were made of the radiolysis of solutions of a number of other substances, which decompose readily to form radicals (peroxides, azo-compounds, disulphides), in different solvents (toluene, cyclohexane, ethyl acetate, styrene, etc.). It was shown that effective sensitisation of the decomposition of the solutes takes place only when both the solvent and the solute are aromatic compounds. The yield for the decomposition of the acceptors at first increases sharply with concentration and then, from a concentration ~ 0.01 M, the yield increases less rapidly and follows a linear relation (Fig.3).

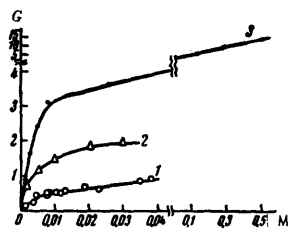


Fig. 3. Variation of the radiochemical yield for the decomposition of solutes with their concentration in benzene:
1) $C_6H_5-N=N-C(C_6H_5)_3$;
2) $C_6H_5-S-S-C_6H_5$;
3) $C_6H_5-\overset{\overset{O}{\|}}{C}-O-O-\overset{\overset{O}{\|}}{C}-C_6H_5$.

In accordance with reaction scheme (5), we can obtain, for the yield for the decomposition of the solute $G(-B)$, the relation

$$G(-B) = \frac{100Ne_A k_{A^*} k_{AB} k_B^* [B]}{(k_A^* + k_A + k_{AB}[B])(k_B + k_B^*)} + \frac{100Ne_B k_{B^*} k_B^*}{k_B^* + k_B}, \qquad (18)$$

where N is Avogadro's number.

At low concentrations the direct action of radiation on the solute is small and the second term in Eqn.(18) can be neglected. $1/G(-B)$ should then be linearly dependent on $1/[B]$ and for the benzene solutions studied, at concentrations < 0.01 M, a linear relation does hold. This makes it possible to determine the ratio $k_{AB}/(k_A^* + k_A)$, characterising the efficiency of the transfer of energy from the solvent to the solute and the ratio $k_A{}^* k_B^*/(k_B^* + k_B)$, characterising the probability of decomposition of the resulting excited acceptor molecules.

The corresponding values for dilute solutions of some substances in benzene are compared in Table 4 which shows that the efficiency of the transfer of energy in dilute solutions of these substances is greater by about two powers of ten than that in the binary systems described in the preceding section. As already mentioned, this efficiency is observed only when both components are aromatic. The difference in the yields for the decomposition of solutions of the substances listed in Table 4 is due chiefly to the difference in the probabilities of decomposition of the excited molecules. An interesting feature is that the probability of decomposition of the excited molecules of these compounds is not directly related to the dissociation energy, which is approximately the same for all of them (~ 30 kcal mole^{-1}).

TABLE 4.

Acceptor	$\frac{k_{AB}}{k_A^* + k_A}$, litre mole^{-1}	$\frac{100\, k_{A^*} k_B^* N}{k_B^* + k_B}$
Benzoyl peroxide	380	3
Phenylazotriphenylmethane	430	0.35
Diphenyl disulphide	370	1.4

It may be suggested that the slower increase in $G(-B)$ at acceptor concentrations > 0.01 M arises because all the excited benzene molecules are able to transfer energy to the acceptor molecules before their deactivation and that the subsequent increase in $G(-B)$ is due to the direct action of radiation. A more detailed examination[34] shows, however, that at higher concentrations transfer of energy from another type of excited molecule is also possible and this takes place with a much lower efficiency.

Let us try to estimate the interaction distance for the interaction of excited molecules of the solvent with acceptor molecules R assuming that at concentrations 0.01 M all the excited molecules are able to transfer energy to the acceptor. Inside the sphere of radius R described around each excited solvent molecule taking part in the effective transfer of energy there is at least one molecule of solute. Since the average distance between the solute molecules at a concentration 0.01 M is

$$\left(\frac{3.2\times10^{-21}}{0.01}\right)^{1/3} \simeq 70\times10^{-8} \text{ cm},$$

we have $R \simeq 35$ Å. The value of R obtained in this way shows that the energy transfer takes place at a distance about 10 times greater than the kinetic radii of the molecules. This "long-range action" in the non-radiative transfer of energy from some molecules to others was first detected in a study of luminescence in multicomponent systems. As early as 1922, Frank and Cario[49] showed that the irradiation of a mixture of mercury and thallium vapour by light corresponding to the resonance line of mercury leads to the emission of fluorescent light whose spectrum contains, in addition to the mercury lines, lines characteristic of thallium. The authors showed that this phenomenon cannot be attributed to the trivial reabsorption, by the thallium atoms, of light emitted by the mercury; therefore this sensitisation of the luminescence was interpreted as the result of the non-radiative transfer of the energy of electronic excitation from the mercury atoms to the thallium atoms.

Sensitised fluorescence was later detected in solutions of a number of organic dyes[50,51].

Studies of the concentration dependence of the yield or the intensity of fluorescence, together with fluorometric measurements of the lifetime of the excited molecules, have indicated that in the sensitisation of the fluorescence the transfer of energy takes place at a distance considerably greater than the effective kinetic radii of the molecules. To explain the long-range action in the transfer of excitation energy in solutions, the theory of the so-called resonance transfer of excitation energy has been developed[52]. Förster[52], considering the resonance transfer of energy as the result of the dipole–dipole interaction of excited and unexcited molecules, obtained for the probability of energy transfer (n) from donor to acceptor the following dependence on the distance between the molecules (R):

$$n = \frac{1}{\tau}\left(\frac{R_0}{R}\right)^6, \qquad (19)$$

where τ is the average life time of the excited molecules of the energy donor and R_0 the critical distance at which the probability of energy transfer is equal to the probability of spontaneous deactivation of the excited molecules of the donor. The theory makes it possible to calculate R_0, which is greater, the greater the overlap of the fluorescence spectrum of the energy donor and the absorption spectrum of the energy acceptor. For solutions, R_0 is usually 20–80 Å.

The luminescence of liquid organic scintillators under the action of ionising radiation is evidently also related to the resonance transfer of energy[53]. These scintillators consist of dilute solutions of aromatic compounds with condensed nuclei (anthracene, p-terphenyl, 2,5-diphenyloxazole, etc.) in organic solvents[54]. The applied ionising radiation is absorbed almost completely by the solvent, which transfers the energy to the molecules of the solute, which is an efficient phosphor. Furst and Kallmann[55] determined the dependence of the intensity of fluorescence of various liquid scintillators on the concentration of the solutions and estimated the efficiency of the energy transfer from the solvent to the phosphor (Table 5).

Table 5 shows that the efficiency of the energy transfer, determined by the fluorescence method, is of the same order of magnitude as the efficiency of the transfer in the radiolysis of the dilute solutions considered above (Table 4). It may be that resonance transfer of energy also takes place in the sensitised radiolysis of dilute solutions.

As a rule, the highest luminescence yield is given by scintillators in aromatic solvents[56]. This is apparently related to the overlap of the spectra of the components being a maximum, which may also explain the fact that effective transfer of energy in radiolytic reactions is observed only when both components of the solution are aromatic.

To confirm the suggestion that the mechanisms of the transfer of energy in the case of fluorescence excited by ionising radiation and in the sensitised radiolysis of dilute solutions are similar, a study was made of the radiolysis of three-component benzene–benzoyl chloride–phosphor solutions[57]. It was shown that small quantities of added organic phosphors (anthracene and phenanthrene) protect the benzoyl peroxide from decomposition. This appears to indicate that the benzoyl peroxide and the phosphor compete for the same excited solvent molecules in the process of energy transfer. Taking this into account, let us try to estimate by a somewhat different method the distance for the transfer of energy in the radiolysis of solutions.

Let us assume that the transfer of energy from an excited solvent molecule to a molecule of solute requires that they approach to a certain distance (irrespective of whether the energy transfer takes place as a result of the collision of molecules or at much greater distances). This suggestion was put forward by Galanin *et al.*[58], who showed that in ordinary aromatic solvents (benzene, toluene, xylene, etc.) the diffusion displacement during the lifetime of the excited molecules of the solvent may be commensurate with and even greater than the critical distance of resonance interaction R_0. As a result, the

TABLE 5. Values of $k_{AB}/(k_A + k_A)$ litre mole^{-1} for liquid solutions of luminescent materials.

Luminescent material	Solvents				
	benzene	toluene	xylene	cumene	p-dioxane
Anthracene	425	318	336	254	89
Anthranilic acid	260	228	182	125	76
Diphenylbutadiene	550	443	330	166	102
Phenyl-α-naphthylamine	550	447	365	115	54
p-Terphenyl	380	280	384	190	41

transfer takes place with a much greater probability than would be expected on the assumption that the molecules are immobile during the transfer. Calculating the probability of energy transfer as the probability of the "collisions" whose effective cross-section is determined by the distance for resonance transfer, Galanin obtained satisfactory agreement with experiment. The suggestion that approach by diffusion to the distance of "long-range action" is necessary also agrees with the hypothesis of Burton *et al.*[59], of the excited molecules of solvent forming characteristic "aggregates" with the surrounding solvent molecules. A characteristic feature of these aggregates is that the collision of the molecules of an acceptor with any of the molecules in the aggregate is equivalent to collision with the initially-excited molecule. It is therefore possible to use Eqn.(17) to estimate the interaction distance.

The value of τ for excited benzene molecules was estimated by Burton and Dreeskamp[60], who studied the concentration dependence of the time required for quenching of the fluorescence, initiated by X-rays, of *p*-terphenyl dissolved in benzene. By extrapolating the observed values of the time required for quenching to zero concentration, these authors found for the characteristic lifetime of the excited benzene molecules taking part in the energy transfer the value $\tau = 2 \times 10^{-8}$ sec. A similar value of τ was obtained by Knau[61] in a study of the photo- and radio-luminescence of solutions of anthracene in benzene.

Assuming $k_{AB}/k'_A + k_A = 380$ (Table 4), we obtain from Eqn.(17) $R \simeq 30$ Å, which agrees with the value estimated above by a different method.

The sensitised radiolytic decomposition of substances of the type $X-CH_2-C_6H_5$, where X is Cl, OH, HCOO, CH_3COO, H, $C_6H_5-CH_2$, in cyclohexane solutions was studied by McLachlan[62]. With the exception of toluene and dibenzyl, all the above substances decompose in 0.1 M solutions with a radiochemical yield, $G(C_6H_5CH_2X) \simeq 4$, which is much greater than the maximum possible yield due to the direct action of radiation. Taking into account the fact that $G(-C_6H_5CH_2Cl)$ is independent of the concentration of the solute (in the range 0.05–0.5 M) and dose rate, the author concludes that the radiolytic decomposition of this compound does not take place by a chain mechanism. Radiolysis of the solutions in the presence of radical acceptors such as cyclohexene and iodine decreases considerably the yield for the decomposition of solutes but does not suppress it completely. From this it is concluded that the high yield for the decomposition of $C_6H_5CH_2Cl$ cannot be due entirely to reaction with radicals formed from the solvent but is to a considerable extent related to the transfer of energy from the solvent. The fact that $G(-C_6H_5CH_2Cl)$ is independent of the concentration appears to indicate that at concentrations > 0.05 M, the reaction of a solute with the species transferring the energy reaches saturation. The absence of data on the radiolysis of more dilute solutions where saturation is not reached makes it impossible to determine the efficiency of the energy transfer.

Schuler and Burton *et al.*[63-65] showed that the addition of small quantities of I_2, CH_3I, C_2H_5I, CH_3Br, bromobenzene and cyclohexylbenzene (10^{-2}–10^{-3} M) decreases sharply the yield of hydrogen in the radiolysis of cyclohexane. In the radiolysis of solutions of iodine in cyclohexane the quantity of HI formed is much less than the corresponding decrease in $G(H_2)$. They therefore consider that the protective action of iodine and alkyl halides is not related to the capture by the solutes, of the H· atoms formed in the radiolysis of hexane, but is due to the deactivation of the excited or ionised cyclohexane molecules by the molecules of the additive, *i.e.* by the transfer of energy from the solvent to the solutes.

If the decrease in the yield of hydrogen is related to the deactivation of the excited cyclohexane molecules by the additive, we have, according to scheme (5),

$$G(H_2) = G(-A) = \frac{100 N k_{\dot{A}} k_A \cdot e_A}{k_A + k_{\dot{A}} + k_{AB}[B]}. \qquad (20)$$

Using the data of Burton *et al.*[65] and Eqn.(20), it is possible to estimate the efficiency of the postulated energy transfer in dilute solutions of iodine and bromobenzene in cyclohexane, the values found being 70–100 litre mole^{-1}. This high efficiency of transfer of excitation energy is characteristic of solutions of "absorbing" acceptors, *i.e.* substances whose absorption spectra overlap the fluorescence spectrum of the solvent. In this case there is no such overlap of spectra. Burton *et al.* suggest that the transfer of energy takes place as a result of the capture, by the molecules of the additive, of the thermal electrons formed in the radiolysis.

Kolbanovskii *et al.*[66,67] consider that the action of small amounts of both absorbing and non-absorbing acceptors is based on the same mechanism. Their quantitative examination of the interaction of excited molecules of an energy donor with acceptor molecules shows that at low solution concentrations the protective action is proportional to the concentration of additive to the power 2/3.

It should be noted that these studies give no unambiguous proof that the decrease in the yield of hydrogen in the presence of iodine is related to the transfer of energy. Moreover, Dyne and Jenkinson's data[11] indicate that the decrease in $G(H_2)$ in the radiolysis of cyclohexane in the presence of iodine is due to the reaction of the iodine with atomic hydrogen. These authors measured the yield of D_2, HD, and H_2 from $C_6H_{12} + C_6D_{12}$ mixtures. Extrapolation of the dependence of $G(D_2)$ on the C_6D_{12} concentration in the mixture to zero C_6D_{12} concentration gives the yield of "molecular" D_2 formed, apparently, according to the scheme $C_6D_{12}^* \rightarrow C_6D_{10} + D_2$. The addition of I_2 decreases the total yield of hydrogen (D_2 + HD + H_2) but has almost no effect on the yield of molecular D_2. This is evidently because iodine is only a "trap" for radicals, particularly H· atoms, but is not an energy acceptor. That the yield of HI, measured by Schuler and Burton *et al.*[63,65], is much less than expected from the decrease in $G(H_2)$, is possibly due to secondary reactions such as R· + HI → RH + I.

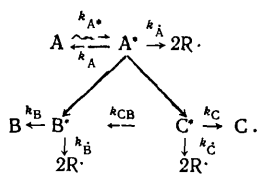
Of particular interest are the features of the redistribution of the initially absorbed energy in three-component systems containing two energy acceptors.

As already stated, the addition of small quantities of phenanthrene and anthracene to solutions of benzoyl peroxide in benzene decreases the yield for the decomposition of the peroxide. A similar effect is shown by other energy acceptors such as benzoic anhydride, aromatic azo-compounds, and disulphides[47,48]. The protective action of the second energy acceptor is apparently due to competition between the acceptor and the peroxide in the process of energy transfer from the solvent.

Increasing the concentration of the second acceptor in the solution sometimes enables the decomposition of the

peroxide to be almost completely suppressed, but in a number of cases (Fig.4) the yield for the decomposition of benzoyl peroxide reaches a limiting value and does not decrease further with increase in the concentration of the second acceptor[48,57]. In these solutions transfer of energy apparently also takes place from the second acceptor to the peroxide, and at sufficiently high concentrations of the second acceptor this compensates for its protective action.

For processes taking place in the radiolysis of three-component systems, we may then write the following kinetic scheme¶:



(21)

The steady-state equations have the form

$$I k_{A^\bullet} = k_A [A^\bullet] + k_{\dot{A}} [A^\bullet] + k_{AB} [A^\bullet][B] + k_{AC} [A^\bullet][C],$$
$$k_{AB} [A^\bullet][B] = k_B [B^\bullet] + k_{\dot{B}} [B^\bullet] - k_{CB} [C^\bullet][B], \quad (22)$$
$$k_{AC} [A^\bullet][C] = k_C [C^\bullet] + k_C [C^\bullet] + k_{CB} [C^\bullet][B],$$

from which

$$\frac{G(-B)}{G^0(-B)} = \frac{1 + k_{AC}/k_{AB}[C]/[B]\ \alpha}{k_{AC}/k_{AB} \cdot [C]/[B]} \Big/ \frac{1 + k_{\dot{A}} + k_A \cdot k_{AB}}{1/[B] + 1}, \quad (23)$$

where $G^0(-B)$ and $G(-B)$ are the yields for the decomposition of component B in the absence and in the presence of the component C, and $\alpha = \dfrac{k_{CB}[B]}{k_C + k_C^{\bullet} + k_{CB}[B]}$. When [B] = const,

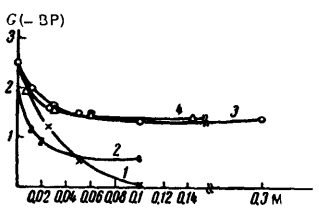
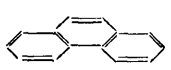


Fig. 4. Variation of the radiochemical yield for the decomposition of benzoyl peroxide with the concentration of protective additives at a constant concentration of the peroxide in benzene of ~ 0.05 M:
1) $C_6H_5-HN-N=N-C_6H_5$;
2) $C_6H_5-C(=O)-S-S-C(=O)-C_6H_5$;
3) $C_6H_5-C(=O)-O-C(=O)-C_6H_5$;
4)  .

¶ For sufficiently dilute solutions, the direct action of radiation on the solutes can be neglected; $\epsilon_A \sim 1$.

Eqn.(23) can be rearranged to a form convenient for the determination of α and $k_{AC}/k_{\dot{A}} + k_A$, if $k_{AB}k_{\dot{A}} + k_A$ is known[43,48].

When the direct exchange of energy between two acceptors does not take place, for example in the benzene–benzoyl peroxide–diazoaminobenzene system, *i.e.* when k_{CB} and α are zero, Eqn.(23) acquires the simpler form

$$\frac{G^0(-B)}{G(-B)} - 1 = \frac{(k_{AC}/k_{\dot{A}} + k_A)[C]}{1 + (k_{AB}/k_{\dot{A}} + k_A)[B]}. \quad (24)$$

The values of the efficiency of the transfer of energy from benzene to dibenzyl disulphide and phenylazotriphenylmethane, determined from their protective action [Eqns.(23) and (24)] and from the sensitised decomposition of these acceptors in solutions [Eqn.(18)]† show satisfactory agreement.

Thus in those cases where the energy acceptor does not fluoresce and does not undergo chemical change under the influence of the energy which it accepts, its efficiency can be estimated from its protective action in three-component solutions.

b. Solid phase. There are few radiochemical papers devoted to the intermolecular transfer of energy in glasses and polymers, although the analogous processes for the luminescence of scintillation plastics and glasses have been studied in considerable detail[68].

Chilton and Porter[69] studied the radiolysis of dilute solutions of triphenylmethane in organic glasses, for example a frozen mixture of methylcyclohexane and isopentane, at -196°. The yield of triphenylmethyl radicals was much higher than the value corresponding to the direct action of radiation. The efficiency of the energy transfer, determined from the dependence of the yield of radicals on the triphenylmethane concentration, was 830 litre mole^{-1}. The high efficiency of the energy transfer in glasses, observed by Chilton and Porter and by other workers[70,71], who studied sensitised fluorescence in polymers and glasses, does not agree with the theory of the ordinary resonance transfer of energy. Calculation shows[72] that the energy transfer takes place at distances much greater than the usual distances for resonance interaction between molecules (the probability of resonance transfer decreases sharply with distance and is inversely proportional to R^6). Since in glasses the approach of the excited donor molecules to the acceptor molecules by diffusion is excluded, it must be assumed that the energy migrates either in the form of excitons or in some other form not associated with spatial displacement of the molecules (for example the migration of holes or the resonance transfer of charge)[73]. In this case we may assume that the excitation is transferred from one molecule of solvent to another until an excited solvent molecule is found at the interaction distance from a solute molecule. If the "free path" of this excitation is much less than its total displacement, it may be assumed that in this case the migration of energy is diffusional in character[74]. We are then justified in using Eqn.(17) to calculate the radii of interaction in glasses, but in this case D is the diffusion coefficient of the excitation[72].

Since in Chilton and Porter's experiments the spectra of the substrate (solvent) and additive do not overlap, it

† Eqns.(22) and (23) appear to contain errors and are ambiguous. For a detailed treatment of this topic the interested reader is advised to consult A.J.Swallow, "The Radiation Chemistry of Organic Compounds", Pergamon, New York. 1960 [Ed. of Translation].

may be suggested that the transfer of energy from the excited molecules of the substrate to the molecules of the additive takes place at distances close to the molecular radii (R = 5 Å). In other words, for the transfer of energy, the electronic excitation in the substrate should be displaced from the molecule in which it originated to one lying close to molecules of the additive. Assuming that the lifetime of the excitation is of the same order of magnitude in the vitreous state as in the liquid state, we may assume that for methylcyclohexane $\tau = 5 \times 10^{-10}$ sec. Since $k_{AB}/k'_A + k_A$ = 830 litre mole^{-1}, the diffusion coefficient of the excitons, determined from Eqn.(17), is $D \simeq 4.5 \times 10^{-3}$ cm^2 sec^{-1}, from which the mean square displacement of the exciton, *i.e.* the distance at which the transfer of energy takes place in glasses during the lifetime of the excited state, is

$$\bar{x} = \sqrt{2D\tau} = 200\,\text{Å}. \qquad (25)$$

Intermolecular transfer of energy in solid mixtures of dicyclohexyldodecane and diphenyldodecane at -196° was observed by Voevodskii *et al.*[75]. Determination of the yield of radicals for each component separately and for their mixtures, by the EPR method, showed that the energy is transferred from the first component to the second.

The decrease in the radiochemical yield for the destruction or cross-linking of a number of polymers in the presence of small quantities of certain substances, so-called antirads, is apparently associated in many cases with the transfer of energy from the polymer to the antirad.

Alexander and Charlesby[76-78] studied the influence of the addition of various substances on the destruction, by radiation, of poly(methylmethacrylate) and found that the greatest protective action is shown by aromatic compounds (anthracene, naphthalene, benzophenone, 8-hydroxyquinoline, naphthylamine, etc.). Comparison of the protective action of 8-hydroxyquinoline and naphthalene showed that, whereas the efficiency of the former decreases during the radiolysis, the efficiency of the latter remains almost unchanged. Experiments with naphthalene labelled with ^{14}C showed that the quantity of naphthalene reacting with the polymeric molecules is too low for its action to be due to the combination of macroradicals, formed during radiolysis, *via* the naphthalene molecule. The protection of poly(methyl methacrylate) by naphthalene is evidently due chiefly to the transfer of energy from the polymer to the naphthalene molecules, which scatter it in the form of heat (sponge type protection).

The addition of small quantities (~ 0.2%) of a number of the aromatic amines and phenols normally used as antioxidants (phenyl-β-naphthylamine, di-β-naphthyl-*p*-phenylenediamine, di-t-butyl-4-methylphenol, etc.) decreases considerably the rate of cross-linking of polyethylene. Certain fatty acids, for example stearic acid, also prevent cross-linkage in polyethylene. Here it was found that the yield for the decomposition of the acid in the polymer, calculated for the direct action of the radiation, is 25 times greater than that in the pure acid. It may be assumed that in this case sacrificial protection of the polymer by the acid takes place. Salts of the acids do not exhibit the protective action, indicating the important part played by the mobile proton in the mechanism of protection. The part played by the transfer of energy in the prevention of cross-linking in polyethylene is not yet clear[79]. If the transfer of energy is significant, an important part is apparently played by the migration of energy along the hydrocarbon chains. It has been shown[27,75] that the energy taken up by molecules during radiolysis is readily transferred along aliphatic chains.

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The data at present available on the radiolysis of organic solutions are insufficient for a detailed examination of the mechanism of the intermolecular transfer of energy in radiochemical reactions. Nevertheless the study of the kinetics of these reactions enables systems to be differentiated according to the efficiency of the energy-transfer processes taking place in them. At high transfer efficiencies ($k_{AB}/k'_A + k_A = 10^2 - 10^3$ litre mole^{-1}), deviations from additivity are observed even at low acceptor concentrations (< 0.01 M), and at low efficiencies ($k_{AB}/k'_A + k_A \sim 1$) they are observed at higher concentrations (> 0.01 M). Sometimes, in the radiolysis of a given system in different ranges of acceptor concentration, the transfer of energy takes place with different efficiencies, indicating apparently that different excited or ionised states can take part in the energy transfer. This division of energy-transfer processes according to efficiency is not sharp and is to some extent arbitrary, since the efficiency of transfer depends both on the interaction cross-section of the molecules and on their lifetime in the excited state. However, it enables certain suggestions regarding the mechanism of energy transfer to be made.

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APPLICATION OF THE KINETIC ISOTOPE EFFECT OF TRITIUM TO THE INVESTIGATION OF THE MECHANISM OF HYDROGEN SUBSTITUTION AND TRANSFER REACTIONS

F.S. Yakushin

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I. INTRODUCTION

The velocity of a reaction is affected when the atom involved is replaced by its isotope in the molecule if the bond between this atom and another element is ruptured during the rate-determining stage of the reaction. The effect is expressed as the ratio of the rate constants for

the molecules containing the different isotopes, and is called the kinetic isotope effect. Theoretical calculations of kinetic isotope effects and their experimental determination have been widely studied. The latter is of special importance, because sufficiently accurate theoretical calculations are possible only for comparatively few reactions. Study of kinetic isotope effects provides information on reaction mechanisms, the nature of the transition state, etc. Such investigations have been carried out mainly with isotopes of hydrogen, nitrogen, and carbon, and to a lesser extent with those of oxygen, chlorine, etc. Several reviews[1-10] have been published on kinetic isotope effects.

The present review is concerned with recent work in which tritium has been used to study the mechanism of heterolytic reactions involving the substitution, exchange, and transfer of hydrogen. This radioactive hydrogen isotope has the advantage over deuterium that its greater mass results in a larger kinetic isotope effect (where it is observed). Use of tritium and deuterium together enables the kinetic isotope effect in hydrogen exchange to be investigated.

The concentrations of tritium used to investigate reaction mechanisms should be small, since otherwise its natural β-radiation may affect the course of the reaction[11].

II. THEORY OF THE KINETIC ISOTOPE EFFECT

Theoretical analysis of the kinetic isotope effect is often confined to a consideration of the most important factor responsible for its appearance, which is the difference in the zero-point energies of the bonds formed by the isotopes of a given element with some other atom. The potential-energy curves for the bond with protium will then generally be identical with the curves for the bond formed by the same atom with deuterium or with tritium: *i.e.* the classical activation energies for the reactions of such molecules can be regarded as identical. The difference in reaction rates is due to the difference in vibrational energy of the lowest levels in the initial and the transition states.

At or near room temperature almost all bonds are in the lowest energy state, and the vibrational energy is approximately the same as at the absolute zero, *i.e.* E^0. The zero-point energy is related to the vibration frequency ν_i of a bond as follows.

$$E^0 = \frac{1}{2}\,\Sigma h\nu_i. \qquad (1)$$

For a harmonic oscillator, the vibration frequency of the bond is

$$\nu_i = \frac{1}{2\pi}\sqrt{\frac{f}{m^*}}, \qquad (2)$$

where f is the force constant and m^* the reduced mass.

For comparatively heavy molecules containing protium, deuterium, and tritium, the reduced masses may be regarded as in the proportions

$$m_H^* : m_D^* : m_T^* = 1 : 2 : 3, \qquad (3)$$

if it is assumed that the force constants of bonds formed by different isotopes are identical.

Thus the zero-point energy for a bond with deuterium will be less by a factor of about $\sqrt{2}$, and that for a bond with tritium by a factor of about $\sqrt{3}$, than the value for a bond with protium.

The true activation energy is defined by the relation

$$E^a = E_{cl} + E_{\neq}^0 - E^0, \qquad (4)$$

where E_{cl} is the classical activation energy, E^0 the zero-point energy of the bond in the initial state, and $E_{\neq}^0$ the zero-point energy in the transition state.

The difference in activation energy for the rupture of X–H and X–T bonds will be

$$E_{X-H}^a - E_{X-T}^a = [(E_{\neq}^0)_{X-H} - (E^0)_{X-H}] - [(E_{\neq}^0)_{X-T} - (E^0)_{X-T}]. \qquad (5)$$

The first difference on the right-hand side of this equation is smaller than the second difference, and therefore $E_{X-H}^a < E_{X-T}^a$: *i.e.* the activation energy for rupture of a bond with protium will be less than that for the bond with tritium.

Fig. 1 shows the maximum difference in activation energy, and hence the maximum isotope effect, assuming that the bond in question is completely ruptured in the transition state.

An example of the way in which the effect of the difference in the zero-point energies of bonds on reaction velocities is estimated is provided by Melander's approximate calculation[12] for ordinary benzene and benzene in which a hydrogen atom has been replaced by an atom of deuterium or of tritium. The basic assumption is that all bonds other than that directly involved in the reaction, which is assumed to be ruptured, are unchanged in the transition state. The difference in activation energy, and hence in reaction velocity, will then be determined only by the difference in the zero-point energies of the C–H, C–D, and C–T bonds in the initial state. For the case of protium and tritium in benzene molecules, this difference can be written as follows:

$$E_{C-T}^0 - E_{C-H}^0 = \frac{1}{2}Nh(\Sigma\nu_{C_6H_6} - \Sigma\nu_{C_6H_5T}) = \frac{1}{2}Nhc(\Sigma\omega_{C_6H_6} - \Sigma\omega_{C_6H_5T}), \qquad (6)$$

where $\omega_{C_6H_6}$ and $\omega_{C_6H_5T}$ are the wave numbers of the initial states of the C–H and C–T bonds respectively. The wave numbers corresponding to an aromatic C–H bond are 3000, 1100, and 700 cm^{-1}. Since it follows from Eqn. (2) that, with appropriate assumptions,

$$\omega_{C-T} : \omega_{C-H} \simeq 1/\sqrt{3}, \qquad (7)$$

then

$$E_{C-T}^0 - E_{C-H}^0 = \frac{1}{2}(1-1/\sqrt{3})\,\Sigma'\omega_{C_6H_6}, \qquad (8)$$

where Σ' relates only to the single C–H bond. Hence

$$E_{C-T}^0 - E_{C-H}^0 = \frac{1}{2}(1-1/\sqrt{3})(3000+1100+700) = 1020\ cm^{-1}. \qquad (9)$$

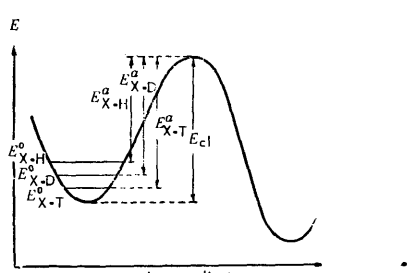


Fig. 1. Relation between the classical activation energy and zero-point bond energies of isotopic molecules.

A similar calculation for deuterium gives

$$E^0_{C-D} - E^0_{C-H} = \frac{1}{2}(1-1/\sqrt{2})\,\Sigma'\omega_{C_6H_6} = 703 \text{ cm}^{-1}, \quad (10)$$

which agrees well with experimental results obtained for deuterated benzenes (Table 1)

In energy units

$$E^0_{C-T} - E^0_{C-H} = \frac{1}{2} NhC \cdot \Sigma'\omega_{C_6H_6} = 2900 \text{ cal mole}^{-1}. \quad (11)$$

The ratio of the Arrhenius exponential functions of the rate constants for the tritium–protium pair at room temperature is as follows:

$$\frac{e^{-E^0_{C-T}/RT}}{e^{-E^0_{C-H}/RT}} = e^{-\frac{2900}{600}} = 1/125. \quad (12)$$

The corresponding ratio for the deuterium–protium pair under the same conditions and with the same assumptions is approximately 1/29.

The main assumptions in calculations of the kinetic isotope effect relate to the nature of the reactive bond in the transition state. It is supposed in one of the limiting cases that this bond is completely ruptured, *i.e.* in the transition state the isotopic atom is at an infinite distance from the rest of the molecule. Calculations by Bigeleisen[13] for such a case give values for the maximum isotope effect at room temperature of 60 for the proton–tritium pair and 18 for the protium–deuterium pair.

In the other limiting case, in which the state of the reactive bond remains about the same in the transition state as in the initial state, calculations give the following ratios of the rate constants for "light" and "heavy" molecules, depending on their mass:

$$k_H/k_D \simeq \sqrt{\frac{\dot{m}_D}{\dot{m}_H}} \simeq \sqrt{2} \quad (13)$$

and

$$k_H/k_T \simeq \sqrt{3}. \quad (14)$$

Real conditions represent an intermediate case in which the reactive bond is not completely ruptured in the transition state, but is only more or less deformed.

The difference in the zero-point energies of the bonds in the transition state cannot in general be neglected. Its effect is to diminish the maximum isotope effect. The ratio of the rate constants is affected also by interaction with the solvent, which is different for isotopic substrate molecules. This interaction results in different degrees of polarisation of the reactive bonds, which affect the magnitude of the kinetic isotope effect[4,12,14]. Furthermore, with hydrogen atoms a non-classical penetration of the energy barrier (the tunnel effect) is possible. Bell[15] showed its effect on the velocity-constant ratio for several reactions involving hydrogen transfer. In some cases this effect can be allowed for in the theoretical calculation. In general it is small and decreases on passing from hydrogen to deuterium and tritium.

TABLE 1.

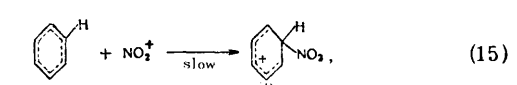
Compound	$\frac{1}{2}\Sigma\omega$, cm^{-1}	ΔE^0, cm^{-1}
Benzene	21536	
Monodeuterobenzene	20838	698
1,4-Dideuterobenzene	20172	666
1,3,5-Trideuterobenzene	19506	666
1,2,4,5-Tetradeuterobenzene	18801	705
Hexadeuterobenzene	17431	2×685

Depending on these circumstances, the magnitude of the kinetic isotope effect can vary between quite wide limits. Replacement of protium by deuterium in a reactive bond X–H usually results in a decrease in reaction velocity by a factor of 3–8, and with replacement of protium by tritium the corresponding factor is 6–20 at the rate-determining stage. Thus an estimate of the magnitude of the kinetic isotope effect must as far as possible take into account all the following factors: isotopic mass, temperature, character of bonds in the transition state, *i.e.* in effect the structure of the latter, etc. Otherwise, such an estimate is difficult, and can be carried out only by analogy with similar systems which have already been investigated, or by using hypothetical models of the transition state, which frequently yields the correct order of magnitude for the kinetic isotope effect.

III. KINETIC ISOTOPE EFFECT OF TRITIUM IN ELECTROPHILIC AROMATIC SUBSTITUTION REACTIONS AND IN THE ACID EXCHANGE OF HYDROGEN

Two methods have been used for the experimental determination of the kinetic isotope effect, the first, a comparison of the experimental rate constants for the same reaction carried out with the usual and the isotopic compounds, and the second, undoubtedly the more accurate, a determination of the change in the isotopic composition of substrate molecules or reaction products corresponding to a definite fractional change during the reaction. Appropriate relations between these quantities have been obtained for various cases[16–18] and refs.5 and 12 contain an analysis of the range of application of such relations depending on the conditions of measurement.

1. Nitration. Melander[19,20] used data on the kinetic isotope effect to determine the mechanism of several reactions involving the electrophilic substitution of hydrogen in aromatic compounds. The reaction which was investigated most thoroughly was the liquid-phase nitration of aromatic compounds. The nitrating agent is the nitronium ion NO_2^+, whose existence has been demonstrated by many investigators[21,22]. A detailed study of this reaction led to the conclusion that it occurs in two stages:



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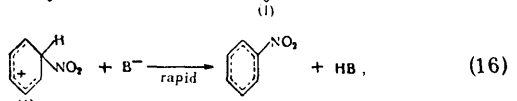


(16)

where B^- represents a base which combines with the proton. Melander[20] tested this scheme experimentally by measuring the kinetic isotope effect in the nitration of a series of aromatic compounds labelled with tritium. The presence of tritium in the aromatic molecule was found to have no appreciable effect on the reaction velocity with any of the compounds investigated (benzene, bromobenzene, *o*-, *m*-, and *p*-toluene, napthhalene, etc.). It can be seen from Table 2 that the velocity-constant ratio k_T/k_H is close to unity at 350°K.

TABLE 2.

Compound	Position	Lower limit of k_T/k_H
Benzene	—	0.84
Nitrobenzene	3	0.74
Toluene	2	0.85
Bromobenzene	2	0.78
p-Bromonitrobenzene	2	0.81
Naphthalene	α	0.77

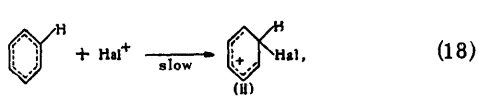
No isotope effect has been detected by other investigators[23] in the nitration of benzene containing ~91% of monodeuterobenzene.

To explain the absence of an appreciable kinetic isotope effect, the investigators assume that the rate of nitration is apparently determined, not by the rupture of a C–H bond attached to the aromatic ring, but by the addition of a nitronium ion with formation of the intermediate complex (I), the structure of which is similar to that postulated by Wheland[24]. Decomposition of this complex with the splitting off of a proton takes place rapidly†.

The influence of the polarity of the solvent on the rates of formation and disappearance of the nitronium ion also agrees with a two-stage mechanism for nitration. The solvent effect on the kinetics of the process casts doubt on the possibility of nitration by a termolecular mechanism:

$$NO_2^+ + Ar{-}H + B^- \rightarrow [NO_2^+ \ldots Ar \ldots H \ldots B^-] \rightarrow ArNO_2 + HB. \quad (17)$$

2. Bromination. Study of the kinetic isotope effect in the bromination of aromatic compounds is complicated by simultaneous hydrogen exchange between the aromatic compound and the hydrogen bromide formed when metal bromides are used as catalysts[12]. If, however, iodine is used as catalyst, the exchange takes place slowly, and the velocity-constant ratio for the dibromination of tritiated benzene and isomeric bromobenzenes at 85° ± 2° has been found to differ only slightly from unity. This indicates that, as in the case of nitration, the rate of bromination is probably not controlled by the proton removal from a carbon atom of the aromatic ring. This conclusion is consistent with the scheme of aromatic halogenation suggested by Robertson *et al.*[26]:



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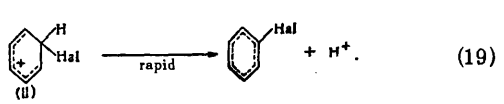
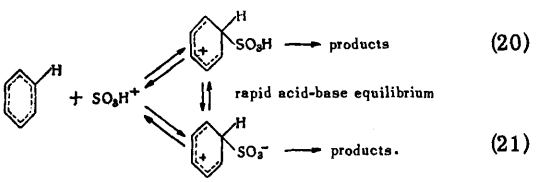


(19)

The intermediate complex (II) is assigned by Melander a structure similar to that of the complex (I).

3. Sulphonation. In contrast to the above reactions, the sulphonation of bromobenzene and *p*-bromotritiobenzene with oleum (some of the experiments were carried out in the presence of nitrobenzene as solvent) showed a slight isotope effect ($k_T/k_H = 0.55 \pm 0.09$ at 0°)[27]. This effect was later shown[28] to change very little when the temperature was raised from 0° to 50°. The reaction is assumed to have a two-stage aromatic electrophilic substitution mechanism, like those of nitration and halogenation, the difference in the rates of sulphonation of ordinary and tritiated molecules arising in the second stage, elimination of a proton in the transition state, which is partly rate-determining. The overall reaction scheme is as follows:



(20)

(21)

In contrast to nitration and bromination in the presence of iodine, the first stage in sulphonation, consisting in the attack of the sulphonating agent on the aromatic molecule, is reversible, and a quasi-stationary state can be assumed between the intermediate complex and the starting materials[7]. The velocity of the reaction

$$Ar{-}H + X^+ \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} Ar^+\!\!\begin{array}{l}\diagup X\\ \diagdown H\end{array}, \quad (22)$$

$$Ar^+\!\!\begin{array}{l}\diagup X\\ \diagdown H\end{array} + B \xrightarrow{k_2} Ar{-}X + HB^+, \quad (23)$$

can then be written, according to Bodenstein,

$$v_1 = k_1[ArH][X^+] = v_{-1} = k_{-1}\left[Ar^+\!\!\begin{array}{l}\diagup X\\ \diagdown H\end{array}\right] + k_2\left[Ar^+\!\!\begin{array}{l}\diagup X\\ \diagdown H\end{array}\right][B], \quad (24)$$

where v_1 and v_{-1} are the rates of formation and consumption of the intermediate complex.

Hence we find that

$$\left[Ar^+\!\!\begin{array}{l}\diagup X\\ \diagdown H\end{array}\right] = \frac{k_1[ArH][X^+]}{k_{-1} + k_2[B]}. \quad (25)$$

Representing the rate of formation of the final product by the equation

$$\frac{d[ArX]}{dt} = k_2\left[Ar^+\!\!\begin{array}{l}\diagup X\\ \diagdown H\end{array}\right][B], \quad (26)$$

and substituting for $[Ar^+HX]$ in Eqn. (26) from (25), we obtain

$$\frac{d[ArX]}{dt} = \frac{k_2 k_1 [B]/k_{-1}}{1 + k_2[B]/k_{-1}}[ArH][X^+]. \quad (27)$$

Inspection of this equation shows that, when k_{-1} is small, the denominator becomes $k_2[B]/k_{-1}$, and Eqn. (27) then takes the form

$$\frac{d[ArX]}{dt} \simeq k_1[ArH][X^+], \quad (28)$$

whence it follows that no isotope effect will occur on replacement of protium by deuterium or tritium in the Ar–H molecule, since only the rate constant k_2 is affected by such substitution. In the other extreme, when k_{-1} is large, the rate of the process will be roughly proportional

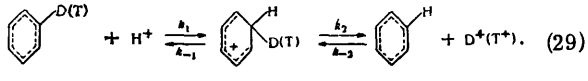
† Hammond[25] remarks that such a conclusion is not always necessary (see later, p.128).

to the rate constant k_2, and a kinetic isotope effect should then appear. This is evidently the case when an isotope effect was observed in sulphonation, *i.e.* the second stage is not too rapid compared with the reverse reaction of the first stage. A similar phenomenon has been noted by Zollinger[7] with azo-coupling, where a still greater isotope effect was observed when protium was replaced by deuterium in an aromatic molecule. In his view this effect, and other observations, is consistent with a two-stage mechanism of electrophilic hydrogen substitution [see scheme (22)–(23)], provided that a quasi-stationary stage is present.

Notable difficulties arise in the investigation of the isotope effect in sulphonation — absence of a homogeneous reaction system, formation of side-products if the solvent is nitrobenzene, and finally the possibility of hydrogen exchange.

4. Acid hydrogen exchange. The combined use of tritium and deuterium enables us to study the kinetic isotope effect in hydrogen exchange. Several examples showing the close connection between acid hydrogen exchange and electrophilic hydrogen substitution in aromatic compounds have been examined in detail in Shatenshtein's book[29].

The treatment of the kinetic isotope effect observed in reactions involving acid hydrogen exchange in aromatic compounds takes account of the similarity of their mechanism to that of chemical reactions involving electrophilic hydrogen substitution. Melander and Olsson[30,31] measured the effect of the difference in the rates of hydrogen exchange in deuterated and tritium-labelled benzene and isomeric toluenes in 80% sulphuric acid at 25°. They describe the process of hydrogen exchange using a two-stage mechanism similar to that adopted for the electrophilic substitution of hydrogen



(29)

According to such a scheme, the magnitude of the kinetic isotope effect in an exchange reaction involving deuterium or tritium will depend on the ratio of the velocity constants:

$$k = \frac{k_1 k_2}{k_{-1}+k_2} = \frac{k_1}{k_{-1}/k_2 + 1} . \qquad (30)$$

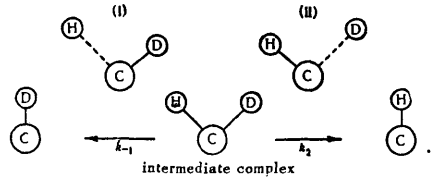
Comparison of the rate constants for the exchange of tritium and deuterium yields the ratio

$$k_T/k_D = \frac{(k_{-1}/k_2)_D + 1}{(k_{-1}/k_2)_T + 1} , \qquad (31)$$

it being assumed that replacement of deuterium by tritium does not appreciably affect the rate of the first stage, defined by the constant k_1 [*i.e.* that $(k_1)_T/(k_1)_D = 1$]. Thus the observed isotope effect will be determined by k_{-1}/k_2, the ratio of the velocity constant for the splitting off of protium to that for the splitting off of deuterium or tritium. The value of k_T/k_D can be roughly estimated if the intermediate complex is assumed to behave as a normal molecule. Actually, the usual value of k_D/k_H at room temperature is $\frac{1}{4}$, *i.e.* in this case $(k_{-1}/k_2)_D = 4$. The corresponding value for $(k_{-1}/k_2)_T$ can be obtained from the relation

$$k_H/k_T = (k_H/k_D)^{1.44}, \qquad (32)$$

deduced by Swain *et al.*[32] and extended by Melander[33] and Olsson[34] to isotopic hydrogen exchange in an acid medium, where the intermediate complex is supposed to contain both hydrogen isotopes. The isotope effect will be determined mainly by the vibrations of the carbon–hydrogen bonds in the transition states (I) and (II), and will not depend on the vibrations of bonds in the intermediate complex[35], which is common to both reactions:



In this model of acid hydrogen exchange C represents the active centre and a carbon atom in the aromatic ring; the broken line represents the bond which is ruptured in the transition state. The relation obtained between the protium–tritium and protium–deuterium isotope effects,

$$(k_{-1}/k_2)_T = (k_{-1}/k_2)_D^{1.44}, \qquad (33)$$

gives $(k_{-1}/k_2)_T = 4^{1.44} = 7.4$. A value of 0.60 is then obtained for the ratio k_T/k_D [from Eqn. (31)]. The value obtained experimentally agrees with this estimate (Table 3)‡.

The relative rates of exchange for tritium and deuterium in the *ortho*-, *meta*-, and *para*-positions in toluene are then

47 : 1 : 41 and 51 : 1 : 46.

No generally accepted view yet exists as to the detailed mechanism of the acid exchange of hydrogen in aromatic compounds. In Melander's opinion the intermediate product which is formed has the structure of a σ complex (see above scheme). The carbon atom at which substitution takes place is linked with other atoms by four sp^3 bonds. Two π electrons are involved in the formation of one of them, and the remaining π electrons form a pentadiene system. Satchell[36] postulates the presence, in the exchange with sulphuric acid, of at least three stages with two types of intermediate complexes: the proton first interacts with all the ring π electrons to form an intermediate π complex:

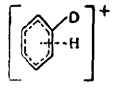


TABLE 3.

Isotopically substituted compound	k_T/k_D
Toluene, *ortho*-position	0.53
Toluene, *meta*-position	0.59
Toluene, *para*-position	0.52
Benzene	0.65

‡ Olsson[34] gives more accurate values for the ratio k_T/k_D under the same conditions, but the general character of the dependence of k_T/k_D on the position of the hydrogen in the ring remains the same.

This then rearranges to a σ complex, the decomposition of which results in formation of the products of the exchange.

According to Gold *et al.*[37], the experimental values of the kinetic isotope effects can be explained both by Melander and Olsson's scheme and by that given by Gold and Satchell. The rate of exchange of tritium in the *o*-tritio-*p*-cresol molecule with aqueous sulphuric acid is less by a factor of 2–3 than the rate of exchange of deuterium in the corresponding deutero-compound. On the basis of the reaction mechanism

$$H_3O^+ + Ar{-}H^* \underset{-1}{\overset{1}{\rightleftarrows}} (H\ldots Ar - H^*)^+ + H_2O \underset{-2}{\overset{2}{\rightleftarrows}} (H - Ar\ldots H^*)^+ + H_2O \rightarrow H{-}Ar + H^*H_3O^+, \quad (34)$$

these investigators explain the difference in the rates of exchange of deuterium and tritium by different degrees of weakening of the bond with the hydrogen isotope which is split off at the slow stage.

The great influence exerted by the nature of the substrate and by the reaction medium on the character of the bonds in the transition state has been noted above, and these can also affect the magnitude of the kinetic isotope effect. Melander and Olsson[30] pointed out that the decrease in reactivity is accompanied by some decrease in the kinetic isotope effect (see Table 3). Thus the value of k_T/k_D for the *ortho*-position in toluene is 0.53, while for the less reactive *meta*-position this ratio is 0.59. The velocity-constant ratios for the exchange of tritium and deuterium in the *para*-position of toluene compared with benzene differ still more (0.52 and 0.65 respectively). The ratio of the velocity constants for the exchange of the *para*-hydrogen in toluene and of a hydrogen atom in benzene with sulphuric acid is 200-300. In order to obtain a more reliable test of the dependence of the isotope effect on the reactivity of a fixed position in the molecule, Östman and Olsson[38] used thiophen, since the rates of exchange of hydrogen atoms in positions 2 and 3 in its molecule differ by a factor exceeding 900[39]. With 57% sulphuric acid at 24.6° the values obtained for k_T/k_D were 0.51 in position 2 and 0.59 in position 3. Thus the same kind of variation of the kinetic isotope effect with reactivity is observed as in the above work[30]. For hydrogen exchange with sulphuric acid, differences in reactivity among non-equivalent positions are to a considerable extent levelled out. To study this effect, it would probably be more suitable to use liquid hydrogen bromide, which Shatenshtein *et al.*[29,40] have shown to be a differentiating solvent in the acid exchange of hydrogen.

5. Some difficulties in the interpretation of reaction mechanisms on the basis of the kinetic isotope effect. Hammond[25] remarks that a very small isotope effect in the electrophilic substitution of hydrogen with the intermediate formation of a σ complex is still not a definite proof that the reactive C–H bond is not ruptured in the rate-determining stage. In his opinion a small effect can also be observed when the proton loss is preceded by a very slight weakening of the C–H bond in the intermediate complex. Such a conclusion differs from those of Melander[3] with regard to the isotope effect in the nitration of aromatic compounds.

Other investigators have observed that substitution of a heavy isotope for hydrogen in an aromatic compound has different effects on the rate of halogenation depending on the nature of the compound, the halogenating agent, and the medium.

Thus Vainshtein and Shilov[41] found that, whereas the iodination of some aromatic amines shows no isotope effect, with others it is small (k_H/k_D = 1.4) or considerable (k_H/k_D = = 4), the latter value being obtained also in the iodination of phenol[42]. Farrell and Mason[43] found a value of 1.8 for this ratio in the bromination of dimethylaniline with bromine in sulphuric acid at 25°. They point out that the character of the bond in the transition state depends on the nature of the aromatic molecule which is attacked and on the substituting reagent employed. Myhre[44] found that replacement of hydrogen by tritium in the bromination of 1,3,5-tri-t-butylbenzene in the presence of silver perchlorate and perchloric acid in the acetic acid–dioxane–bromine system lowers the reaction velocity by a factor of approximately 10. Because of this and the absence of an isotope effect in the bromination of benzene in the presence of iodine as catalyst[12] or with hypobromous acid[45], he suggests that the velocity-constant ratio is affected by a steric factor. The great bulk of the substituent *ortho* to the site at which hydrogen is substituted tends to make the second stage in the general scheme of electrophilic substitution [Eqns. (22) and (23)] become rate-determining.

Existing measurements of the kinetic isotope effect in aromatic halogenation do not yet permit a definite relation between the magnitude of the effect and the factors which affect this reaction to be formulated. As Vainshtein and Shilov[46] have shown, such a relation is difficult to discover even in a study of a single reaction, such as the bromination of aromatic amines.

IV. KINETIC ISOTOPE EFFECT OF TRITIUM IN METALLATION AND HYDROGEN EXCHANGE WITH A BASE

Shatenshtein and his collaborators[29] have repeatedly pointed out the great similarity between the laws governing hydrogen exchange with bases and metallation with alkali-metal alkyls. All the known facts lead to the conclusion that these reactions take place *via* a stage which can be represented in the general form

$$\equiv C{-}H + B^- \rightarrow \equiv C\ldots H^{+\sigma}\ldots B^{-\sigma} \rightarrow \equiv C^- + BH. \quad (35)$$

The base attacks the hydrogen of the C–H bond and initiates protolysis. Replacement of protium by a heavier isotope of hydrogen can be expected to affect the reaction velocity if the hydrogen–carbon bond is ruptured at the rate-determining stage. Bryce-Smith *et al.*[47] measured the rate of metallation of benzene and toluene with ethylpotassium, and observed a positive isotope effect, varying with temperature, when the hydrogen of the aromatic molecule was replaced by deuterium. Gronowitz and Halvarson[48] compared the rates of metallation with butyllithium of ordinary thiophen and of thiophen labelled in the α-position with tritium, and found that protium is replaced by lithium about six times as rapidly as is tritium. The investigators in both cases suggest that the existence of an isotope effect indicates that a carbon-hydrogen bond is ruptured in the transition state as a result of attack by the carbanion part of the metallating agent on the hydrogen of the aromatic C–H bond. Further investigations[49] on orientation effects in 3-substituted thiophens make improbable the electrophilic mechanism of Morton[50] for metallation reactions.

Isotopic mass has the same effect on reaction velocity in hydrogen exchange with a base. Fluorene which has been deuterated in the methylene group and methyl 2-naphthyl ketone containing deuterium in the methyl group exchange

TABLE 4.

Catalyst	k_H/k_T
H^+	9.7
CH_3COOH	11.4
CH_3COO^-	10.2
HO^-	12.9

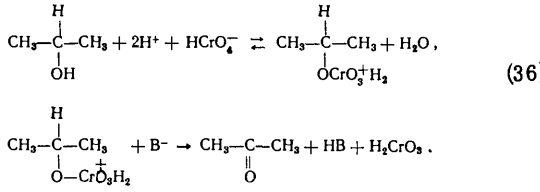
with ammonia at 25° twice as rapidly as the corresponding compounds containing tritium[51,52]. This difference in the rates of exchange can be ascribed to different activation energies for the rupture of C–D and C–T bonds in the transition state, just as with metallation reactions.

Streitwieser[53] obtained a value of $k_D/k_T = 3.0 \pm 0.3$ in an investigation of the stereochemistry of base-catalysed hydrogen exchange in the methylene group of ethylbenzene with lithium cyclohexylamide in cyclohexylamine (at 49.9°), and quoted a result of Langworthy's, who obtained values of 2.75 and 2.98 for the ratio on substituting deuterium and tritium in the methyl group of toluene. As in aromatic electrophilic substitution and hydrogen exchange with an acid, the reactivity of the reactants and the nature of the substituents and the medium must be considered for metallation and hydrogen exchange with bases. Depending on the conditions, these reactions take place by either a molecular or an ionic mechanism, and it thus becomes possible to study the effect of these conditions on the magnitude of the kinetic isotope effect. That this line of attack can give a deeper understanding of the reaction mechanism is shown by the work of Swain *et al.*[32] on the enolisation of ketones. The k_H/k_T ratio depends on the nucleophilic reagent used. It increases with increase in the basic strength of the reagent, since the proton is less firmly held in the transition state when a stronger base is involved. This relation can be seen from Table 4, which lists measurements of the kinetic isotope effect of tritium in the enolisation of 3-methyl-1-phenylbutyl phenyl ketone.

V. KINETIC ISOTOPE EFFECT OF TRITIUM IN HYDROGEN TRANSFER REACTIONS

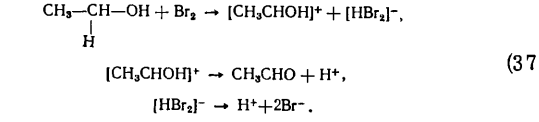
A considerable amount of work based on the kinetic isotope effect has been done on reaction mechanisms involving hydrogen transfer. In most cases the change in reaction velocity when protium is replaced by deuterium has been determined. Great attention has been paid to various reactions involving the oxidation and reduction of organic compounds, the Cannizzaro reaction, the Meerwein–Pondorf reaction, etc. Miklukhin and Rekasheva[54,55] used in particular the kinetic isotope effect of deuterium to investigate the mechanism of reactions of this type. We shall consider briefly some work in which tritium was employed.

The large kinetic isotope effect found[56] in the oxidation of 2-deuteropropan-2-ol with chromic acid and in the oxidation of benzaldehyde with chromic acid, permanganate, and other oxidants indicates that the C–H bond is ruptured in the rate-determining stage of the reaction. The magnitude of the isotope effect is found to depend on the acidity of the medium. These fundamental conclusions were confirmed and supplemented in an investigation of these and similar reactions, with partial substitution of hydrogen for tritium in the reactant molecules. According to Brown and Kaplan[8], the experimental k_T/k_H ratio found for the oxidation of propan-2-ol varies from 0.13 to 0.26 when the chromic acid concentration changes from 0.3 to 2 M. In the presence of manganous ions, which convert Cr^{IV} into Cr^{III} ions, the ratio is 0.04. Thus change in the acidity of the medium has an appreciable influence on the isotope effect. On the basis of these results, the following scheme was suggested[57,58] for this process



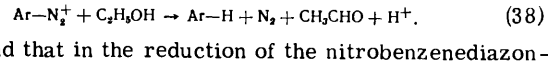
(36)

$k_H/k_T = 5$ at 37.5° has been found in the chromic acid oxidation of benzyl alcohol labelled with tritium at the α carbon atom. In the bromine oxidation of tritium-labelled ethanol an isotope effect equivalent to $k_H/k_T = 6.7$ was observed at the α carbon atom[59]. This result, like those obtained in the work mentioned above, is evidence of the occurrence of a slow stage in which a hydrogen atom is split off and added to the attacking reagent, the Br_2 molecule. This *ipso facto* casts doubt on the intermediate formation of ethyl hypobromite, which has been suggested to precede that of acetaldehyde which is the final product[60]. The following reaction scheme is claimed to be more probable[60]:



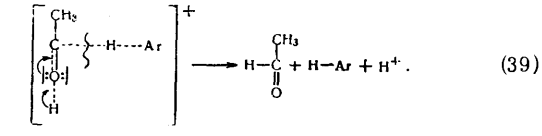
(37)

The very slight isotope effect observed when the Cannizzaro reaction is carried out with benzaldehyde labelled with either deuterium or tritium in the aldehyde group indicates that rupture of the C–H bond with transfer of a hydride ion does not occur[4]. An isotope effect was observed in the reduction of diazonium salts with alcohols[3,61] containing tritium (or protium) attached to the α carbon atom, the general scheme of this reaction being



(38)

It was found that in the reduction of the nitrobenzenediazonium ion the alcohol labelled with tritium (CH_2TOH or CH_3CHTOH) is used up at a rate about one-seventh of that with the alcohol containing no tritium. This led Melander[61] to infer a reduction mechanism similar to Dewar's for reactions of this type. In the reduction of a diazonium salt hydrogen transfer is apparently effected in a single bimolecular act, which Melander regards as an electrophilic S_E2 hydrogen substitution. The magnitude of the isotope effect indicates a rate-determining rupture of the carbon–hydrogen bond in the transition state, whose structure can be represented, if the process is ionic in character, as follows:



(39)

It is possible, however, as Miklukhin and Rekasheva[62] remark, that this reaction may occur homolytically, by a free-radical mechanism.

VI. APPLICATION OF THE KINETIC ISOTOPE EFFECT OF TRITIUM TO THE INVESTIGATION OF THE MECHANISM OF SOME OTHER REACTIONS

The kinetic isotope effect can be used to study a great variety of reactions. Apart from the work discussed in the present review, several other investigations are of great interest. Work on the kinetic isotope effect in the acid and base catalysis of ionic reactions in solution, discussed in a review by Wiberg[4], is very important.

Assarsson[63-65] has studied the kinetic isotope effect using tritium in the neutralisation of carbanions. These investigations are especially important because very many substances labelled with hydrogen isotopes are actually prepared by decomposing the corresponding Grignard compounds with water or alcohol.

Some work[67,68] has been done on the mechanism of the hydrolysis of trialkylsilanes using deuterium and tritium.

Antonovskii and Berezin[69-71] used the isotope effect substituting tritium for hydrogen in benzene and in a number of paraffins, in studies of the mechanism of the reaction of these compounds with methyl radicals in the liquid phase.

In the field of heterogeneous catalysis the kinetic isotope effect of deuterium and tritium has been used[72] to study the mechanism of the exchange between cyclohexene and water on a platinum catalyst. The kinetic isotope effect was used by Boreskov[73,74] to determine the molecularity of exchange reactions, in particular of hydrogen with deuterium and tritium on metallic catalysts.

A great deal of work using the kinetic isotope effect has been done on reactions in the gas phase. Weston[75] used this method to make an experimental test of the kinetic scheme for the occurrence of a unimolecular reaction as a function of the pressure. The isotope effect of tritium has proved useful in the study of gaseous chain reactions for determining the rate-determining stage in the photochemical reaction of hydrogen with chlorine[76] and in the branched-chain oxidation of hydrogen containing tritium under the influence of the β-rays from tritium[77].

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Tritium is widely used in reaction-mechanism studies. This review has been restricted to work in which the kinetic isotope effects of tritium and deuterium have been used in reactions involving the substitution, exchange, and transfer of hydrogen. It is clearly possible to obtain in many cases a more precise idea of the mechanism of a given reaction, especially when measurement of isotope effects is reinforced by an investigation of other aspects of the reaction. Nevertheless, several facts connected with the interpretation of the values obtained for the kinetic isotope effects have not yet received adequate explanation.

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THE CHEMISTRY OF DEPSIPEPTIDES†

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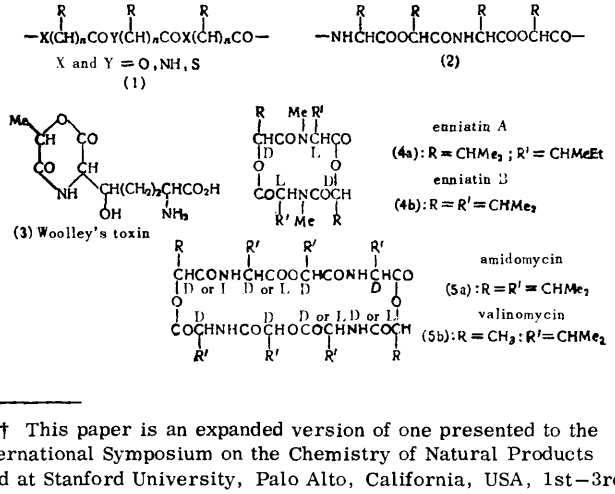
Depsipeptides is a term we have applied[1,2] to a group of compounds of type (1) made up of residues of hydroxy-acids and amino-acids linked together by amide and ester bonds. Various representatives of this group are frequently met among natural products, and recently intense research has started on methods for their synthesis. Thiodepsipeptides, made up of residues of mercapto- and amino-carboxylic acids, are related to depsipeptides in structure and modes of synthesis.

Not long ago Russell[3] suggested the name *peptolides* for compounds of type (1), but this was unsuitable because it is applicable only to cyclic and not to linear compounds. Therefore Russell[4] soon gave up his term, regarding the name *depsipeptides* as more correct.



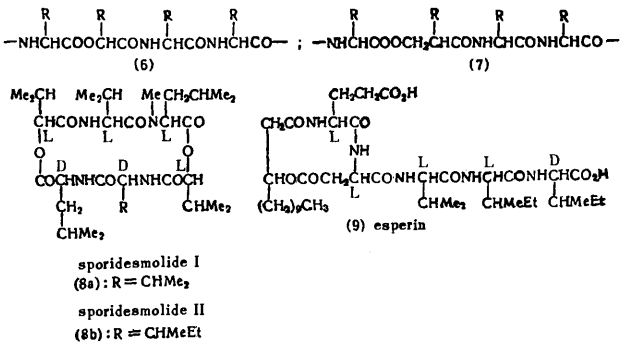
Natural and synthetic depsipeptides are now known which possess both linear and cyclic structures, and can be divided into several types. The first group of depsipeptides contain a regular alternation of residues of α-amino and α-hydroxy-acids (2). All natural compounds in this group are cyclodepsipeptides. The simplest of them is the phytopathogenic toxin (3) described in 1955 by Woolley[5], which proved to be a cyclodidepsipeptide. Being a derivative of dioxomorpholine, it is analogous to dioxopiperazine in the cyclopeptide series. This group also includes several depsipeptide antibiotics — the cyclotetradepsipeptides enniatin A (4a) and enniatin B (4b), the structure of which has been investigated by Plattner and others[6-17], and also the two cyclooctadepsipeptides amidomycin and valinomycin. According to Vining's results[18-20] amidomycin possesses the structure (5a), and valinomycin, which has been studied by Brockmann[21,22], is probably (5b), although the sequence of hydroxy-acid and amino-acid residues in the latter was not completely elucidated. There are still several little known antibiotics which are evidently related to the above compounds — enniatin C,[11] sambucinin, avenacein, fructigenin, lateritiin II,[12,14] baccatin A,[16] and fusafungin[17] — but these have not been obtained in a pure form, and their individuality still remains obscure‡.

The second group of depsipeptides comprises compounds having an irregular alternation of hydroxy-acid and amino-acid residues. It can include compounds containing α-hydroxy-acids, *e.g.* type (6), and also those containing β-hydroxy-acids, type (7). Among natural compounds of the former type are sporidesmolides I and II, investigated by Russell[3,4] in 1960, which are metabolic products of the fungus *Sporidesmium bakeri*. No pharmacological, or in particular antibiotic, activity has yet been detected in these compounds. They are both cyclohexadepsipeptides, sporidesmolide I possessing the structure (8a), while

† This paper is an expanded version of one presented to the International Symposium on the Chemistry of Natural Products held at Stanford University, Palo Alto, California, USA, 1st–3rd March, 1961.

‡ It has been shown quite recently that baccatin A is a mixture of enniatins A and B.[23]

sporidesmolide II is evidently its homologue with the structure (8b).



(5) (7)

(9) esperin

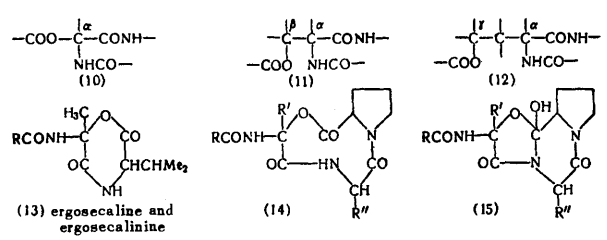
sporidesmolide I
(8a): R = CHMe$_2$

sporidesmolide II
(8b): R = CHMeEt

Depsipeptides of this group which contain β-hydroxy-acid residues, type (7), include the antibiotic esperin, whose structure (9) has recently been elucidated by Japanese workers[24]§.

The third group of depsipeptides are characterised by the presence of one or more residues of an aminohydroxy--acid, containing both the amine and hydroxyl functions in the same molecule. This group can be subdivided into compounds containing residues of α-amino-α-hydroxy--acids (10), α-amino-β-hydroxy-acids (11), α-amino-γ--hydroxy-acids (12), etc.

The first subgroup includes among natural products two new ergot alkaloids — ergosecaline and ergosecalinine — discovered in 1959 by Japanese workers[26], for which the cyclodidepsipeptide structure (13) has been proposed. However, the long known ergotamine and ergotoxine groups of alkaloids can also be included in this subgroup if they are accepted as having the cyclotridepsipeptide formula (14) of Jacobs and Craig[27] and of Barger[28] or the isomeric Stoll formula (15),[29,30] which is produced from it by transannular interaction between one of the amide groups and an ester group.



(10) (11) (12)

(13) ergosecaline and ergosecalinine (14) (15)

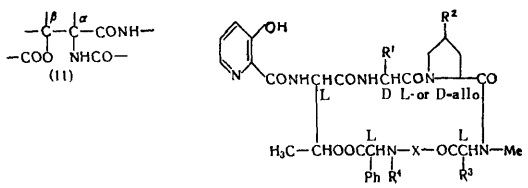
R-Lysergic acid	R′	R″	R-Isolysergic acid
Ergocristine	CHMe$_2$	CH$_2$Ph	ergocristinine
Ergotamine	Me	CH$_2$Ph	ergotaminine
Ergokryptine	CHMe$_2$	CH$_2$CHMe$_2$	ergokryptinine
Ergocornine	CHMe$_2$	CHMe$_2$	ergocorninine
Ergosine	Me	CH$_2$CHMe$_2$	ergosinine

§ According to Todd[25] the peptide antibiotic ostreogrycin A, the structure of which has not yet been finally established, contains an ester link formed by the hydroxyl group of a δ-hydroxy--acid residue.

Quite recently a new antibiotic serratamolide has been described[78], which has proved to be a cyclotetradepsipeptide composed of two L-serine residues and two residues of a β-hydroxy-acid (3-hydroxydecanoic acid).

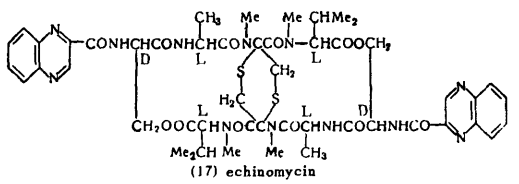
However, the question of the structure of the peptide part of the ergot alkaloids has not yet been finally settled, and forms a special subject of investigation by my colleagues and myself.

The second subgroup embraces a large number of diverse substances of type (11) which contain, in addition to residues of various α-amino-acids joined by amide links, one or more α-amino-β-hydroxy-acid (or α-amino-β--mercapto-acid) residues linked with other amino-acid residues not only by an amide but also by an ester (or thioester) link¶. The natural products include several interrelated antibiotics — etamycin (16a),[32-34] staphylomycin S (16b),[35,36] and ostreogrycin B (16c)[37,38]† — the molecules of which all contain one threonine residue incorporated in the depsipeptide ring not only by an amide but also by an ester link, the amino-group of the threonine being acylated by a hydroxypicolinic-acid residue. Still another closely related antibiotic is echinomycin (17),[39-41] the depsipeptide ring of which contains two serine residues incorporated in the ring by ester and amide links.



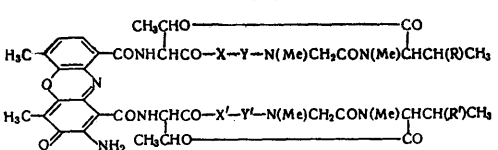
(11)

(16a): etamycin; R^1 = iso-Bu; R^2 = OH; R^3 = H; R^4 = Me; X = L-DiMeLeu-L-Ala
(16b): staphylomycin S; R^1 = Et; R^2 = H; R^3 = CH$_2$C$_6$H$_5$; R^4 = H; X = L-oxopipecolinic acid
(16c): ostreogrycin B; R^1 = Et; R^2 = H; R^3 = CH$_2$C$_6$H$_4$NMe$_2$-p; R^4 = H; X = L-olinic acid



(17) echinomycin

All actinomycin antibiotics of general formula (18), which have been studied in greatest detail by Brockmann[42,43], contain two cyclodepsipeptide groups, each of the rings always including one threonine residue, while the other α-amino-acid residues can vary greatly.



(18) actinomycins

Actinomycin	X and X′	Y and Y′	R and R′	Actinomycin	X and X′	Y and Y′	R and R′
I ($X_0\beta$)	Val	Pro; HyPro	CH_3	E_1	alleu	Pro	CH_3; C_2H_5
II (F_8)	Val	Sar	CH_3	E_2	alleu	Pro	C_2H_5
III (F_9)	Val	Sar; Pro	CH_3	F_1	alleu; Val	Sar	CH_3
IV (C_1)	Val	Pro	CH_3	F_2	alleu; Val	Sar; Pro	CH_3
V (X_2)	Val	Pro; γ-OPro	CH_3	F_3	alleu	Sar	CH_3
VI (C_2)	alleu*; Val	Pro	CH_3	F_4	alleu	Sar; Pro	CH_3
VII (C_3)	alleu	Pro	CH_3	$X_1\alpha$	Val	Sar; γ-OPro	CH_3
				$X_0\delta$	Val	Pro; HyPro	CH_3

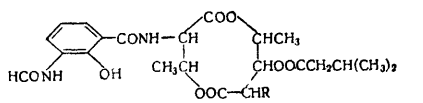
* Alleu = alloisoleucine (Ed. of Translation).

¶ Compounds of type (11) are sometimes termed *O*-peptides.[31] However, this name cannot in general be applied to depsipeptides, since *O*-peptides actually mean depsides.

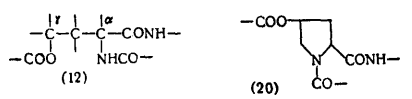
† According to Todd's most recent results[25], two further antibiotics, ostreogrycins B_1 and B_2, can be added to these compounds.

Antimycin A_1 (19a) and antimycin A_3 (19b), the structures of which were established in 1960,[44-46] differ substantially and stand apart from the above compounds. Both these antibiotics contain a threonine residue, but, in contrast to all the previous depsipeptides, three ester links are present for every peptide link.

The subgroup of depsipeptides of type (12), the molecules of which contain α-amino-γ-hydroxy-acid residues, are of peculiar interest, since they include the proteins of connective tissue, procollagen and collagen. The amino--acid residues in these proteins are joined together not only by peptide but also by ester links, and it has recently been shown[47] that the latter are formed between the hydroxyl group in hydroxyproline and the carboxyl group of glutamic or aspartic acid (20).

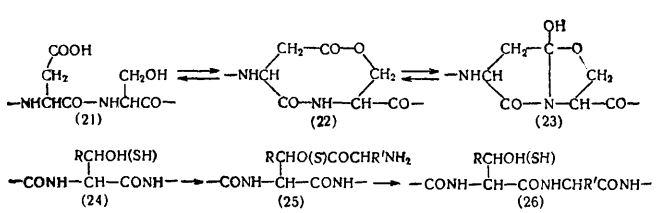


antimycin A_1 (19a) : R = $(CH_2)_5CH_3$
antimycin A_3 (19b) : R = $(CH_2)_3CH_3$



(12) (20)

Thus the class of depsipeptides includes the most varied representatives of natural products, extending from alkaloids and various antibiotics to several proteins. Moreover, depsipeptide groupings can evidently arise in the course of biochemical changes. Thus from Bernhard's results[48] it is quite possible that the action of esterases is associated with the ability of their active centre (21) to undergo changes leading to the formation of a cyclodepsipeptide grouping (22) and the tautomeric or isomeric cyclol structure (23). According to Brenner[49,50], on the other hand, the synthesis and the change in structure of some protein molecules of the type (24) may be associated with the intermediate formation of the corresponding depsipeptides and thiodepsipeptides (25), which then rearrange under the influence of enzymes to produce a normal peptide chain (26):

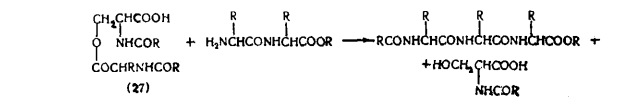


(21) (22) (23)

(24) (25) (26)

An important general property of all depsipeptides is that, under conditions of alkaline hydrolysis, they are readily cleaved only at the ester linkages. This fact affects fundamentally the procedures and methods used to study depsipeptides compared with those applicable to peptides. The possibility of the alkaline cleavage of depsipeptides into fragments at precisely located sites in the molecule greatly facilitates the investigation of their structure, in particular the determination of the optical purity of synthetic depsipeptides.

Little work has yet been done on the relation of the ester and the amide links in depsipeptides to the corresponding enzymes, although several facts suggest that interesting features can be expected here. Thus Botvinik has shown recently[51-54] that, under the influence of chymotrypsin, depsipeptides of type (27) not only undergo hydrolysis at the ester linkage but also, in the presence of esters of amino-acids or dipeptides, transfer their aminoacyl residue to the latter with formation of esters of the correspond ing dipeptides or tripeptides.



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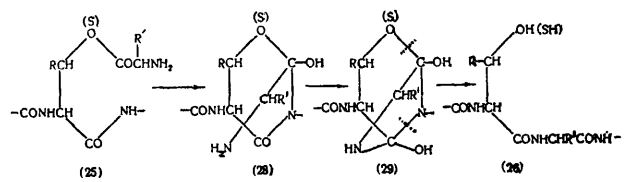


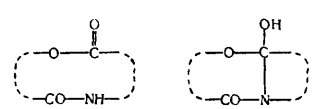
(25) (28) (29) (26)

Another characteristic feature of the same particular group of depsipeptides of type (25), containing residues of α-amino-β-hydroxy- or α-amino-β-mercapto-acids, is their tendency to undergo the above-mentioned rearrangement into the compounds (26), which according to Brenner[49,50] results from intramolecular reactions, first between an amide and an ester group (28), and then between an amide and an amino-group (29).

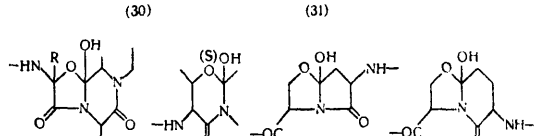
Such a tendency of amide and ester groups to undergo intramolecular reaction may perhaps be a general property of both linear and especially cyclic depsipeptides. With the latter (30) such transannular interaction should lead to the formation of bicyclic compounds of type (31). This question has been raised several times in the literature, by Witkop[55] in connection with the ergot alkaloids (32), by Brenner[49,50] when discussing the rearrangement (33) which he discovered, and by Bernhard[48] in connection with the mechanism of the action of esterases (34).

Experimentally, however, the possibility of intramolecular interaction between amide and ester groups remains so far completely unproven.

We are now studying this question with a series of model compounds analogous to those which have been cited, and especially with the ergot alkaloids, where the general method for synthesising α-substituted α-amino-acids and their peptides, which we worked out a few years ago[56-59], constituted a prerequisite for the synthesis[60,79] and study of the peptide moiety of the ergot alkaloids‡.



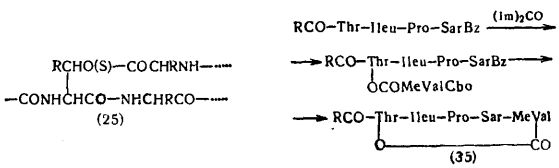
(30) (31)



ergot alkaloids (32) Brenner's rearrangement (33) esterases (34)

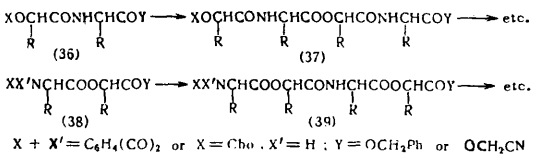
‡ Quite recently Swiss investigators have published a preliminary communication on the synthesis of one of the ergot alkaloids — ergotamine[61].

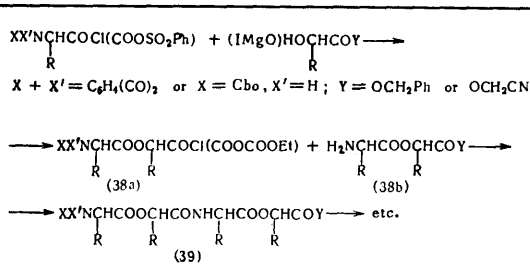
The general question of the synthesis of depsipeptides has not arisen until recently, although in isolated cases concerning depsipeptides of type (25), incorporating residues of α-amino-β-hydroxy- or α-amino-β-mercapto-acids (serine, threonine, cysteine), the desired compounds were synthesised. It was usually found that an ester (thioester) link was formed only after the peptide links, and it evidently proved best to use the carbodiimide and mixed anhydride methods (Shchukina[62-64], Brenner[65-67], and others[68-70]), which enable depsipeptides and thiodepsipeptides of type (25) to be obtained in high yield and in crystalline form. In the successful synthesis of actinomycin C_3 by Brockmann[71,72] the ester link of the cyclodepsipeptide part of the molecule (35) was formed at an intermediate stage by means of *NN'*-carbonyldiimidazole, cyclisation being effected by formation of a peptide link.



An experimental investigation of general paths for the synthesis of various types of depsipeptides was begun under the direction of Shemyakin and Shchukina a few years ago in view of the ever increasing interest aroused by this new class of compounds. By the present time Vinogradova, Lur'e-Feigina, Aldanova, and Oladkina[2,73] have worked out general methods for building up a depsipeptide chain with either a regular or an irregular arrangement of residues of optically active α-amino- and α-hydroxy-acids, and have shown the possibility of converting linear into cyclic depsipeptides.

Linear depsipeptides based on a regular alternation of α-amino-acid and α-hydroxy-acid residues can be synthesised in two fundamentally different ways. The first is to combine appropriate residues of a hydroxy- and an amino-acid by an amide link (36), remove either one (X) or the other (Y) protective group, and then join the resulting fragments together by an ester link (37); the whole depsipeptide chain is then built up by the repeated formation of ester links alone. In the second method substituted residues of an amino- and a hydroxy-acid would be combined by an ester link (38), then either one (X) or the other (Y) protective group would be removed and the resulting fragments connected by an amide link (39); here the further building up of the whole depsipeptide chain will be achieved by the repeated formation of amide links alone. Since methods of forming an amide link, and also procedures for introducing and removing protective groups, are quite well developed in peptide chemistry, the second path was preferred. In this case, however, it was necessary to reckon with the permanent presence in the molecules of labile ester groupings, which restricts the choice of methods applicable to the synthesis of a depsipeptide chain.





The choice of protective groupings should be governed by the possibility of their subsequent removal without affecting the ester links of the depsipeptide. It was found that, in preparing compounds of types (38) and (39), it was advisable to protect the carboxyl of the α-hydroxy-acid component by converting it into a benzyl or a cyanomethyl ester. If necessary, the cyanomethyl ester of the depsipeptide could be hydrolysed under mild alkaline conditions without greatly affecting the ester bonds of the depsipeptide itself, whereas the benzyl ester could be more suitably cleaved by hydrogenolysis§. The amino-group could be most suitably protected with a phthaloyl or a benzyloxycarbonyl group, since the former could be removed with hydrazine, and the latter with hydrogen bromide, under conditions which had little effect on the ester links of the depsipeptides; a benzyloxycarbonyl group could also be removed, of course, by hydrogenolysis. The removal of protective groups is not accompanied by racemisation.

Formation of an ester link in the synthesis of compounds of type (38) takes place with some difficulty, since the hydroxyl group of the α-hydroxy-acid component is usually secondary, and therefore many methods which are often employed for the acylation of alcohols cannot be utilised here. Production of such an ester link requires strong activation of the carboxyl group of the acylating amino-acid component, which is achieved by converting it into a mixed anhydride or the acid chloride. By itself, strong activation of the carboxyl is not dangerous with respect to racemisation of *N*-acylamino-acids: in the absence of bases, racemisation does not occur even with phthaloyl-D-valyl chloride, in which the α hydrogen atom should possess considerable reactivity owing to the presence of two strongly electron-accepting groups. However, acylation of the hydroxyl group of the α-hydroxy-acid component, by either anhydrides or chlorides of *N*-acylamino-acids, frequently takes place only in the presence of bases (pyridine, triethylamine), which strongly favour racemisation. Thus in the preparation of a mixed anhydride by the action of benzenesulphonyl chloride on phthaloyl-D-valine in the presence of excess of pyridine, complete racemisation of the phthaloyl-D-valine has occured even before it reacts with the α-hydroxy-acid component. Nevertheless, racemisation can be avoided if acylation with chlorides of phthalimido-acids is carried out in the presence of strictly equimolecular quantities of pyridine. Acylation can also be accomplished in the absence of bases, but then the hydroxyl group of the α-hydroxy-acid component must first have been activated, for example, by preparing one of the alkoxymagnesium halides. In the case of benzyloxycarbonylamino--acids, acylation can be carried out by the mixed anhydride method (with benzenesulphonyl chloride) and in excess of pyridine, since, in contrast to the phthalimido-acids, no

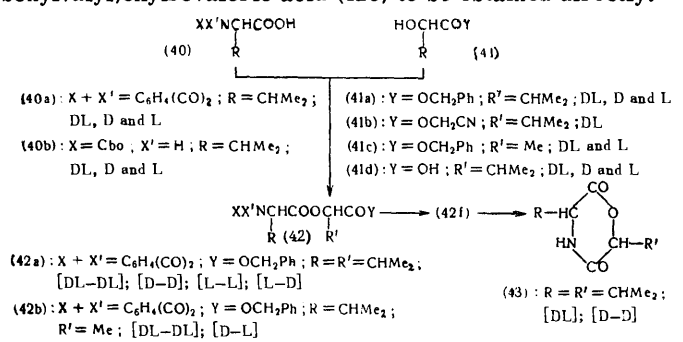
§ Recently we have begun to make extensive use of protection of the carboxyl group by converting it into a t-butyl ester, which is stable under alkaline conditions but unstable in acid media.

racemisation is observed at all here. The method suggested not long ago by Gibian and Lübke[74,75] and subsequently used by Schwyzer[76] for preparing compounds of type (38) by acting on diazoacetic esters and amides with *N*-acylamino-acids cannot be of general significance, since it provides no opportunity for synthesising depsipeptides containing residues of optically active hydroxy-acids¶.

Among methods of forming an amide link in preparing linear depsipeptides of type (39) the most promising proved to be the mixed anhydride method and especially the acid chloride method. Their use does not cause racemisation, because it is only the carboxyl of the hydroxy-acid residue of compounds of type (38a) which undergoes activation, whereas the amino-acid component of compounds of type (38b) does not require activation and its racemisation is excluded. This makes it possible to use the above two methods to synthesise various tetra- and octa-depsipeptides in high yields without appreciable racemisation.

Thus the scheme which we have worked out enables the preparation of optically active depsipeptides to be accomplished under far harsher conditions than the synthesis of the corresponding peptides. As a result, the preparation of depsipeptides is considerably simpler, and it does not involve the complications usually associated with the synthesis of optically active peptides.

It will be useful to consider in greater detail a number of actual examples of the synthesis of depsipeptides. Preparation of the first fragment of a depsipeptide chain — of racemic and optically active compounds of type (42) — was effected initially starting from phthaloylvaline (40a) or benzyloxycarbonylvaline (40b) and benzyl (41a) or cyanomethyl (41b) α-hydroxyisovalerate, or also benzyl lactate (41c). The racemic compounds (42a)–(42d), which are either crystalline solids or oils which can be distilled in a vacuum, were readily synthesised in yields of 65–70% by the mixed anhydride method (by the action of benzenesulphonyl chloride and excess of pyridine at 0°–2°). The same procedure was employed for the condensation of benzyloxycarbonylvaline (40b) with α-hydroxyisovaleric acid (41d), which enabled a 70% yield of α-(*N*-benzyloxycarbonylvalyl)oxyisovaleric acid (42e) to be obtained directly.



In the synthesis of optically active compounds of type (42), however, this method can be used only when benzyloxycarbonylamino-acids are used as starting materials. Thus benzyl α-(benzyloxycarbonyl-D-valyloxy)-D-isovalerate (42c) has been obtained in an optically pure state in 65% yield, whereas condensation under the same conditions of phthaloyl-D-valine (40a) with benzyl D-α-hydroxyisovalerate (41a) or L-lactate (41c) was accompanied by complete racemisation of the phthaloyl-D-valine. Variation of the reaction conditions (quantity of pyridine, temperature, sequence in which the components were introduced) did not eliminate the racemisation. If the protective group is a phthaloyl residue, optically active compounds of type (42) can be obtained in a different way, by condensing phthalimido-acid chlorides with esters of α-hydroxy-acids in the presence of one mole of pyridine in benzene. Benzyl phthaloyl-D-valyl-L-lactate (42b), for example, was obtained under these conditions in 95% yield. Good results were achieved also by the action of phthalimido-acid chlorides on the alkoxymagnesium halides formed by esters of α-hydroxy-acids, benzyl α-(phthaloyl-D-valyloxy)-D-isovalerate (42a) being synthesised in 70% yield.

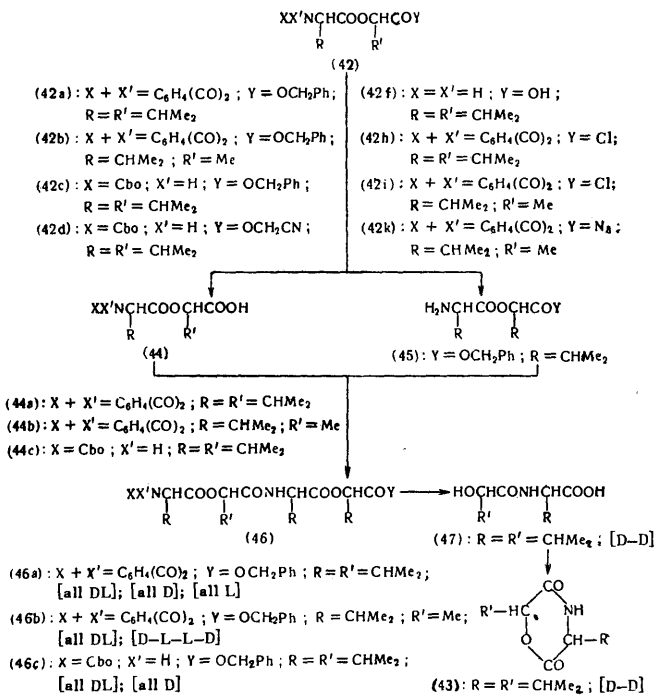
In order to demonstrate the optical activity of the compounds of type (42) obtained, their protective groups were removed, and then the following two procedures were used: (1) thermal cyclisation into easily sublimed substituted morpholines (43); (2) acid hydrolysis with subsequent isolation of optically active α-amino- and α-hydroxy-acids, the optical purity of the D-α-amino-acids being checked additionally with D-amino-acid-oxidase, and that of L-lactic acid with the corresponding dehydrogenase. Thus the compounds (42a, D–D) and (42c, D–D) yielded *via* (42f, D–D) a morpholine (43, D–D) identical with that isolated previously in an investigation of the structure of the antibiotic amidomycin, and acid hydrolysis of the compounds (42f, D–D) and (42g, D–L) led to the isolation of the corresponding optically active amino- and hydroxyl-acids uncontaminated with racemates.

The depsipeptide chain was built up further by splitting off the protective groups from the carboxyl or the amino-group of compounds of type (42) and then condensing the fragments (44) and (45) into racemic and optically active tetradepsipeptides (46). The benzyl group in the compounds (42a) and (42b) was eliminated by hydrogenolysis under normal conditions, when the acids (44a) and (44b) were obtained in yields reaching 80%. But hydrogenolysis of the compound (42c), of course, led to the formation of the compound (42f) containing free amino- and carboxyl groups. The phthaloyl group in (42a) was eliminated by heating with an alcoholic solution of one mole of hydrazine hydrate; under these conditions benzyl α-valyloxyisovalerate (45) is formed with a yield of ~80%. This same aminoester was obtained in 60% yield by eliminating the benzyloxycarbonyl group from compound (42c) by the action of HBr in glacial acetic acid. The acid chloride method was used to join fragments (44) and (45) by an amide link: the action of thionyl chloride on (44a) and (44b) yielded the corresponding acid chlorides (42h) and (42i), reaction of which with the aminoester (45) in the presence of triethylamine or pyridine led to the formation of substituted tetradepsipeptides of type (46). Thus 75% yields of the optically active tetradepsipeptides (46a, all D) and (46a, all L) have been obtained in the crystalline state by this method, while the optically active tetradepsipeptide (46b, D–L–L–D) separated as an oil in almost quantitative yield. This last compound has also been obtained by the azide method *via* the acid chloride (42i) and the azide (42k), but the yield is only

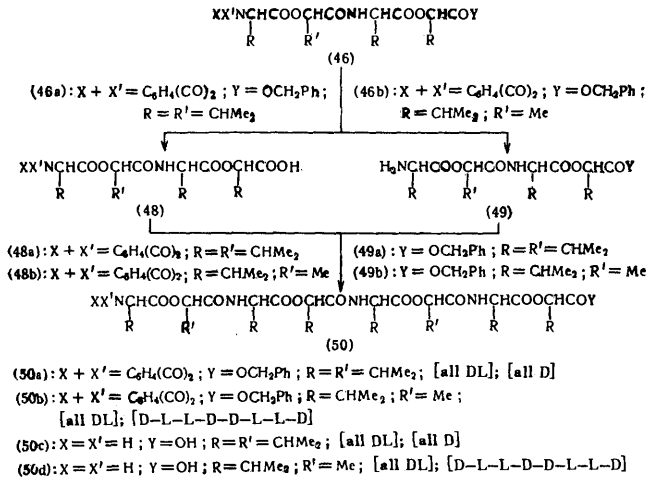
¶ The same drawback is possessed by the method, published at the end of 1961, for preparing tridepsipeptides by the condensation of acylamino-acids, aldehydes (ketones), and esters of α-isocyanocarboxylic acids[77].

50%. The compounds (46a, all D) and (46c, all D) were also synthesised, with yields of ~70%, by the mixed anhydride method, by treating (44a) or (44c) under normal conditions with ethyl chloroformate followed by the aminoester (45). Attempts to use the cyanoethyl ester (42d) to synthesise the tetradepsipeptide (46c), however, led to negative results, as this ester proved to be insufficiently reactive to condense with the aminoester (45).

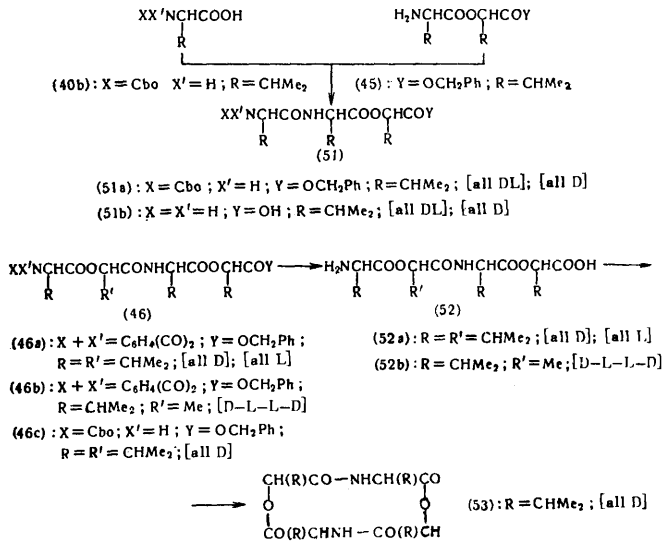
The optical purity of tetradepsipeptides of type (46) was determined by partial alkaline hydrolysis leading to a selective cleavage of the ester links and the formation of compounds of type (47) containing free hydroxyl and carboxyl. Thermal cyclisation of these compounds with simultaneous sublimation in a vacuum results in formation of the substited morpholines (43). The optically active tetradepsipeptide (46a, all D), for example, yielded the morpholine (43, D–D), identical with that isolated previously in studying the structure of amidomycin. On the other hand, complete acid hydrolysis of the tetradepsipeptide (46b, D–L–L–D) with subsequent determination of D-valine with D-aminooxidase and of L-lactic acid with the corresponding dehydrogenase also confirmed the absence of appreciable racemisation during synthesis of tetradepsipeptides in this way.



The tetradepsipeptides (46) were converted into racemic and optically active octadepsipeptides (50) in a similar manner to that in which they had been formed from compounds of type (42). Hydrogenolysis of the compounds (46a) and (46b) yielded the phthalimido-acids (48a) and (48b), and elimination of the phthaloyl group from (46a) and (46b) by means of hydrazine led to the aminoesters (49a) and (49b), which were condensed with (48a) and (48b) respectively by the acid chloride method, removal of the protective groups from the resulting compounds (50a) and (50b) being effected under the same conditions as with the corresponding substituted tetradepsipeptides. In this way, for example, an 80% yield of the octadepsipeptide (50a, all D) was obtained in the crystalline state. The above process for lengthening a depsipeptide chain with regularly alternating residues of α-hydroxy- and α-amino-acids can be continued further.



The above synthetic path can also be used to obtain linear depsipeptides having an irregular arrangement of α-amino-acid and α-hydroxy-acid residues. Thus benzyloxycarbonylvaline (40b) was condensed by the mixed anhydride method with the aminoester (45) to give an 80% yield of the compounds (51a, all DL) and (51a, all D), hydrogenolysis of which led to the tridepsipeptides (51b, all DL) and (51b, all D) containing two amino-acid residues together. Depsipeptides having any alternation of α-amino- and α-hydroxy-acid residues can be synthesised in this way.



Linear tri-, tetra-, and octa-depsipeptides having free amino- and carboxy-end-groups can serve as starting materials for the synthesis of cyclodepsipeptides. Such

unsubstituted linear depsipeptides can be prepared in various ways. Thus hydrogenolysis of the optically active tetradepsipeptide (46c, all D) gave an 80% yield of α-(D-valyloxy)-D-isovaleryl-α-(D-valyloxy)-D-isovaleric acid (52a), which can be obtained also, though in lower yield, from the tetradepsipeptide (46a, all D) by removing the protective groups in stages, first the phthaloyl group (by means of hydrazine) and then the benzyl group (by hydrogenolysis). The cyclisation of linear depsipeptides, for example of the tetradepsipeptide (52a) into the cyclotetradepsipeptide (53), is most simply accomplished by the acid chloride method, the acid chloride of this tetradepsipeptide being cyclised in very dilute benzene solution in the presence of triethylamine.

The influence of various structural and especially steric factors on the cyclisation of linear depsipeptides, ring-closure by formation of an ester link, and also several other problems of the chemistry of depsipeptides having regular and irregular alternations of various amino- and hydroxy-acids form the subject of our current investigations.

The methods which we have worked out can be further utilised for the synthesis of various natural depsipeptides, in particular antibiotics. Furthermore, these methods open up the possibility of synthesising a new type of analogues of biologically active peptides in which some of the peptide links are replaced by ester links, *i.e.* in which residues of various α-amino-acids are replaced by residues of the corresponding α-hydroxy-acids. In this connection it is of particular interest to introduce α-hydroxy-acid residues into peptides which exhibit enzyme or hormone activity, since it is quite possible that, among such analogues, substances will be found which possess a strong antagonistic effect. At the present time our interests in this field are concentrated on two peptides — glutathione, which displays a broad spectrum of biological activity, and bradykinin, which possesses appreciable hypotensive activity.

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ORGANOPHOSPHORUS COMPOUNDS† OBTAINED FROM α-OXIDES

E. L. Gefter and M. I. Kabachnik

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† In this translation names of these compounds have been changed to conform to the 1952 rules of the Chemical Society and American Chemical Society, where authors' intentions are clear. In the Russian text derivatives of phosphonous and phosphinous acids are both referred to as phosphinites (Ed. of Translation).

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I. INTRODUCTION

The importance of organophosphorus compounds in chemical science and industry has grown during the post-war years. Many substances of this type are effective insecticides, medicinals, catalysts for various reactions, plasticisers, flameproofing agents for various materials, additives for improving the properties of lubricating oils, etc. This has naturally aroused interest in the development of simple and efficient methods for synthesising various types of organophosphorus compounds, as noted particularly by several authors at the Second All-Union Conference on the Chemistry and the Applications of Organophosphorus Compounds (Kazan, November 1959)[1-3].

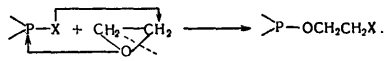
The present review deals with the reactions of cyclic oxides with some phosphorus compounds and also the properties, reactions, and applications of the products. The only short summary in this field, dealing with the addition of α-oxides to halogen compounds of phosphorus, was written by one of us in 1947[4]. During the past years many facts have accumulated, the applications of this reaction have been extended, and many new compounds of the β-substituted "organoelemental" type have been prepared. This trend in the chemistry of organophosphorus compounds has developed considerably during recent years in relation to the practical exploitation of organophosphorus compounds synthesised from α-oxides. Other methods for the preparation of such compounds have usually been less effective, and are difficult to use, even if they are possible at all. α-Oxides and phosphorus compounds usually undergo ready addition without the formation of by-products. In organic chemistry reactions of this type — the addition of ethylene oxide to alcohols, amines, and other compounds containing a reactive hydrogen atom — have for a long time been extensively used for the preparation of 2-hydroxyethyl compounds[5-9].

II. INTERACTION OF PHOSPHORUS COMPOUNDS CONTAINING REACTIVE HALOGEN ATOMS WITH α-OXIDES. PROPERTIES OF THE RESULTING PRODUCTS

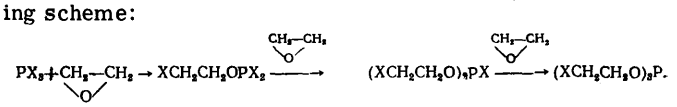
1. Addition of α-Oxides to Halogen Compounds of Tervalent Phosphorus

The addition of α-oxides (epichlorohydrin) to phosphorus trichloride was first described by Hanriot[10]; fifty-four years later Lommel and Engelhardt[11] patented the addition of ethylene oxide to PCl_3 for the preparation of chloroethyl esters of phosphorous acid. In neither case was the structure of the products of these reactions established.

The systematic investigation of this reaction was begun by Soviet scientists. Kabachnik and Rossiiskaya studied the reaction of phosphorus trichloride and tribromide and also of various ester chlorides of phosphorous acid with ethylene oxide[12-15]. Smooth addition of the components to one another was observed in all cases, the oxide ring opening with formation of a P–O–C link, while halogen, previously combined with the phosphorus, added to the β carbon atom



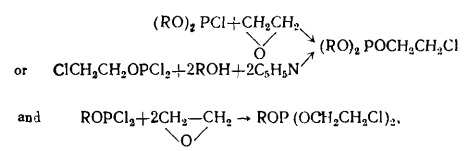
The valency of the phosphorus remains unchanged during this reaction. Addition of ethylene oxide to tervalent phosphorus halides takes place in stages according to the following scheme:



Products formed by the addition of one, two, and three molecules of the oxide to PCl_3 [12] and PBr_3 were isolated[13].

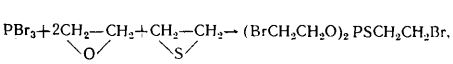
The process can be stopped at any desired stage, depending on the amount of ethylene oxide introduced, making it easy to obtain various derivatives of the 2-halogenoethyl phosphorous acids (see below).

Kabachnik, Rossiiskaya, and other investigators obtained also mixed esters of phosphorous acids containing either one or two 2-chloroethyl groups, according to the following schemes:

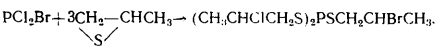


where R = phenyl[14], ethyl[15,16], some 1-cyanoalkyls[17], and other radicals[15,18].

Interesting mixed 2-halogenoalkyl esters of phosphorous acid with different bonds (P–O–C and P–S–C) or with different halogens were synthesised by De Witt[19] by the reaction of phosphorus tribromide with a mixture of ethylene oxide and ethylene sulphide:



and also by the reaction of phosphorus bromodichloride with propylene sulphide:



The preparation of such unsymmetrical compounds is sometimes complicated by disproportionation processes, which readily occur with some esters of tervalent phosphorus acids. For example, 2-chloroethyl diphenyl phosphite[14], 2-chloroethyl *o*-phenylene phosphite[14], and 2-chloroethyl cyanoalkyl phosphites[17] were synthesised in good yields, whereas the preparation of 2-chloroethyl diethyl phosphite yielded only a certain amount of this product together with other theoretically possible compounds — triethyl phosphite, bis-2-chloroethyl ethyl phosphite, and tris-2-chloroethyl phosphite[15,16] — formed by disproportionation. Similar behaviour was found in the synthesis of bis-2-chloroethyl phenyl phosphite[14] and dialkyl 2,2-dichloro-1-methylethyl phosphite[20]; incidentally, the preparation of 2-chloroethyl methyl phosphite from phosphorus trichloride and a mixture of methanol and ethylene chlorohydrin was also accompanied by formation of other possible products, dimethyl and bis-2-chloroethyl phosphites[21].

Ethylene oxide reacts extraordinarily readily with tervalent phosphorus halides with much heat evolution, the tribromide reacting more vigorously than phosphorus trichloride.

Another possible method for obtaining ester chlorides [phosphoro-chloridites and -dichloridites (Ed. of Translation)] and 2-chloroethyl esters of phosphorous acid (symmetrical and mixed) is by reaction of phosphorus trihalides with ethylene chlorohydrin. However, the accompanying evolution of hydrogen chloride makes this procedure less convenient, reduces the yields of products owing to partial rupture of ester links, and often requires special apparatus owing to the corrosive action of the hydrogen chloride evolved. Sometimes this last product must be combined with organic bases, which complicates the process.

The preparation of bis-2-chloroethyl hydrogen phosphite [bis-2-chloroethyl phosphonite? (Ed. of Translation)] may well be the only case in which the use of ethylene chlorohydrin provides a simpler process than that with ethylene oxide, the former reaction taking place in a single stage[21,22]

$$PCl_3+3HOCH_2CH_2Cl \rightarrow HPO(OCH_2CH_2Cl)_2+2HCl+ClCH_2CH_2Cl,$$

whereas the latter occurs in two stages, *via* tris-2-chloroethyl phosphite[23]

$$2PCl_3+6CH_2\!-\!CH_2 \rightarrow 2P(OCH_2CH_2Cl)_3 \xrightarrow{H_3PO_2} 3HPO(OCH_2CH_2Cl)_2.$$

However, in this case also the use of ethylene oxide is to be preferred, since both the above stages take place readily, with excellent yields, and without the formation of by-products.

The use of ethylene bromohydrin, by analogy with the chlorohydrin, to obtain 2-bromoethyl esters of phosphorous acid, *e.g.* $BrCH_2CH_2OPBr_2$ [really 2-bromoethyl phosphorodibromidite (Ed. of Translation)], is apparently impossible, since hydrogen bromide cleaves ester links far more readily than does hydrogen chloride[24]; it is for this reason that the reaction of phosphorus tribromide with alcohols is a universal method for preparing alkyl bromides.

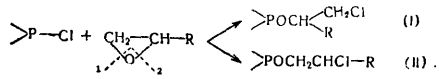
Hence for the preparation of 2-halogenoethyl derivatives of phosphorous acid the above reaction of ethylene oxide with phosphorus trihalides has no equal for simplicity and the ease with which it can be carried out.

Technically it is more convenient to pass gaseous ethylene oxide into the phosphorus trihalide than to carry out the reaction in the reverse order. The yields of the reaction products remain substantially unaffected by the order in which the components are added to one another. Although according to Efimova's results[25] the addition of PCl_3 to liquid ethylene oxide gives a higher yield (64.6%) of tris-2-chloroethyl phosphite than does bubbling gaseous ethylene oxide through phosphorus trichloride (56.5%), these results are not typical, since the vacuum distillation of the reaction product occurred in this case at high temperatures (owing to a poor vacuum), so that isomerisation of the tris-2-chloroethyl phosphite took place at an appreciable rate. In a good vacuum this substance distils almost quantitatively[23].

Until recently only 2-halogenoalkyl esters of phosphorous acid were known, *i.e.* compounds containing P–O or P–X bonds, where X represents a halogen. Comparatively recently, the addition of ethylene oxide to alkyl-[26-28] and aryl-phosphonous dichlorides[29-31] and to diethylphosphinous chloride[32] has been studied. These reactions, which were more vigorous than in the case of phosphorus trichloride, led to the preparation of mono- and bis-2-chloroethyl esters of methyl-,[26] ethyl-,[27,28] and phenyl-phosphonous acids[29-31] and the 2-chloroethyl ester of diethylphosphinous acid[32].

The comparatively little studied reactions of unsymmetrical α-oxides with tervalent phosphorus halides are interesting. The addition of propylene oxide[23,25,33-35], styrene oxide[23,36], epichlorohydrin[33], and glycidyl‡ phenyl ether [1-phenoxypropane-2,3-diol (Ed. of Translation)][33] to phosphorus trichloride has been described, as well as that of propylene oxide to methyl-,[36] ethyl-,[26] and phenyl-phosphonous dichloride[36] and of propylene sulphide to phosphorus tribromide and bromodichloride[19]. The reaction is fundamentally the same as with ethylene oxide, the oxide ring opening with formation of 2-halogenoalkyl esters or thioesters of phosphorous acid.

Theoretically the reaction can go in two ways, the radical of the α-oxide being attached to either an α or a β carbon atom in the reaction product:



Little experimental work has been done on this problem, and the results are inconclusive. Thus Shuikin and Bel'skii[35] obtained a good yield of 2-chloropropan-1-ol by hydrolysing the addition product of propylene oxide and phosphorus trichloride, which indicates the second type of reaction. Efimova[25] carried out the same investigation and isolated 1-chloropropan-2-ol (although without giving the yield), which can be obtained only by the first type of reaction. Nevertheless, most chemists consider from general principles that these processes are of the second type, *i.e.* that the oxide ring is opened at the bond between oxygen and the secondary carbon atom[19,23,33-36]:

$$>P\!-\!Cl+CH_2\!-\!CH\!-\!R \rightarrow >POCH_2CHCl\!-\!R.$$

The only case of the reaction of phosphorus trichloride with an α-oxide (*e.g.* epichlorohydrin) in the presence of aluminium chloride so far described[37] is one yielding the

‡ The term ***glycidyl*** used throughout this review derives from ***glycidol***, 2,3-epoxypropan-1-ol (Ed. of Translation).

dichloride of 3-chloro-2-hydroxypropylphosphonic acid $ClCH_2.CH(OH).CH_2.POCl_2$. The mechanism of this reaction was not given.

2. Some Properties of 2-Halogenoalkyl Derivatives of Tervalent Phosphorus Acids

Compounds containing the grouping $>P-O.CH_2.CH_2X$ (where X = Cl or Br) display all the properties characteristic of esters or ester halides of tervalent phosphorus acids. They can add on oxygen, sulphur, and halogens, the phosphorus becoming quinquevalent:

$$>POCH_2CH_2X+A \rightarrow >P(A)OCH_2CH_2X,$$

where A = O, S, Cl_2, or Br_2. Such addition occurs more readily with phosphonous esters than with derivatives of phosphorous acid. Thus tris-2-chloroethyl phosphite could be oxidised to the phosphate with potassium permanganate[38] and sodium hypochlorite[39], while bis-2-chloroethyl phenylphosphonite is readily oxidised to the phenylphosphonate ester even in the air[31].

The addition of sulphur to 2-chloroethyl phosphorodichloridite[40], bis-2-chloroethyl phosphorochloridite[41], bis-2-chloroethyl phenylphosphonite[31], tris-2-chloroethyl phosphite[42,43], and methylphosphonochloridite esters (the 2-chloroalkyl ester)[26] has been described. The action of chlorine on 2-chloroethyl *NN*-diethylphosphoramidochloridite was investigated by Malatesta and D'Atri[40]. 2-Halogenoethyl phosphites are hydrolysed quite readily, ultimately giving phosphorous acid[12,14].

The variety of behaviour of these 2-chloroethyl derivatives on storage (in absence of air or moisture) and on heating is noteworthy[12]. Among the three well-known substances:

$$\underset{(I)}{ClCH_2CH_2OPCl_2}, \quad \underset{(II)}{(ClCH_2CH_2O)_2PCl}, \text{ and } \underset{(III)}{(ClCH_2CH_2O)_3P},$$

I and III are quite stable on storage; I is stable when heated to 190°–200°, but begins to decompose at higher temperatures; III is stable at temperatures below 140°–150°, but at about 140° it begins to isomerise at an appreciable rate, as will be discussed in detail below. Product II is in general unstable, gradually changing into a mixture of I and III:

$$2(ClCH_2CH_2O)_2PCl \rightarrow ClCH_2CH_2OPCl_2+(ClCH_2CH_2O)_3P.$$

This process is accelerated on heating, and the decomposition becomes more complicated.

Various mixed 2-chloroethyl derivatives of phosphorous acid have been prepared using the reactivity of the chlorine atoms attached to phosphorus in 2-chloroethyl phosphorodichloridite. One or both of these atoms were replaced by fluorine by the action of metal fluorides[40,44] by diethylamino- and anilino-groups by the action of the amines[40], and by the corresponding alkoxy-groups by the action of ethanol in the presence of pyridine[15] and of cyanomethyl alcohol[17].

Walsh found that trialkyl phosphites, including those containing 2-chloroalkyl groups, are able to react with phosphorous acid to form dialkyl phosphonates[23]

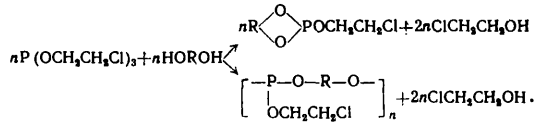
$$2P(OR)_3+H_3PO_3 \rightarrow 3HPO(OR)_2.$$

By this method Walsh obtained excellent yields of bis-2-chloroethyl, bis-2-chloropropyl, and bis-2-chloro-2-phenylethyl phosphonates. The hydrogen in these bis-2-chloroalkyl esters possesses the usual reactivity of compounds of this type. Aldehydes, for example, add to bis-2-chloroethyl phosphonate to form the corresponding bis-2-chloroethyl 1-hydroxyalkylphosphonates[45-47]. This offers great scope, little used as yet, for the synthesis of 2-halogenoalkyl esters of various phosphonic acids.

Tris-2-chloroethyl phosphite on moderate heating with alcohols and diols undergoes transesterification to other esters or polyesters of phosphorous acid[48,49] presumably according to such schemes as:

$$P(OCH_2CH_2Cl)_3+ROH \rightarrow ROP(OCH_2CH_2Cl)_2+ClCH_2CH_2OH,$$

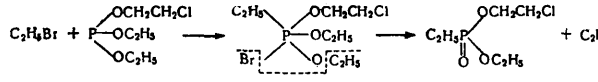
and



The Arbuzov rearrangement of tris-2-chloroethyl phosphite occurs under the influence of alkyl halides[21,25] acetyl chloride[21], halogenated ethers[25], and chlorine[50]. As anticipated, bis-2-chloroethyl esters of the corresponding phosphonic acids were obtained, while chlorine yielded bis-2-chloroethyl phosphorochloridate:

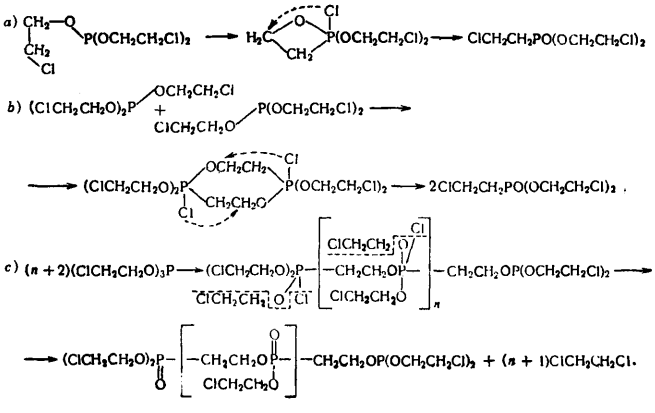
$$Cl_2+P(OCH_2CH_2Cl)_3 \rightarrow \left[\begin{matrix}Cl\\Cl\end{matrix}\right]P(CH_2CH_2Cl)_3 \rightarrow ClPO(OCH_2CH_2Cl)_2+ClCH_2CH_2Cl.$$

It is interesting that the Arbuzov rearrangement of 2-chloroethyl diethyl phosphite in the presence of ethyl bromide takes place in only one of the two theoretically possible ways, a mixed 2-chloroethyl ethyl ethylphosphonate being obtained[16]:



A remarkable property of 2-halogenoalkyl esters of tervalent phosphorus acids is their ability to undergo Arbuzov isomerisation merely on heating, without the addition of any halogen compounds or other agents[12,50]. In these cases the 2-halogenoethyl groups themselves act as the halogen-containing agents causing the rearrangement.

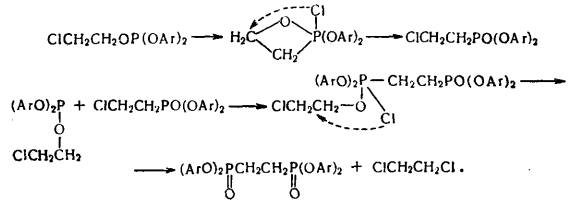
Kabachnik and Rossiiskaya investigated the course of the thermal isomerisation of tris-2-chloroethyl phosphite, and suggested that this isomerisation can take place both as an intramolecular[50] and as an intermolecular[50,51] process:



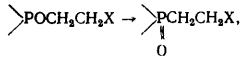
In the first two cases a single product, bis-2-chloroethyl 2-chloroethylphosphonate, is formed by the isomerisation; the third case results in non-volatile resinous products of polyester type, containing both C–O–P and C–P bonds. Such polyester resins may be formed to some extent also as a result of the thermal polycondensation of 2-chloroethyl esters of acids of phosphorus, which has been investigated by Korshak *et al.* (phosphonic esters)[52] and by Acker (a phosphorochloridic ester)[53].

Isomerisation of other 2-halogenoalkyl esters of tervalent phosphorus acids not containing Ar–O–P groups apparently occurs similarly[13,15,25,27-32,50].

Compounds containing such groups, *e.g.* mixed aryl 2-chloroethyl phosphites, however, isomerise according to a different mechanism, forming esters not of 2-chloroethylphosphonic but of ethylenediphosphonic acid[14] according to the following scheme:



Clearly, the former type of thermal isomerisation makes it easy to prepare organophosphorus compounds containing 2-halogenoethyl groups combined directly with the phosphorus. Thus 2-bromo- and 2-chloro-ethylphosphonic esters have been obtained from 2-halogenoethyl phosphites[13,15,50] ethyl-2-chloroethylphosphinic[27,28] and phenyl-2-chloroethylphosphinic esters from bis-2-chloroethyl ethyl- and phenyl-phosphonites[29-31] and 2-chloroethyldiethylphosphine oxide from 2-chloroethyl diethylphosphinite[32]. The common feature of all these reactions is

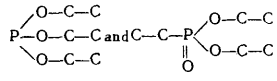


where X = Cl or Br.

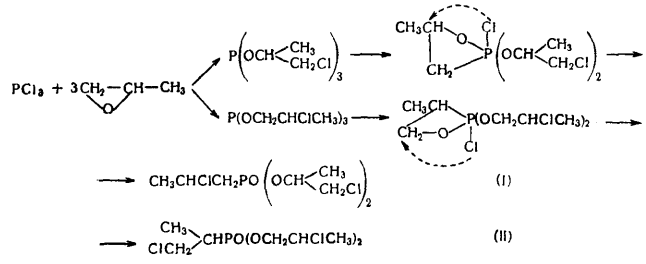
A peculiarity of the thermal isomerisation of 2-halogenoethyl esters of tervalent acids of phosphorus is that, up to a certain temperature (which is different in each case), the process is quite slow, but at some point, especially if local overheating is present, the reaction becomes comparatively rapid, sometimes with considerable heat evolution. This fact, first noted by Kabachnik and Rossiiskaya[50], presented serious danger even in work with small amounts of these substances, and of course hindered their extensive investigation.

A safe method for isomerising 2-chloroethyl esters of tervalent phosphorus was worked out by one of us[54-56] and independently by German chemists[57], who described the isomerisation of tris-2-chloroethyl phosphite in various solvents, which were boiling and well stirred. The agitation prevented local overheating, and the boiling of the solvent absorbed the heat of isomerisation evolved. Moreover, the presence of solvents diminished the probability of polycondensation, so that the yields of the isomeric product increased. For example, thermal isomerisation of tris-2-chloroethyl phosphite in the absence of solvent yielded 40% of the monomeric isomer, bis-2-chloroethyl 2-chloroethylphosphonate[50], whereas the yield increased to 65–70%[55] and sometimes even to 90%[57] when isomerisation was carried out in solvents. The solvents used should be inert towards the isomerising substances and should possess sufficiently high boiling points for isomerisation to take place at a satisfactory rate. In addition, the solvents must not form azeotropic mixtures with the products of isomerisation, nor must they have similar boiling points, so that they can be easily separated. Suitable solvents for the isomerisation of tris-2-chloroethyl phosphite are aromatic hydrocarbons[55,57], halogenated aromatic hydrocarbons[56,57], and some phosphoric esters[57]; ethylbenzene[27,28] can be used for bis-2-chloroethyl ethylphosphonite, decalin[30,31] for the corresponding phenylphosphonite, and toluene[32] for 2-chloroethyl diethylphosphinite.

The thermal isomerisation of the addition products of unsymmetrical α-oxides with phosphorus trihalides have been far less investigated than that of tris-2-halogenoethyl phosphites. A qualitative difference between these two processes involves the hydrocarbon skeletons, which are the same for the tris-2-halogenoethyl phosphites and their isomerisation products, consisting of three chains each of two carbon atoms



The isomerisation of any other tris-2-halogenoalkyl phosphite, however, shows a different pattern, for example



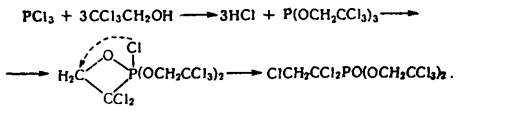
It can be seen from this scheme that during isomerisation the hydrocarbon skeleton of the acid part of the ester molecule changes its structure, while that of the ester part remains as before. This was shown by Efimova[25] for tri-(2-chloro-1-methylethyl) phosphite, and by Kuznetsov and Valetdinov[58] and Khairulin *et al.*[20] for tri-(2-chloro-1-chloromethylethyl) phosphite (this compound, obtained together with others by the action of PCl_3 on glycerol 1,3-dichloride, can be formed by the addition of epichlorohydrin to PCl_3 according to mechanism I).

The thermal isomerisation of 2-halogenoalkyl phosphites, like the usual Arbuzov rearrangement, depends on the readiness with which the components of alkyl halides add to the tervalent phosphorus atom in each individual compound. Steric factors and also the type of radical in the alkoxy-groups apparently play an important part.

Whereas tris-2-chloroethyl, tri-(2-chloropropyl), tri-(2-chloro-1-chloromethylethyl), and similar phosphites when heated isomerise quite readily into corresponding compounds of quinquevalent phosphorus, some mixed phosphorous esters containing cyanoalkoxy-groups do not isomerise and do not undergo radical redistribution[17].

The information on tris-2,2,2-trichloroethyl phosphite is contradictory: according to Gerrard *et al.*[59] this ester is incapable of thermal isomerisation, but according to Rydon

and Tonge[60] it is already converted into the normal isomerisation product, bis-2,2,2-trichloroethyl 1,1,2-trichloroethylphosphonate during preparation by the interaction of PCl_3 and trichloroethanol in the cold:



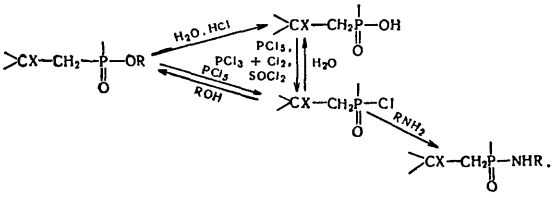
It is clear that thermal isomerisation of the addition products of α-oxides and phosphorus trihalides can be used to obtain more or less readily compounds containing one, two, or three phosphorus–carbon bonds (depending on the initial phosphorus compounds taken), where one of the radicals combined with phosphorus will necessarily be a 2-halogenoalkyl group. Compounds of this type form, in turn, starting materials for the preparation of halides of phosphinic acids and oxides of tertiary phosphines containing 2-halogenoalkyl and 1,2-unsaturated radicals.

3. 2-Halogenoalkylphosphonic Acids and Their Derivatives

Phosphorus–carbon, C–P, bonds are usually more stable, except in a very few cases, than bonds of the ester, C–O–P, type. It is not surprising, therefore, that treatment of 2-halogenoalkylphosphonic esters (among which bis-2-chloroethyl 2-chloroethylphosphonate has been studied the most thoroughly) with water, hydrochloric acid[50,51], hydrogen chloride[61,62], or phosphorus pentachloride[13,27-30,50,51,61,62] results in rupture of the C–O–P bonds, while the C–P bonds remain unchanged. In the first three cases 2-halogenoalkylphosphonic acids are obtained, and in the last case their chlorides. Phosphorus pentachloride splits off one ester group, especially a 2-chloroethyl group, very readily[27-30,50,51,62], while the second ester link reacts incompletely even on moderate heating. Preparation of the acid dichloride from bis-2-chloroethyl 2-chloroethylphosphonate therefore requires more severe conditions. For example, the ester has been heated with PCl_5 to 150°–160° under pressure[51]; PCl_5 has been added to the ester heated to the same temperature in the presence of some metal chlorides[61]; and the ester has first been converted into 2-chloroethylphosphonic acid with hydrogen chloride, and the acid subsequently treated with phosphorus pentachloride, a mixture of phosphorus trichloride and chlorine[61], or thionyl chloride[61].

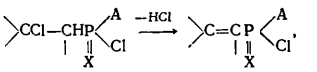
Chlorides of 2-halogenoalkylphosphonic acids, which contain reactive chlorine atoms in the molecule, more or less readily form the corresponding acids, esters, and amides on treatment with water[29,30,50,62,63], alcohols[27-30,62,63], or phenols[63,64], and amines[51,63] respectively.

These reactions of derivatives of 2-halogenoalkylphosphonic acids can be represented by the following scheme:



4. Compounds Containing αβ-Unsaturated Groups Attached to Phosphorus§

2-Halogenoalkyl radicals attached to phosphorus are quite inert towards acid reagents and towards heating for a short period up to about 300°. They are not stable at higher temperatures, especially in the presence of some metal salts, nor to the action of basic reagents. Kabachnik and Medved', Soborovskii and Zinov'ev, and subsequently others, have described the preparation of several chlorides of αβ-unsaturated phosphonic and phosphonothioic acids by dehydrochlorination¶ according to the following general scheme:

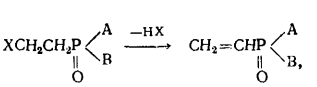


where X = O or S, and A = Cl, alkyl, or aryl.

Dehydrochlorination in the presence of barium salts or activated carbon at about 300°, for example, yielded chlorides of vinylphosphonic[66,67], propenylphosphonic[68], and ethylvinylphosphinic[27,28] acids, while dehydrochlorination with triethylamine has given the chlorides of vinylphosphonic[69], vinylphosphonothioic[70], and phenylvinylphosphinic[71] acids. Finally, the chloride of vinylphosphonic acid was synthesised in a different way, by treating esters of this acid with phosphorus pentachloride[72,73].

Hydrolysis of several chlorides of αβ-unsaturated phosphonic acids yielded the corresponding acids[67,71,74] and also the anhydride of vinylphosphonic acid[67].

Treatment of 2-halogenated alkylphosphonic esters or tertiary phosphine oxides with alcoholic alkalis[27-30,71,75,76], triethylamine[29,30,32,64,71,77-82], diethylamine in non-aqueous medium[83], or alkali-metal acetates[56,84], readily splits off hydrogen halide to form an αβ-unsaturated group attached to phosphorus, for example



where A and B are ester, alkyl, or aryl groups. In aqueous medium dialkylamines react differently with a 2-halogenoalkyl group attached to phosphorus, replacing halogen by dialkylamino groups: *i.e.* dialkylaminoethylphosphonic instead of unsaturated phosphonic esters are formed[76]:

If esters containing no 2-halogenoalkyl group in the alcoholic part of the molecule are subjected to dehydrohalogenation, all the above basic reagents act in the same way to give about the same yields of esters of αβ-unsaturated phosphonic acids. If, however, 2-chloroethyl groups are present in both acid and alcoholic parts of the ester molecule, as for example in bis-2-chloroethyl 2-chloroethylphosphonate, these basic reagents will have differing

§ The properties of such compounds and a series of methods for preparing them are given in a monograph written by one of us[65]. The present review includes a short account of methods for synthesising these compounds and material which has been published since the appearance of the monograph.

¶ The starting materials for the dehydrochlorination were obtained also by methods not discussed in the review.

effects. Alkali-metal acetates act selectively, reacting only with the 2-chloroethyl radical attached to phosphorus, practically without affecting the P–O–CH_2.CH_2Cl group. Alkalis, and to a lesser extent amines, react quite readily with both acid and alcoholic 2-chloroethyl groups, giving rise to side-reactions[56,84], which will be considered below. Here we note only that, by carrying out the reaction with triethylamine slowly, we can obtain satisfactory yields of 2-chloroethyl esters of vinylphosphonic[78] and arylvinylphosphinic[71] acids, whereas with alcoholic alkali only small yields of these substances can be isolated.

Esters and also amides of $\alpha\beta$-unsaturated phosphonic acids can be prepared in other ways, for example by treating chlorides of $\alpha\beta$-unsaturated phosphonic acids with alcohols[27,28,66,67], glycols[67], phenols[27,28,67], or amines[67].

Specific methods for the preparation of vinylphosphonic esters are the dehalogenation of 1,2-dihalogenoalkylphosphonic esters with zinc dust[79], and also (for divinyl vinylphosphonate) reaction of 2-chloroethylphosphonic dichloride with acetaldehyde and triethylamine[85,86].

$$ClCH_2CH_2POCl_2+2CH_3CHO+3N(C_2H_5)_3 \rightarrow CH_2=CHPO(OCH=CH_2)_2+3N(C_2H_5)_3\cdot HCl.$$

Among tertiary phosphine oxides containing $\alpha\beta$-unsaturated groups are diethylvinylphosphine, dipropylvinylphosphine, and ethylphenylvinylphosphine oxides, prepared by dehydrochlorination (by heat or with triethylamine) of the corresponding tertiary phosphine oxides containing 2-chloroethyl groups[32]. These and some other dialkylvinylphosphine oxides are synthesised by means of organomagnesium compounds[87].

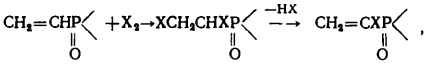
5. Properties of Compounds Containing $\alpha\beta$-Unsaturated Groups Attached to Phosphorus

These unsaturated organophosphorus compounds can add nucleophilic reagents at the double bond, take part in diene syntheses, in polymerisation and copolymerisation, and sometimes, depending on their structure, in polycondensation and polytransesterification reactions.

An account of these processes, studied mainly with vinylphosphonic esters, and of the properties of the products, has been given in the monograph[65] mentioned earlier, and we shall confine ourselves to a discussion of information not given there.

The addition of halogens at the double bond in derivatives of $\alpha\beta$-unsaturated phosphonic acids has been investigated. Kabachnik and Medved'[67,75] showed that bromine is readily added to diethyl vinylphosphonate to give the corresponding 1,2-dibromoethylphosphonate. This ester proved to be thermally quite unstable, and on heating (during vacuum distillation) it partially split off hydrogen bromide to form the bromovinylphosphonic ester. Similar behaviour was observed by Tsivunin and Kamai, who brominated and chlorinated ethylvinylphosphinyl chloride[28,88]. In both cases the halogens added smoothly at the double bond, but the stability of the products differed. The unstable bromination product split off hydrogen bromide during distillation, being converted into bromovinylethylphosphinic chloride. The chlorine addition product, on the other hand, was quite stable, and it could be dehydrochlorinated over a mixture of barium carbonate and activated carbon at 330°–350°.

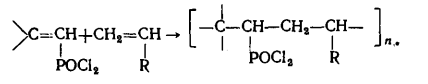
The position of the halogen remaining in the products of dehydrohalogenation has not yet been rigorously established, but all the investigators mentioned consider that it is located on the α carbon atom. Thus the above changes can be represented by the following scheme



where X = Cl or Br.

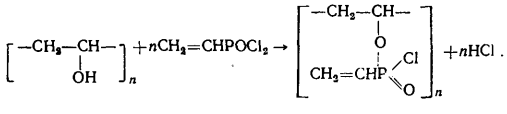
Addition of halogens to such a halogenovinyl group is very difficult[88]. The kinetics of the bromination of diethyl vinylphosphonate was investigated by Kabachnik and Balueva, who showed it to be a radical process[89].

Apart from halogenation it has been found, for example, that chlorides of $\alpha\beta$-unsaturated phosphonic acids can undergo polymerisation and copolymerisation[90-92] with formation of chlorides of polymeric phosphonic acids:



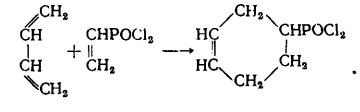
Such acid chlorides, of fairly high molecular weight, react readily with water, alcohols, silanols, and other hydroxy-compounds, the chlorine atoms being replaced by the corresponding groups[91,93]. It can be seen from the scheme above that as in polymers and copolymers of vinylphosphonic esters, the phosphorus atoms surround the main carbon chain and are directly linked to it in these compounds.

In the reaction of poly(vinyl alcohol) with the chloride of vinylphosphonic acid, however, the resulting carbon-chain polymers (of either linear or three-dimensional structure depending on the reaction conditions) contain the phosphorus linked to the carbon chains by bonds of ester type[94]:



The second chlorine atom can react with a hydroxyl group on the same or a different macrochain, leading in the latter case to cross-linking of the chains with formation of a three-dimensional macromolecule.

Chlorides of $\alpha\beta$-unsaturated phosphonic acids can take part in diene syntheses, forming chlorides of the corresponding cyclic $\gamma\delta$-unsaturated phosphonic acids[95], for example



Ester fluorides of alkoxyvinylphosphonic acids have been obtained by treating the acid dichlorides with alcohols and metal fluorides[96].

It has been found comparatively recently that derivatives of 2-chloroethyl- and especially vinyl-phosphonic acids can form the starting materials for the preparation of phosphorus-containing polyesters that may be toughened by heat treatment. The problem of producing such polyesters is of both

theoretical interest and practical importance. Until recently all known phosphorus-containing polyesters had linear structures[65], and there were no methods for preparing three-dimensional polyesters (apart from one not entirely clear patent specification[97]).

Most such linear polyesters possessed, together with their well-known useful properties (incombustibility, chemical stability, adhesion to many materials), not very high softening points, unless starting materials which were not readily available were used. This fact diminished the value of such polyesters. At present several methods are known for obtaining thermo-hardening phosphorus-containing polyesters based on derivatives of 2-chloroethyl- and vinyl-phosphonic acids.

The fundamental possibility of producing such polyesters was shown by Gefter and Rubtsova[98], who condensed 2-chloroethylphosphonic dichloride with aromatic diols. The resulting linear polyesters were subjected to heat treatment or the action of basic reagents, which caused dehydrochlorination of the 2-chloroethyl side-chains to vinyl groups. These latter groups polymerised, cross-linking the linear chains to form three-dimensional polyesters which were incombustible, infusible, and insoluble in organic solvents. This principle of two-stage preparation of hardenable polyesters (production of linear polyesters with unsaturated side-chains, and cross-linking of chains by means of the double bonds in the unsaturated groups) was later worked out in detail, especially its first stage.

Rubtsova *et al.* prepared the initial linear polyesters by reaction of the dihydroxy-compounds with the chloride of vinylphosphonic acid (polycondensation)[69,99] and also with the diphenyl ester of this acid (polytransesterification)[99,100]. They also refined the older method (see above)[98] of obtaining the initial linear polyesters (*via* the chloride of 2-chloroethylphosphonic acid[69,99]).

Kabachnik *et al.*[101] based their synthesis of linear polyesters containing vinyl groups in the side-chains on a different principle. They prepared a series of cyclic esters of vinylphosphonic acid (by the method described previously[67]) and polymerised them by ring-opening hydrolysis.

The linear polyesters obtained by any of the methods described form three-dimensional polymers by cross-linking of the unsaturated side-chains on heating with radical initiators. The hardened polyesters do not dissolve in organic solvents, do not burn in a naked flame, and do not melt, but merely soften somewhat on heating; above 250°–300°, however, they gradually char.

Among other new work must be mentioned that on the polymerisation and copolymerisation of dibutyl vinylphosphonate by the molecular beam method[102] and also a preliminary study of the polymerisation capacity of saturated and unsaturated (allyl) esters of ethylvinyl- and ethylchlorovinyl-phosphonic acids in the presence of radical initiators[27,28,88].

Alkyl ethylvinylphosphinates slowly polymerise into linear polymer gels of low molecular weight; the corresponding ethylhalogenovinylphosphinates show hardly any appreciable change in viscosity under similar conditions.

Allyl esters of ethylvinyl- and ethylchlorovinyl-phosphinic acids polymerise quite readily into tacky, rubber-like substances, which swell but do not dissolve in a number of organic solvents.

6. Addition of α-Oxides to Acid Halides of Quinquevalent Phosphorus

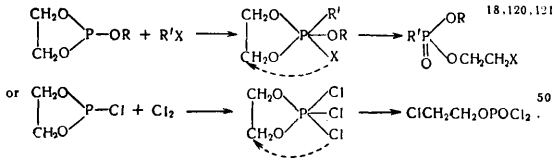
The reactions of α-oxides with acid halides of tervalent and quinquevalent phosphorus follow a fundamentally similar course, with opening of the oxide ring and formation of 2-halogenoalkyl derivatives of the phosphorus acid in both cases, the processes occurring in stages involving the addition of one, two, or three molecules of alkene oxide. However, the difference in valency of the phosphorus in the initial acid halides causes substantial differences in reactivity, and especially in the properties of the products. In contrast to the tervalent acid halides, the corresponding derivatives of quinquevalent phosphorus react less vigorously with α-oxides, and usually under the influence of catalysts — halides of metals or (less often) non-metals, organometallic compounds, metal alkoxides, tertiary amines, etc.

The addition has been described of ethylene oxide (more rarely of propylene oxide and epichlorohydrin) to phosphoryl chloride in the presence of small amounts of phosphorus trichloride[103]; the chlorides of aluminium[104,105], tin[104,105], antimony[104,105], nickel[104], cadmium[104], zinc[104], cobalt[104], lead[104], titanium[105–107], zirconium[106,107], and other metals; tetrabutyltin[105]; aluminium triethoxide[105]; titanium tetrabutoxide[105]; tertiary amines[108]; etc.

Among other acid halides which have been used are thiophosphoryl chloride[109]; the dichlorides of phenylphosphonic[105,110,111], substituted phosphoramidic[106,107], and other acids, and of aryl dihydrogen phosphates[106,107,111]; and monohalides of dimethylphosphinic[112] and other[111,113] acids and of diethyl[110] and dibutyl[106,107] hydrogen phosphates.

Among cyclic oxides which are rarely employed in the above reaction may be mentioned those of but-1-ene and but-2-ene[106], styrene[105], undecene[105], and stilbene[108], the glycidyl esters of unsaturated carboxylic acids[111], 1,3-diepoxybutane[105], and also hexitol mono- and di-anhydrides in which the free hydroxyl groups are protected[103].

Other methods also exist for obtaining 2-halogenoalkyl derivatives of the acids of quinquevalent phosphorus, such as, for example, reaction of alkene β-halogenohydrins with phosphorus pentahalides[22,58,114–119] (sometimes in the presence of organic bases) or the Arbuzov rearrangement of some cyclic derivatives of phosphoric acid according to the following general scheme:



The original method of preparing bis-2-chloroethyl phosphorochloridate from phosphorus trichloride, ethylene glycol, and chlorine[122] stands on its own:

$$2PCl_3+3HOCH_2CH_2OH \rightarrow 4HCl+ ClCH_2CH_2Cl+C_4H_{10}O_6P_2$$

(structure presumably $HOP(OCH_2CH_2O)_2POH$)

$$C_4H_{10}O_6P_2+2Cl_2 \rightarrow ClPO(OCH_2CH_2Cl)_2+HPO_3+HCl\,.$$

None of these methods is as suitable as the method which has been discussed.

The inadvisability of using alkene halogenohydrins instead of alkene oxides has been discussed above (see Section 1).

Arbuzov isomerisation of cyclic derivatives of phosphorous acid can be employed for the synthesis of a limited range of compounds, whereas the last method can be used for only one substance.

The addition of oxygen or sulphur to 2-halogenoalkyl derivatives of acids of tervalent phosphorus discussed above (see Section 2) is not, of course, a distinct method for synthesising 2-halogenoalkyl derivatives of acids of quinquevalent phosphorus.

7. Properties of 2-Halogenoalkyl Esters and Ester Halides of Acids of Quinquevalent Phosphorus

The presence of the phosphorus atom in its higher valency state makes these compounds relatively stable chemically and deprives them of many of the synthetic possibilities existing with 2-halogenoalkyl derivatives of acids of tervalent phosphorus, notably the ability to undergo addition reactions, Arbuzov rearrangement, thermal isomerisation, etc.

The characteristic $>CX-\underset{|}{C}H-O-P=O$ groups in these components behave peculiarly towards chemical reagents.

Upson found that treatment of 2-chloroethyl phenylphosphonates and 2-chloroethyl diethyl phosphate with alcoholic alkali, sodium carbonate, or triethylamine yields the corresponding vinyl esters or (depending on the conditions of dehydrochlorination) polymers of them[110].

Allen and his collaborators[123], however, were unable to repeat this, in spite of the simplicity of the experiments. A detailed account of Allen's results and arguments is beyond the scope of this review, and we will merely point out that he was able to prepare only small amounts of unsaturated compounds of somewhat indeterminate composition. Nevertheless, these workers accomplished the dehydrobromination of 2-bromoethyl diethyl phosphate to diethyl vinyl phosphate by means of such a specific reagent as sodium hydride.

Kabachnik showed that alcoholic alkali exerts its dehydrochlorinating action mainly on the acid portion of the bis-2-chloroethyl 2-chloroethylphosphonate molecule, forming bis-2-chloroethyl vinylphosphonate[75]. Alkali-metal salts of organic acids are even more effective[56,84]. Ward considers that the alcoholic alkali replaces chlorine by hydroxyl in the $ClCH_2CF_2OP<$ group to form a 2-hydroxyethyl group[124]:

$$NH_2PO(OCH_2CH_2Cl)_2+2NaOH \rightarrow NH_2PO(OCH_2CH_2OH)_2+2NaCl.$$

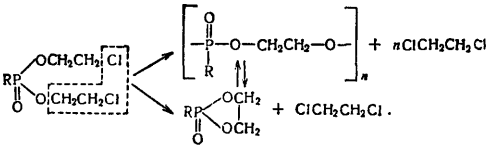
Tertiary amines react quite readily with 2-halogenoalkoxy groups attached to phosphorus[78,114] forming comparatively stable crystalline addition products of the same type as quaternary ammonium salts. Primary amines, however, react by replacing the halogen with an alkylamino group.

A reaction of such a type, that of bis-2-chloroethyl vinylphosphonate with ethanolamine and aminoheptanoic acid, yielded interesting compounds — a glycol and a dicarboxylic acid — containing phosphorus, nitrogen, and a double bond in the molecule[125], for example:

$$CH_2=CHPO(OCH_2CH_2Cl)_2+2NH_2CH_2CH_2OH \rightarrow$$
$$\rightarrow CH_2=CHPO(OCH_2CH_2\underset{\underset{HCl}{|}}{N}HCH_2CH_2OH)_2 \xrightarrow{2C_6H_5ONa}$$
$$\rightarrow CH_2=CHPO(OCH_2CH_2NHCH_2CH_2OH)_2+2NaCl+2C_6H_5OH.$$

Acid reagents — hydrochloric acid, hydrogen chloride, phosphorus pentachloride — rupture the C–O–P bonds more or less easily, replacing the 2-halogenoalkoxy groups by hydroxyl[50,61,62] and chlorine[12,13,27-30,50,51,61,62] respectively. Substances containing 2-halogenoalkoxy groups attached to phosphorus undergo various (intramolecular or intermolecular) condensation reactions on heating.

Korshak and his coworkers showed that, when bis-2-chloroethyl alkyl- and aryl-phosphonates as well as tris-2-chloroethyl phosphate are heated above 200°, dichloroethane is evolved with the formation of a mixture of cyclic and linear products, between which an equilibrium probably exists[52]:



It cannot yet be stated definitely whether the primary process is intermolecular elimination of dichloroethane (formation of a linear polyester of low molecular weight) or the intramolecular reaction (formation of a cyclic ester), or whether they occur simultaneously. It may be noted that conversion of purified cyclic esters of phosphorus acids into linear polyesters occurs quite readily (for example with various catalysts, moderate heating, and sometimes simply on standing[65]), whereas the reverse process is possible only in the case of thermal degradation of the polyesters, *i.e.* under more severe conditions[52,126].

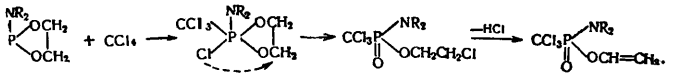
Acker[53] has described the liberation of dichloroethane and the formation of polyester chains in the thermal homopolycondensation of 2-chloroethyl phenyl phosphorochloridate.

A reaction of a different type was investigated by Lecoq, who showed that hydrogen chloride is evolved and cyclic ethylene hydrogen phosphate is formed when an aqueous solution of 2-chloroethyl dihydrogen phosphate is boiled[127]:

$$ClCH_2CH_2OPO(OH)_2 \xrightarrow{-HCl} \begin{matrix} CH_2O \\ CH_2O \end{matrix}\!\!>P(O)OH.$$

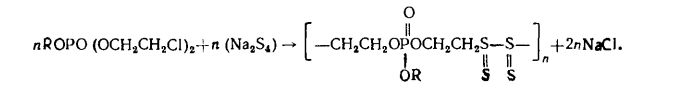
These reactions (or one of them) are the cause of the decomposition of various 2-halogenoalkyl esters of phosphorus acids when distilled at high temperatures (at atmospheric pressure or under a poor vacuum). There is, it is true, the patent of Winkle *et al.*[128], which is inconsistent with these results. According to this patent, interaction of some cyclic esters of substituted phosphoramidous acids with carbon tetrachloride at 200° leads to the formation of vinyl esters of trichloromethylphosphonamidic acids. The formation of such substances can apparently be represented

as a result of consecutive reactions — (1) Arbuzov rearrangement with opening of the ring and formation of 2-chloroalkoxy-groups attached to phosphorus, and (2) thermal dehydrochlorination of these groups:

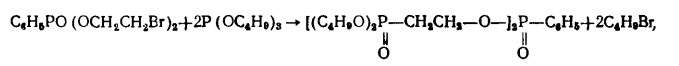


The hydrolysis of 2-halogenoalkyl phosphates has been investigated by German and French scientists. Dilute alkalis and acids in aqueous-alcoholic media have been found to split off 2-halogenoalkoxy-groups with comparative difficulty[38], and the halogens in these groups more easily[38], whereas the phenoxy-groups in 2-halogenoethyl diphenyl phosphates and bis-2-halogenoethyl phenyl phosphates are split off quite easily under these conditions[118,119]. Therefore 2-halogenoethyl diphenyl phosphates can be used to introduce $(OH)_2PO(OCH_2CH_2)$ groups into various organic compounds.

It has been found comparatively recently that the halogen atoms in 2-halogenoalkoxy-groups linked to phosphorus react quite readily with sodium and calcium polysulphides forming special "Thiokols"† containing phosphorus[2,20,129]



Bis-2-halogenoalkyl alkyl- and aryl-phosphonates have been used as special dihalogenoalkanes in the Arbuzov rearrangement of phosphorous or phosphonous esters, for example:



and for the Michaelis-Becker reaction[130].

2-Halogenoalkyl phosphorochloridates possess the normal reactivity characteristic of acid halides of phosphorus. They react with alcohols and amines to form alkyl 2-halogenoalkyl phosphates[114] and 2-halogenoalkyl *N*-mono- or *NN*-di-alkylphosphoramidates[131] respectively. Tertiary amines add readily to such ester chlorides (obviously at the P-Cl bond), forming hygroscopic crystalline products which are insoluble in inert solvents (ether, benzene, etc.) and which decompose on contact with water or alcohols[132].

Substantial differences in chemical behaviour are thus observed between 2-halogenoalkyl groups combined with quinquevalent phosphorus directly or through oxygen.

These differences are briefly as follows. (1) Basic reagents in non-aqueous media dehydrochlorinate 2-halogenoalkyl groups attached to phosphorus comparatively readily, converting them into $\alpha\beta$-unsaturated groups[27-30,56,64,69-72,75,84]. 2-Halogenoalkyl groups linked to phosphorus *via* oxygen under similar conditions have their halogens replaced by other groups[124,125], add on tertiary amines[78,114], or else do not react at all[56,84]. More severe action of certain basic reagents produces changes which have not yet been elucidated, resulting in polymeric or resinous substances[123]. (2) Acidic reagents — hydrochloric acid, hydrogen chloride, PCl_5 — rupture the C-O-P ester bonds more or less readily, replacing the 2-halogenoalkoxy-groups by hydroxyl or chlorine, but (up to certain temperatures) do not affect 2-halogenoalkyl groups attached to phosphorus[13,27-30,50,51,61,62,72,73]. (3) The action of high temperatures on 2-halogenoethyl groups attached to phosphorus results, especially in the presence of certain salts or of activated carbon, in their dehydrohalogenation with the formation of vinyl groups attached to the phosphorus[27,28,66-68]. 2-Halogenoalkoxy-groups, however, split off dichloroethane and hydrogen chloride and undergo other changes, but, except in one case[128], it has not been possible to isolate vinyl esters of phosphorus acids[52,53,127].

8. Reactions of α-Oxides with Phosphorus Halides Not Involving Formation of C-O-P Bonds

It was shown above that α-oxides and sulphides readily add to halides of tervalent and quinquevalent phosphorus (except PCl_5 and PBr_5) at the P-X bonds, forming 2-halogenoalkyl derivatives of the corresponding acids of phosphorus.

Similar reactions of β-oxides have not been described, while reaction of γ- and δ-oxides with such phosphorus halides is more difficult than, and of a different type from, that of α-oxides. Such reactions, studied mainly in the case of $POCl_3$, occur only in the presence of catalysts — zinc chloride, sulphuric acid, aluminium chloride, etc. The oxide ring is broken, but formation of a P-O-C bond is not observed. Under mild conditions a halogen-carbon bond is formed, the ring oxygen atom being preserved in the product molecule. Under more severe conditions two halogen-carbon bonds are produced with simultaneous elimination of the ring oxygen. The final products of these processes are thus halogenated ethers and dihalogenoalkanes. The latter are obtained also by the reaction of any cyclic oxides or their homologues with phosphorus pentachloride and pentabromide. We may note that PBr_3, PCl_5, and PBr_5 (in contrast to the less vigorous reagents, PCl_3 and $POCl_3$) undergo such reactions in the absence of any catalyst. Thus ethylene and trimethylene oxides react with phosphorus pentachloride to form 1,2-dichloroethane[133] and 1,3-dichloropropane[133a] respectively.

Treatment of tetrahydrofuran with phosphoryl chloride under mild conditions, with small additions of sulphuric acid or zinc chloride, yields mainly bis-4-chlorobutyl ether $Cl.[CH_2]_4.O.[CH_2]_4.Cl$ [134,135] (with phosphorus trichloride the yields are poor[134]) and to a less extent 1,4-bis-4'-chlorobutoxybutane $Cl.[CH_2]_4.O.[CH_2]_4.O.[CH_2]_4.Cl$.[134] If large quantities of zinc chloride are used in this reaction, 1,4-dichlorobutane is obtained[135], while the action on tetrahydrofuran of phosphorus tribromide[136] and of phosphorus and iodine[137] or phosphoric acid and potassium iodide[138] leads to the formation of 1,4-dibromo-[136] and 1,4-diiodo-butanes[137,138] respectively.

2-Methyltetrahydrofuran on treatment with phosphorus tribromide forms 1,4-dibromopentane[138a].

In no case was the formation of 3-halogenoalkyl esters of the phosphorus acids observed during these reactions, as suggested in Bretschneider's patent[108], and his statement that a γ-oxide (tetrahydrofuran) can react with phosphorus halides in the same way as α-oxides must be regarded as incorrect.

† Trade mark of Thiokol Chemical Corp. for various products; here denotes polysulphide synthetic rubbers (Ed. of Translation).

δ-Oxides react with phosphorus halides with still greater difficulty than do γ-oxides. Tetrahydropyran on treatment with phosphoryl chloride in the presence of sulphuric acid forms a mixture of comparatively small quantities of bis--5-chloropentyl ether and 1,5-dichloropentane[134]. Nevertheless, in the well-know Braun reaction this same δ-oxide and a substituted nitrogen analogue (*N*-benzoylpiperidine) react with phosphorus pentachloride and pentabromide under severe conditions to give respectively 1,5-dichloropentane[139,140] and 1,5-dibromopentane[140].

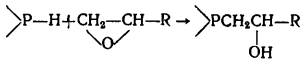
A few cases of reaction of phosphorus halides with furan, thiophen, and pyridine, which have aromatic properties, have been described[141,142] but do not come within the scope of the present review.

III. INTERACTION OF PHOSPHORUS COMPOUNDS CONTAINING A REACTIVE HYDROGEN ATOM WITH α-OXIDES. PROPERTIES OF THE PRODUCTS

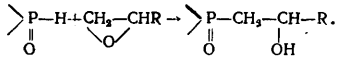
1. Addition of α-Oxides to Phosphorus Compounds (at a Phosphorus–Hydrogen Bond)

Comparatively little research has been done on reactions of this type.

During the addition of α-alkene oxides at a phosphorus–hydrogen bond the oxide ring is opened with formation of a phosphorus–carbon bond, and at the β-carbon atom a hydroxyl group is produced from the oxygen of the oxide and the hydrogen of the phosphorus compound, the valency of the phosphorus remaining unchanged:

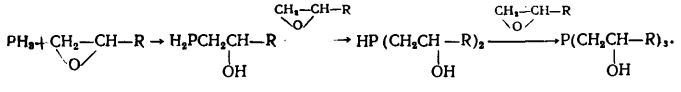


or

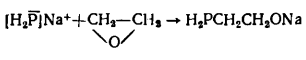


Two types of reactions of this nature have been described involving the addition of α-oxides to phosphine and to dialkyl hydrogen phosphites.

Knunyants and Sterlin[143] showed that the difficulty in reaction between phosphine and ethylene and propylene oxides lay in the very feeble dissociation of PH_3 under normal conditions. They were able to make these components combine with one another only under pressure and on heating, but even then the yields of the reaction products were not very high. The reaction obviously took place in stages:

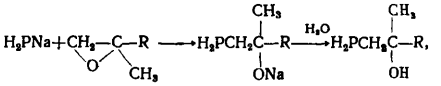


Products formed by addition of one and three (but not two) oxide molecules to the PH_3 were mainly obtained. When sodium dihydrogen phosphide in liquid ammonia was used instead of phosphine, reaction took place very readily and with good yields:



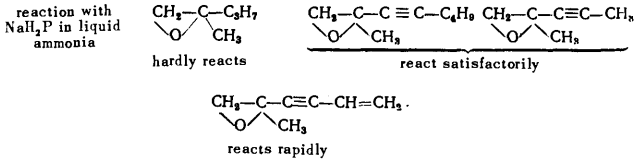
Decomposition of the resulting alkoxide with water gave free 2-hydroxyethylphosphine.

Sodium dihydrogen phosphide in liquid ammonia was used also by Perveev and Rikhter[144], who effected the addition of several acetylenic α-oxides to it



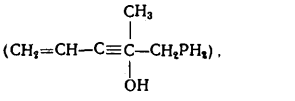
where R contains a triple bond.

If R were a saturated radical (propyl), such a reaction would be extraordinarily difficult[144]. The ability of substituted α-oxides to react with sodium dihydrogen phosphide is apparently governed primarily by the electronic state of the molecule of the particular oxide and only secondarily by steric factors. In fact the reactivity of the following four α-oxides increases with the occurrence and strengthening of conjugation between the multiple bonds in the substituent group and the oxide ring



The 2-hydroxyalkylphosphines known at the present time are colourless mobile liquids with the disagreeable odour characteristic of phosphines. Simple representatives of this group are readily soluble in water and pyridine, but less soluble in ether and benzene[143]. More complex members of this class dissolve well in several organic solvents, but do not dissolve in water[144].

Hydroxyalkylphosphines, and especially *O*-acyl derivatives of the lower members, oxidise easily[143]. When an attempt was made to replace hydroxyl by halogen in several 2-hydroxyalkylphosphines, the phosphorus–carbon bond was ruptured with the formation of phosphine itself and halogenated unsaturated hydrocarbons[143]. A 2-hydroxyalkylphosphine containing a conjugated double and triple bond



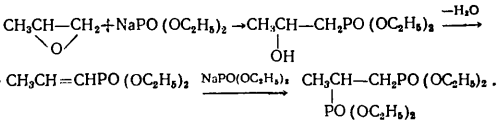
polymerised so rapidly that it could not be isolated, although it was very readily formed[144].

No other methods exist as yet for the synthesis of 2-hydroxyalkylphosphines. Compounds containing the reactive hydrogen attached to quinquevalent phosphorus react with α-oxides with still greater difficulty.

In the absence of catalysts, dialkyl hydrogen phosphites do not react at all with α-oxides. A qualitative experiment on the addition of ethylene oxide to sodium diethyl phosphite was carried out by Chelintsev and Kuskov[145].

Pudovik and Ivanov[16], Preis *et al.*[146], and Kreutzkampf[147] have shown that addition of α-oxides to sodium dialkyl phosphites does take place, but the yields are not very high. The addition of propylene oxide to sodium diethyl phosphite[146] is noteworthy, for tetraethyl propylene-1,2-diphosphonate was unexpectedly isolated. According to Preis *et al.*, the reaction proceeds normally at first, *i.e.* with the

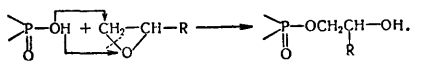
formation of diethyl 2-hydroxypropylphosphonate, which is then dehydrated, and a second molecule of the phosphite adds on to the double bond thus formed:



Sulphuric acid proved to be a feeble catalyst for the addition of α-oxides to dialkyl hydrogen phosphites[16]. Rather better yields were obtained for the addition of ethylene oxide, cyclohexene oxide, and 1-ethoxypropane-2,3-diol to several dialkyl hydrogen phosphites by heating a mixture of the components in the presence of boron trifluoride–diethyl ether under pressure[16].

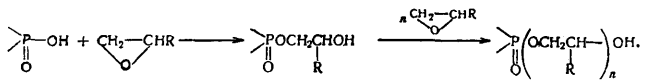
2. Addition of α-Oxides and Their Analogues to Hydroxyl Groups Attached to Phosphorus (at an Oxygen–Hydrogen Bond)

Compounds containing one or more hydroxyl groups combined with phosphorus are more or less strong acids. They usually react readily with α-oxides in the absence of any catalyst. If one molecule of alkene oxide adds on at an O–H bond, 2-hydroxyalkyl esters of the corresponding acids of phosphorus are formed. The oxide ring opens, the P–O–H bond is converted into a P–O–C bond, and a hydroxyl group is formed at the β carbon atom:



This main reaction is accompanied by some side-reaction, polymerisation of α-oxides under the influence of the acids of phosphorus. The addition has been reported of various α-oxides (principally those of ethylene and propylene) to phosphorous acid and its salt[148,149], phosphoric acid[148], its salts[148,150], and acid esters[151–153], including polymeric forms[154], and also to alkylphosphonic acids[155,156].

Since the substances obtained in this way always contain hydroxyl groups in the β position, this reaction can proceed stepwise by ring-opening and addition of the next oxide molecule, and so on



Such secondary processes takes place less readily in the presence of excess of the corresponding α-oxide[148,153,155,156], on heating[153,155,156], sometimes under pressure, in the presence of catalysts, for example aluminium hydrosilicate[155,156].

Dickey and McNally oxidised unsaturated ketones, acids, ethers, and esters, and treated the products (obviously containing α-oxide groups) with various phosphorus acids or their salts. The reactions went normally, *i.e.* with opening of the oxide ring and addition of the components to one another[157–159].

2-Hydroxyalkyl esters of phosphorus acids are more or less viscous oily liquids, soluble in water and the lower alcohols. The hydroxyl groups in these compounds can be replaced by chlorine by the action of phosphorus trichloride[148].

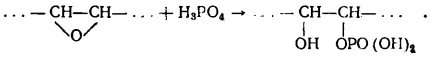
Sulphur and nitrogen analogues of α-oxides — ethylene sulphide[148], aziridine (ethyleneimine)[160], and the 2-methyl[148] and 2-ethyl[148] derivatives of the latter — have been added to phosphoric acid. The course of the reactions is similar, with mercapto- and amino-groups respectively replacing the hydroxyl groups in the final products. The properties of such compounds have hardly been investigated. It is known only that some 2-aminoalkyl esters are hard crystalline substances[160].

3. Addition of Polyepoxides to Hydroxyl Groups Attached to Phosphorus

Interesting and promising work has been carried out on the interaction of polyepoxides with phosphoric acid and its acid esters.

Polyepoxides are copolymers of unsaturated compounds containing one double bond with various proportions of epoxy compounds also containing one double bond in the molecule.

On moderate heating of a polyepoxide with phosphorus acids, the α-oxide ring of the polyepoxide is opened, and a macromolecular acid of phosphorus is formed according to the following general scheme:



Patents cover the reaction of phosphoric acid with dioxan solutions of the copolymers 1-allyloxypropane-2,3-diol/styrene[161,162], 1-allyl glycidyl ether/butyl methacrylate[163], glycidyl methacrylate/butyl methacrylate[163], etc.[161–164]

The interaction has also been described of alkyl- and aryl-phosphonic acids with glycidyl polyethers of dihydric and polyhydric phenols, polymers of allyl glycidyl ether, and other compounds of high molecular weight containing epoxy-groups[164]. These reactions are usually carried out in solution with the aim of minimising premature formation of three-dimensional polymers. Dioxan is the most suitable solvent, since it is miscible with water, and enables aqueous solutions of phosphoric acid to be used.

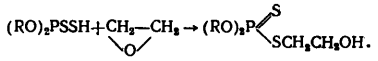
The polymeric acids of phosphorus thus obtained are soluble in dioxan, acetone, benzene, several other organic solvents, and sometimes, depending on the structure of the original polyepoxides, in water and aqueous alkalis. Polymeric phosphoric acids based on copolymers of allyl glycidyl ether and vinyl acetate, for example, are soluble in aqueous solutions of alkalis, while those based on copolymers of glycidyl methacrylate with other methacrylates are insoluble.

Depending on the extent of copolymerisation of the original monomers, the molecular weights of the polymeric phosphoric acids vary between 1500 and 50000 (mainly 2000–10000)[164], their consistency varying from semi-liquid to solid[164].

On being heated, or treated with diisocyanates, they are converted into three-dimensional polymers possessing hardness, strength [or stability (Ed. of Translation)], and good adhesion to many materials [161-165].

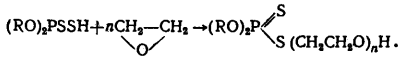
4. Addition of α-Oxides and Sulphides to Mercapto-Groups Attached to Phosphorus

α-Oxides add readily to *OO*-dialkyl hydrogen phosphorothiolothionates [166] and also to *OO*-alkaryl and *OO*-diaryl hydrogen phosphorothiolothionates [167]. The reactions are accompanied by the evolution of heat, but if the process is carried out slowly and at moderate temperatures the addition takes place practically quantitatively:



The resulting 2-hydroxyalkyl esters of substituted phosphoro- and phosphono-dithioic acids are viscous liquids which can be distilled in a vacuum (sometimes with slight decomposition). They are quite readily oxidised by nitric acid, and decomposed by alkalis. The 2-hydroxy-groups in them are acetylated by acetic anhydride and replaced by chlorine on careful treatment with phosphorus pentachloride.

If the alkene oxide is added rapidly, and the temperature is not controlled, the reaction mixture becomes very hot, and syrupy substances are formed which cannot be distilled in a vacuum. Kabachnik and his coworkers claim that stepwise addition of many oxide molecules then occurs [166]:

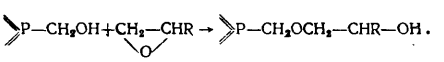


Cyclic 1,2-sulphides react similarly to, but less vigorously than the oxides [167,166]. The dialkyl *S*-2-mercaptoethyl phosphorothiolothionates $(RO)_2P(S)SCH_2CH_2SH$ formed in this reaction have in general similar properties to their hydroxy-analogues, but differ from the latter in their insolubility in water, lower thermal stability, and the ease with which the mercapto-group is methylated by diazomethane.

5. Addition of α-Oxides and Aziridine to Hydroxymethyl and *p*-Hydroxybenzyl Groups in Phosphorus Compounds

Tetrakishydroxymethylphosphonium chloride and trishydroxymethylphosphine oxide are quite widely known as flameproofing agents for various synthetic and natural materials [65]. It has recently become known that monomers for epoxide resins containing phosphorus have been produced on the basis of these interesting substances.

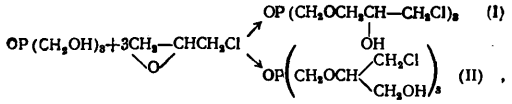
The hydroxymethyl groups in these compounds, the hydrogen in which is quite reactive, can add at the O–H bond to α-oxide compounds of normal type comparatively readily, ether links being formed in the phosphorus compound and hydroxyl groups in the β position relative to them



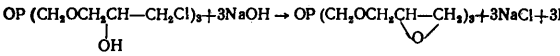
The reaction is carried out simply by boiling a mixture of the components, sometimes in the presence of acid catalysts.

Descriptions have appeared of the addition to tetrakishydroxymethylphosphonium chloride, to trishydroxymethylphosphine oxide, and to substances containing the group $\gg P-CH_2OH$, of ethylene oxide [169], epichlorohydrin [169-171], epibromohydrin [171], poly(glycidyl ether) ("Epon 562"‡) [171,172] poly(glycidyl dihydrophenol ether) ("Epon 1007"‡) [171], ethyleneimine [173-175], etc.

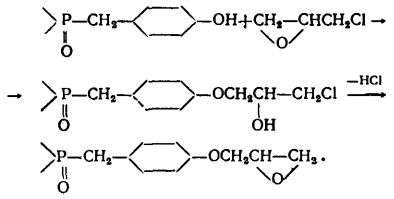
Monomers for phosphorus-containing epoxide resins (mentioned above) were prepared by adding epichlorohydrin to trishydroxymethylphosphine oxide in the presence of acid catalysts. Of the two possible compounds



only the first is formed. Dehydrochlorination and closure of the α-oxide ring occur readily on treatment with alkalis



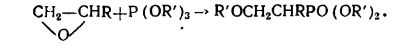
As the accompanying equations show, this method enables us to obtain organophosphorus compounds containing epoxy-groups. Apart from the above phosphorus compounds, tertiary phosphine oxides containing one, two, or three *p*-hydroxybenzyl groups [176,177] were also subjected to this reaction. Their reactions with epichlorohydrin go as follows:



IV. INTERACTION OF PHOSPHORUS COMPOUNDS WITH α-OXIDES AND SULPHIDES INVOLVING THE LONE ELECTRON PAIR OF THE PHOSPHORUS ATOM

1. Addition of Components to One Another

Reactions of this type are almost uninvestigated. Scott patented a process for preparing dialkyl alkoxyalkylphosphonates by heating certain alkene oxides with trialkyl phosphites under pressure [178]

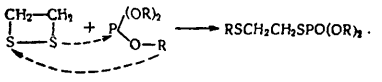


However, numerous investigations have shown that the α-oxides react with trialkyl phosphites in a different way (see Section 2). Scott's actual patent [178] (so far the only communication of this kind) did not give the yields of the

‡ Epon resins are condensation products of epichlorohydrin and bisphenol-A [2,2-bis-(4-hydroxyphenyl)propane], made by Shell Chemical Co. (Ed. of Translation).

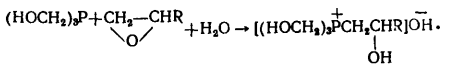
products obtained, and it therefore seems to us that addition of α-oxides to trialkyl phosphites (which is quite possible theoretically) occurs as a side-reaction and is not the main reaction.

Trialkyl phosphites react with cyclic disulphides with the formation of *OO*-dialkyl *S*-alkylthioalkyl phosphorothiolates[179]. This interesting reaction can be represented (in the simplest case) as follows:



The addition of α-oxides to trishydroxymethylphosphine has been described by Reuter *et al.*[180]. These reactions occur at 50°–100° in water, the lower alcohols, acetonitrile, dimethylformamide, etc. Two competing reactions are possible in a given case — addition of the alkene oxides to the hydroxymethyl groups at the O–H bonds (which was considered in Section 5 (Part III) or to the tervalent phosphorus — but it was found that the latter reaction takes place far more readily and practically completely.

Reuter and his coworkers patented the addition to trishydroxymethylphosphine of ethylene and propylene oxides, epichlorohydrin, glycidol, bivinyl dioxide, triglycidyl cyanurate, and polyepoxides. The process apparently corresponds to the following scheme:



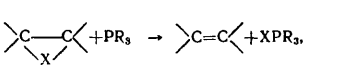
Quaternary phosphonium compounds can be obtained in this way.

2. Formation of Unsaturated Substances Together with Quinquevalent Organophosphorus Compounds

The possibility of synthesising these compounds results from the strong affinity of tervalent phosphorus for oxygen and sulphur. It was found that certain structures (α-oxides and sulphides) containing these latter elements readily give them up on reacting with certain compounds of tervalent phosphorus.

Culvenor and his coworkers, investigating the reaction of ethylene and propylene sulphides and of several other alkene sulphides with triethyl phosphite and tertiary phosphines, were the first to note that these organophosphorus compounds readily add sulphur to form triethyl phosphorothioate and tertiary phosphine sulphides respectively[181]. They did not study the transformations of the alkene sulphides.

Other investigators have found that, in these and similar reactions (with α-oxides), the cyclic components lose oxygen or sulphur and are converted into unsaturated compounds. Thus the general scheme of this reaction can be represented as



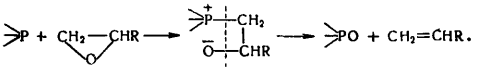
where X = O or S; and R = alkyl, aryl, or alkoxy.

Accounts have been published of the reaction of ethylene oxide with triethyl phosphite[182,183] and triallyl phosphite[183], propylene oxide with triethyl phosphite[182,183], 2,3-epoxybutane with tributylphosphine[184], styrene oxide with triethyl phosphite[183] and triphenylphosphine[185], and finally of the oxide of ethyl cinnamate with triphenylphosphine[185].

The analogous reactions of cyclic α-sulphides have been investigated no less thoroughly.

The interaction has been studied of ethylene sulphide and 2-methylpropylene sulphides with triethylphosphine[181]; of propylene sulphide with triethylphosphine[181], triphenylphosphine[186], and triethyl phosphite[187]; of 3-chloropropylene sulphide with triethylphosphine[181] and triethyl phosphite[187], and of but-2-ene sulphide with triphenylphosphine[184,188], tributylphosphine[188], and triethyl phosphite[188]. The reactions have also been studied of 3-methoxypropylene sulphide with triethyl phosphite[187] and of cyclohexene sulphide with triethylphosphine[181], triphenylphosphine[181,186], and triethyl phosphite[181,186].

Apparently the components first add to one another, with rupture of a C–O (C–S) bond and production of a C–P bond. This is followed by formation of a stable P=O (P=S) bond and rupture of the less stable second C–O (C–S) bond[185].



This reaction usually takes place very smoothly, the sulphides reacting more readily than the cyclic oxides with tervalent phosphorus compounds, sometimes simply when a mixture of the components is allowed to stand in the cold[181]. It goes practically to completion, and the yields are good in all cases.

It is interesting that interaction of triallyl phosphite with ethylene oxide yields only triallyl phosphate practically no epoxidation of the double bond being observed[183].

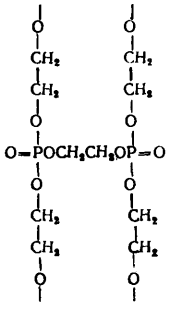
The formation of olefines in this reaction is accompanied by an interesting stereochemical phenomenon: whereas the *cis*-and *trans*-isomers of but-2-ene sulphide are practically entirely converted into *cis*- and *trans*-but-2-enes respectively[187,189], the oxygen analogues of this sulphide (namely *cis*- and *trans*-2,3-epoxybutane) give mixtures of isomers in which the stereoisomer of opposite structure to that of the original oxide predominates[184].

V. OTHER REACTIONS OF PHOSPHORUS COMPOUNDS WITH α-OXIDES

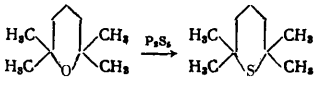
Ethylene oxide, propylene oxide, and epichlorohydrin add to phosphorus pentoxide[190], phosphorus pentasulphide[190], and also to the product formed by reaction of P_2S_5 with certain petroleum products[191]. Liquids or solids are formed depending on the reaction conditions.

The reactions of α-oxides with P_2O_5 and P_2S_5 occur quite readily on moderate heating of mixtures of the components, 3–7 moles of the alkene oxide being taken per mole of the phosphorus compound.

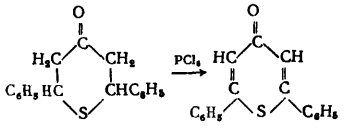
According to the patent literature[190] units of the following type are present in the substances (whose structure has not been completely elucidated):



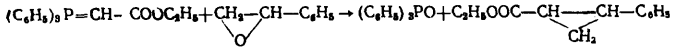
The action of phosphorus pentasulphide on 2,2,6,6-tetramethyltetrahydropyran does not involve addition, as in the case of α-oxides, but the replacement of oxygen by sulphur[142]



Substituted tetrahydrothiapyrones are dehydrogenated into thiapyrones by the action of PCl_5,[142]



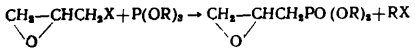
An interesting reaction has been described by Denney and Boskin: when cyclic oxides react with certain organophosphorus compounds of methylenephosphine type R.CH=P$\lessdot$, the CHR group is replaced by oxygen, and a cyclopropane ring is formed[192]:



VI. INTERACTION OF PHOSPHORUS COMPOUNDS WITH α-OXIDES AND THEIR ANALOGUES NOT INVOLVING THE OXIDE FUNCTION

1. Arbuzov Rearrangement and Michaelis-Becker Reaction of Phosphorous Esters with Halogenated α-Oxides and Their Analogues

The Arbuzov rearrangement of trialkyl phosphites under the influence of epihalogenohydrins has been studied[146,177,193-195]:



(X is halogen).

This reaction is carried out in a similar manner to an ordinary Arbuzov rearrangement, *i.e.* the trialkyl phosphite and the epihalogenohydrin are mixed, and the mixture is heated until the alkyl halide ceases to separate; the reaction product is isolated by vacuum distillation. Various 2,3-epoxypropylphosphonic esters have been prepared in this way.

2-Tetrahydrofurfurylphosphonic esters have been obtained in a similar manner from tetrahydrofurfuryl bromide[193]. Since all these reactions conform to the well-known rules of the Arbuzov rearrangement, they will not be discussed in greater detail here.

2,3-Epoxypropyl- and 2-tetrahydrofurfuryl-phosphonic esters have also been obtained by the reaction of epihalogenohydrins and 2-tetrahydrofurfuryl halides with sodium dialkyl phosphites[193,194], *i.e.* by the Michaelis-Becker reaction.

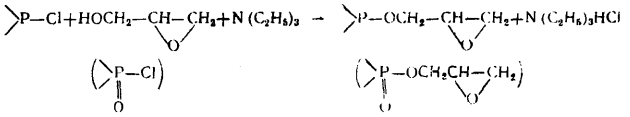
It is interesting that 2-bromotetrahydropyran reacts normally with sodium diethyl phosphite[193], whereas 2,3-dibromotetrahydropyran does not form an organophosphorus compound at all under these conditions, but undergoes dehydrobromination[193]. Rearrangements of trialkyl phosphites by more complex halogenated heterocycles (containing two oxygen atoms, nitrogen, etc.) have been systematised by Arbuzov.[196]

2. Reaction of Acid Halides of Phosphorus with Alcohols Containing Epoxy Groups

Little work has been done on this reaction. It is known to require more care than that of the corresponding acid halides with ordinary alcohols.

The α-oxide ring is readily opened by various reagents, and this side-reaction can sharply diminish the yield of the epoxyalkyl esters of the phosphorus acids.

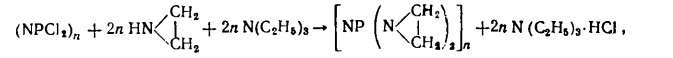
Patent specifications[197,198] have described the reaction of glycidyl alcohol with phosphorus trichloride phenyldichlorophosphine, and phosphoryl chloride, of 2,3-epoxybutane-1,4-diol with dimethylphosphinic and dibutylphosphinous chlorides, etc. Other alcohols containing α-oxide groups, such as 2,3- and also 3,4-epoxyhexanol and 4,5-epoxyoctanol, have been used in addition to the most readily available glycidyl alcohol. Triethylamine was used to combine with the hydrogen chloride liberated in these reactions:



The yields of the reaction products have not been stated. The organophosphorus compounds containing epoxy-groups resulting from this reaction and also the reaction discussed in Section 1 can be obtained by another method, the epoxidation of allyl or other unsaturated groups combined with phosphorus either directly or *via* oxygen. The epoxidation of allylphosphonic esters[195], tertiary phosphine oxides containing allyl groups[170,176,177], and also allyl esters of various phosphorus acids[198] has been reported.

3. Reaction with Aziridine of Phosphorus Compounds Containing a Reactive Chlorine Atom

This reaction and the products formed have been discussed elsewhere[65] and they will not be considered here. Among new work is that on the reaction of tri- and tetra-mers of phosphonitrilic chloride with aziridine in the presence of triethylamine[199]. The chlorine atoms are completely replaced by aziridine rings:

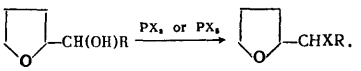


where n = 3 or 4.

4. Reactions Not Resulting in Formation of Organophosphorus Compounds

The relative stability of γ-oxides towards phosphorus halides has been pointed out in Section 8 (Part II). If however, hydroxyl is present in the γ-oxide molecule, it is readily replaced by halogen, but the corresponding ester of an acid of phosphorus (as in the case of glycidyl alcohol) is not formed.

The interaction of tetrahydrofurfuryl alcohol and its derivatives with phosphorus trichloride and tribromide (sometimes in the presence of pyridine) and also with phosphorus pentachloride has been described. Tetrahydrofurfuryl halides are formed in these cases[200-202]



Note that when sodium diethyl phosphite reacts with 2,3-dibromotetrahydropyran the latter is dehydrobrominated to 3-bromodihydropyran[193].

VII. APPLICATIONS OF ORGANOPHOSPHORUS COMPOUNDS OBTAINED BY THE PROCESSES DISCUSSED

Many compounds synthesised by these reactions have found use in a number of branches of the national economy, while other substances are undergoing production trials, and yet others have been recommended or patented for use in various branches of industry. Results are interesting, though not yet quite definite, and additional investigation is required.

Plasticisers

Phosphoric esters containing 2-halogenoalkyl groups have been widely explored as plasticisers for various polymeric materials[103-108,203-210].

Such esters as tris-2-chloroethyl phosphate§, tris-2,3-dichloropropyl phosphate, and tris-2-chloropropyl phosphate have found industrial application under various commercial names – "Celluflex CEF"§, "Cetamol Q", "Celluflex Fr-2"¶, "Cetamol P", etc. These esters are readily compatible (often in combination with other plasticisers) with poly(vinyl chloride), polyesters, cellulose acetate and nitrate, polyurethanes, phenol–formaldehyde plastics, and epoxy and other resins. These polymers thus acquire flame resistance and in some cases (for example cellulose derivatives) resistance to light, durability, and elasticity[204-208].

Various aryl 2-halogenoalkyl phosphates[106,107], phosphoric and phosphonic esters containing epoxyalkyl groups[195,198] products formed by addition of alkene oxides to phosphonic acids[155] and acid phosphoric esters[153], and also *OO*-dialkyl *S*-alkylthioalkyl phosphorothiolothionates[179] have been proposed as plasticisers.

Flameproofing Agents for Various Articles, Plastics, Textiles, etc.

It is well known that many phosphorus compounds make various materials flameproof (or more so)[3,65]. The compounds of various classes described here have also been used for this purpose. Almost all the plasticisers considered above increase the fire resistance of the polymers[103-108,153,195,203-210]. 2,3-Dibromoalkyl phosphates, especially tris-2,3-dibromopropyl phosphate, have proved particularly effective flameproofing agents for polystyrene foams[211-213]. The use has been patented of poly(bis-2-chloroethyl vinylphosphonate), which here acts as a special kind of plasticiser, to confer incombustibility on polycondensation resins[214]. Flameproof coatings have been obtained by the polymerisation of the addition products of acid halides of quinquevalent phosphorus to glycidyl esters of methacrylic and other unsaturated carboxylic acids[111].

Flameproof polymers can be produced by incorporating phosphorus in macromolecules using the acid chlorides and some esters of 2-chloroethyl- and vinyl-phosphonic acids. In contrast to the 2-halogenoalkyl phosphates, these compounds are not simply present in the mass of the polymer, but are chemically combined with it. The phosphorus enters the main polymer chains (in thermosetting phosphorus-containing polyesters[69,98-101]), or is located in the side-chains (in the case of copolymers of an acid chloride and vinylphosphonic esters[90-92,102,215]), or even in the cross-links between the linear chains of the organic polymers of, for example, unsaturated polyesters[216-219].

Since in these cases the phosphorus components are combined with the macromolecules by stable chemical bonds, the flameproof properties are practically unaffected by any treatment which does not destroy the polymer.

Products of the reaction of aziridine with phosphonitrilic chloride[199], phosphoryl chloride, or thiophosphoryl chloride[220-227] and of α-oxides or aziridine with tetrakishydroxymethylphosphonium chloride or trishydroxymethylphosphine oxide[169-175] (and their combinations with other substances) have proved useful for making various materials, and particularly textiles, flameproof. Solutions of 2-chloroethyl phosphoric acid[228], and also the addition products of phosphoryl chloride and its derivatives with glycidyl methacrylate, oleate, and crotonate[111], have been employed for the same purpose.

Recently Monsanto Chemical Co. has developed several compounds containing phosphorus and halogens under the general name "Phosgard", which confer good fire resistance on synthetic resins, fibres, wood, and paper[229]. The exact compositions of these compounds are not yet known, but it has been stated that the starting materials for them are in several cases 2-halogenoalkyl derivatives of phosphorous acid.

§ Tris-2-chloroethyl phosphate, made by Amcel Co. Inc., affiliated with Celanese Corp. of America (Ed. of Translation).

¶ Tris-dichloropropyl phosphate, made by Amcel Co. Inc., affiliated with Celanese Corp. of America (Ed. of Translation).

Additives for Motor Fuels

Several 2-halogenoalkyl phosphorothio-ites and -ates, phosphonothioates, and also (more rarely) phosphites and phosphates have proved to be effective additives for petrol and other fuels for internal combustion engines [19,34,36,42,43,108,109,230,231]. Their value lies in preventing the premature ignition of fuel, thereby raising its octane number, and they diminish the formation of carbon deposits. The Phosgard compounds (see above) have been proposed for the same purpose [229].

Additives for Lubricating Oils

2-Halogenoalkyl phosphites and phosphates, as well as their sulphur analogues, improve the quality of lubricating oils (in particular those used in friction units operating under very high loads) [108,109,232,233].

Among compounds which have proved useful additives for lubricating oils are bis-2-chloroethyl vinylphosphonate [217], Phosgard compounds [229], esters and thioesters of 2-chloroethylphosphonic acids [234], and products of the addition of α-oxides and sulphides to phosphoric acid [148], its acid esters [153], diaryl- and alkylaryl-phosphinodithioic acids [167], phosphorus pentasulphide [190], and finally to substances formed by reaction of petroleum hydrocarbons with P_2S_5. [191]

Stabilisers for Polymers

Salts of vinylphosphonic and alkylvinylphosphinic acids stabilise several polymers and copolymers (particularly those of vinyl chloride and acrylonitrile) towards light and heat [235-237].

Among antioxidants are several 2-halogenoalkyl esters of phosphorus, phosphoric, phosphonothioic, and phosphorothioic acids [103,108,238]. Cable plastics can be stabilised for tropical use with tris-2-chloroethyl phosphite and bis-2-chloroethyl 2-chloroethylphosphonate [239,240]. Epoxyalkyl esters [195,198] and "ethyleneimides" of phosphorus acids [241-243], and also *OO*-dialkyl alkylthioalkyl phosphorothioates [179], are good stabilisers for poly(vinyl chloride).

Textile-Finishing Agents

Products of the interaction of various α-oxide compounds with acids of phosphorus, their acid esters, and phosphates of aliphatic amines have found application in the textile industry mainly as antistatic agents [151,152,157-159,244].

It has been suggested that textiles should be treated with epoxyalkyl esters of phosphorus acids to make them crease-resistant [245].

Other Fields of Application and Prospects

Several 2-halogenoalkyl, vinyl, and alkylthioalkyl esters of acids of phosphorus have been suggested as insecticides [131,179,246-248].

2-Halogenoalkyl and also epoxyalkyl derivatives of phosphorus acids are intermediates in the synthesis of various organophosphorus monomers [3,65,195] and Thiokols [2,20,129].

Products of the addition of polyepoxides to phosphoric acid give hard and durable corrosion-resistant coatings for various materials [161-165].

Bis-2-chloroethyl hydrogen phosphite is apparently of interest for some biological investigations [249].

Finally, research on the preparation of organophosphorus compounds containing epoxy-groups [176,177,193-195,197,198] is extremely important and promising. In particular, it is suggested that such substances can be used to produce flameproof and very heat-resistant plastics [176,177,250].

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The reaction of phosphorus compounds with α-oxides provides then a very simple, convenient, and cheap method for obtaining various organophosphorus compounds containing 2-halogenoalkyl and hydroxyl groups, $\alpha\beta$-unsaturated radicals attached to the phosphorus, and also reactive epoxide and aziridine rings. The majority of such compounds are obtained in good yields, and are easily separable from the reaction mixture. They have already found some application, and will probably be more extensively used in the near future.

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EFFECT OF ANIONS ON THE KINETICS OF THE DISSOLUTION OF METALS

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The dissolution of metals in electrolyte solutions is electrochemical in nature, and its velocity depends not only on the usual variables of chemical kinetics — concentration and temperature — but also on the electrochemical properties of the system, primarily on the electrode potential and the structure of the electrical double layer at the metal–solution interface. This point, obvious to electrochemists, has often been neglected, and is not always taken into account now by workers on corrosion.

From the laws of electrochemical kinetics, the dependence of rate of dissolution on potential can be represented in the simplest case by the equation

$$i_1 = k_1 \exp\left(\beta \frac{F}{RT}\varphi\right), \quad (1)$$

where i_1 is the rate of dissolution expressed as an electric current, φ the electrode potential, β the transfer coefficient, and k_1 a constant depending on the nature of the metal and the state of its surface.

Eqn. (1) is valid for a process which can be written in the general form

$$M \rightarrow M^{n+} + ne. \quad (2)$$

In the spontaneous dissolution of a metal in an acid, reaction (2) is balanced by the simultaneous cathodic discharge of hydrogen ions:

$$2H^+ + 2e \rightarrow H_2, \quad (3)$$

the kinetics of which can be expressed by the equation

$$i_2 = k_2[H^+]\exp\left(-\alpha \frac{F}{RT}\varphi\right). \quad (4)$$

On combining Eqns. (1) and (4) we find that the dependence of the rate of spontaneous dissolution of a metal on the acid concentration should be given by the equation

$$v = k_3[H^+]\frac{\beta}{\alpha+\beta}, \quad (5)$$

which in several cases shows good agreement with experiment[1-3].

In many cases, however, the rate of dissolution of metals in acid electrolyte solutions depends not only on the concentration of hydrogen ions, which are directly involved in the process, but also on the nature and the concentration of the anions, which at first sight do not appear to take part in the process. Recent investigations in this laboratory[4-9] have shown that a change in the anionic composition of the solution can lead to a change both in the cathodic process (hydrogen evolution) and in the anodic process.

The activating effect of anions on the anodic process is often associated with their influence on the state of the passivating film, *i.e.* on the magnitude of the diffusion barrier. However, recent data indicate that anions are directly involved in the discharge and the formation of metal ions[8-14].

Kolotyrkin and Medvedeva[8] have shown that the dependence of the rate of anodic dissolution of cadmium on the potential in solutions containing halides is represented by a Tafel straight line having a slope of 0.035 V, which gives a value of 1.66 for β (reckoning that $\alpha + \beta = 2$), the position of this curve depending markedly on the nature and the concentration of the added halide. The curve for the dependence of rate of dissolution on KI concentration at a given electrode potential (Fig. 1) shows that, after a certain critical concentration of the salt, in this case 0.1 N, a tenfold increase in the salt concentration is accompanied by an almost thousandfold increase in the rate of the anodic process. Bromide and chloride solutions give similar results, but with the difference that replacement of I^- by Br^- and Cl^- resulted in an increase in the critical concentration of the added salt.

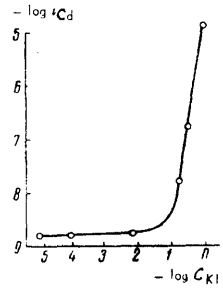


Fig. 1. Dependence of rate of dissolution of cadmium (at constant potential) in a solution of 1.0 N H_2SO_4 + x KI on the concentration of KI.

Analogous results were obtained recently by Losev and Molodov[9], who investigated the effect of the nature and the concentration of anions on the anodic dissolution of indium amalgam. They used a radioactive tracer method to determine the exchange current i_0 between the amalgam and an indium salt solution at the equilibrium potentials, and also the rate of the true anodic process of the ionisation of indium at other potentials near the equilibrium value. Combination of this method with ordinary polarisation measurements enabled the kinetics of the anodic reaction also to be investigated.

The results show that the dependence of the velocity of the anodic process on potential is also characterised by a Tafel straight line, with a slope of 0.025 V. This value of the slope, and hence the transfer coefficient $\beta = 2.3RT/b_a F = 2.32$ (on the condition that $\alpha + \beta = 3$), remained unchanged with change in the nature and the concentration of the halide in the solution. Variation in the anionic composition of the solution did, however, lead to a change in the overpotential of the process, as shown in Fig. 2, which gives curves for the dependence on the halide concentration of the rate of the anodic reaction at constant potential (-0.330 V for Cl^- and -0.276 V for Br^- and I^-). After a certain concentration, further increase in the halide concentration leads to a systematic increase in the rate of dissolution.

This critical concentration increases appreciably in the series $I^- \rightarrow Br^- \rightarrow Cl^-$, having values of 2×10^{-3}, 5×10^{-2}, and 5×10^{-1} N respectively, the corresponding increases in the rate of dissolution of the amalgam for a subsequent tenfold increase in concentration of the added salt being almost $\times$ 10, $\times$ 10^2, and $\times$ 10^3, respectively.

It can be concluded from these data that the dissolution of metals involves the direct participation of halide ions, and consequently that the kinetics of these reactions can be written in the following form (at constant pH):

$$i_a = kC^{\delta} \exp\left(\beta \frac{F}{RT} \varphi\right), \qquad (6)$$

where C is the concentration of the halide salt and δ is a constant having a value of 3 for the dissolution of cadmium in the presence of I^- ions, and 1, 2, and 3 for the dissolution of indium amalgam in iodide, bromide, and chlorine solutions respectively.

Interesting results on the mechanism of the activating effect of halide ions on the anodic dissolution of certain metals have recently been obtained by Medvedeva for the silver electrode (compare references cited elsewhere[7]) with which an appreciable decrease in overpotential for the anodic process also occurs on passing from a solution of pure sulphuric acid to one containing KI. The adsorption of iodide ions on the electrode surface at different potentials was investigated by a radioactive tracer method using ^{131}I. Preliminary experiments showed that iodide ions are very strongly adsorbed on the silver surface, which enabled adsorption measurements to be made on smooth electrodes with low initial concentrations in the solution (10^{-9}–10^{-7} N).

The results showed primarily that adsorptive and chemical interaction between iodide ions and the surface silver atoms occurs at potentials which are appreciably more negative than those for the dissolution of this metal, the degree of coverage of the metal surface with adsorbed ions and the strength of bonding of these ions with the surface metal atoms increasing appreciably with potential. Fig. 3 shows that, for the range of polarisation investigated, the amount (A) of I^- ions adsorbed varies linearly with the potential of the silver. If it is assumed that such a relation is maintained even at very low degrees of coverage, it follows from the above data that at a KI concentration of 2.6×10^{-9} N this interaction begins at -1.15 V, which is almost 1.5 V more negative than the potential at which silver is observed to dissolve in the corresponding solution.

It is noteworthy that this adsorption is reversible in the sense that, with a given KI concentration in the solution, the quantity of I^- ions adsorbed is determined unambiguously by the potential: change to a more negative potential always leads to the desorption of a definite quantity of ions.

A study of the rate of desorption of I^- as a function of the potential to which the electrode has first been polarised indicates that the strength of the adsorption increases with potential. Since these experiments were carried out in solutions having a very low KI concentration, it was easy to reach a potential at which iodide ions were completely adsorbed from the solution. The same degree of coverage of the surface corresponded to different potentials more positive than this value.

Fig. 4 shows the results of one such experiment, curves *1* and *2* representing the rate of desorption of ions at -0.335 V after preliminary polarisation of the silver at -0.174 and -0.124 V respectively, corresponding to the same coverage of the surface, 16.9×10^{11} ions cm^{-2}. A shift in the preliminary polarisation potential towards more positive values is seen to lead to a considerable slowing

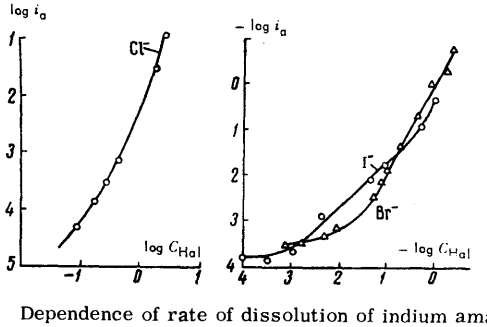


Fig. 2. Dependence of rate of dissolution of indium amalgam (at constant potential) in a solution of 0.01 N $In(ClO_4)_3$ + + 0.01 N $HClO_4$ + x NaHal on the concentration of NaCl, NaBr, and NaI.

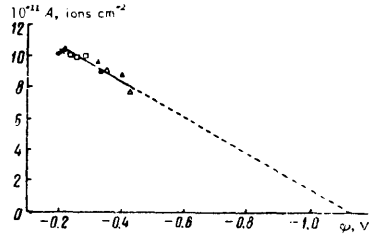


Fig. 3. Dependence of quantity of iodide ions adsorbed per cm^2 of a silver electrode on its potential in a solution of 1.0 N H_2SO_4 + 2.6×10^{-9} N KI.

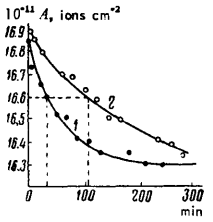


Fig. 4. Dependence of rate of desorption of iodide ions at -0.335 V on potential of preliminary polarisation of silver electrode: 1) -0.174 V; 2) -0.124 V.

down of desorption. Thus, for example, the time required for the desorption of the same amount of KI, 3×10^{10} ions cm^{-2}, was 27 min in the first case and 110 min in the second.

On the basis of these results the specific adsorption of anions, beginning at considerably more negative potentials than the solution potential of the electrode metal, must be regarded as the start of the formation of the corresponding salt (by means of covalent bonds). In the initial stages of adsorption, however, the strength of this bond differs appreciably from that in the corresponding free compound. As the potential shifts towards more positive values, this difference decreases, and finally disappears altogether. Starting from this potential, the metal ions begin to pass into solution in the form of complexes with the adsorbed anions. In this case the mechanism of metal dissolution can obviously be represented by two consecutive reactions[8]:

$$M + \partial Hal^- \rightarrow MHal_{\partial}^{\partial-}, \quad (7)$$

$$MHal_{\partial}^{\partial-} \rightarrow MHal_{\partial}^{(n-\partial)+} + ne, \quad (8)$$

the first of which corresponds to the specific adsorption of an anion on the surface of the metal with the formation of a surface complex, and the second to the ionisation of the metal atom in this complex.

In explaining the mechanism of the effect of anions on the kinetics of electrode processes, we must take into account the change in structure of the electrical double layer caused by their adsorption and the appearance of a negative ψ_1 potential at the metal–solution interface. However, allowance for these effects alone is insufficient for a satisfactory interpretation of many of the existing experimental results. In particular, it is obvious that a change in the ψ_1 potential should lead to identical changes in the rates of the forward (anodic) and the reverse (cathodic) reactions, and consequently to a change in the exchange current i_0. However, such a parallelism is not generally observed[9]. It has been established, for example, that an increase in chloride concentration to 0.5 N, while accompanied by an appreciable increase in the rate of the anodic dissolution of indium amalgam, does not lead to an increase in the exchange current, which remains the same as in the original $NaClO_4$ solution (without added NaCl)†.

† To explain this effect by the ψ_1 potential alone, it would be necessary to assume that only In^{3+} ions take part in the electrode process, and that the retardation of the cathodic reaction with increase in the KCl concentration, resulting from the decrease in concentration of the In^{3+} ions due to complex formation, is exactly double the accelerating influence of the ψ_1 potential on the anodic process.

It can be concluded from present results that direct participation of the components of a solution in the elementary act of ionisation of metal atoms is evidently a necessary stage in these processes. Of course, it is mainly those components that possess the greatest chemical affinity for the electrode metal under the given conditions which are involved in this way. Recent experiments by Losev have shown, for example, that not only specifically adsorbed anions but even water molecules can act in this way. These experiments established that the rate of the anodic dissolution of indium amalgam in acidified concentrated perchlorate solutions, which are known to exhibit no tendency to specific adsorption, is appreciably retarded with decrease in the concentration of free water in the solution. These results evidently indicate that hydration (at least partial) of the metal ion occurs before the latter passes from the metal lattice into the solution.

It follows from these ideas that the activating effect of a given anion on anodic dissolution can be exerted only when a definite critical potential is reached, at which the strength of the bond between a surface metal atom and the adsorbed ion is equal to that of the covalent bond in the corresponding free compound. Different anions should obviously correspond to different critical potentials. When, therefore, the electrode potential of the metal is maintained at values at which only one of the components of the solution can exert an activating influence on the anodic process, the adsorption on the surface of other components, active at more positive potentials, must be expected to lead to a retardation of dissolution. In other words, if several components of a solution are adsorbed simultaneously on the surface of a metal at a given potential, not all of the surface complexes formed can pass into solution, but only those for which the strength of the chemical bond has reached the necessary value. This can evidently explain the passivating influence of iodide and chloride ions on the spontaneous dissolution of iron and its alloys in sulphuric acid[15–23], in spite of the fact that at more positive potentials these ions are extremely corrosive reagents.

The Passivation of Metals

We can evidently explain not only the activation of the anodic dissolution of an electrode metal by adsorbed components of the solution but also the passivation of the metal surface.

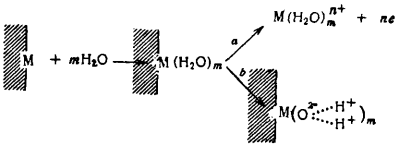
Recent results show more and more convincingly that many features of the electrochemical behaviour of passivated metals cannot be explained on the phase theory of passivity without resorting to additional and frequently improbable hypotheses. A fundamental principle of this theory is the irreversibility of anodic passivation in the sense that, when a definite potential has been reached, at which film formation takes place, the metal becomes inert, and that this inertness will be maintained subsequently at all more positive potentials; any breakdown of the passivating film, leading to an increase in the rate of dissolution of the metal, should also result in a shift in the electrode potential towards more negative values.

Recently it has been clearly established, however, that this view of the effect of passivity is incorrect. Detailed investigations on chromium, nickel, stainless steels, and other metals and alloys have shown that in many cases the passive state remains stable only within a comparatively narrow potential range dependent on the nature of the metal

and the pH of the solution, and that on the more positive side of this range the metal again begins to dissolve readily. The most surprising fact is that the rate of such dissolution varies with potential in conformity with the usual Tafel straight line, *i.e.* in conformity with the ordinary laws of electrochemical kinetics[24-35]. Such a dependence under conditions far removed from equilibrium obviously indicates the absence of diffusion hindrances to the process, which is incompatible with the presence of a continuous film on the surface of the metal.

Such a discrepancy is avoided by the adsorption theory of passivity. However, the further hypothesis is then necessary that the usual adsorption of water, which accelerates the anodic dissolution of the metal as ions of a lower degree of oxidation, is accompanied by chemisorptive interaction of the surface metal atoms with the oxygen of the water, resulting in passivation, the link between the passivating oxygen and the surface atoms being similar in nature to that in oxygen complexes of metal ions of a higher degree of oxidation, such as $Cr_2O_7^{2-}$. This means that such adsorption is to be regarded as the start of the formation of a metal salt of a higher degree of oxidation.

This hypothesis is quite reasonable in view of the above statement that halide ions start to interact with the metal surface also at appreciably more negative potentials than those at which the metal dissolves in the presence of these ions. The interaction of water molecules (or OH^- ions) with the surface metal atoms can then be represented by the following scheme



(8a)

(8b)

which is similar to that which was once suggested by Kabanov *et al.*[36] for the passivation of iron in alkalis. However, their work contains no hypotheses as to the nature of the bond between the passivating oxygen and the surface metal atoms.

It is natural to suppose that the link between oxygen and the metal atom will change and become stronger the longer the adsorbed H_2O (or OH^-) remains on the metal surface. This should evidently be favoured by an increase in the pH of the solution and a shift in the electrode potential to more positive values. It is now known that passivating reactions begin to take place at an appreciable rate only when a definite potential (the passivation potential) is reached, the value of which for a given metal increases as the pH of the solution falls. It is extremely likely that passivating adsorption first begins on the most active portions (centres) of the surface, and only afterwards, as the potential becomes more positive, does it extend to other sites.

In conformity with this, a passivating oxide of this type may remain on the surface and inhibit the anodic reaction up to a certain potential, at which it is able to pass into solution in the form of a complex with a metal ion of higher oxidation state. At such positive potentials the surface complex will obviously be readily regenerated, which will lead to a continuous dissolution of the metal by this mechanism.

Electrochemical Basis of the Pitting of Metals

It is now known that the passive state of a metal or an alloy can in many cases be broken down (either partly or completely) by introducing certain anions, expecially Cl^-, Br^-, and I^-, into the solution.

Numerous experimental observations have shown that the presence of these ions in solution is frequently a cause of irregular corrosion, leading to the formation of deep pits in the metal surface. This type of corrosion is, of course, most dangerous, since with relatively small overall corrosion losses it can put metal structures or individual parts completely out of action.

Many investigators have studied pitting corrosion, without, however, being able to elucidate the mechanism of this process. In spite of this, several workers[37] are inclined to regard it as a purely chemical process, not an electrochemical one. To the writer, however, such a conclusion appears to be completely unjustified. Analysis of available data shows that, with certain, quite plausible assumptions, the occurrence and development of pitting can be satisfactorily explained on the basis of an electrochemical mechanism for the dissolution of metals.

Available data indicate that the presence of Cl^-, Br^-, or I^- ions in the solution is a necessary but not a sufficient condition for the acceleration of corrosion and the formation of pits. Often the corrosive action of these ions is observed only at potentials which are more positive than a certain critical value[38,39], which depends on the nature and the concentration of the halide ion in the solution and also on the nature of the metal itself and several other factors. Data recently obtained by Gil'man[40] show conclusively that, under conditions of spontaneous dissolution of metallic zirconium in pure 1.0 N H_2SO_4, the passive state remains stable and the rate of corrosion of the zirconium (with hydrogen depolarisation) does not exceed 5×10^{-7} A cm^{-2}. A very important fact is that this rate does not change appreciably as the potential becomes more positive right up to 2.0 V (see Fig. 5, curve *1*). Addition to the acid solution of chloride, bromide, or iodide also produces no appreciable change in the rate of spontaneous dissolution or the steady-state potential of the zirconium. These ions do, however, exert a corrosive action when anodic polarisation is applied and the electrode potential is shifted to a certain value which increases regularly in the series Cl^-, Br^-, I^-.

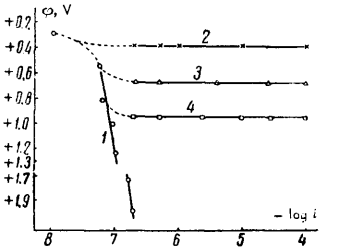


Fig. 5. Dependence of rate of dissolution of zirconium on potential in solutions of: 1) 1.0 N H_2SO_4; 2) 1.0 N HCl; 3) 1.0 N H_2SO_4 + + 1.0 N KBr; 4) 1.0 N H_2SO_4 + 1.0 N KI.

As Fig. 5 (curves *2–4*) shows, the value of this critical potential under stationary conditions is practically independent of the anodic polarising current density, and hence of the rate of dissolution of the zirconium, although immediately after the current has been stepped up (or down) a momentary shift of the potential in the positive (or negative) direction is observed followed by its quite rapid return to the original value (see Fig. 6). Visual observation showed that under these conditions the zirconium does not dissolve uniformly over its whole surface, the dissolution being distinctly local in character and leading to the formation of pits.

The critical potential can be reached not only by polarising the electrode but also by introducing an oxidant into the solution. The oxidant employed by Gil'man[40] was a ferric salt, sufficiently high concentrations of which in chloride solutions shifted the potential of zirconium to the critical value and resulted in pitting of the metal surface.

The behaviour of zirconium in solutions containing chlorides, bromides, or iodides does not differ fundamentally from that of several other metals (iron, magnesium, aluminium, chromium, etc.) and alloys.

Since the solution potential of zirconium in acid chloride solutions is definitely irreversible, its independence of the current can be satisfactorily explained on the assumption that under these conditions the effective surface S increases in proportion to the growth in the current I, when we can write

$$\varphi = K + \log \frac{I}{S}. \qquad (9)$$

It follows from Eqn. (9) that the constancy of φ is a consequence of that of the quantity I/S. This hypothesis is consistent with data obtained for aluminium, whose critical solution potentials in acid chloride, bromide, and iodide solutions are more negative than the corresponding values of the reversible hydrogen potential. Tomashov and Modestova[41] have shown that in this case a shift in the electrode potential to the critical value is accompanied by an increase not only in the overall rate of dissolution but also in the rate of spontaneous dissolution, which is shown in an increase in the amount of gaseous hydrogen evolved (negative differential effect). It was clearly established that the rate of hydrogen evolution increases linearly with increase in the polarising current. Since in this case the corrosion has a well-defined local character, and the evolution of hydrogen is strongly retarded at the passive portions of the surface, such a relation between current and rate of hydrogen evolution evidently indicates that the effective surface of the active sites increases linearly with increase in the polarising current. This conclusion agrees with visual observations of these workers, indicating a growth in the number of pits with increase in the current.

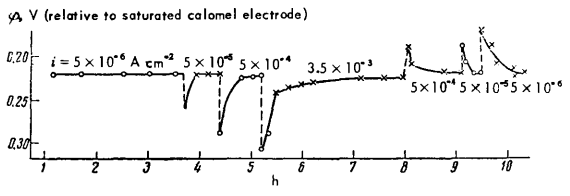


Fig. 6. Variation of potential with time when the current density is increased or decreased during the anodic dissolution of zirconium in 1.0 *N* HCl.

The observed momentary deviations of the potential from the critical value immediately after the current has been stepped up or down are obviously due to the fact that, with a rapid change in polarisation, the quantity S has insufficient time to keep pace with the growth in I.

It can be concluded from the experimental coincidence of the forward and reverse polarisation curves that depassivation of a metal surface by halide ions is reversible in the sense that, when the factors producing activation of the surface are eliminated, the latter again passes into the passive state. Hence it appears that two competing processes are occurring on the metal surface under these conditions — the passivating adsorption of the oxygen of water (8b) and the activating adsorption of chloride ions — which can be represented schematically as follows

$$\text{M}(\text{O}^{2-}\cdots\text{H}^{+})_m + p\text{Cl}^- \rightleftharpoons \text{M}(\text{Cl})_p^{p-} + m\text{H}_2\text{O}. \qquad (10)$$

The possibility of displacing such an equilibrium to the right should obviously depend not only on the electrode potential but also on the concentration of halide ions near the metal surface. Engell and Stolica[37] have recently shown that the activating influence of chloride ions on the corrosion of a passive iron electrode (accompanied by pitting) is observed only when a certain critical concentration of these ions in the solution is reached.

Naturally the question arises as to why the dissolution of a metal under these conditions has a well-defined local character. In the reviewer's opinion the experimental dependence of the area of active sites on the polarising current is of considerable importance for an understanding of this phenomenon. The existence of such a relation can be understood and explained if it is assumed that the supply of chloride ions to the metal surface is effected by transport by the current. This hypothesis agrees well with experimental data showing that the corrosive effect of chloride or other halide ions can be diminished or completely eliminated by raising the concentration of the main electrolyte in the solution. Thus, Gil'man[40] has recently shown that the effect of chloride ions on the anodic dissolution of zirconium in sulphate solutions disappears completely when the concentration ratio of sulphate to chloride is brought close to 5. If, however, perchlorate, whose anion is singly charged, is employed as the main electrolyte, the critical concentration ratio is practically doubled, *i.e.* it is brought close to 9–11.

Such a hypothesis is supported also by the data of Engell and Stolica[37], who showed that, with passive iron at a specified potential, the activating effect of chloride ions on the anodic dissolution of this metal is not observed immediately after chloride has been introduced into the solution, but only after the lapse of a period of time, which is longer the lower the chloride concentration in the solution. Under conditions such that the bulk concentration of chloride remains below the critical value, the appearance of such an induction period may be due to the time required for the Cl^- concentration next to the electrode to reach the critical value.

Since the dissolution of solid metals always takes place irregularly (even when they are passive), so that the current is always distributed irregularly over the surface, it is reasonable to assume that the critical concentration of Cl^- ions will be reached soonest close to those portions of the metal surface which dissolve at the greatest rate. If the current is maintained constant, the activation of these portions which has already begun will inevitably lead to a still greater localisation of the current, and hence to a still more rapid supply of activating ions to them, which will result in a self-accelerating dissolution process. It is very probable that the dissolution of metal at active sites will be limited by diffusion‡, so that further increase in the anodic current will inevitably result in an increase in the area of these portions.

It is easy, with the same postulates, to explain the formation and development of pitting in the absence of external anodic polarisation, *i.e.* under conditions such that corrosion is due to the reduction of an oxidant present in the solution, in particular, of oxygen. Data on the electrochemical properties of passive metals show that it is reasonable to suppose that the cathodic reaction will occur mainly on the passivated part of the surface. A local current then inevitably arises, which can play the same part as an external current.

It follows that pitting can develop on a metal surface in the presence of Cl^-, Br^-, or I^- ions in the solution only if the critical solution potentials (φ_c^{Hal}) for the metal in the presence of these ions are more positive than the passivation potential (φ_p) of the metal. This evidently implies that the affinity of the metal for oxygen should considerably exceed its affinity for the corresponding halogens. If the opposite relation holds ($\varphi_p > \varphi_c^{Hal}$), the adsorption of halide ions will obviously prevent the passivating adsorption of the oxygen of water and favour dissolution of the metal in the active state. With zirconium such a condition is realised by introducing into the solution fluoride ions[42], which possess a greater affinity for this metal than has oxygen. The zirconium surface is then completely activated in acid solution, and its rate of dissolution considerably increased. It follows from what has been said that analogous conditions are realised also in the dissolution of silver, cadmium, lead, and indium amalgam in acid solutions of chlorides, bromides, and iodides.

The condition formulated above ($\varphi_p < \varphi_c^{Hal}$) is necessary but not sufficient for pitting to develop in the absence of external polarisation. Even when this condition is satisfied, introduction into the solution of a corrosive anion can obviously lead to pitting only if the steady-state potential of the corroding metal is more positive than φ_c^{Hal}, *i.e.* if the following relation holds: $\varphi_{st} \geq \varphi_c^{Hal} > \varphi_p$. Since the value of φ_{st} depends on factors which determine not only the kinetics of the anodic but also that of the cathodic reaction, the realisation of this latter condition may depend on the concentration of the oxidising component in the solution, on the rate of supply of this component to the metal surface, and finally on its true rate of reduction. This conclusion agrees well with numerous experimental observations showing that, in the presence of aggressive anions in the solution, the development of pitting corrosion is favoured by the presence of an oxidant in the system, in particular molecular oxygen, ferric ions, etc. The maximum permissible concentration of oxidant should obviously depend on several conditions, including the nature of the corroding metal, the pH, the nature and concentration of the aggressive anion, the temperature, and the rate of stirring of the solution.

The relation between φ_p and φ_c^{Hal} may be affected by a change in composition of the solution. According to numerous data, the value of φ_p for any given metal or alloy depends on the pH of the medium, becoming more positive with increasing acidity of the solution[25,43-45]. The value of φ_c^{Hal}, however, varies appreciably with a change in concentration of the aggressive anion, and is practically independent of pH. Thus according to Gil'man's results[40], obtained with zirconium, a tenfold increase in Cl^- concentration is accompanied by a shift in φ_c^{Hal} of approximately 58 mV towards more negative values (see Fig. 7).

Following these ideas and assuming, as in Eqn. (10), that the activating effect of halide ions on the anodic dissolution of metals with pitting is due to the participation of these ions not only in the depassivation of individual portions of the surface but also in the elementary act of ionisation of the metal atoms, we could reasonably expect that the process would be retarded by the slowness of supply of aggressive anions to the metal surface. Experimental data do not, however, confirm this conclusion. Experiments with zirconium have shown that, even with comparatively low concentrations of chloride ions, an increase in the anodic polarising current density (calculated on the apparent surface) right up to 10^{-1} A cm^{-2} produces no appreciable deviation of the electrode potential from the critical value. In the reviewer's opinion this result can be understood and explained, bearing in mind that pitting can develop only when the affinity of the metal for oxygen exceeds its affinity for the corresponding halogen. The stable form of the metal ion in the bulk of the solution will then be its oxygen complex of the type ZrO^{2+}.

It is very probable that under normal conditions dissolution of a metal involves the direct formation of such ions, whereas when the critical potential is reached conditions are created which favour the formation of complex ions of the metal with the aggressive anion as primary product. As such ions diffuse from the metal surface into the solution, however, they can be expected to hydrolyse completely with

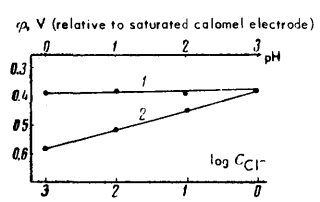


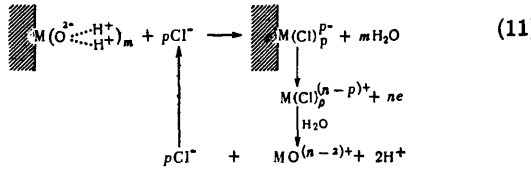
Fig. 7. Dependence of critical solution potential of zirconium on:
1) pH value at constant Cl^- concentration;
2) concentration of chloride ions at constant pH.

‡ Such a hypothesis is quite reasonable if it is remembered that the potentials at which pitting occurs are usually appreciably more positive than the corresponding passivation potentials. On the assumption that the kinetics of metal dissolution is characterised by roughly the same Tafel straight line at pitted regions as on the active metal in the potential range of the preceding passivation, it can be easily shown that the true rate of dissolution of the metal will then considerably exceed the rate of diffusion of the reaction products from the metal phase into the solution.

TABLE. Solution potentials of some metals in the presence of halide ions (N).

Metal	Potential, V (relative to saturated calomel electrode)		Ref.
	Cl^-	Br^-	
Magnesium	−1.419	−1.269	46
Aluminium	−0.509	−0.369	41
Zirconium	+0.380	+0.660	40

the formation of oxygen complexes and free halide ions, which can take part in the process afresh. Under such conditions the concentration of halide ions at the metal surface, as also in the bulk of the solution, will remain unchanged, and they will act as a kind of corrosion catalyst. The mechanism of the dissolution of a metal under such conditions can obviously be represented by the scheme:



(11)

The fact that the corrosive effect of halide ions is exerted in each case only when a definite electrode potential is reached indicates that their chemical activity increases with increase in the positive charge on the metal surface, the role of which is evidently to polarise such ions. Hence the potential at which ions of a given halogen are able to displace the passivating oxygen from the metal surface should vary with the zero-charge point of the metal and its affinity for oxygen§, and consequently should depend not only on the nature and concentration of the halide ions but also on the nature of the metal itself. This conclusion agrees well with available experimental data.

It is clear from the Table that, of the three metals compared, zirconium, which possesses the greatest affinity for oxygen, is characterised by the most positive solution potentials in the presence of chloride and bromide ions.

In conclusion, halide ions are not exceptional in their ability to cause pitting. Results obtained by Kabanov and Vanyukova[38], for iron[39], and recently by Gil'man[40] for zirconium show that perchlorate ions also possess a similar ability, but the solution potential then has considerably more positive values.

§ Since in this case we are dealing with a specific interaction between the surface atoms of the metal and oxygen, the affinity between them can be usefully measured not by the total energy of interaction but only by the part of it associated with the covalent bond.

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METHODS FOR INCREASING THE RESISTANCE OF POLYMERS TO LOW-TEMPERATURES

V. V. Chernaya and R. L. Vol'chenko

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1. INTRODUCTION

The rapid growth of technology places increasing demands on the properties of polymeric materials; in particular, an increase in the temperature limits of their applicability is needed.

This article reviews the methods for increasing their low-temperature resistance, *i.e.* the ability of parts made from polymeric materials to retain their serviceability at low-temperatures. An insufficient low-temperature resistance in polymers may be due to vitrification or crystallisation†, which produce increased hardness, brittleness, and loss of elastic properties. According to modern views[1,2], the vitrification of polymers is caused by a sharp decrease in the intensity of the thermal motion of the polymer chains, a decrease in their flexibility, closer approach of the molecules, and an increase in their interaction. The temperature at which the polymer becomes vitreous is called the glass point (T_g). Polymers typically show a range of glass points, and not a single temperature T_g, since the values of T_g obtained by different methods do not coincide. Moreover, as Aleksandrov and Lazurkin[3], Lazurkin[4,5], and Bartenev[6-8] have shown, the temperature at which the material loses its properties can vary by several tens of degrees, depending on the rate of deformation: T_g increases with the rate of deformation; thus in evaluating T_g for polymers, the actual conditions of use must be taken into account‡.

As the temperature is reduced, the tendency of crystallising polymers to vitrify increases. Crystallisation takes place over a range of temperatures, and its rate increases sharply over a definite section of this temperature range[2]. Thus for unstretched natural rubber this range extends from +15° to -50°, with a maximum rate of crystallisation at -26°. No crystallisation occurs below -50°, since the mobility of the macromolecular chains is too small to form orderly structures. Polychloroprene polymers crystallise over the temperature range +32° to -32°, with a maximum rate of crystallisation at 0°.[2]§

Articles made of polymeric materials often cannot be used even at temperatures above the glass point, because of crystallisation. Thus goods of natural rubber, which has a glass point of the order of -73°, sometimes cannot be used at -10° to -40°, because of incipient crystallisation and loss of elastic properties. Methods are now known for reducing the glass point and decreasing the extent of crystallisation in polymeric materials.

2. REDUCTION OF THE GLASS POINT IN POLYMERS BY PLASTICISING

Until recently the only method for increasing the low-temperature resistance of polymeric materials was by plasticising them, which comprises compounding the polymer with substances which reduce the glass point of the initial polymer. The most widely used plasticisers were phthalic, sebacic, and phosphoric esters.

For a long time, however, the experimental data on the plasticising of polymers had no theoretical foundation, because of the absence of any clear views on the structure of polymers. The investigation of the physical basis of plasticising became possible after the studies of Kobeko[1], Aleksandrov and Lazurkin[3], and Kargin and Slonimskii[15] on the structure of polymers and their behaviour on deformation.

According to modern views there are two mechanisms for the action of plasticisers, for polar and non-polar polymers. After studying the plasticisation of polar polymers by polar or easily polarised plasticisers, Zhurkov[16-19] concluded that the plasticising effect is independent of the chemical nature or molecular dimensions of the plasticiser. The plasticising effect was directly proportional to the molar concentration of the plasticiser:

$$\Delta T = kn,$$

where ΔT is the plasticising effect and n is the molar concentration of plasticiser. k was constant for several plasticisers (tetrachloroethane, acetone, benzyl alcohol, and others). Zhurkov explained this action of plasticisers on polar polymers as the blocking of the individual active centres in the polymer molecule, and showed that this should be determined only by the number of molecules introduced, irrespective of their nature or shape. This is known as the Zhurkov rule of molar concentrations.

† For polymers which crystallise.

‡ The processes occurring in vitrification have been described in more detail in special publications[9,10].

§ The processes occurring in crystallisation have been described in more detail[2,11-14].

The same dependence of the plasticising effect on the number of molecules introduced, irrespective of their chemical structure or shape, was found by Sokolov and Fel'dman[20] in the plasticising of poly(vinyl chloride) with various phthalates and phosphates, and by Kozlov and Russkova[21,22] on cellulose nitrate and acetate.

Kargin and Malinskii[23,24] have shown that the rule of volumetric concentrations applies for non-polar or weakly polar polymers: the decrease in the glass point is proportional to the volumetric concentration of the added plasticiser; this rule was established in the plasticising of poly(vinyl chloride) and polystyrene.

According to Kargin and Malinskii, vitrification of a polymer system is due to a sharp decrease in the mobility of the macromolecular chains; with non-polar or weakly polar polymers, when the plasticiser is introduced there is a purely geometric decrease in the steric hindrance to motion of the polymer chains, because of the increased mean distance between them. Nielsen and Levreault[25] obtained analogous data on the dependence on the plasticising effect on the volume concentration of the plasticiser.

The volumetric and molar concentration rules indicate that the plasticising effect is independent of the type of plasticiser, but recent published work has shown that the chemical structure, and the molecular size and shape of plasticisers can influence the plasticising effect.

On the basis of a study on the deformational properties of polymers, Slonimskii[26] has shown that the various properties of plasticised compositions depend as a whole on the types of plasticiser used; in this respect plasticisers are not mutually interchangeable.

TABLE 1. Mechanical properties of films prepared with various plasticisers.

Plasticiser	Poly(vinyl chloride) : plasticiser : : stabiliser ratio	Tensile strength, kg cm^{-2}	Elongation, %
1*	100 : 100 : 1.5	166.5	203
2	100 : 100 : 1.5	105.5	175
3	100 : 100 : 1.5	101.5	168

* 1) 1-Nitromethyl-2-chlorocyclohexanol;
2) acetyl 1-nitromethylcyclohexane;
3) 1-nitromethylcyclohexanol.

TABLE 2. T_g of polymers and plasticisers.

Property	Polymers			
	styrene – acrylonitrile copolymer	poly(vinyl chloride)	poly(vinyl acetate)	poly(chloroprene)
T_g of polymer, °C	+151°	+116°	+84°	−9°
	Plasticiser			
	dimethylcyclohexyl phthalate	tricresyl phosphate	di-n-heptyl phthalate	dibutyl adipate
T_g of plasticiser, °C	+6°	−30°	−57°	−85°

Voskresenskii and Kozlov[27] have studied the influence of the chemical nature of plasticisers on the plasticising effect in poly(vinyl chloride), and found it to vary with different plasticisers, being dependent on their chemical nature and structure (particularly their polarity). Equimolecular proportions of different plasticisers (see Table 1) give films with different mechanical properties.

Films obtained using equimolecular amounts, or the same contents by mass, of different plasticisers show different low-temperature resistances. Films plasticised with tributyl phosphate are more resistant (T_{brit} = -45°) than those plasticised with tricresyl phosphate (T_{brit} = -15°).

Jenckel[28,29] has shown that the plasticising effect depends not only on the chemical structure of the plasticiser, but also on the glass point of the plasticisers themselves. Table 2 gives the characteristics of the polymers and plasticisers which he studied. The results obtained with 16 different compositions fit the equation:

$$\frac{1}{T_g} = C_{pol}\frac{1}{T_{g\,pol}} + C_{plast}\frac{1}{T_{g\,plast}},$$

where T_g is the glass point of the mixture, and C_{pol} and C_{plast} are the concentrations of polymer and plasticiser respectively.

It follows from the above equation that the greater the difference $T_{g\,pol} - T_{g\,plast}$, the greater will be the reduction in T_g. If this difference is negative, the plasticiser acts as a "thickener", *i.e.* its addition will increase T_g for the mixture.

Pollack[30] has shown that some plasticisers form eutectic mixtures with polymers, and in this case the plasticising effect is a maximum. Forman[31] has investigated the influence of some plasticisers on neoprene rubbers; his results are given in Table 3. He showed that the best plasticising effect at low temperatures is given by plasticisers of high viscosity, high boiling point, and as low vapour pressure as possible.

In his study of the plasticising effect of esters of organic acids, Felix[32] showed that the most effective were esters of C_{6-8} acids. Esters of higher acids tend to freeze out.

TABLE 3. Mechanical properties of neoprene films with various plasticisers.

Plasticiser	Amount added, %	GN neoprene				FR neoprene			
		tensile strength, kg cm^{-2}	elongation, %	molecules at 300%** kg cm^{-2}	T_{brit}, °C	tensile strength, kg cm^{-2}	elongation, %	molecules at 300%** kg cm^{-2}	T_{brit}, °C
—	—	235	995	12	−51	85	785	59	−57
Dibutyl sebacate	15	110	770	40	−62	88.5	1000	28	−57
ditto	30	—	—	—	—	74	1055	19	−68
Tributoxyethyl phosphate	15	119	640	38	−51	89	975	22	−62
ditto	30	105	655	24	−62	80	1160	8.5	−68
Flexol 360*	30	109	820	32	−62	—	—	—	—
Tricresyl phosphate	15	—	—	—	—	82	1010	32	−57
ditto	30	107	730	28	−57	—	—	—	—
Dicapryl phthalate	30	112	800	32	−46	75	1075	15	−68
Petroleum oil	30	124	875	32	−57	—	—	—	—

* Flexol 360 is triethyleneglycol di-2-ethylhexyl ether [made by Union Carbide Corp. (Ed. of Translation)].

** In the rubber industry, modulus at 300% denotes tensile stress to produce 300% strain; it is not the modulus of elasticity (Ed. of Translation).

Lel'chuk and Sedlis[33-35] have attempted to generalise the theory of the action of plasticisers on polar and non-polar polymers. They suggest that the plasticiser molecules penetrate between the polymer macromolecules, force them apart, solvate them, separate the reacting groups, and destroy the regularity and order of the macromolecules; this weakens the intermolecular and intramolecular forces and increases the mobility of the molecules and polymer chains. Consequently, the greater the length, degree of branching, and volume of a molecule, the greater will be its efficiency as a plasticiser. However, increasing the size of the plasticiser molecule decreases its mobility and hinders its penetration into the polymer. Table 4 gives results[33-35] which support these suggestions.

For the quantitative determination of the compatibility of the polymer with the plasticiser, the usual method is to measure the free energy of mixing or the lowering of vapour pressure or change in specific viscosity of the mixture[36,37].

The above data relate to low-molecular plasticisers, the main disadvantage of which is that in addition to reducing the glass point of the polymer, they worsen its mechanical properties, electrical conductivity, dielectric properties, etc.

Recently, polymeric plasticisers have come to be used for plasticising polymers, since they reduce the glass point but do not worsen the other properties[20,38,39]. Thus Voyutskii and his coworkers[38,39] have plasticised poly(vinyl chloride) with high-molecular butadiene–nitrile copolymers as plasticisers; they consider that the plasticising of poly(vinyl chloride), which is a polar polymer, requires a plasticiser containing both polar and non-polar groups, the polar groups reacting with the polar groups of the polymer and so increasing the compatibility of the plasticiser with the polymer. The non-polar groups of the plasticiser screen the polar groups of the polymer and so decrease the interaction between its molecules.

If the plasticiser molecule has a large number of polar groups, it will be highly compatible with the polymer, but its plasticising effect will be slight. It was found that in plasticising poly(vinyl chloride) with butadiene–nitrile copolymers, the optimum effect is obtained with the copolymer containing two butadiene groups for each nitrile group, and that the use of a high-molecular plasticiser provides a poly(vinyl chloride) of considerably better mechanical properties than the use of the low-molecular plasticiser dibutyl phthalate.

In the light of new theories on the structure of amorphous polymers — the micellar structure[40] — two mechanisms have been proposed for the action of plasticisers, an intramicellar and in intermicellar mechanism[41].

TABLE 4. Main properties of plasticisers.

Plasticiser	Efficiency, °C	Compatibility (swelling); tricresyl phosphate = 1	Plasticiser	Efficiency, °C	Compatibility (swelling); tricresyl phosphate = 1
Tricresyl phosphate	9.4	1	Dibutyl adipate	12.4	1.60
Diethyl phthalate	9.8	3.75	Dioctyl adipate	13.1	0.01
Dibutyl phthalate	10.6	1.5	Dibutyl sebacate	13.8	0.275
Dioctyl phthalate	11.9	0.438	Dioctyl sebacate	15.1	0.0087

Intramicellar plasticising takes place when the interaction between the plasticiser and the polymer is stronger than that between the polymer molecules. This occurs with complete miscibility of the polymer and plasticiser.

Intermicellar plasticising takes place when the intermolecular interaction in the polymer is greater than that between the plasticiser and the polymer. This is found when there is a limited compatibility of the polymer with the plasticiser.

The mechanical properties of the plasticised polymer will depend on the type of plasticising which takes place. With intramicellar plasticising one would expect to find increased elasticity in the polymer, a reduction in its glass point and reduced mechanical strength. With intermicellar [intra- in Russian (Ed. of Translation)] plasticising, the glass point would not be reduced, the mechanical strength would be high, and the elasticity of the plasticised polymer would be determined by the Hooke elasticity of the "clusters", which are highly asymmetric in shape, *i.e.* by the elastic deformation of these secondary structural formations.

3. REDUCTION OF THE TENDENCY OF POLYMERS TO CRYSTALLISE

As the literature cited above shows, plasticising can reduce the T_g of a polymer and therefore increase its resistance to low-temperatures. Crystallising polymers lose their elastic properties at reduced temperatures because of increasing crystallisation.

Ritter[42,45] has shown that when crystallising polymers are plasticised their tendency to vitrify increases, because of the increased mobility of the chains and the creation of more favourable conditions for the formation of crystal structures.

One of the known methods for reducing the tendency of polymers to crystallise is the copolymerisation of monomers[10,46]. Recent investigations[42-76] have shown modifying a polymer can reduce its tendency to crystallise by a factor of hundreds or even thousands. The low-temperature resistance of the modified polymer is considerably increased thereby.

A. Copolymerisation

The close connection between crystallisability and regularity of molecular structure is well known. Reduction in the regularity of structure produces a sharp decrease in the tendency of the polymer to crystallise. The introduction of side groups of various structure in the linear polymer chain (by copolymerisation) is often used in practice to obtain non-crystallising polymers.

By copolymerising chloroprene with styrene Mayo[46] obtained a new non-crystallising rubber, neoprene FR. The destruction of the regular structure of the rubber by adding small quantities of styrene prevented the rubber crystallising. Mayo gives comparative data on the tendency of neoprene rubbers to crystallise (Figs. 1 and 2). The diffraction patterns were taken after conditioning the films at 15° for 4 days (Fig. 1) or after straining the vulcanised films 400% (Fig. 2). The full lines indicate the tendency of the various types of rubber to crystallise, and the broken lines indicate the amorphous halo formed when the crystals are destroyed (Fig. 1) or before they appear

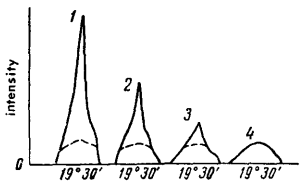


Fig.1. X-Ray diffraction intensity before and after 4 days exposure of the specimen at 15°:
1) neoprene CG; 2) neoprene CN;
3) neoprene RT; 4) neoprene FR;
broken lines: before conditioning; full lines: after conditioning.

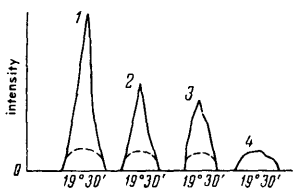


Fig.2. X-Ray diffraction intensity before and after stretching by 400%:
1) neoprene CG; 2) neoprene CN;
3) neoprene RT; 4) neoprene FR;
broken lines: unstretched; full lines: stretched.

(Fig. 2). The greatest tendency to crystallise is shown by neoprene CG, and is less with neoprene CN and slight with neoprene RT; the neoprene–styrene copolymer FR has no tendency to crystallise.

B. Modification

Another and comparatively new method for greatly reducing the crystallisation effect at low temperatures is by modifying the polymers. This can be carried out with thio-acids[42-44,47-53,55-65], butadiene sulphone[5,67], sulphur dioxide[54,67], titanium tetrachloride, triisobutylamine, or powdered selenium[68]. The reactions of polymers with thio-acids were first described in du Pont patents[47-49]. This work was carried out to stabilise polymers to the action of solvents by the saturation of the double bonds¶.

The reaction of natural rubber with thio-acids to prevent its crystallisation has been described by Ritter and Cunneen in patents[51,52]. Commencing in 1956 there have been a large number of investigations by Ritter[42-44], Cunneen[53-56,63-65], and others, on the conditions for the reaction of thio-acids with solid rubber (in the roller mill, Banbury mixer, and extruder), in solution, and in latex; in each case the modified rubbers crystallised hundreds and sometimes thousands of times more slowly than the initial natural rubber.

Gent[57-59] has studied the kinetics of crystallisation of natural rubber at low temperatures, and has evaluated the effect of the degree of cross-linking on the rate of crystallisation, showing that the formation of chemical cross-links reduced the rate of crystallisation. Moreover, Gent showed that combined sulphur in the side groups can also substantially reduce the rate of crystallisation.

On this basis, Ritter[44] suggested that the thio-acids react with natural rubber at the double bonds to form side chains which hinder crystallisation because of the resulting irregular structure.

If the side groups contain more carbon atoms than thiobenzoic acid, they tend to crystallise themselves, so that high-molecular-weight modifiers are ineffective.

According to Ritter[44], the addition of thio-acids to natural rubber proceeds as follows:

$$\mathrm{RCOSH} \rightarrow \mathrm{RCOS^*}$$

$$-\mathrm{CH_2C(CH_3)=CH-CH_2}- + \mathrm{RCOS^*} \rightarrow -\mathrm{CH_2C^*(CH_3)CH(SCOR)CH_2}-$$

$$-\mathrm{CH_2C^*(CH_3)CH(SCOR)CH_2}- + \mathrm{RCOSH} \rightarrow$$

$$\rightarrow -\mathrm{CH_2CH(CH_3)CH(SCOR)CH_2}- + \mathrm{RCOS^*},$$

where R is alkyl or aryl.

Thiobenzoic acid was the most effective modifier in respect of reducing the rate of crystallisation and yielding products of satisfactory strength and technological properties. The addition of 0.5–2 moles of thiobenzoic acid per 100 isoprene groups reduces the rate of crystallisation by a factor of hundreds.

Since the changes were considerably greater than would be expected from the "action of side group mechanism"[57,72], it had to be assumed that thio-acids produce some other structural changes in the isoprene macromolecules.

Ritter's suggestion[44] that the double bonds in the macromolecule are transposed to form side methylene groups has not been confirmed by infra-red spectroscopy.

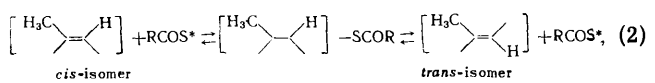
Cunneen[63-65], Cunneen and Shipley[53,54], Watson[67], and Golub[61] and others have observed that the action of thiol acids on natural rubber causes isomerisation, some of the *cis*-bonds becoming *trans*-bonds. Earlier attempts to isomerise natural rubber by the action of ultra-violet light or various chemicals did not give substantial *cis*-*trans*-isomerisation[73,74]. Before Golub's work[75] configurational changes of polyolefines with non-conjugated double bonds were unknown. The method of infra-red spectroscopy used by Cunneen and coworkers[64] was specially developed by them, and could only be used for homopolymers and for mixtures of homopolymers of *cis*-*trans* 1–4 polyisoprenes; it is based on differences observed in the spectra at frequencies of 1125 and 1145 cm^{-1}, and can give a quantitative analysis of the configurational changes taking place in natural rubber and gutta-percha, even with less than 5% isomerisation.

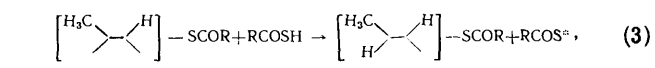
¶ For similar work on the modification of polyisoprene by saturating it with mercaptans to obtain a product stable to the action of ozone, ultra-violet light, and sunlight, see Meyer and coworkers[69-71].

Fig. 3 shows detailed stereochemical results. After reaction with sulphur dioxide, natural rubber and gutta-percha were converted into products containing 57% *trans*-bonds and 43% *cis*-bonds. Analogous isomerisation can be achieved by treating the polymers with thio-acids or butadiene sulphone.

The isomerisation, according to Cunneen and his coworkers[53], must proceed as follows:

$$A^{*}+RCOSH \rightarrow AH+RCOS^{*}, \quad (1)$$





where A* is a radical formed either by the action of initiators (in solution or in latex) or by rupture of the rubber molecules on the roller mill. The isomerisation thus proceeds through a reversible stage in the addition reaction. The addition proceeds by a free-radical mechanism; in step (2) the thioacyl radicals add across the double bonds to form a complex radical, which can then either react further with the acid to form the addition product, as shown in step (3), or can undergo *cis-trans*-isomerisation. If step (2) is much more rapid than step (3), a considerable number of double bonds will be isomerised for each thio-acid molecule added on to the chain. These structural changes, as would be expected, considerably reduce the tendency of natural rubber to crystallise at low temperatures.

This has been confirmed by Kraus[76], who showed that polybutadienes with a high content of *cis*-bonds crystallise rapidly at low temperatures, while those containing 20–75% *trans*-bonds are amorphous.

The rate of crystallisation has been determined by various methods: by measuring the stress relaxation in the specimen[55], dilatometrically[59], and by measuring the temperature retraction[44].

The stress relaxation has been measured at -26°, the temperature at which the rate of crystallisation of unvulcanised and vulcanised natural rubber is maximum[55]. The vulcanised specimens were held under a constant strain (usually 150%) at this temperature. The time for the volume to decrease by 50% of the total change (in the dilatometric method), or for the tension in the stretched specimen to decrease to a half of the initial value (in the stress relaxation method), is called the crystallisation half-life[55].

Fig. 4 shows the crystallisation half-lives for modified and unmodified natural rubber[64]. The former is seen to be greater than the latter. The retardation factor (the ratio of the crystallisation half-life for the modified rubber to that for the corresponding control) is in this case 100:1.

The rate of crystallisation can also be determined by the standard ASTM procedure[77,78] by the temperature retraction of specimens. In this procedure the specimen is stretched by 400–500%, cooled to between -70° and -80° and held at this temperature for a definite period of time. The stretching force is then removed and the temperature of the specimen raised. The temperatures are recorded at which the specimen contracts by 10, 30, 50, and 70% of the initial length (TR 10, TR 30, TR 50, and TR 70 respectively).

Fig. 5 shows the temperature retraction of unmodified natural rubber.

Using this procedure, Ritter[44] has determined the degree of crystallisation as follows: the specimen was stretched by 50–100% (crystallisation does not occur, even in unmodified rubber) and held at -70°. TR 70 was measured, the specimen stretched by 400–500%, and TR 70 again measured. The difference between these two values of TR 70 characterises the tendency of the rubber to crystallise; the greater the difference, the greater the tendency. For a non-crystallising rubber the difference is zero. To obtain additional information on the rate of crystallisation at low temperatures, Ritter[44] has slightly modified the above TR method. The specimens were not stretched at

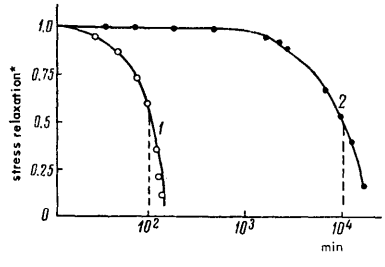


Fig. 4. Comparison of the crystallisation half-lives of vulcanised rubbers:
1) unmodified; 2) modified natural rubber.

* Stress/initial stress (Ed. of Translation).

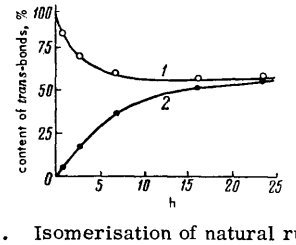


Fig. 3. Isomerisation of natural rubber and gutta-percha at 140° under the action of sulphur dioxide:
1) gutta-percha; 2) natural rubber.

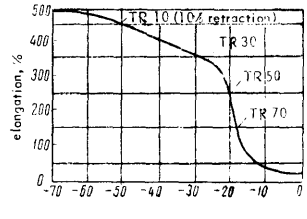


Fig. 5. Temperature retraction (TR) of unmodified natural rubber.

room temperature, but were first cooled to the desired low temperature, and then stretched at that temperature; the stretched samples were held under these conditions for a definite period of time, the straining force was removed, and the permanent set measured as a function of crystallisation time at the given temperature.

At -50° the permanent set of modified rubbers containing 0.5 and 1% thiobenzoic acid was 28 and 16% respectively. Unmodified rubbers had a permanent set of 32% at -20°, 200% at -30°, 300° at -40° and 280% at -50°.

Fig. 6 shows the permanent set curves for modified rubbers; low-temperature plasticisers increase the rate of crystallisation of the unmodified natural rubber. This cannot be detected with the normal TR techniques described above, since the vulcanised rubbers crystallise very rapidly at room temperature and the increase in the rate of crystallisation when the plasticiser is introduced is negligible at this temperature.

Moreover, it was found[44] that the temperature at which the crystallisation rate is a maximum, which is -26° for unstretched natural rubber, may be different when the rubber is stretched, *e.g.* -50°. The introduction of low-temperature plasticisers shifts this optimum crystallisation temperature towards higher temperatures (Fig. 7).

Modification of natural rubber in the solid. Ritter[42-44] has modified natural rubber with thio-acids in the roller mill and the Banbury mixer, using thioacetic, thiocaprylic, thiostearic, thiochloroacetic, thiobenzoic, thionaphthoic, benzoic [*sic.* (Ed. of Translation)], bromothiobenzoic, nitrothiobenzoic, and dinitrothiobenzoic acids. The thio-acids were added to the plasticised rubber in amounts of 0.1, 0.25, 0.5, 1, and 2 mole% and mixed for 10 min. The vulcanising agents were added the following day. The addition of more than 2 mole% of the thio-acids was difficult because of scorching. The rate of scorching could be reduced by replacing the sulphur used for vulcanising by Sulfasan R† (4, 4′ dithiodimorpholine). Figs. 8 and 9 show Ritter's results on the rate of scorching[47].

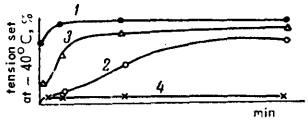


Fig. 6.* Low-temperature tension set at -40° and 400% elongation; racking periods 5, 30, 120, and 380 min:
1) dried latex film, unvulcanised; 2) smoked sheet, vulcanised; 3) smoked sheet + tributyl phosphate; 4) rubber (1 mole % added thiobenzoic acid) + + tributyl phosphate, vulcanised.

* Captions taken from original paper[44] (Ed. of Translation).

† Made by Monsanto Chemical Co.

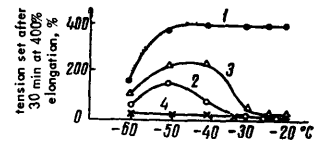


Fig. 7.* Dependence of the low-temperature tension set on the test temperature.
1)–4) See Fig. 6.

* Captions taken from original paper[44] (Ed. of Translation).

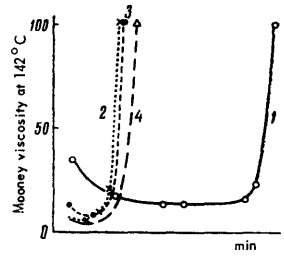


Fig. 8.* Tendency to scorching as a function of the content of various thio-acids:
1) smoked sheet; 2) thiobenzoic acid modified rubber; 3) trichlorothioacetic acid modified rubber; 4) β-thionaphthoic acid modified rubber. (At 2, 4, etc. up to 20 min).

* Captions taken from original paper[44] (Ed. of Translation).

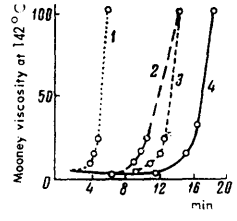


Fig. 9.* Influence of substitution of sulphur by Sulfasan R on the vulcanisation of rubber. 100 g of thiobenzoic acid-modified rubber contain:
1) 2.5 g of sulphur; 2) 1 g of Sulfasan R;
3) 2 g of Sulfasan R; 4) 4 g of Sulfasan R.

* Captions taken from original paper[44] (Ed. of Translation).

Thiobenzoic acid was the most effective of those studied in reducing the crystallisability of natural rubber; the addition of up to 2 mole% produced a sharp reduction in the tendency towards crystallisation.

Fig. 10 shows the effect of thiobenzoic acid on the crystallisation of natural rubber. The rate of crystallisation

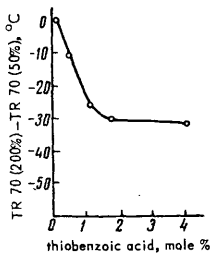


Fig.10. Crystallisation of natural rubber as a function of the thiobenzoic acid content.

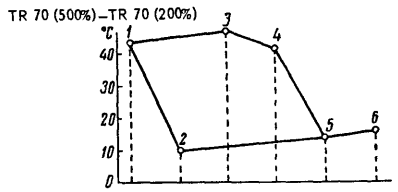


Fig.12. Influence of plasticisers and modifiers on the tendency of smoked sheets to crystallise: 1) unmodified sheet; 2) thiobenzoic acid-modified rubber; 3) rubber + tributyl phosphate; 4) rubber + + plasticiser TP90B; 5) thiobenzoic acid-modified rubber + tributyl phosphate; 6) thiobenzoic acid--modified rubber + plasticiser TP90B.

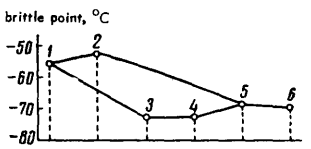


Fig.13. Influence of plasticisers and thiobenzoic acid on the brittle point: 1)–6) see Fig.12.

decreases as increasing amounts of thiobenzoic acid are added, the glass point of the mixture is simultaneously raised (Figs. 11–13); this increase is negligible with up to 2 mole% of the thio-acid, but the tendency to crystallisation is reduced by a large factor by the addition of these amounts. Moreover, Ritter[44] has shown that when a modifier and a plasticiser are used together, non-crystallising rubbers with a low glass point can be obtained. The strength of the rubber decreases as the thio-acid is added to natural rubber.

By analogy with SBR-type copolymer rubbers reinforced with carbon black, Ritter[44] considered modified natural rubber as a "quasi-polymer" and used carbon black to reinforce rubber modified with thiobenzoic acid. Table 5 shows his results.

Modification of natural rubber in latex. The isomerisation of natural rubber in the latex has been studied in detail by Cunneen[53], who used ordinary concentrated latex, containing 60% rubber, preserved with ammonia. To avoid immediate neutralisation of the thio--acid by the ammonia, the stabilised latex was acidified with dilute hydrochloric acid to pH 0.6. The most effective stabilisers were (ethylene oxide)–amine condensation products, particularly the condensation product of stearylamine with 50 moles‡ of ethylene oxide used in an amount of 2–2.5% by weight of the rubber. Ascaridole§, t-butyl hydroperoxide, cumene hydroperoxide, and α,α'-azo-bis-isobutyronitrile were used as catalysts for the reaction.

The catalyst was usually added in an amount of 10–20 wt.% of the thio-acid as a benzene solution or as an emulsion; the thio-acids were also added in benzene solution or as an emulsion. The addition of catalyst and thio--acid in solution gave products whose crystallisation rates were lower than those of products obtained when the additives were used in emulsion. The reaction was continued for 5 h at 60° when using 0.16 wt.% thiobenzoic acid. Above 60° the latex thickened or coagulated, while below 40° the reaction was very slow. Reaction for more than 5 h did not give products with a further reduction in the rate of crystallisation. The latex was coagulated with a polar solvent, such as ethanol or acetone, and the coagulum was extracted with acetone and dried in vacuum, or washed on a wash mill and dried in a thermostat. The rate of crystallisation was determined as described above, or dilatometrically for unvulcanised samples, or by the stress relaxation method[59].

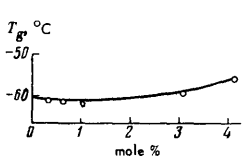


Fig.11. Dependence of the glass point of natural rubber as a function of the thiobenzoic acid content.

TABLE 5. Comparative data on the mechanical properties of modified natural rubber reinforced with carbon black.

Added thiobenzoic acid, mole %	Combined acid, mole %	Modulus at 100% elongation, kg cm^{-2}	Modulus at 300% elongation, kg cm^{-2}	Modulus at 500% elongation, kg cm^{-2}	Tensile strength, kg cm^{-2}	Elongation, %	Tear strength, kg cm^{-2}	Hardness Shore A
With carbon black								
0	0	43	106	—	307	425	109	66
1.2	0.8	47	100	—	221	410	96	67
2.5	1.8	41	83	—	224	500	89	65
4.9	3.2	48	90	—	216	450	95	70
9.8	4.6	89	—	—	135	175	—	83
Without carbon black								
0	0	10	24	78	304	700	29	43
1.2	0.8	5	12	24	140	820	14	35
2.5	1.8	5	11	25	141	825	13	14
4.9	3.2	6	16	23	168	750	14	37
9.8	4.6	6	14	30	72	675	11	35

‡ Mole % ? (Ed. of Translation).

§ 1,4-Peroxido-*p*-menth-2-ene (Ed. of Translation).

TABLE 6. Influence of thiobenzoic acid on the crystallisation half-life.

Added thiobenzoic acid, %	Crystallisation half-life, days
0.04	0.15
0.08	0.69
0.16	28

TABLE 7. Influence of thio-acids on the crystallisation half-life.

Thio-acid	Amount used, %	Crystallisation half-life, days	Thio-acid	Amount used, %	Crystallisation half-life, days
Thiostearic	0.16	0.42	2-Thionaphthoic	0.32	14
»	0.64	1.08		1.28	69
o-Hydroxythiobenzoic	0.16	2.6	2-Hydroxy-3--thionaphthoic	0.32	9.7
	0.32	8.3		1.28	140
	5.12	210			

TABLE 8. Dependence of the retardation factor on the properties of the latex.

Catalyst	pH 1.0	pH 0.6	Precipitated latex, pH 0.6	Repeatedly centrifuged latex, pH 0.6
—	no retardation	6:1	300:1	12:1
Ascaridole	2:1	110:1	750:1	1000:1

TABLE 9. Influence of thio-acids on the crystallisation half--life.

Thio-acid	Amount used, %	Crystallisation half-life, days	Thio-acid	Amount used, %	Crystallisation half-life, days
Thiochloracetic	0.4	3.1	α-Thionaphthoic	0.1	1.2
»	0.6	8.3		0.2	4.2
»	0.8	21		0.4	140
Thiotrichlor-acetic				0.6	140
	0.3	0.83		0.8	140
»	0.7	5.4			
»	1.0	29			

Table 6 gives data on the influence of thiobenzoic acid on the crystallisation half-life, and Table 7 gives similar data obtained with other thio-acids. The hydroxythio-acids are considerably less effective than thiobenzoic acid.

Products prepared under identical conditions from different batches of latex often have very different crystallisation retardation factors (the ratio of the crystallisation half-life of the modified rubber to that of the corresponding untreated rubber). According to Cunneen[62] this difference is due to the different reactivities of the latex. Considerably better results were obtained when the pH of the latex was reduced to 0.6 using precipitated latex, or by using latex which had been repeatedly centrifuged. Table 8 gives some results obtained by these methods.

Reaction in solution. Cunneen[63] and Ritter[44] have reacted natural rubber with thio-acids in solution; the thio-acids were added to 2% solutions of deproteinised crepe in benzene. No catalysts were used. The reaction mixtures were evacuated and heated at 100° for 6 h; the modified rubbers were precipitated with methanol, extracted with acetone in a Soxhlet apparatus for 20 h in an atmosphere of nitrogen, and dried in vacuum. Table 9 gives the results obtained[59] by modifying rubber in solution. The crystallisation half-life increases with the amount of thio--acid added.

Natural rubber can also be isomerised by treatment with sulphur dioxide[67] or butadiene sulphone. The latter is more convenient for modifying natural rubber in the dry state on an industrial scale[65,68]. This method of isomerisation consists in heating the natural rubber for several minutes at 160° with 2% butadiene sulphone. The reaction can also be carried out in internal mixers or injection moulders. The resulting product has properties identical with those of rubber obtained by modification with thio-acids.

This review has shown that three methods exist for increasing the low-temperature resistance of polymeric materials: plasticising, copolymerising, and modifying. Plasticising reduces the glass point of the polymer. Modification and copolymerisation are used to increase the low--temperature resistance of crystalline polymers (to reduce their tendency to crystallise at low temperatures). Modification and copolymerisation do not reduce the glass point of the polymer, so that if it is necessary to increase the low-temperature resistance of a crystallising polymer which has a comparatively high glass point, plasticisers and modifiers must both be used, or copolymerisation must be followed by plasticising of the copolymers.

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USE OF INFRA-RED SPECTROSCOPY TO INVESTIGATE ADSORPTION AND THE STRUCTURE OF SURFACE CHEMICAL COMPOUNDS

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I. INTRODUCTION

Up to the present time formal empirical or semi-empirical modes of description have been widely used in the field of adsorption, and little work has been done on elucidating the structure and condition of the adsorbing surface, ascertaining the mechanism of the adsorption process, and determining the thermodynamic properties of adsorption systems on this basis. Formally empirical modes of describing the results of adsorption measurements (for example, the "potential theory"[1,2] and the "non-uniform surface theory"[3], which are completely unconcerned either with the chemical nature of the surface and its physical structure or with the nature of adsorption interaction) are due to the qualitative character of the results which are usually obtained. Although the potential theory is of great value in classifying measurements of the adsorption of vapours by porous adsorbents and in predicting the temperature dependence of the adsorption of vapours by active carbons[2], it is unable to assist in clearing up fundamental questions of surface structure and the nature of the act of adsorption. The theory of adsorption on non-uniform surfaces[3] enables us to obtain formally energy distribution functions for adsorption sites from experimental adsorption isotherms, but these give no physical picture of the non-uniformity[4], and furthermore are based on the application of the Langmuir theory to individual sites on the surface, although the postulates of this theory are completely inapplicable to adsorption on non-uniform surfaces†.

Nevertheless, during the past fifteen years many accurate investigations have already been carried out, both on adsorption itself and on the differential heats of adsorption of adsorbates with different structure on adsorbents whose geometrical configuration and surface chemistry have been so fully characterised that the adsorption properties of the corresponding adsorbate–adsorbent systems can be expressed quantitatively in terms of numbers which describe the physicochemical characteristics of these systems quite reliably[7]. Such quantitative physicochemical characterisation of adsorption systems urgently requires corresponding changes in the theory of adsorption, in particular the formulation of a statistical thermodynamic theory of adsorption equilibria based on detailed information about the potential field of the surface and the motion of the molecules in adsorption complexes[7].

† The artificial assumption that individual portions of a mosaic surface are uniform[5,6] does not save the situation, since with the diminution in size of these portions which is necessary for the description of a non-uniform surface, their boundary regions begin to play a predominant part.

This task of theory in turn makes new demands on the experimental investigations. Among methods which enable us to obtain a comparatively detailed picture of the chemical structure of a surface and of the motion of the molecules in an adsorption complex, spectroscopic methods are extremely important. They have already given extremely valuable information on surface chemical compounds, which often determine the adsorption, chemisorption, and catalytic properties of a solid, and in the near future will probably also give direct information on the frequencies of vibration and rotation of molecules in adsorption complexes. Comparison of these frequencies obtained directly from spectra with frequencies calculated theoretically by means of potential-energy functions[8-11] is extremely important both for verifying the theory of adsorption forces and as a basis for complete statistical thermodynamic calculations of thermodynamic functions and adsorption equilibria solely from the geometrical, electrical, and magnetic properties (the geometrical and electronic structures) of the adsorbate and the adsorbent separately.

Apart from these tasks, which are important in developing a theory of adsorption, the spectroscopic method of investigating surface chemical compounds and adsorption complexes is also of great practical value. The preparation of effective fillers for media of different chemical types, particularly for polymers, the improvement of the properties of pigments, the improvement of adsorbents, supports for fixed liquid and solid phases, and capillaries for gas chromatography[12] and the production of specific adsorbents and catalysts by chemical modification of a solid surface make infra-red spectroscopy which is one of the main methods for analysing molecular structure, extremely useful for studying the properties of these systems. This method was first applied to the investigation of surface chemistry and adsorption in 1940[13], and was subsequently developed by Terenin and his coworkers[14-17]. An increasing amount of work is now being done in this field, even abroad, and the investigation of adsorbed molecules is regarded as an important new task of applied spectroscopy[18]. Several reviews[16,19-21] have been concerned mainly with catalysis, while others[14,15,17,22] have discussed the results of spectroscopic investigations of surface compounds and adsorption without relation to the problems and data of adsorption investigations. In conformity with the main lines of our work on the chemical modification of solid surfaces[12,29] and the theoretical calculation of the energy of adsorption[7,24-30] and of adsorption equilibria[9-11,30], this review will, therefore, survey research which makes it possible to apply infra-red spectroscopy to the solution of the fundamental problems of surface chemistry: the mechanism of adsorption interaction, the energy of adsorption forces, and the thermodynamics of adsorption.

II. TECHNIQUE FOR THE SPECTROSCOPIC INVESTIGATION OF SURFACES OF HIGHLY DISPERSE SUBSTANCES

Infra-red bands result from the absorption of energy in transitions between rotational and vibrational levels of molecules. The position of a band in the spectrum — corresponding to a wavelength λ (in μ) or a frequency $\nu = 1/\lambda$ (usually expressed in cm^{-1}) — is determined by the nature of the vibrations, and primarily by the energy of the bond and the mass of the vibrating atoms or groups. As a result of this, the vibrational bands of certain groups of atoms (for example OH, CH, NH, etc.) have similar frequencies in different molecules. Slight differences in the

position of the bands of these groups may be due to the effect of neighbouring groups in the molecule or to intermolecular interaction. Infra-red structural analysis is based on the identification of bands in the unknown spectrum by comparison with spectra of molecules having known structure. A quantitative measure of the number of particular groups in a molecule or of molecules per unit volume of a substance can be made from the intensity of the corresponding bands in the infra-red spectrum.

Infra-red spectroscopy can be used to solve a great variety of adsorption problems associated both with the weak interaction of physically adsorbed molecules with the adsorbent and also with the chemisorption of molecules leading to the formation of new surface compounds, *i.e.* to the chemical modification of a solid surface.

In the case of physical adsorption the spectroscopic method is used to investigate changes in the nature of bonds and the geometrical structure of adsorbed molecules and the state of surface groups on adsorption. Investigation of chemisorption and surface chemical compounds solves problems analogous to those involved in the structural analysis of organic compounds.

The absorption bands of adsorbed molecules are superimposed on a background of absorption by the adsorbent. Consequently the possibility of studying physical and chemical adsorption by this method is governed to a considerable extent by the success in overcoming the difficulties associated with interpretation of the spectrum and with preparation of the specimen for investigation, which should be transparent and yet contain several thousand surfaces of separation, covered with the compounds under investigation or with adsorbed molecules, in the path of the infra-red beam. At the present time, interpretation of the spectra of physically and chemically adsorbed molecules is based solely on empirical comparison with the spectra of compounds of known structure. However, the limitation on the sensitivity with which surface compounds and adsorbed molecules, and especially changes in their structure, can be detected is often very slight, and is due mainly to the intrinsic absorption of the adsorbent and the strong scattering of infra-red radiation by powders, the form in which adsorbents of practical interest with large surface areas, are generally used.

However, very important adsorbents of this type — active oxides, such as silica and aluminosilicates — have wide ranges of transparency, limited only by strong absorption bands due to skeletal (lattice) vibrations lying mainly in the region below 1000 cm^{-1}. Silicon dioxide, for example, possesses such absorption bands[31] in the neighbourhood of 1000–1200, 800, and 500 cm^{-1}.

Most of the infra-red radiation is lost by scattering. This is diminished by investigating adsorption processes on thin sheets of adsorbents like porous glass[32] or on specimens prepared from particles of adsorbent powder smaller than the wavelength of the radiation employed.

Such particles are selected either by sedimentation[33] or by precipitation in an electric field[34]. The scattering of infra-red radiation by powders is still further diminished by moistening them with liquid paraffin or by making them into thin disks by compressing the powdered adsorbent with KBr powder[35]. This latter method, however, makes further treatment of the adsorbent difficult, and in several cases leads to ion exchange between its surface compounds and the KBr[36]. From this point of view compressing the adsorbent alone into thin disks is more satisfactory[37].

Surface compounds and chemisorption on metals are usually investigated by depositing them on a support "Aerosil"‡[38-41] or aluminium oxide[42,43]. In this case, too, the scattering of the infra-red radiation can be diminished by pressing the carrier and the metal into disks[44,45]. This leads to some decrease in the metal surface available for chemisorption. In the preparation of disks from palladium on Aerosil, for example, an increase in pressure from 25 to 125 kg mm^{-2} decreases the metal surface available for chemisorption from 5.1 to 3.1 $m^2 g^{-1}$.[45]

In several cases chemisorption on oxides and metals is investigated by depositing them on surfaces which do not scatter infra-red radiation: porous glasses[46,47] or an aerogel[48]. It has proved possible to obtain spectra of surface compounds by passing the infra-red beam through metallic films[20,49] or by reflecting the beam from metallic mirrors[50,51].

All the researches on adsorption by Terenin and his coworkers[52-55] between 1948 and 1952 were carried out in the overtone region of the spectrum using a two-beam infra-red spectrometer of high dispersion having a glass optical system designed by Terenin and Yaroslavskii[56,57]. In this region it is possible to investigate the first overtones of the stretching vibrations of OH, NH, and CH groups in adsorbed molecules and surface compounds using high-sensitivity infra-red detectors and glass cells, which considerably facilitate the handling of the adsorbent specimen. In 1954 Sidorov[58] extended the investigations of adsorption processes into the fundamental region of the spectrum, where the absorption bands of almost all the fundamental frequencies of the vibrational spectrum are located. At the present time the first attempts are being made[59] to extend the investigations into the long-wavelength region of the spectrum (below 500 cm^{-1}), in which absorption bands of vibrations and rotations of chemisorbed and adsorbed molecules relative to the adsorbent surface may appear.

Most of the work now being carried out is in the fundamental region of the spectrum and uses double-beam infra-red spectrometers, which give every opportunity for obtaining differential spectra eliminating the absorption bands of the adsorbent skeleton. The spectra of surface compounds of adsorbed molecules are investigated with the specimen in a special vacuum cell. Existing designs of cells usually provide for the possibility of vacuum treatment at elevated temperatures and for obtaining the spectrum both of the specimen and of the bulk gas phase. Detachable cells of simplified design[60] enable the specimen to be treated by means of a separate vacuum apparatus. Most of the types of cells which have been described[39,61-64] are connected directly to a vacuum line and to a system for measuring out the material; they are intended to be fixed permanently in front of the spectrometer slit. Fig. 1 illustrates one of the best cells of this type[48], made of quartz with CaF_2 windows, which allows the spectrum to be obtained with the specimen placed in the infra-red beam, and the gas to be investigated and the specimen to be heat-treated up to 1000° when the latter is lifted by means of an electromagnet. Vacuum treatment of the specimen is considerably simplified by using cells made entirely of glass[65].

The cells are connected to a conventional vacuum system enabling the sample to be evacuated normally to 10^{-5}–10^{-6} mm Hg. The specificity of the conditions under which

‡ *I.e.* Cab-o-Sil, which is anhydrous, particulate, colloidal silica made by Cabot Corp. (Ed. of Translation).

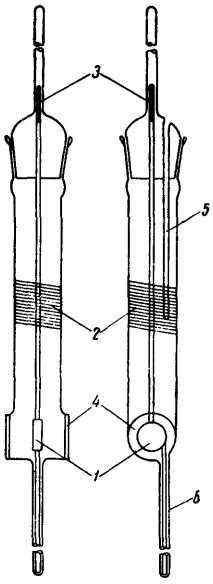


Fig.1. Quartz cell for the spectroscopic investigation of adsorption[48]:
1) specimen holder; 2) heater; 3) sealed-in iron rod for raising the specimen with an electromagnet; 4) windows; 5) well for thermocouple; 6) extension for fixing the holder in place.

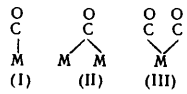
the spectra are obtained (the specimen being heated by the infra-red radiation) and of the conditions under which the powdered specimen has been prepared (by pressing), as well as the presence in the cell of windows made of hygroscopic materials (NaCl, LiF), make it difficult to investigate adsorption equilibria directly in the optical cell. The values of the degree of coverage of the surface with adsorbed molecules which are required are usually obtained from the vapour pressure on the basis of adsorption equilibrium measurements made in a special apparatus with an identical specimen of the adsorbent prepared under the same conditions.

III. SURFACE CHEMICAL COMPOUNDS AND CHEMISORPTION

1. Surface Compounds on Metals

The investigation of surface compounds on metals is of interest both for elucidating the mechanism of their catalytic action and for characterising their corrosion and getter properties. The most detailed research on metals using infra-red spectroscopy has been on the structure of the surface compounds of carbon monoxide, mainly in the USA by Eischens *et al.*[19,20,38,39,41] and by Garland[42,43]. Most of this work has been carried out on disperse metals distributed on the surface of carriers – Aerosils, porous glass, and aluminium oxide – by impregnating the carrier with a salt of the metal (for example, $RhCl_3.4H_2O$,[42] $Ni(NO_3)_2.6H_2O$[43]), decomposing the salt to the oxide, and then reducing the latter to the metal with hydrogen. Terenin[13] had previously suggested depositing the metal on a carrier by thermal decomposition of the metal carbonyls.

The structure of the surface compounds was determined from an investigation of the spectrum of the CO streching vibrations (in the 1800–2200 cm^{-1} range). Comparison of the position of the corresponding absorption band in the surface compounds and in carbonyls of known structure indicated[38,39,42] the existence of compounds of different structures on the surfaces of metals: linear, *i.e.* with a CO molecule linked with one metal atom (I); bridged, *i.e.* with a CO molecule linked to two metal atoms (II); and possibly two CO molecules linked with one metal atom (III);



From the intensities of the absorption bands it was concluded that with some metals (Cu,[20,38] Fe,[20] Pt,[38,39]) the linear configuration of the chemisorbed CO molecules predominates, while with other metals (Ni,[38,39] Pd,[38,39,66-68]) the bridge configuration is more important (Fig.2). In the case of chemisorption on Rh [42] (Fig.2) and Ni[16] all three types of compounds have been noted. As remarked elsewhere[39], with a linear configuration the position of the vibrational absorption band of CO is not very sensitive to the nature of the metal. The vibrational frequency of the bridge configuration is more sensitive to the type of metal, the effect of the carrier, and the type of surface treatment. Thus in the case of platinum deposited on Aerosil, the CO molecules exist predominantly in the linear form (the bridge forms amount to only 15%)[38,39] (Fig.3). When platinum is deposited on Al_2O_3, however, about half the total number of chemisorbed molecules are now in the bridge form[20] (Fig.3).

The effect of the carrier on the spectrum of carbon monoxide chemisorbed on nickel was also determined from

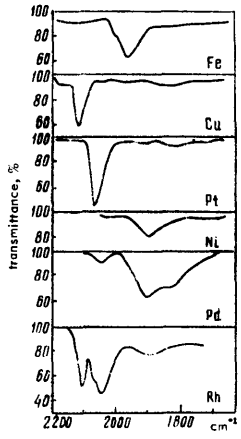


Fig.2. Spectra of carbon monoxide chemisorbed Fe,[20] Cu,[38] Pt,[38] Ni,[38] and Pd,[38] deposited on Aerosil, and on Rh [42] deposited on aluminium oxide.

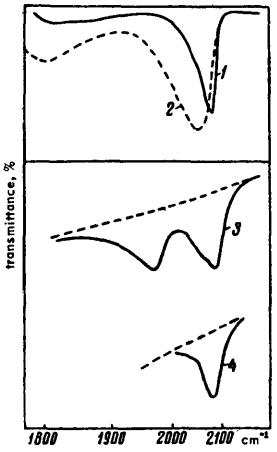


Fig. 3. Effect of carrier on spectrum of chemisorbed oxide[20]:
1) Pt deposited on silicon dioxide;
2) Pt deposited on aluminium oxide; and of surface treatment[43]: 3) freshly reduced Ni; 4) Ni poisoned with CS_2.

the relative intensities of the bands of the linear and the bridged CO structures when the nickel was deposited on aluminium oxide, titanium dioxide (anatase), and silica[65]. It was found that aluminium oxide and titanium dioxide have an appreciable influence on the strength of adsorption and the relative proportions of linear and bridged forms, while the effect of silica is slight.

The properties of the surface compounds of CO are affected also by the state of the metal on the carrier (aluminium oxide) surface. Yates and Garland[69] have shown that absorption bands of bridged and linear forms of surface compounds are observed on the surface of nickel in the crystalline phase (concentration of Ni by weight 25%). Only linear structures are formed on nickel which is highly dispersed (concentration 1.5%) on the carrier surface, and the strength of bonding of the surface compounds with the metal is decreased. Poisoning the metallic nickel surface with CS_2 vapour[43] causes blocking of the adsorption centres involved in the formation of the bridge type of surface compounds with CO (Fig. 3). The interaction of the CO surface compounds with O_2 and H_2 molecules is just as varied. The action of O_2 on CO chemisorbed on Fe [20] is accompanied by a considerable shift (0.4 μ) of the CO absorption band towards shorter wavelengths. With Cu [20] this displacement is less marked (0.04 μ). Treating the CO-metal surface compounds with hydrogen shifts the bands in the opposite direction. This phenomenon is especially marked when reactions are carried out in the surface layer at 200°.[66-68] When surface compounds of CO on Pd are treated with hydrogen (Fig. 4*a*)[67,68] a decrease in intensity of the absorption bands is observed for both linear (2085 cm^{-1}) and bridged (1960 cm^{-1}) structures, the latter band being clearly displaced towards lower frequencies. Treatment with oxygen (Fig. 4*b*) results in a greater decrease in intensity of the bands and their displacement in the opposite direction to 1995 and 2120 cm^{-1}. The observed difference in displacement of the absorption bands of the surface compounds of CO can be explained[20] by a change in the electronic state of the metal surface brought about by oxygen and hydrogen molecules chemisorbed in the course of the reaction.

Direct information on the structure of the surface compounds can be obtained from an investigation of their metal-carbon bonds. The absorption bands of chemical bonds of this type should lie at frequencies above 500 cm^{-1}. It is difficult to obtain a spectrum in this region mainly because of the strong infra-red absorption of the carrier (silica or alumina). Up to the present time it has only been possible to observe a band at 21 μ, which can be ascribed to a Pt–C chemical bond in the linear type of surface compound[20], with surface compounds of CO on highly disperse Pt pressed into KBr powder. In addition, with hydrogen and deuterium chemisorbed on platinum, absorption bands have been observed[70] at 4.74 and 4.87 μ, and also at 6.60 and 6.76 μ, which are ascribable to stretching vibrations of Pt–H and Pt–D bonds.

Among simple molecules of other types, the spectra of chemisorbed nitric oxide have been investigated in detail. The position of the absorption band of the NO molecule is an extremely sensitive criterion of its behaviour as an electron donor or an electron acceptor. This property of the molecule was used by Terenin and Roev to characterise the adsorption centres on the surfaces of the transition metals Fe, Ni, and Cr, their salts, and their oxides[71-74].

Investigation of the structure of surface compounds formed by the chemisorption of organic compounds on metals is of considerable interest. Compounds of ethylene and acetylene chemisorbed on a nickel surface have been studied in detail[20,40,41]. The spectrum of ethylene chemisorbed on a nickel surface covered with hydrogen shows absorption bands due to the stretching vibrations of the CH

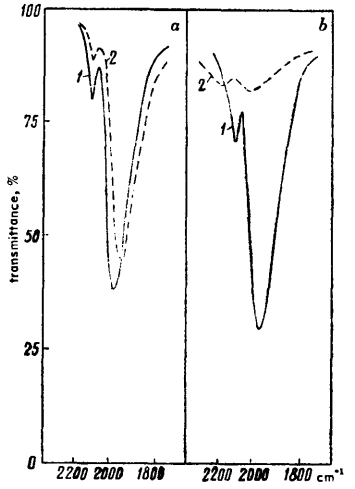


Fig. 4. Change in spectrum of carbon monoxide chemisorbed on Pd deposited on Aerosil, resulting from reaction with (*a*) hydrogen and (*b*) oxygen:
1) original spectrum; 2) after reaction[67].

bond of saturated hydrocarbons and a band due to the deformation vibrations of CH_2, the development of which indicates that a compound of type $\diagup CH_2 \cdot CH_2 \diagdown$ is formed on the surface. The intensity of the CH absorption bands is less in the spectrum of ethylene chemisorbed on a pure nickel surface (Fig.5). This evidently indicates the formation of a surface compound of type $\diagup CHCH \diagdown$ in this case. The increase in the CH absorption band intensity and the appearance of a band due to CH deformation vibrations in the CH_3 group when the surface compounds are treated with hydrogen (Fig.5) show that the surface compounds are hydrogenated to form ethyl radicals of the type $\diagup CH_2CH_3$ on the surface. The decrease in intensity of the CH absorption bands on evacuation may in turn indicate dehydrogenation of the surface radicals and their conversion into surface carbides.

The spectrum of the surface compounds in the chemisorption of acetylene on nickel is similar to that of surface ethyl radicals.

Analysis of the relative intensities of the 2950 and 2920 cm^{-1} bands, due to vibrations of the CH bond in CH_3 and in CH_2 groups, enables us to determine the relative proportions of these groups in surface radicals $[CH_2]_n.CH_3$. It was concluded on this basis[20] that the hydrogenation products of surface compounds of ethylene contain a large proportion of butyl radicals $CH_2CH_2CH_2CH_3$. The relative intensities of absorption bands due to stretching vibrations of the CH bonds at 2950, 2920, and 2870 cm^{-1}, the last of which is due to a group of type $-\overset{|}{C}H-$ or $-\overset{|}{C}H-\overset{|}{C}H_2$ in the surface compound, in turn indicate the number of carbon atoms in the surface compound which are directly linked to metal atoms. In this way it was deduced that butene molecules chemisorbed on nickel are joined to the nickel surface by all four carbon atoms[20].

Little *et al.*[47] estimated the intensities of the absorption bands of surface compounds of ethylene and acetylene chemisorbed on Pd, Cu, and Ni, and compared the results with those for the original compounds. The spectrum of C_2H_2 chemisorbed on Pd and Cu showed the presence of surface groups of olefinic type. In the chemisorption of C_2H_4 on Pd, absorption bands due to CH in saturated compounds were also observed. Treatment with hydrogen of surface compounds on these metals was also accompanied by an intensification of the absorption bands of saturated compounds and a decrease in the intensity of those of unsaturated compounds (Fig.5). The relative intensities of the absorption bands of CH_2 and CH_3 groups in the hydrogenated surface compounds indicate the existence on the surface of alkyl radicals of type $M.[CH_2]_n.CH_3$, and also that $n > 5$ for the hydrogenation of compounds of C_2H_2 on Pd and Cu, and that $n \simeq 3$ for C_2H_4 on Pd.

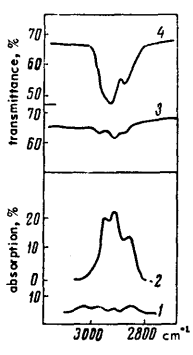


Fig.5. Spectrum of ethylene chemisorbed on Pd[47]: 1) before treatment with H_2; 2) after treatment with H_2; and on Ni[20]: 3) before treatment with H_2; 4) after treatment with H_2.

Such methods for investigating the structure of surface compounds can be considerably extended and used to study the surface compounds of hydrocarbons of the most varied structures. Furthermore, the possibilities of the method can be considerably increased by employing compounds obtained by replacing the hydrogen in the hydrocarbons by deuterium and by other atoms or groups.

The spectroscopic method has been employed also to investigate surface compounds of formic acid[44,75-77] and of stearic acid[51] on metals. The spectra observed in the chemisorption of the former acid agree satisfactorily with the hypothesis that the formate ion is produced on the metal surfaces.

2. Surface Compounds on Oxides

(*a*) Hydration and dehydration. All the various amorphous and crystalline forms of silica carry on their surface so-called "structural water" as a result of their production from aqueous solutions (silica gels), being leached with aqueous solutions (porous glasses), hydration of the surface formed at high temperatures (Aerosils, vitreous quartz), or being ground in water (crystalline silicas). From chemical and adsorption data, Kiselev[78] showed that this structural water consists of the hydroxyl groups of silicic acid chemically combined with the surface atoms of silicon. The absorption band due to the stretching vibrations of hydroxyl groups (7326 cm^{-1}) was detected in the overtone region of the spectrum in the very first spectroscopic investigations by Terenin and his coworkers on porous glass[52,54,55] and aerogel[53]. This band also appears clearly in the fundament range (3749 cm^{-1}) in the spectra of porous glass[58,60,79,80], silica gel[81-86], and Aerosil[37,87,88]. The observed bands are due to hydroxyl groups chemically combined with the surface atoms of silicon, since they remain in the spectra of specimens treated in a vacuum under conditions (heating to 150° and above) which remove the absorption band due to deformation vibrations of adsorbed water molecules[84,86], and where adsorption data[89-93] show that the adsorbed water is removed reversibly from the surface. The hydroxyl groups are located mainly on the surface of the different forms of silica, since the infra-red spectrum shows that they are perturbed by the adsorption of even feebly adsorbed substances, for example argon and nitrogen[94], and are readily substituted, being converted into OD by reaction with molecules of D_2O vapour[37,60,84-86,95,96]. The absorption band of the stretching vibrations of surface hydroxyl groups on strongly dehydrated forms of silica is very narrow, indicating the absence of interference between these groups. The half-width of the absorption band for porous glass treated in a vacuum at 550° is 50 cm^{-1} in the overtone range[54], and less than 15 cm^{-1} in the fundamental

range[94] (in the spectrum of Aerosil treated in a vacuum at 400°). This fact served as the basis for the view adopted in several papers[14,15,60,94] that the distribution of OH groups over a silica surface is completely "free".

Kiselev and Lygin[79,80] noted, however, that the narrow absorption band is observed only when the silica has been treated at high temperatures, with removal of most of the hydroxyl groups. But if adsorbed water has been removed from the surface of silica by vacuum treatment with moderate heating (up to 200°), the absorption band due to the stretching vibrations of the hydroxyl groups is considerably broadened and is unsymmetrical. This asymmetry in the spectrum of porous glass has been explained[60] by the presence of adsorbed H_2O molecules remaining on the surface after vacuum treatment at 470°, and the asymmetry in the spectrum of Aerosil powder by the Christiansen effect[94]. Neither of these causes can serve as an explanation, however, since under such conditions of treatment as heating in a vacuum to 470° all the adsorbed water is removed, while the Christiansen effect does not appear, since the same band contour is observed in the spectrum of silica powder moistened with liquid paraffin[37,80].

The observed form of the hydroxyl absorption band was explained by Kiselev and Lygin[79,85] who determined the spectra of silica gel and compared them with the hydroxyl concentrations on the surface obtained from the loss on heating of specimens[92] which had previously been subjected to a vacuum at different temperatures. Under conditions of complete hydration of the surface (treatment in a vacuum up to 200°) the mean distance between hydroxyl groups was found to be ~4 Å. Irregularity in the packing of the silicon–oxygen tetrahedra bearing hydroxyl groups, and in the orientation of their angles and edges, which is always present owing to the amorphous structure of silica gel produces a large number of hydroxyl group spacings of less than 3 Å on its surface, when treated under such conditions, so that hydrogen bonds can be formed between them. Hence the surface contains both "free" hydroxyl groups, separated from one another by more than 3 Å and not interacting with one another, and "combined" hydroxyl groups, which are close together (separated by < 3 Å) and are favourably oriented for the formation of hydrogen bonds between them.

In conformity with Terenin's first interpretation[15,52-55] the narrow bands were ascribed to such non-interacting "free" hydroxyl groups. The absorption in the longer-wavelength part of the band due to stretching vibrations of the surface hydroxyl groups, however, belongs to those groups on the same surface which are quite close together and are favourably oriented geometrically, interacting with one another by a weak hydrogen bond[79,80,85]. This view of the structure of the hydroxyl surface covering on silica is now adopted in many papers[37,97-100]. The idea of the existence of hydroxyl groups combined with one another on the surface of silica is used by Folman and Yates[97-99] to explain the variation in length of a rod of porous glass and in the spectrum of its hydroxyl groups when NH_3, $(CH_3)_2CO$, SO_2, and CH_3Cl are adsorbed on it.

The form of the absorption band due to the hydroxyl groups indicates that the relative proportions of free and interlinked groups are different on specimens of silica of different origin and subjected to different treatments (Fig. 6)[37]. Interlinked hydroxyl groups predominate on the surface of silica gels, the globules[23] in whose skeleton consist of arbitrarily packed silicon–oxygen tetrahedra resulting from polymerisation of the most hydrated form (monomeric molecules of orthosilicic acid); the absorption band due to the hydroxyl groups is, therefore, considerably broadened (Fig. 6*a*). Free hydroxyl groups predominate, however, on the surface of Aerosils, which have not undergone additional hydration (Fig. 6*b*), giving a narrow absorption band. These widely spaced free hydroxyl groups are very resistant to thermal dehydration. Even on treatment at high temperatures their absorption band only slowly decreases in intensity (Fig. 7)[37].

When hydrated silicas are dehydrated, the absorption band due to interlinked hydroxyl groups is the first to become weaker. When a not very strongly dehydrated silica surface is rehydrated, it is neighbouring hydroxyl groups, linked together by a hydrogen bond, which are restored first (Fig. 8)[84]. After partial thermal dehydration of the surface of silica gel at 400°, the hydroxyl covering can be completely reestablished by renewed hydration in water vapour[83,84]. When silica gel is treated above 400°, however, it is dehydrated irreversibly[83].

A hydroxyl covering exists on the surface of other oxides. Bands at 3698, 3737, and 3795 cm^{-1}, due to unlinked surface hydroxyl groups, remain in the spectrum of γ-aluminium oxide[48] after vacuum treatment, while the corresponding absorption bands in the spectrum of a deuterated specimen are at 2733, 2759, and 2803 cm^{-1}. With low treatment temperatures, each band is asymmetric towards low

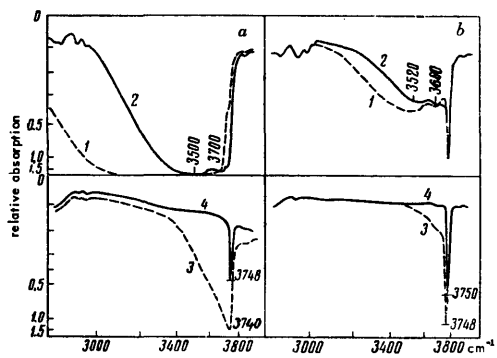


Fig. 6. Spectrum of hydroxyl groups of (*a*) silica gel and (*b*) Aerosil:
1) original specimen; 2) after vacuum treatment at 30° for 3 h; 3) at 500° for 30 min; 4) at 940° for 8 h.[37]

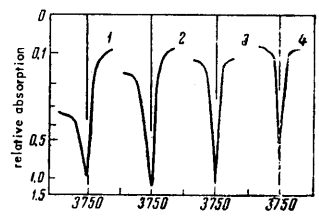


Fig. 7. Spectrum of Aerosil:
1) original; 2) after vacuum treatment at 500° for 30 min; 3) at 940° for 15 min; 4) at 940° for 8½ h.[37]

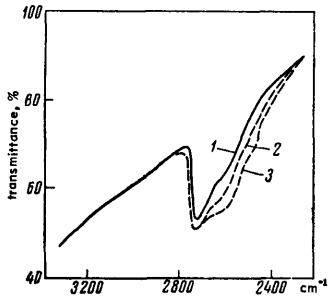


Fig. 8. Spectrum of deuterated silica gel: 1) vacuum treatment at 400°; 2) after contact with D_2O vapour for 30 sec and evacuating; 3) after contact with D_2O vapour for 2 h and evacuating[84].

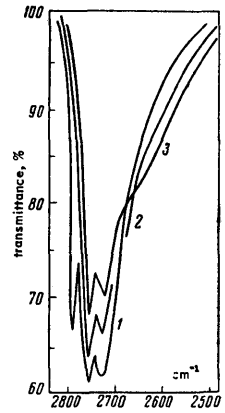


Fig. 10. Change in spectrum of surface OD groups on aluminium oxide during adsorption of acetylene[101]: 1) after treatment with deuterium at 600°; 2) on adsorption of acetylene at a pressure of 2 mm Hg; 3) at 5.9 mm Hg.

frequencies, owing to the superposition of absorption bands due to hydroxyl groups which are close together and interact with one another.

Each band can be ascribed to a set of hydroxyl groups possessing distinctive properties. The difference in properties between these groups is shown primarily by the order in which they are removed on dehydration, by their reactions with butene and NH_3, and by their ability to exchange with deuterium. With D_2, for example, the hydroxyl groups responsible for the absorption bands of highest and lowest frequency exchange first (Fig. 9), the intermediate band showing the slowest exchange.

A difference in properties between the various surface hydroxyl groups on aluminium oxide is observed also in the adsorption of acetylene and its derivatives[101] (Fig. 10). Thus when C_2H_2 is adsorbed on aluminium oxide covered with OD groups, the high-frequency OD band (2790 cm^{-1}) disappears first, whereas the other two OD absorption bands (2755 and 2735 cm^{-1}) merely decrease in intensity. Adsorption of C_2D_2 involves the disappearance of the high-frequency OH absorption band (3785 cm^{-1}) and the appearance of the high-frequency OD band (2785 cm^{-1}) indicating that only these groups take part in isotope exchange. The molecules of all adsorbates interact most strongly with hydroxyl groups corresponding to the high-frequency absorption band.

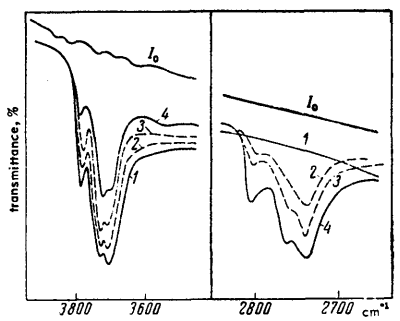


Fig. 9. Exchange between D_2 and H in OH groups of γ-aluminium oxide at 250°: 1) spectrum of original specimen; 2) after exchange for 15 min; 3) 45 min; 4) 18 h.[48]

A difference in properties between surface hydroxyl groups appears also in the spectrum of the different modifications of titanium dioxide[102]. The spectrum of anatase heated at 150° in a vacuum shows absorption bands due to stretching vibrations of hydroxyl groups around 3675 cm^{-1} and in the range 3350–3100 cm^{-1} (Fig. 11). Vacuum treatment of a specimen at 350° leads to splitting of the band at 3675 cm^{-1}. Treatment of rutile under analogous conditions (evacuation at 350°) yields a spectrum with only one OH absorption band, at about 3680 cm^{-1}. The 3320 cm^{-1} band in the spectrum of rutile is due to surface NH groups formed in the preparation of the specimen. The hydrogen of the hydroxyl groups on titanium dioxide exchanges with deuterium at a greater rate than in the case of silica and aluminium oxide.

Several absorption bands due to surface hydroxyl groups are observed in the spectrum of an aluminosilicate catalyst[103].

(*b*) Surface esterification of oxides and hydroxides. Surface reactions yielding new compounds by the creation of a bond with the surface atoms of the adsorbent skeleton or by the replacement of existing surface groups provide wide possibilities of altering the properties of adsorbents. The hydrophilic properties of a hydrated silica surface can be replaced by hydrophobic properties by the formation of esters on the surface. The reaction of a silica gel surface with methanol was first observed by Kiselev and his coworkers[104] and then elsewhere[105-107]. Methylation on porous glass was investigated spectroscopically by Sidorov[58,60]. Adsorption of methanol on this material decreases the intensity of the absorption band of the surface hydroxyl groups (3750 cm^{-1}) and causes the

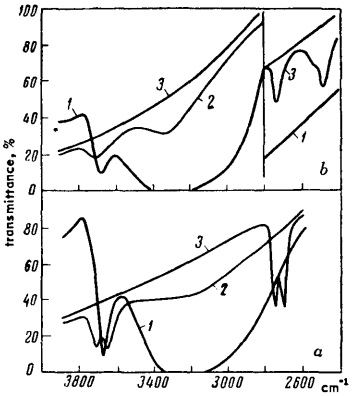


Fig. 11. Spectrum of (*a*) anatase evacuated at: 1) 150°; 2) 350°; 3) after exchange with deuterium at 350°; *b*) spectra of rutile obtained under the same conditions[102].

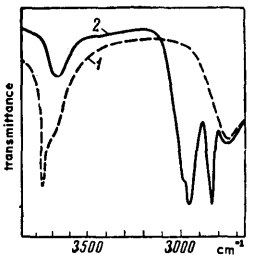


Fig. 12. Spectrum of porous glass after: 1) vacuum treatment at 430°–470°; 2) treatment three times in saturated methanol vapour at 430°–470° followed by evacuation at 430°–470°.[123]

appearance of bands due to C–H stretching vibrations in the methyl groups (2965 and 2862 cm^{-1}) (Fig. 12). Treatment of the surface with methanol at elevated temperatures (up to 470°) leads to an increase in the degree of methylation. However, it is not possible to replace all the surface hydroxyl by methoxy-groups§. The change in intensity of the hydroxyl absorption band indicates that 30% of them are methylated when Aerosil is heated in a current of methanol vapour[94]. The impossibility of complete replacement of surface OH by CH_3 groups is probably explained by steric hindrance[94]. Surface methyl groups are stable to heat treatment, and their absorption bands remain in the spectrum on heating to 400°.[60,94] The reverse reaction, the replacement of methyl by hydroxyl groups, is very slow[60].

Formation of new hydroxyl groups on the surface is also possible during methylation. Thus Stober[105] and Kiselev and Belyakova[107] found that the chemisorption of methanol increases with increasing dehydration of the surface. This indicates that methylation of the surface of silica gel can take place by rupture of Si–O–Si bonds with the formation of hydroxyl and methoxy-groups on the surface.

Esterification was also investigated spectroscopically with other oxides. For example, Babushkin and his coworkers[63,108,109] studied the reactions of methanol and ethanol with aluminium oxide. The spectrum of the chemisorbed alcohols contained bands due to the ether O—C link and to Al–O in surface compounds of the type $>Al-O-CH_3$.

Roev and Terenin[110] found a great variety of forms of surface compounds in an investigation over the range 800–1700 cm^{-1} of the spectra of methanol and ethanol chemisorbed on chromium oxide (Fig. 13). The bands at 942 and 859 cm^{-1} were interpreted as due to deformation vibrations of surface OH groups. The band at 1580 cm^{-1} in the case of the chemisorption of CH_3OH, and that at 1563 cm^{-1} with C_2H_5OH, as well as a series of bands within the range

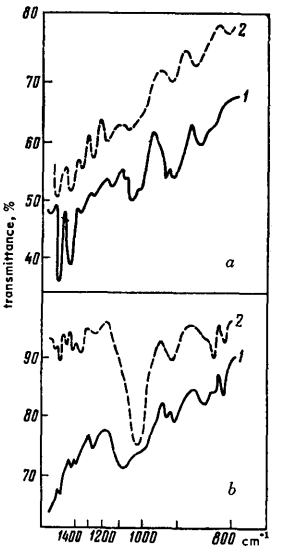


Fig. 13. Spectra of surface compounds obtained on treatment of chromium oxide with: *a*) ethanol; *b*) methanol: 1) treatment and desorption at 20°; 2) treatment at 150° and desorption at 200°.[110]

800–1000 cm^{-1}, were taken as indicating the presence of surface compounds containing a C=C bond. The absorption bands in the range 1000–1200 cm^{-1} were in turn assigned to surface compounds of the type $Cr-O-\underset{|}{\overset{|}{C}}-$ in the case of the chemisorption of methanol, and to compounds of the type $Cr-O-\underset{|}{\overset{|}{C}}-\underset{|}{\overset{|}{C}}-$ with ethanol.

§ In this and the following paragraph there seems some confusion as to whether CH_3 or CH_3O groups are present (Ed. of Translation).

(*c*) Trimethylsilylation of hydroxide surfaces. The most complete coverage of a silica surface by chemically grafted compounds was achieved in surface reactions with trimethylsilyl chloride. The extent of coverage of an Aerosil surface with trimethylsilyl groups was found[111] to be increased by preliminary hydration of the surface. In this case, however, hydroxyl groups still remained on the surface, and affected the adsorption properties, especially with respect to small molecules[7]. The accessibility of such remaining hydroxyl groups to absorbed water molecules was studied[112] from the infra-red spectra obtained by means of isotopic exchange of the OH groups of Aerosil with D_2O molecules. Exchange of surface OH groups by OD in an atmosphere of D_2O vapour is complete (Fig. 14*a*), apart from groups blocked at the point of contact by Aerosil particles. With a strongly modified Aerosil specimen (Fig. 14*b*), however, exchange is considerably less. This indicates that Aerosils which are strongly modified by trimethylsilyl groups, have a proportion of the hydroxyl groups remaining on the surface which are screened by the trimethylsilyl groups chemically grafted to the surface, and are therefore inaccessible to isotopic exchange with D_2O molecules.

Trimethylsilyl groups, located above the remaining surface hydroxyl groups, perturb the vibrational motion of the latter, so that the absorption maximum of the OD groups on a modified porous glass is shifted to 2740 cm^{-1} (Fig. 15)[113]. The spectrum shows that heating porous glass to 400° does not remove trimethylsilyl groups (2968 cm^{-1}) from the surface. It is only after the surface has been heated at 500° that OD groups alone remain, giving an absorption band at 2761 cm^{-1}, as in the spectrum of the original unmodified specimen.

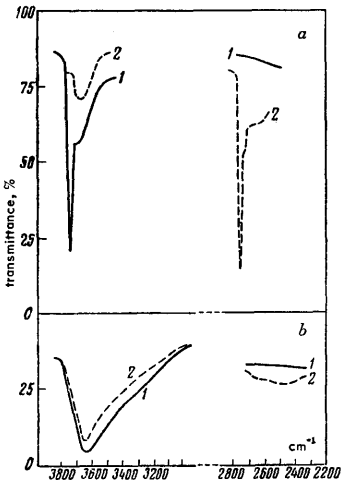


Fig. 14. Change in spectrum of surface OH groups of original Aerosil (*a*) and Aerosil modified with trimethylsilyl chloride (*b*), on treatment with D_2O:
1) original spectrum; 2) after reaction with D_2O.[112]

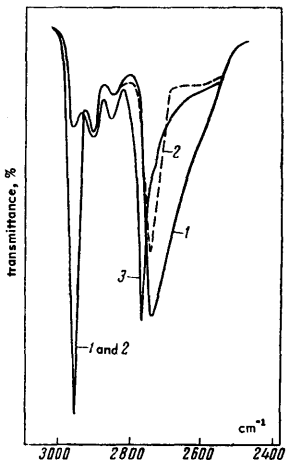


Fig. 15. Spectrum of porous glass modified with trimethylsilyl chloride after vacuum treatment at:
1) 200°; 2) 400°; 3) 500°.[113]

Infra-red spectroscopy has been used in conjunction with nuclear magnetic resonance to investigate surface compounds of formic acid on silica and alumina[114,115]. Organic radicals can be formed on oxide surfaces as a result of the chemisorption of a great variety of compounds. Little[46], for example, detected absorption bands of methyl and methylene groups in the spectra of ethylene chemisorbed on the oxides of Ni, Cu, and Pd. Infra-red spectra indicate that compounds similar to the carboxylate ion are formed when CO is adsorbed on the surface of zinc oxide[116].

3. Chemical Compounds on the Pore Surfaces of Zeolites

The surface chemistry of the channels in zeolites plays an extremely important part in the properties of the latter as adsorbents and molecular sieves. Work on the properties of zeolite surfaces is only now beginning to be developed, and only preliminary attempts have been made at applying infra-red spectroscopy to the investigation of surface chemical compounds on zeolites. Kington and Frohnsdorff[117,118] detected no absorption bands of OH groups in the spectrum of Linde zeolite type A heated at 400°. The spectrum of Linde zeolite type NaX and NH_4X was found[119] to contain a narrow band at 3500 cm^{-1}, which was assigned to surface OH groups of the zeolite. The mechanism of hydration of the zeolite surface was traced, a decrease in intensity of the absorption band of the NH group in the NH_4^+ ion being observed with the simultaneous appearance and increase in intensity of the OH band when a zeolite of type NH_4X was heated. The decrease in intensity of the OH band observed on heating above 400° was explained by the condensation of neighbouring groups with the elimination of H_2O.

Surface OH groups on zeolites are difficult to exchange for OD in saturated D_2O vapour. The absence of such exchange has been noted previously by Terenin in the case of the natural aluminosilicate bentonite[115].

4. Oxygen Compounds on the Surfaces of Carbon Adsorbents

It is difficult to obtain infra-red spectra of high quality for surface compounds on carbon adsorbents, including carbon blacks, owing to the great loss in infra-red radiation by scattering and to the continuous background absorption. Infra-red spectroscopy is therefore employed at the present time as an ancillary method for investigating surface chemical compounds only on a small number of carbon blacks which are most suitable for spectroscopic investigation, such as oxidised carbon black of the "Carbolac" type¶,[120] a highly disperse channel black of particle size 80–100 Å,[121] a channel black which has been specially oxidised with sodium hypochlorite solution, and a carbon black obtained by thermal decomposition of graphite oxide[122]. The spectra show the absorption bands of carbonyl groups and vibrations of the COH group, evidently forming part of phenolic, enolic, and lactone compounds, whose existence has been suggested on the basis of chemical investigations. The infra-red spectra also confirm that carbonyl and hydroxyl groups in these compounds which are close together are linked by hydrogen bonds. Far greater success in investigating the structure of surface chemical compounds on carbon adsorbents can evidently be achieved by employing electron paramagnetic resonance and spectroscopy in the far infra-red, where carbon adsorbents are more transparent.

IV. SIMULTANEOUS CHEMISORPTION AND PHYSICAL ADSORPTION

Interaction between molecules and an adsorbent surface can occur both by the strong interactions alone considered above, being in the limiting case chemical reactions with surface groups and atoms, and also as a result of weak forces, causing concentration of the molecules in the surface layer without any substantial change in their geometric structure or chemical properties. Depending on the chemical nature of the adsorbed molecules, the peculiarities of the electron density distribution in them, the nature and structure of the adsorbent surface, and the temperature, these processes can take place simultaneously and make different contributions to the total adsorption.

The chief spectroscopic manifestation of physical adsorption on surfaces covered with chemical groups is a decrease in intensity of the absorption band due to the surface groups, accompanied by the appearance of a new and usually broader band due to these groups displaced to longer wavelengths. The spectrum of the adsorbed molecules undergoes comparatively little change on adsorption. All changes in spectrum accompanying physical adsorption are completely reversible: vacuum treatment restores the original intensity of the adsorbent bands and removes those due to the adsorbed molecules.

Chemisorption may have spectroscopic features similar to those of physical adsorption. Thus the intensity of the absorption bands due to surface groups on the adsorbent may diminish during chemisorption owing to substitution of these by other groups. The absorption bands of many groups in chemisorbed molecules (for example, CH_2 and CH_3) may undergo little change on chemisorption. The distinguishing feature of chemisorption is the irreversibility of the spectroscopic changes in surface groups and chemisorbed molecules which accompany it. The type of changes undergone by a molecule on a surface can be most reliably established by studying its whole spectrum in order to determine whether its structure is preserved or destroyed and to determine the type of link between the molecule and a surface adsorbent atom. The results of chemical and adsorption measurements must also be taken into account.

In many cases, however, the whole spectrum cannot be studied owing to the overlapping of absorption bands due to the adsorbent skeleton and the adsorbed molecule, while investigations in the far infra-red, in which bands due to bonds between the molecule and the surface may appear, are only beginning. Owing to this difficulty, complete spectroscopic investigations of adsorption, in which proper account is not taken of chemical and adsorption data, may lead to contradictory conclusions as to the predominance of physical or of chemical adsorption and as to the part played by different adsorption "centres".

Nikitin *et al.*[60] observed no change in intensity of the absorption band due to free surface hydroxyl groups in an investigation of the adsorption of water on porous glass which had been heated in a vacuum at 470°. On desorption of water from the surface of the porous glass, however, the spectrum still contained absorption bands due to the stretching vibrations of OH groups, somewhat displaced relative to the absorption band of the "free" hydroxyl groups. These facts were interpreted as indicating that adsorption of water takes place not on the surface hydroxyl groups but on other sites on a porous glass surface. In later work with thin sheets of porous glass, Sidorov[123] noted a decrease in intensity of the absorption band of the "free" hydroxyl groups on a silica surface only at high relative pressures of water vapour. It was therefore concluded that hydroxyl groups provide adsorption centres only at high degrees of surface saturation of a porous glass surface. These conclusions did not agree with the adsorption data (see discussions elsewhere[124,125]).

Simultaneous processes of physical adsorption and other molecular changes appear in still more complicated form in the adsorption of ammonia on a partly dehydrated porous glass surface. The absorption band due to surface hydroxyl groups almost completely disappears on adsorption of ammonia, but vacuum treatment at 20° restores its original intensity[126]. The spectrum still contains the absorption bands due to stretching vibrations of NH groups at 3370 and 3280 cm^{-1} (Fig.16)[123]. A similar pattern of spectral change was observed by Sidorov[123] in the adsorption of phenol and chloroform on porous glass, and by Folman and Yates[97-99]

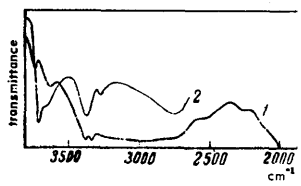


Fig.16. Spectrum of porous glass 0.5 mm thick: 1) in the presence of ammonia at 50 mm Hg; 2) after vacuum treatment for 15 min.[123]

¶ Series of channel carbon blacks made by Cabot Corp. (Ed. of Translation).

in the adsorption of methanol and ammonia. The preservation of absorption bands due to individual bonds in adsorbed molecules on evacuation of a specimen was explained, as in the case of water, by the adsorption of the molecules on "secondary" adsorption centres, the bonding energy of which was greater than the energy of a hydrogen bond.

Since the secondary centres are not directly represented in the spectra, great uncertainty in establishing their nature is noted in many papers[17,97,99,127]. This vagueness also arises because secondary centres are introduced in most cases to explain an adsorption process on dehydrated silicas; on the latter, however, physical adsorption can also be accompanied by *chemisorption*, the spectral manifestations of which are very similar to those used to justify the "secondary" centres of *physical* adsorption.

Ideas based on the existence of secondary centres of physical adsorption and their decisive role in the adsorption of water are incompatible with results in the overtone region of the spectrum previously obtained by Yaroslavskii[54]. The conclusions of Nikitin *et al.*[60] on the absence of interaction between adsorbed water molecules and surface hydroxyl groups are also inconsistent with results obtained by McDonald[37] in the fundamental region of the spectrum for the adsorption of water on Aerosil. In a recent paper Sidorov[100] remarks on the great part played by surface hydroxyl groups in the adsorption of water.

Finally, direct results on the adsorption of water and methanol[90-93,128] do not support the assumed existence of other surface centres, more active than hydroxyl groups, for their *physical* adsorption.

Direct measurements of the heats and entropies of adsorption of water vapour[93], ether[129], and t-butyl alcohol[130] on silica gels having hydrated and partly dehydrated surfaces showed that, firstly, these substances are reversibly adsorbed many times more strongly on a hydrated than on a dehydrated surface, and secondly that the decrease in heat of adsorption on dehydration of the surface is particularly large in the case of ether, the molecules of which can form hydrogen bonds only with surface hydroxyls, but not with one another, and do not react chemically with the dehydrated surface. A particularly important fact is that the decrease in heat of adsorption of ether due to dehydration just corresponds to the energy of two hydrogen bonds. Thirdly, the heats of adsorption of ether and t-butyl alcohol on hydrated silica gel exceed those of the hydrocarbons of corresponding structure – n-pentane and neopentane – also by the energy of two hydrogen bonds. Nevertheless, ether and n-pentane, and also isolated molecules of t-butyl alcohol and neopentane, have similar energies of adsorption on a non-polar adsorbent, graphite, where adsorption takes place essentially only under the influence of electrokinetic (dispersion) forces[7,131]. These new data leave no room for doubt that the most favourable sites for the reversible adsorption of oxygen-containing molecules, which can form hydrogen bonds with hydroxyl groups on the surface, are pairs of favourably arranged hydroxyl groups, and not dehydrated parts of a silica surface.

Nevertheless, the above facts indicate that the interpretation of the results of some spectroscopic investigations on complicated surfaces (on partly dehydrated silicas in the simplest case) is difficult and hence sometimes contradictory, while the mechanism of adsorption suggested on this basis does not explain all the phenomena, especially purely adsorption ones. Therefore further spectroscopic investigations are obviously necessary. With specimens of known surface structure and adsorption capacity, these would enable the effects of reversible physical adsorption to be separated from chemisorption (for example, hydration of the surface), and would allow us to establish the predominant role and detailed character of these processes when the chemical structure of the surface is varied in different ways.

V. PHYSICAL ADSORPTION

1. Mechanism of Physical Adsorption

(*a*) Change in spectrum of surface hydroxyl groups during adsorption. Direct and most reliable information on the mechanism of physical adsorption on hydroxylated surfaces is obtained by spectroscopic investigation of the interaction between the surface hydroxyl groups of silica and adsorbed molecules. The sensitivity of surface hydroxyl groups to adsorption interaction was first used by Terenin and Yaroslavskii in an investigation in the overtone range of the adsorption on porous glass of benzene, toluene, aniline, pyridine, phenol[14,52], water[54], nitrogen, and oxygen[55]. Kurbatov and Neuimin investigated in the overtone range the adsorption of chloroform, phenol, acetone, and water on aerogel[53]. Filimonov used the spectroscopic method to study the adsorption from the gaseous phase and from solution of a number of organic compounds on porous glass, on silica gel, and on an aluminosilicate catalyst[132,133]. Lyubimov and Egorov investigated the adsorption of water in the overtone range[134]. With saturated hydrocarbons and molecules having spherical symmetry like CCl_4, whose interaction with surface hydroxyl groups involves mainly dispersion forces, the absorption band due to these groups remains narrow and its displacement towards lower frequencies does not exceed 1%. The situation is similar in the adsorption of molecules possessing quadruple moments or small dipole moments. A typical case is the change in the absorption band of OH groups when N_2 molecules are adsorbed on porous glass at -180° (Fig. 17)[55]. The spectrograms show during adsorption a gradual disappearance

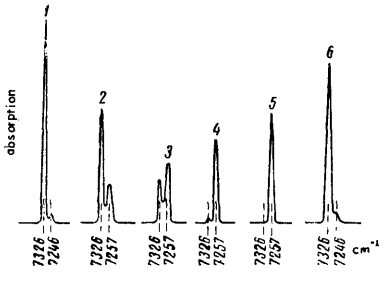


Fig. 17. Change in spectrum of surface hydroxyl groups of porous glass after adsorption of nitrogen at -180°:
1) original specimen; 2) after 1 min; 3) after 10 min; 4) after 20 min; 5) 2 h after admission of nitrogen; 6) heated with adsorbed nitrogen to +20°.[55]

of the absorption band at 7326 cm^{-1} due to free hydroxyl groups, and the appearance of a band at 7257 cm^{-1} due to hydroxyl groups perturbed by the adsorbed N_2 molecules. A typical feature of physical adsorption in this case is the restoration of the original band when the temperature of the specimen is raised to 20°, *i.e.* on desorption of the nitrogen.

The adsorption of molecules having large dipole moments, and especially of molecules able to form a hydrogen bond with surface hydroxyl groups, is accompanied by a large displacement (> 3%) and a broadening of the band due to the hydroxyl groups. With the adsorption of acetone, for example, the hydroxyl absorption band is displaced by 1000 cm^{-1} and is considerably broadened[132,133].

A typical effect of adsorption interaction involving formation of a hydrogen bond with surface hydroxyl groups is observed in the overtone range during the adsorption of water on porous glass[54]. The spectrum of the latter (Fig. 18) shows a decrease in intensity of the band at 7326 cm^{-1} due to surface OH groups and the appearance of an absorption band at 7140 cm^{-1} due to the adsorbed water molecules. At high vapour pressures absorption appears in the region of 6850 cm^{-1}, caused by molecules condensed in the capillaries and by surface hydroxyl groups which have formed hydrogen bonds with adsorbed water molecules.

The effect of dehydration of a silica surface on the adsorption of water is shown clearly on the spectrograms (Fig. 19) given by Kurbatov and Neuimin[53]. When water is adsorbed on a slightly dehydrated specimen of aerogel (curve *1*, Fig. 19) there is a considerable diminution in the absorption band of the surface hydroxyl groups accompanied by the appearance of bands due to adsorbed and capillary-condensed water (curve *2*). However, there is far less adsorption of water on a strongly dehydrated aerogel (curve *3*): the intensity of the absorption band due to the surface hydroxyl groups decreases only slightly and the bands due to adsorbed and capillary-condensed water appear only faintly in the spectrum (curve *4*). A satisfactory explanation of the observed variation in the spectrum of the surface hydroxyl groups can be given on the basis of ideas now current in adsorption research[93,124] on the mechanism of the adsorption of water on hydrated and dehydrated silicas. Adsorption data, which indicate a decrease in the amount of adsorption and in the heat of adsorption of water on dehydration of the surface, confirm that adsorption of a water molecule on two neighbouring surface hydroxyl groups, situated close together and favourably oriented, is energetically the most advantageous. In conformity with this,

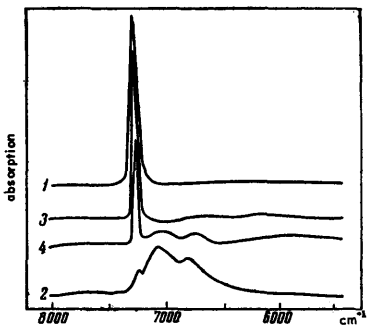


Fig. 19. Change in absorption spectrum of hydroxyl groups of porous glass on adsorption of water; 1) specimen subjected to vacuum treatment at 400°; 2) after capillary condensation of water; 3) vacuum treatment at 900°; 4) after capillary condensation of water[53].

the interaction of water molecules with hydroxyl groups should have a greater effect with a hydrated surface or with one that has been dehydrated at not too high a temperature, as is observed in Fig. 19.

The dominant role of neighbouring surface hydroxyl groups, close together and favourably oriented, in the adsorption of water on a hydrated surface is shown by Sidorov's results, in the fundamental range of the spectrum, on the adsorption mechanism on porous glasses of different degrees of hydration[100]. The spectrograms in Fig. 20[100] clearly show that, with increase in the temperature of vacuum treatment of the porous glass and removal of surface hydroxyl groups situated close together (narrowing of the 3749 cm^{-1} absorption band), the quantity of adsorbed water molecules also decreases. The governing role of surface hydroxyl groups in the adsorption of water molecules on silica was shown by Benesi and Jones[84], and by Kiselev and Lygin[86] in a spectroscopic investigation of the adsorption of water on silica gel having a fully hydrated surface. On adsorption of a monolayer of heavy water on silica gel containing surface OD groups[86], the intensity of the band due to the stretching vibrations of such groups

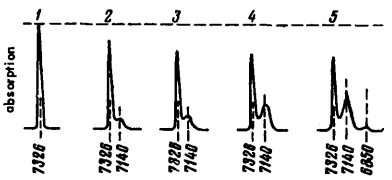


Fig. 18. Change in absorption spectrum of hydroxyl groups of porous glass on adsorption of water: 1) specimen treated in vacuum at 550°; 2) after adsorption of water at 4 mm Hg for 1½ days; 3) at 9 mm Hg for 4 h; 4) at 12 mm Hg for 1 h; 5) in saturated steam for 10 min[54].

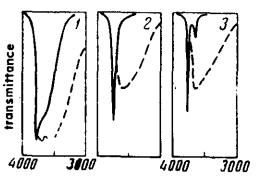


Fig. 20. Full lines: change in spectrum of hydroxyl groups of porous glass after being heated in a vacuum at different temperatures: 1) 300°; 2) 540°; 3) 650°. Broken lines: after remaining in water vapour at 16 mm Hg for 30 min[100].

(2760 cm^{-1}) is considerably diminished, and absorption bands appear due to stretching vibrations of adsorbed D_2O molecules (2680 cm^{-1}) and surface OD groups (2500 cm^{-1}) perturbed by the adsorbed water molecules (Fig. 21). However, the absorption band due to deformation vibrations of the OH groups of the adsorbed H_2O (1620 cm^{-1}) lies between the bands due to the deformation vibration of H_2O molecules in the vapour (1595 cm^{-1}) and in the liquid (1640 cm^{-1}). These facts suggest that the hydroxyl groups of completely hydrated silica gel are the main centres of reversible physical adsorption of water, which takes place by the formation of hydrogen bonds between surface hydroxyl groups and oxygen in the adsorbed water molecules.

The overtone OH band completely disappears on the adsorption of molecules having strong protophilic properties, such as aniline, pyridine[52], benzaldehyde, dioxan, etc.[14] To explain this effect by the formation of a strong hydrogen bond[15], as noted elsewhere[20], is inconsistent with our normal ideas, since formation of a hydrogen bond is always accompanied by a broadening and a displacement of the hydroxyl absorption band, not by its complete disappearance. It is quite possible, however, that overtone bands of perturbed hydroxyl groups are not observed owing to their considerable diffuseness, and perhaps also owing to the potential curve becoming more symmetrical on adsorption, making the OH bond vibration more harmonic, with an associated decrease in intensity of the overtone band of OH when perturbed by adsorption[17].

The possibilities of infra-red spectroscopy for studying the mechanism of adsorption are considerably increased by investigations in the fundamental region of the spectrum. McDonald[94], for example, was able to reveal extremely fine differences in the variation in the spectrum of the surface hydroxyl groups of Aerosil even with the weak van der Waals adsorption of different inert gases. The shift in the hydroxyl absorption band (3749 cm^{-1}) accompanying adsorption was found to be 8 cm^{-1} for argon, 16 for krypton, 12 for oxygen, 24 for nitrogen, and 34 for cyclohexane. The 3749 cm^{-1} band completely vanishes, a new band appearing at 3725 cm^{-1}, with the adsorption on the surface of considerably fewer N_2 molecules than are required for a complete monolayer (Fig. 22). This indicates the preferential adsorption of the first N_2 molecules on the hydroxyl groups of the silica. With the adsorption of argon and oxygen, the hydroxyl band disappears at higher vapour pressures than in the case of N_2, which, in conformity with the smaller shift in the hydroxyl band, indicates a weaker interaction, in comparison with N_2, between these molecules and hydroxyl groups. The stepwise change in position of the hydroxyl absorption band observed on the spectrograms is explained by a change in the mechanism of interaction of N_2 molecules with hydroxyl groups at these vapour pressures.

The polarisability of the adsorbed molecules cannot be the factor explaining the shift in the absorption band of the surface hydroxyl groups, since oxygen and nitrogen, for example, have almost identical polarisabilities, while the displacements are different, amounting to 12 and 24 cm^{-1}. Frohnsdorff and Kington[135] have shown that this latter difference can be explained by the proton–quadruple interaction between the surface hydroxyl groups and adsorbed molecules. These spectroscopic data are consistent with the observed[136] decrease in the adsorption of nitrogen at low degrees of surface coverage on dehydration of a silica surface.

Investigation in the fundamental range of the spectrum[58,123] also revealed a distinct variation in the displacement of the hydroxyl absorption band with the polarity of the adsorbed molecules and their ability to form a hydrogen bond. It has been shown with a large number of organic molecules[88] that the shift in the absorption band of the surface hydroxyl groups of Aerosil varies from 30 cm^{-1} (for the adsorption of cyclohexane) to 845 cm^{-1} (with pyridine).

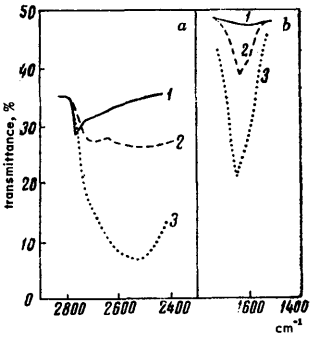


Fig. 21. Spectrum of (*a*) deuterated silica gel: 1) heated in vacuum at 200°; 2) after adsorption of a monolayer of D_2O; 3) under conditions of capillary condensation of D_2O, (*b*) original silica gel: 1) heated in a vacuum at 200°; 2) after adsorption of a monolayer of H_2O; 3) under conditions of capillary condensation of H_2O.[86]

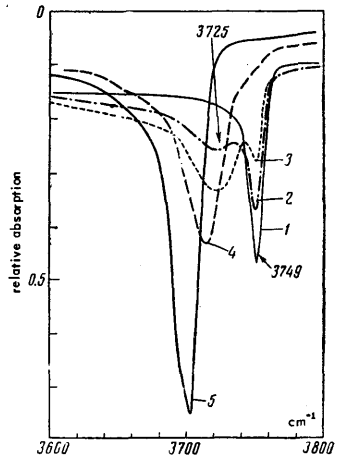


Fig. 22. Change in absorption spectrum of Aerosil on adsorption of N_2:
1) specimen heated in a vacuum at 300°–350°;
2) after adsorption of N_2 at -190° and 1.42 mm Hg;
3) 4.85 mm Hg; 4) 47.3 mm Hg; 5) under conditions of condensation of N_2 at -200°.[94]

Folman and Yates[97] found that the perturbation of the surface hydroxyl groups of porous glass by polar adsorbates increases in the order $CH_3Cl < SO_2 < (CH_3)_2CO < NH_3$; *i.e.* it increases with increasing ability to form a hydrogen bond.

(*b*) Change in spectrum of adsorbed molecules. The mechanism of adsorption interaction can be judged also from the changes in the spectrum of the adsorbed molecules themselves compared with their spectrum in the gaseous and liquid states. The absence from most papers of data on the surface coverage by adsorbed molecules introduces a certain vagueness into the characterisation of physically adsorbed molecules, since their interaction with one another at low degrees of surface saturation is closer to their interaction in the gas, while that at high surface saturations resembles more their interaction in the liquid. Nevertheless, it can be concluded that groups in molecules which do not make a fundamental contribution to the formation of an adsorption link are little perturbed by adsorption. Thus, for example, no displacement of the absorption maximum in bands due to the CH bond in a benzene ring and its aliphatic substituents can be established between the adsorbed and liquid states[123].

Nevertheless, a difference can be noted in the positions of the bands due to the CH bond and of the absorption bands due to stretching and deformation vibrations of the C–C bond in benzene molecules adsorbed at low surface saturations, the gas, and the liquid[137]. In particular, a band at 2223 cm^{-1}, a component of the CH deformation vibrations in the plane of the ring, appears in the spectrum of adsorbed benzene even at low degrees of coverage, although it is absent in the gas (Fig. 23).

The change in spectrum of an adsorbed molecule in turn allows us in several cases to ascertain the chemical group or bond in the molecule by which it is linked to the adsorption centre. Thus the increase in frequency of the absorption bands of the CH groups in benzaldehyde and acetone,

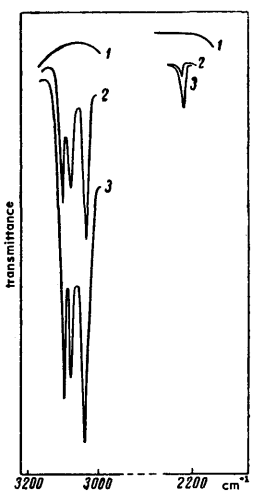


Fig. 23. Infra-red spectrum of: 1) Aerosil; and of benzene on Aerosil: 2) covered with 0.1 monolayer; 3) one monolayer[137].

and the decrease in frequency of the CO group, indicate that these molecules are joined to the surface hydroxyl groups of porous glass by the electronegative oxygen atoms of the carbonyl groups[123]. A change in the spectrum of a similar character is observed in the adsorption of aldehydes and ketones on Aerosil[88]. The formation of a hydrogen bond between surface hydroxyl groups of silica and aluminosilicates and amino nitrogen atoms in adsorbed molecules is indicated by the considerable displacement of the NH absorption band towards lower frequencies[123,132,138]. The change in the spectrum of an adsorbed molecule produced by a controlled variation of the geometrical and chemical structure of the adsorbent can in turn contribute to establishing the nature of the link between the adsorbed molecule and the surface of the adsorbent. The shift in the absorption band due to the OH stretching vibration in a water molecule adsorbed on halides formed by ions of different sizes and electronegativities indicates the formation of a preferential link between the hydrogen atom of the water molecule and the negative halide ion[139].

(*c*) Intensity of absorption bands of surface groups of absorbent and adsorbed molecules. Adsorption methods for obtaining isotherms and heats of adsorption usually give the aggregate effect of the interaction of a large group of molecules with many adsorption centres on the surface.. Apart from the simplest cases[7] this diminishes the possibility of separating the interaction of adsorbate molecules with different adsorption centres on the surface of the adsorbent and with one another. The great selectivity of infra-red spectroscopy eliminates these restrictions to a considerable extent, since in principle infra-red spectra enable us to characterise the state of every chemical group on the surface and every bond in the adsorbed molecule. Up to the present, however, investigations on these lines have not been widely developed owing to the difficulty of intensity measurement and to limitations in the sensitivity with which adsorbed molecules can be detected. In fact the accuracy of the intensity measurements, which is usually limited by distortions introduced by the finite width of the slit and the spectroscopic apparatus, is diminished in the case of adsorption investigations by the large background absorption and the scattering of infra-red radiation by adsorbents. These factors also lower the accuracy with which the concentration of adsorbed substances can be determined.

However, the employment of adsorbents of low scattering power, such as porous glasses and aerogels, and the pressing of powders into transparent disks, now enable measurements of the intensity of absorption bands due to adsorbed molecules to be made at comparatively low degrees of surface saturation. Absorption bands of CH groups in methane molecules adsorbed on porous glass, for example, can be observed at surface coverages below 0.004,[61] and below 0.1 with ethylene,[61,140] 0.01 with CO_2,[41] and 0.001 with butene[141]. At the same time, real values have been obtained for the extinction coefficients of physically adsorbed molecules per unit effective thickness of the layer and per unit volume of adsorbed substance[61] or per unit weight or volume of the adsorbent[46,47,141]. With the aim of employing infra-red spectroscopy to determine numbers of molecules adsorbed, Hoffman and Brindley[142] have investigated the dependence of the extinction coefficient of adsorbed molecules on the surface coverage of the adsorbate. In determining the intensity of absorption bands of adsorbed molecules and surface groups on the adsorbent, the possibility must be borne in mind of anomalous broadening of

the absorption bands[143], as well as the possibility of a change in intensity both as a result of perturbation of chemical bonds by adsorption forces and, perhaps, owing to the simultaneous occurrence of chemical reactions[144].

All these facts confirm that it is now already possible to utilise infra-red spectroscopy, within certain limits, for the quantitative analysis of physically adsorbed molecules at different surface saturations, with the aim of obtaining spectroscopic adsorption and desorption isotherms and comparing them with isotherms both of adsorption itself and of differential heats of adsorption and heat capacities of adsorption systems.

With physical adsorption due to stronger interactions, such as a hydrogen bond, and chemisorption, the task is considerably complicated. In this case the field of the adsorbent changes the bond polarity of the molecules, leading to a change in their absorption coefficient, which depends also on the surface saturation[98]. However, this fact can in turn be utilised to determine the redistribution of charge in the molecule[145,146] and to estimate the field over the adsorbent[61,140]. Investigation of the changes occurring during adsorption and desorption, in the absorption coefficient of the perturbed surface hydroxyl groups and of the groups in adsorbed molecules which interact with them at different degrees of surface coverage can give additional information on the mechanism of adsorption. Investigations of this type have been carried out only by Folman and Yates[98], who obtained curves for the variation of the optical density coefficient of surface OH groups perturbed by adsorbed molecules and for CH and NH groups during adsorption and desorption of CH_3Cl and NH_3 molecules on porous glass.

The combination of research on adsorption equilibria by ordinary adsorption methods with the utilisation of the spectroscopic possibilities noted here for determining adsorption equilibria and characterising the individual bonds in adsorbed molecules during adsorption and desorption will undoubtedly be further developed in the near future.

2. Energy of Adsorption

The most important characteristic of the energy of adsorption interactions is the heat of adsorption. No direct link has yet been found between the heat of adsorption and the spectroscopic observations on adsorption. However, the shifts in the absorption bands of the surface hydroxyl groups and the bonds of adsorbed molecules observed during adsorption are a consequence of the perturbation of surface groups by adsorbed molecules, and are governed by the energy of adsorption interaction.

A definite parallelism is evident between the displacements of the absorption band due to the surface hydroxyl groups of silica (Fig. 24) and the heats of adsorption of water vapour, benzene, and n-hexane[7,147]. These quantities are collated in the Table, the differential heat of adsorption at a moderate surface coverage being calculated both per mole of adsorbate (Q_a) and for the coverage of unit surface (Q_s). The agreement in the sequence of shifts in the absorption band of surface OD and OH groups and of heats of adsorption is shown especially clearly if we compare the displacements $\Delta\nu$ with the differential heats of adsorption calculated not per mole (Q_a) but per unit surface occupied by these molecules (Q_s).

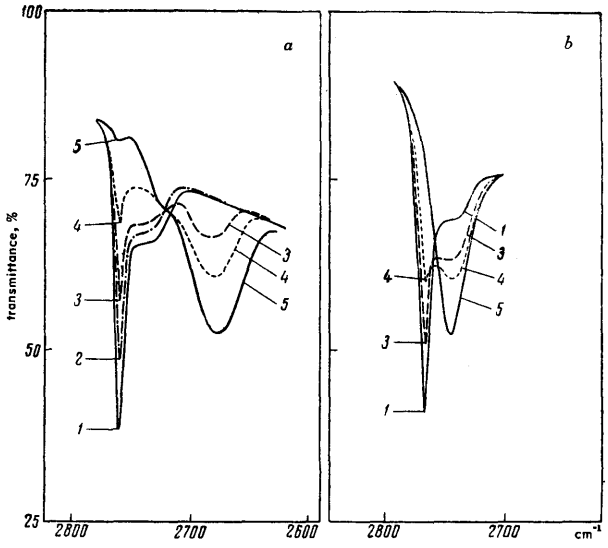


Fig. 24. Spectrum of Aerosil:
1) containing OD groups on the surface and vacuum treatment at 200° for 6 h; and also after adsorption of (*a*) benzene and (*b*) hexane to the extent of: 2) 0.1 monolayer; 3) 0.5 monolayer; 4) 1 monolayer; 5) with capillary condensation[147].

TABLE. Comparison of shifts in absorption band of surface OD and OH groups on silica with differential heats of adsorption per mole Q_a and per unit surface occupied by an adsorbate molecule Q_s with a coverage of half a monolayer.

Adsorbate	Differential heat of adsorption on hydrated silica surface[7,98]		Shift in absorption band of surface groups on adsorption $\Delta\nu$, cm^{-1}	
	Q_a, kcal mole^{-1}	Q_s, erg cm^{-2}	OD	OH
Water	12.5	800	260[112]	330[94]
Benzene	10.2	150	90[147]	110[94]
n-Hexane	8.5	100	26[147]	34[94]*

* Also on adsorption of cyclohexane.

The parallelism noted in the variation of heats of adsorption (which are a measure of the interaction of molecules with all force centres on the surface and in the bulk of the adsorbent) and of the shifts in the hydroxyl absorption bands (which measure the interaction of molecules with the hydroxyl groups alone) confirms that the energy of interaction with these groups makes a large contribution to that of adsorbed benzene and water molecules.

In the formation of relatively stable adsorption complexes (water, methanol, ether, and benzene on hydrated silica) direct spectroscopic determination of the energy of interaction is evidently possible by finding the equilibrium constants of these complexes at different temperatures, as is usually done in determining the bonding energy of complexes in solution[148]. In this connection it is necessary to

investigate both theoretically and experimentally (spectroscopically and calorimetrically) the energy of adsorption of complex molecules on surfaces bearing electric charges or dipoles, allowing for the distribution of electron density in the adsorbate molecules. Such a calculation has been made for the π bonds in the benzene molecule[26], and for the π and σ bonds by the molecular orbital method[28,29].

3. Thermodynamics of Adsorption

In connection with the general problem of the theoretical calculation of heats of adsorption and adsorption equilibria from the properties of the adsorbent and adsorbate alone[7,9-11,23], statistical methods for calculating total and free energy, the entropy of adsorption, and the heat capacity of the adsorbate are of great importance. Whereas with gaseous substances knowledge of the vibrational and rotational spectra of the molecules is sufficient for calculations of thermodynamic functions with an accuracy exceeding that of their direct measurement, the problem is considerably more complicated in the case of adsorbed substances. In the case of localised adsorption, we must have a model of the adsorption complex and know the vibrational and rotational frequencies of the molecule in the complex, as well as have information on the distribution of adsorbate molecules over the surface. In the case of non-localised adsorption, we must know the vibrational and rotational frequencies, and also have information on the migration of molecules along the surface. Up to the present time, entropy calculations (see review[149]) have been based merely on quite arbitrary assumptions as to the movement of molecules along the surface and the possible frequencies of vibration and rotation of an adsorbed molecule relative to the adsorbent surface. Only the first attempts have been made to estimate the frequencies of the vibrations[8-11] and restricted rotations[11] of adsorbed molecules from their theoretically calculated potential energy functions at the surface.

Apart from very rare exceptions, the problem of obtaining the data necessary for the calculation of the thermodynamic functions of adsorbed substances has not in general arisen in spectroscopic work on adsorbed molecules. Therefore only very incomplete data relating to an extremely restricted class of molecules and adsorbents can be obtained from these papers for a study of the thermodynamics of adsorption. Thus the previously considered spectroscopic criteria of the type and stability of the adsorption link can help to solve the question of the degree of localisation of adsorbed molecules. Slight perturbations of the surface hydroxyl groups correspond to weak physical and probably non-localised adsorption. Strong perturbations, corresponding to a stable hydrogen bond, or substitution of the surface hydroxyls by organic or organoelemental compounds indicate firm localisation of the molecules of these compounds on the adsorbent surface.

The slight change in the vibrational spectrum of adsorbate molecules in all cases of physical adsorption, noted earlier, allows us to neglect the change in thermodynamic quantities due to intramolecular motion[11]. In most cases, however, changes in the spectrum of the internal vibrations of adsorbed molecules yield valuable information on the structure of adsorption complexes. The most complete information on the structure of a complex can be obtained from a study of the full vibrational spectrum of molecules adsorbed on adsorbents having an ordered surface structure.

In this connection special interest attaches to the work of Karagounis and Peter on the vibrational spectra of aromatic compounds: 1,3,5-trichlorobenzene, biphenyl, naphthalene, etc., deposited on silver iodide and silica surfaces[145]; and aniline, phenol, *o*-, *m*-, and *p*-phenylenediamines, and *m*-xylene on KBr, AgI, NaCl, AgCl, and TlCl surfaces[146]. The decrease in intensity of the absorption bands due to vibrations perpendicular to the plane of the ring in a molecule having symmetrical substituents, for example, 1,3,5-trichlorobenzene, observed in these cases, indicates a planar arrangement of the molecule on the surface. Data on the intensification and the weakening of the bands due to vibrations in the plane of the ring, taking into account the structure of the molecule and the surface of the crystalline adsorbent, in turn allow us to orientate the adsorbed molecule relative to the force centres on the surface. Changes in intensity of the absorption bands in the vibrational spectra of adsorbed molecules also allow us to assess changes in orientation of the plane of the molecule relative to the force centres of the surface when unsymmetrical substituents are introduced into the benzene ring[146].

The alteration in the spectrum of acetylene and its derivatives on adsorption on aluminium oxide[101] suggests that the molecules of acetylene and methylacetylene are predominantly oriented towards the surface. Dimethylacetylene molecules are arranged parallel to the surface.

In setting up the partition functions, we must also take into account the change in the isomeric composition of adsorbed molecules. Thus Yoschino[150] showed from the intensities of the absorption bands that the relative proportions of the *cis* and *trans* forms of 1,2-dichloroethane and of the keto–enol isomers of acetylacetone are different in the adsorbed state from their proportions in the liquid state and in solution.

Spectroscopic data are of special importance in analysing the possible rotational motion of an adsorbed molecule relative to the adsorbent surface. Sheppard and Yates[61,140] studied the shapes of the absorption bands of methane and hydrogen adsorbed on porous glass with the aim of determining the rotational degrees of freedom of these molecules with respect to the surface. In the case of methane, the observed shape excludes the possibility of free rotation of the molecules about three mutually perpendicular axes. Whereas the shape of the ν_1 and ν_2 bands of adsorbed methane does not allow any conclusions to be reached concerning the restriction of the rotation of these molecules, the ν_3 band (triply degenerate asymmetric vibration of CH groups) is appreciably broader than the ν_1 band, and its shape is consistent with the hypothesis that methane molecules can rotate freely only about one axis. The shape of the ν_4 band (doubly degenerate CH stretching vibration) of CH_3Br molecules adsorbed on porous glass at room and low temperatures, and hence of the ν_3 band of the CH_4 molecule, has been shown[151] to be due solely to rotational motion of the molecules, and not to removal of degeneracy under the influence of the force field of the adsorbent. The change in the rotational structure of the absorption bands of CO_2 molecules on adsorption on Aerosil also provides evidence of the restriction of molecular rotation[41].

Considerably difficulties arise in the spectroscopic investigation of rotations of adsorbed molecules restricted by the existence on the adsorbent surface of potential barriers. Up to the present time it has proved possible to observe combined bands due to deformation vibrations and librations only in the case of water molecules adsorbed on a zeolite[117] and CsI[139] at high surface coverages. The

libration frequencies of the adsorbed water molecules in these cases are close to those of liquid water, and are evidently due to librations of water molecules associated together, not to their librations in the field of the absorbent.

Great uncertainty in calculations of the rotation component of the partition function arises also in determining the moments of inertia and the symmetry groups of adsorbed molecules. The appearance in the infra-red spectrum of absorption bands which are usually evident only in the Raman spectrum, observed in several cases [61,140,145,146], enables us to elucidate the change in symmetry resulting from the action of the force field of the adsorbent on the adsorbed molecule. Thus the appearance in the spectrum of methane adsorbed on porous glass of the 2899 cm^{-1} absorption band (Fig. 25), which is forbidden in the infra-red spectrum, indicates that the adsorbed molecule has symmetry C_{3v} or C_{2v} with respect to the surface, not T_d, which the methane molecule has in the gaseous state. The appearance in the spectrum of adsorbed ethylene of a band at 3010 cm^{-1}, which is absent from the infra-red spectrum, indicates a change in distribution of electron density in the molecule, as a result of which the symmetry of the molecule changes from V_h to C_{2v}, its principal plane being parallel to the surface of the adsorbent. Similarly, the appearance in the spectrum of hydrogen adsorbed on porous glass of the 4131 cm^{-1} band (Fig. 25), which does not occur in the infra-red spectrum, is evidence of a redistribution of charge in the molecule, resulting in a change in symmetry from $D_{\infty h}$ to C_{2v}.

A redistribution of electron density and a change in symmetry are indicated also by the appearance of the ν_5 band (3070 cm^{-1}) in the infra-red spectrum of ethylene adsorbed on porous glass [152], and of the ν_2 band (1950 cm^{-1}) in the spectrum of acetylene adsorbed on aluminium oxide [101]. These bands normally appear only in the Raman spectrum.

The vibration frequencies of adsorbed molecules relative to the surface lie in the inaccessible far infra-red region of the spectrum, and so far have not been investigated at all. Moreover, the vibrational bands of light

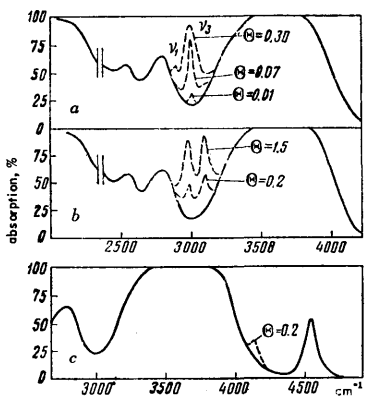


Fig. 25. Spectra of:
a) methane; *b*) ethylene; *c*) hydrogen, adsorbed on porous glass (broken curve: spectrum on adsorbed molecules; full curve: spectrum of porous glass; Θ: surface coverage) [61,140].

molecules, linked to the surface by weak van der Waals forces, are evidently very diffuse, and can barely be observed. The vibrational and rotational bands of heavy molecules, or of molecules linked to the surface by stronger bonds, such as hydrogen bonds, however, should be more clearly developed. Investigation of such vibrations and rotations is of great interest for the solution of thermodynamic problems. At the present time only a few papers on the thermodynamics of adsorption can be cited in which spectroscopic data are utilised. Kington [117,118] studied the infra-red spectra of water adsorbed in the channels of crystals of Linde zeolite type A, and concluded that the water molecule is attached to the surface of the channels by the formation of hydrogen bonds between the hydrogen atoms of the water and the oxygen atoms of the zeolite framework. The molecules are not as strongly held as in liquid water. In Kington's opinion this explains the higher value which he obtained for the specific heat of adsorbed water compared with that of liquid water†.

Kiselev and Lygin [155] attempted to use spectroscopic data to calculate the vibrational, rotational, and configurational entropies of water molecules adsorbed on hydrated silica surfaces. They considered two models, with a water molecule adsorbed on one and on two surface hydroxyl groups. Calculation of the vibrational entropy was based on the frequency of vibration along the hydrogen bond. The rotational entropy was calculated using models of a freely rotating molecule and a restricted rotor. The total calculated value was less than the experimental value, indicating the existence of other degrees of freedom of molecular motion which had not been taken into account, in particular, vibrations of the molecule parallel to the surface. The effect of non-uniformity of the surface on the configurational entropy must also be taken into account [156].

The change in spectrum of the surface hydroxyl groups of aerogel on adsorption of benzene and hexane [147] enabled a model of non-localised adsorption to be chosen for both cases. Calculated and experimental values of the decrease in entropy when half a monolayer is filled with benzene molecules are in satisfactory agreement if it is assumed that the adsorbed molecules possess mainly two-dimensional translational motion and free rotation in the plane of the ring. The entropy of adsorbed hexane considerably exceeds that of benzene, indicating the greater mobility of the adsorbed hexane molecules. This is consistent with spectroscopic and calorimetric data showing a stronger bond between benzene molecules and surface hydroxyls compared with hexane, and with theoretical estimates of the energy of this bond [26,28]. A complete analysis of the degrees of freedom of adsorbed hexane molecules cannot yet be carried out because of the absence of information on the restriction of internal rotations in the molecule on adsorption.

The examples which have been given provide evidence of the great possibilities of infra-red spectroscopy in the study of surface chemistry and molecular adsorption. However, these possibilities are often not fully utilised mainly owing to the absence of close links between spectroscopic and adsorption research. It is quite obvious that the problems which are now arising in the study of the properties of surface compounds and adsorption equilibria, as also the practical tasks of obtaining high-quality fillers or adsorbents

† High values for the specific heat of water, benzene, and hexane adsorbed on fine-pored silica gel having a hydrated surface have been obtained by Berezin *et al.* [153,154]

and supports for chromatography by the chemical synthesis of various compounds on their surface, can be solved only by combining spectroscopic and adsorption methods. It is also obvious that solution of these problems requires further improvement in the spectroscopic method, both by the development of new procedures for preparing specimens for investigation and by increasing the sensitivity and accuracy of determinations of the frequency, intensity, and shape of the absorption bands of adsorbate and adsorbent. It is also necessary to extend the investigations into the long-wavelength region of the spectrum, and to work systematically on the theoretical interpretation of the results of spectroscopic investigations of surface chemistry and adsorption. Combined use of the methods of infra-red spectroscopy and nuclear magnetic resonance will also provide great opportunities for studying the structure of surface chemical compounds and adsorption.

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EFFECTIVE CHARGES AND ELECTRONEGATIVITY

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1. INTRODUCTION

There are concepts which at a certain stage in the evolution of science are useful and progressive, but which in the course of time, with advances in theory and experiment, need revision and critical analysis, because their uncritical employment may become an obstacle to further development. In the present paper our attention will be directed to one such concept, that of electronegativity.

Pauling defines electronegativity as the ability of an atom in a molecule to attract electrons to itself. We are dealing here with the definition of "degree of ionic character" or, to give it a physical formulation, the effective charge on the atom, more exactly the distribution of electron density in the molecule.

Several formulae exist for estimating electronegativity. Pauling was the first to give an empirical formula which defines electronegativity:

$$|X_A - X_B| = 0.208\sqrt{\Delta}, \quad (1)$$

where

$$\Delta = D(A-B) - \tfrac{1}{2}[D(AA) + D(BB)]. \quad (2)$$

Here $X_A - X_B$ is the difference in electronegativity between the atoms A and B, and $D(AB)$, $D(AA)$, and $D(BB)$ are the dissociation energies of the molecules AB, A_2, and B_2. Pauling's formula is empirical and evidently cannot claim to have any theoretical foundation. For an approximate quantum-chemical description, we can set up a wave function of the molecule as a linear combination of functions representing the covalent state (AB), the ionic state with a positive charge on A and a negative charge on B (A^+B^-), and finally the ionic state with a positive charge on B and a negative charge on A (A^-B^+):

$$\psi = \alpha\psi(AB) + \beta\psi(A^+B^-) + \gamma\psi(A^-B^+), \quad (3)$$

where α, β, and γ are coefficients related to the contribution of the state. An attempt to interpret Pauling's formula leads merely to the postulate that the state A^+B^- increases the bonding energy.

The usefulness of this empirical formula is, of course, determined solely by the extent to which it reproduces the experimental results. But the question first arises as to whether the energy is increased by A^+B^- or by A^-B^+. An empirical formula is incapable of answering this question. For a molecule consisting of a "metallic" element A and a "non-metallic" element B, this question seems trivial, but in general it is not so simple. If we consider the CH bond, it follows from data on ionisation potentials and electron affinities that rupture into C^+ and H^- requires a smaller consumption of energy (323 kcal) than rupture into C^- and H^+ (368 kcal), although it is usually supposed that hydrogen forms the positive end of the CH dipole.

A rational definition of electronegativity was given by Mulliken. If the question is posed as to which requires the

smaller consumption of energy — the production of isolated A^+ and B^- ions (in their ground state), or of A^- and B^+ ions, from the separated atoms also in the ground state — the answer is plain. The ionisation potential I and the electron affinity F are the governing factors. Thus the sum $I + F$ may be a measure of electronegativity. But this is true only for isolated atoms and ions in their ground states. The situation is incomparably more complicated in the case of molecules, for it is necessary to know not simply the energy of conversion of an atom A into an ion A^+ in the ground state, but the energy of conversion into an ion having the same electronic configuration as the atom in the ionic state in the molecule. Thus in the ground state the Cl^+ ion has two unpaired electrons ($3p$), and $I = 13.01$ eV, but in the HCl molecule in its "ionic state", which combines with its singlet ground state $^1\Sigma$, Cl^+ should also be in a singlet state, so that the ionisation energy of chlorine must include the energy of excitation of the chlorine ion from the $3p$ to an unknown valence state. The quantity observed physically is the bonding energy, and the energy of the valence state is merely a term entering into the calculation of the bonding energy. Mulliken rightly pointed out the inapplicability of the usual values of I and F, but in effect provided nothing in exchange, since the energy of the valence state is not observed experimentally. Mulliken approximately equated this to the energy $\frac{1}{2}(^1D + {}^1S)$. The proposed empirical quantities for electronegativity cannot be linked with physically observable quantities, such as bonding energies, ionisation potentials, electron affinities, dipole moments, etc. The literature contains indications of a correlation between electronegativity and dipole moments, for example in the molecules HF, HCl, HBr, and HI. In general, however, atomic dipole moments due to lone electron pairs must be taken into account.

Different scales of electronegativity exist, but we shall not dwell on them, for we are interested in analysing the concept itself. The idea of electronegativity evidently originated from the fact that, thirty years ago, any bond was regarded as resulting roughly from the superposition of a covalent and an ionic bond. This was an attempt to regard any bond as in some way intermediate between two types, covalent (prototype H_2) and ionic (prototype, for example, LiF): the concept of electronegativity was assumed by its authors to give some idea of the distribution of electron density, more correctly of the asymmetry of the electron cloud associated with the bond, and an estimate of it by means of an empirical equation.

At the present time such a view of the chemical bond is too simple, and in most cases untenable. We must take into account, together with the possibility of two-centre localised molecular orbitals and ionic bonds, the further possibility of the presence of vacant orbitals, lone electron pairs, donor–acceptor and dative bonds, various types of hybridisation, the possibility of the formation of π complexes, delocalised bonds, which entails the necessity to consider the motion of many electrons in a many-centre field, etc. In the light of these possibilities, the concept of electronegativity oversimplifies the picture of a chemical bond except in a small number of comparatively simple cases. Although many papers have appeared on electronegativity, they are mainly trivial and do not add to our knowledge of the chemical bond. It is no wonder that the concept of electronegativity has been subjected to serious criticism by such eminent experts as Coulson, Moffitt, and others.

Analysis of the concept of electronegativity at the present time should not consist in the application of empirical and semiempirical formulae and their illustration by interatomic distances, energies, etc. The urgent need now is the physical investigation of effective charges. Theoretically an approach can be made to this question by quantum-mechanical calculations of the electron density matrix. But this approach does not hold out much immediate promise: it is a matter for the distant future. At the present time, therefore, the main task is to examine experimental methods for determining effective charges.

2. NUCLEAR QUADRUPOLE COUPLING

One method for determining effective charge is to measure nuclear quadrupole coupling constants. But unfortunately it is impossible to separate, by means of these data alone, the fraction depending on hybridisation from that depending on effective charge[1]. It is impossible to find two unknowns from one determination. For compounds of mixed type (for example with sp hybridisation), therefore, the ionic character of the bond is not determined unambiguously by measurements of the quadrupole coupling constant. Gordy and Townes find the degree of hybridisation by calculating the ionic character of the bond from specified electronegativities. And, conversely, by substituting the degree of hybridisation obtained from some indirect data, they calculate the effective charge. Thus this method is not sufficiently reliable.

3. X-RAY ABSORPTION SPECTRA

Interesting work in this field has been carried out by Barinskii[2,3], Vainshtein[4], and their collaborators. An X-ray quantum expels an electron from the K shell, the atom forming an ion having a charge of +1. The transition of the electron to successive energy levels produces absorption lines in the spectrum. If the atom is involved in a chemical bond and hence has an effective charge X (positive or negative), the resultant charge is $1 + x$ or $1 - x$. The theory of the phenomenon leads to the formulae

$$\varepsilon_n - \varepsilon_\infty = -\frac{e_1^2}{n^2}\,13.6 \text{ eV}, \tag{4}$$

$$\frac{\tau_n}{\tau_\infty} = \frac{4e_1^2 n^2 - 1}{\pi\Gamma n^5}, \tag{5}$$

where ϵ_∞ is the energy of transition of an electron to the limit of the continuous spectrum, ϵ_n the energy of transition of an electron to the np level of the system, τ the height of the n-th absorption line, τ_∞ the height of the continuous spectrum, Γ the width of the absorption lines and of the limit of the continuous spectrum, e_1 the effective charge on the K-ionised atom, in whose field the electron expelled from the K shell moves, and n the effective principal quantum number of the n-th energy level.

Table 1 gives some values found for the effective charge x. The experimental error is said to be 2–10% of the charge increased by unity, so that with a charge of 1.8 the error does not exceed 0.28 unit. The effective charge obtained characterises the physical distribution of charge between the central ion and the surrounding sheath of water molecules within a distance of the order of 1 Å from the nucleus of the central atom. The results indicate that, both in simple molecules of the type H_2S, HCl, and $GeBr_4$, and in complex ions and those of the type CrO_4^{2-}, the bond is predominantly covalent and the effective charges are small.

TABLE 1.

Compound	Atom	Effective charge	Compound	Atom	Effective charge
Gas H_2S	S	−0.1	$ZnSO_4 \cdot nH_2O$	Zn	+2
Gas HCl	Cl	−0.2	Solid $K_3Fe(CN)_6$	Fe	+1
Gas $GeBr_4$	Ge	+0.75	Solid $K_3Mn(CN)_6$	Mn	+0.9
Gas $GeBr_4$	Br	−0.15	$Mn(C_5H_5)_2$	Mn	1.5
Gas $ZnBr_2$	Zn	+0.5	$(C_5H_5)Mn(CO)_3$	Mn	+0.6
Gas $ZnBr_2$	Br	−0.24	$KOsO_3N$	Os	+1.0
Solid $Co(NO_3)_3$	Co	+1.2	K_2OsO_4	Os	+0.8
Solid $Cr(NH_3)_5 \cdot nH_2O$	Cr	1.2	$K_2Os(NO)Cl_5$	Os	+0.7
Cr^{2+}	Cr	1.9	K_2OsCl_6	Os	+0.8
Cr^{3+}	Cr	1.2	OsO_2	Os	+0.8
Solid K_2CrO_4	Cr	±0.1	Gas $Fe(CO)_5$	Fe	+0.4
Solid $Cr(CO)_6$	Cr	+0.4	Liquid $Fe(CO)_5$	Fe	+0.4

TABLE 2.

Compound	Effective charges in fractions of an elementary charge	
	on central atom	on one ring
$Fe(C_5H_5)_2$	+0.7	−0.35
$Fe(C_5H_5)_2^+$	+0.6	+0.2
$Co(C_5H_5)_2$	+0.2	−0.1
$Co(C_5H_5)_2^+$	0.0	+0.5
$Cr(C_6H_6)_2$	+1.5	−0.75
$Cr(C_6H_6)_2^+$	+1.4	−0.2
$V(C_5H_5)_2$	+1	−0.5
$Cr(C_5H_5)_2$	+1.7	−0.85

It is curious and paradoxical that "triply charged ions", for example Co in $Co(NO_3)_3$, have a smaller effective charge (1.2) than have "doubly charged ions", *e.g.* Co^{2+} (1.8). It may be that a so-called "triply charged" ion acts to a far greater extent as an acceptor into its vacant orbitals in relation to the surrounding molecules (ligands), and therefore the lone electron pairs of a ligand (for example H_2O) are very greatly displaced towards the central atom and considerably diminish its effective charge. The results show that not all the charge in complex ions is located on the central atom, but only part of it (sometimes an insignificant part), and hence that the total charge is to a considerable extent dispersed over all the ligands. In some ions the central atom forms practically entirely covalent bonds (CrO_4^{2-}). Therefore references in the literature to multicharged ions are evidently quite unjustified. This unsatisfactory description of the situation is a survival of the past (Kossel, Magnus, van Arkel), when chemists imagined the molecules and crystals as combinations of rigid charged spheres, without considering the magnitude of the effective charge. Modern physical methods enable us to revise these ideas. The data obtained show that the presence of covalent bonds must be taken into account in discussing some complex ions. Electron paramagnetic resonance data and spectroscopic and magnetic properties (g factor, Δ splitting, λ) lead to consistent results if each of the two unpaired electrons in the $Ni(H_2O)_6^{2+}$ ion has a probability of 0.69 of being on the nickel atom and a probability of 0.051 of being on a particular water molecule[5]. In other words, the charge is dispersed over all the atoms in the ion.

Considerable interest attaches to the question of the effective charges in the recently synthesised compounds with new types of bonds, namely in the aromatic complexes of metals. Shustorovich and Dyatkina[6] used the molecular orbital method, the most suitable for molecules of sandwich structure, in their calculations. The effective charges are determined in this method as the normalised sums of squares of the coefficients of the atomic orbitals of a given atom in all the occupied molecular orbitals (the non-orthogonality of the orbitals of the central atom and the ligands being neglected). Calculations were made for neutral molecules and for the corresponding ions with the results shown in Table 2.

Experimental data, obtained from the structure of the K edges of the X-ray absorption spectra, are available for ferrocene and the ferricinium ion. Vainshtein *et al.*[4] found a value of +0.7 for both these compounds, in good agreement with theory. The calculations were published before the experimental check was undertaken. Barinskii's calculations[2,3] based on published experimental data led to the following effective charges on the metal atoms: dibenzenechromium +1.1, cobalticene +0.4, +0.5, and the cobalticinium ion +0.5, +0.6. Thus neutral compounds of this type have a positive charge, varying from metal to metal, on the central atom. It is particularly interesting that the charge on the metal atom does not change during ionisation, for example on passing from ferrocene to the ferricinium ion, as is shown by theory and confirmed by experiment. This implies that the electron is removed from the rings on ionisation. Since the rings bear small effective negative charges in the neutral molecule, the ligands readily lose an electron. In the ion the total charge becomes dispersed over the whole molecule, which is more efficient than localisation of the whole charge on the metal. The positive charge increases from +1 with vanadium to +1.7 with chromium and +2 with manganese, the last giving ionic manganocene $Mn(C_5H_5)_2$ with five unpaired electrons. Such a large charge with manganese probably arises from a gain in energy of the d^5 shell. The presence of a large effective charge, equal to the nominal charge, is characteristic of those molecules in which there are additional conditions for the internal stabilisation of the ion.

4. ATOMIC POLARISATION

It is well known that with several crystals of the NaCl type and others the static, low-frequency dielectric constant ϵ_s is considerably greater than the square of the refractive index n^2. In ionic crystals the difference

$$\Delta\varepsilon = \varepsilon_s - n^2, \tag{6}$$

relating to atomic polarisation is due to the relative displacement of ions of opposite sign, and also to deformation of the electron shells owing to the relative motion of the ions. The characteristic frequencies of displacement of the ions lie in the infra-red range. These shifts contribute a considerable fraction of the static dielectric constant. The ratio of the characteristic frequency of the lengthwise ω_e to the transverse ω_t vibrations is $(\epsilon_s/n^2)^{\frac{1}{2}}$. The relation between $\Delta\epsilon$ and the macroscopic charge was found by Born on the assumption that the ions are not deformed and do not overlap. This theory was subsequently improved by Szigeti[7], who derived the following equation for $\Delta\epsilon$:

$$\Delta\varepsilon = \left(\frac{n^2+2}{3}\right)^2 \frac{2\pi e_1^2}{\omega_t a^3 m}, \tag{7}$$

where e_1 is the effective charge on the ion, a the interionic

distance (2.81×10^{-8} for NaCl), and m the reduced mass. In the derivation of this equation it is assumed that electrostatic forces act between charges e_1 in the lattice, and that the charges of neighbouring ions do not overlap. A ratio $e_1/e < 1$, where e is the elementary charge (4.8×10^{-10}), can be interpreted as due to the superposition of covalent forces. Eqn. (7) enables us to determine the effective charge e_1, since the remaining quantities in the equation are known from experiment. Szigeti showed also that the compressibility K is linked with ϵ_s by the relation

$$\frac{1}{K} = \frac{\epsilon_s + 2}{6(n^2+2)} \frac{m\omega_t^2}{a}. \qquad (8)$$

Table 3 gives values of effective charges[8,9] in fractions of an elementary charge for the most reliable cases, in which K_{calc}/K_{exp} is close to unity. The last column indicates differences in electronegativity ΔX on the Little and Jones scale[10].

Table 3 shows that: (1) the lattices of ordinary binary salts A^IB^{VII} are mainly ionic; (2) even in these salts the effective charges are considerably diminished (by 13–31%) compared with the elementary charge (4.8×10^{-10}); (3) there is in general a qualitative correlation between ΔX and e_1/e. The effective charges in crystals of binary salts of the NaCl type are greater than in the gaseous molecules. The presence of considerable effective charges (even though less than unity) explains the dimerisation of the gaseous molecules. It is curious that, although the effective charges in these substances are reduced (to 69%), the lattice energies calculated by Born's method for single charges agree well with experiment. Thus the energy is not really so sensitive to the magnitude of the effective charge.

In connection with the nature of the chemical bond in semiconductor crystals, it is interesting that compounds of the type $A^{III}B^V$ have three valence electrons on each of the A and B atoms, which give ordinary covalent bonds. In addition, the A atom is an acceptor by virtue of its vacant p orbital, and the B atom a donor owing to its lone pair of s^2 electrons. This is a case of sp^3 hybridisation, and the lattices of these compounds are of the diamond type. The circular infra-red dispersion frequencies have been measured[11], *i.e.* the lattice vibrations for transverse ω_t and longitudinal vibrations ω_e. The effective charges are related to these vibrations as follows:

$$e_1 = \omega_t \left(\frac{\epsilon_s - \epsilon_\infty}{4\pi}\right)\left(\frac{3}{\epsilon_\infty + 2}\right)(mv)^{1/2}, \dagger \qquad (9)$$

TABLE 3.

Compound	ϵ_s	n^2	$\frac{K_{calc}}{K_{exp}}$	$\frac{e_1}{e}$	ΔX
LiF	9.27	1.92	1.0	0.87	3.13
NaCl	5.62	2.25	0.99	0.74	1.82
NaI	6.6	2.91	1.05	0.71	1.20
KCl	4.68	2.13	0.96	0.80	1.92
KI	4.94	2.69	0.99	0.69	1.30

† According to Ref. 11 the first term in brackets should be to the power ½ (Ed. of Translation).

where v is the volume of the unit cell, and ϵ_∞ the optical, high-frequency, and ϵ_s the static, low-frequency dielectric constant.

Table 4 gives the relevant data on effective charges e_1/e and widths of the forbidden gap ΔE in eV.

These data are interesting, since they give an idea of the effective charges arising in the formation of donor–acceptor bonds. Table 4 shows that there is no correspondence between effective charges and the difference in electronegativity. The elements of Group V are generally more electronegative than those of Group III. Since, however, the former are donors, while the latter are acceptors, the result is that the more electronegative atom receives an additional positive charge on interaction, while the more electropositive atom gains a negative charge‡. Further, with nitrogen, phosphorus, and arsenic it is the $2s^2$, $3s^2$, and $4s^2$ electrons respectively which confer donor properties. And although the ionisation potentials characteristic of the removal of the outer p electron fall, the excitation due to the peripheral s electrons and the corresponding ionisation potentials of these s electrons increase, as can be seen from Table 5, compiled from spectroscopic data[12].

Thus the donor properties associated with the ns^2 electrons decrease with increase in n. This is explained by the d subgroup of electrons strengthening the bonding of the

TABLE 4.

Compound	$10^{-13}\omega_t$, sec^{-1}	$10^{-13}\omega_e$, sec^{-1}	$\frac{e_1}{e}$	ΔE, eV
AlSb	5.92	6.32	0.48	1.5
GaAs	5.04	5.35	0.43	1.1
GaSb	4.25	4.40	0.30	0.7
InP	5.74	6.38	0.60	1.25
InAs	3.95	4.38	0.56	0.33
InSb	3.28	3.46	0.34	0.18

TABLE 5.

Element	Electronic configuration of atom	Electronic configuration of ion	Energy required to remove an electron, eV	Difference
N	$2s^22p^3$	$\rightarrow N^+2s^22p^2$	14.54	5.76
N	$2s^22p^3$	$\rightarrow N^+2s2p^3$	20.3	
P	$3s^23p^3$	$\rightarrow P^+3s^23p^2$	11	6.5
P	$3s^23p^3$	$\rightarrow P^+3s3p^3$	17.5	
As	$4s^24p^3$	$\rightarrow As^+4s^24p^2$	9.81	9.14
As	$4s^24p^3$	$\rightarrow As^+4s4p^3$	18.95	

‡ Arsenic as an impurity in silicon is an electron donor, and produces n-type conduction. Conversely, aluminium added to silicon is an acceptor, since it captures an electron from the valence band, creating a positive hole in the latter, which produces p-type conduction. It is easily seen that these facts do not fit into the framework of the so-called electronegativities (As 2.20, Si 1.74, and Al 1.47).

former electrons in their shell. Correspondingly the ionisation potentials of K, Rb, and Cs are less than those of Cu, Ag, and Au. This effect is reflected in a decrease in the effective charges in the sequence InP, InAs. Quantum-mechanical calculations[13] for the compounds $A^{I}B^{VII}$ (CuCl), $A^{II}B^{VI}$ (ZnS), and $A^{III}B^{V}$ (GaAs) give values of 0.4–0.6 for the effective charges, although zinc, for example, is usually regarded as a doubly charged ion.

According to Burstein the effective charge in PbS is 0.8. In coordination lattices a rise in temperature can diminish the role of the covalent bond and increase that of the ionic bond. Accordingly solid InSb has a diamond lattice ($r = 2.8 \times 10^{-8}$) with a covalent sp^3 state; fusion at 540° results in a liquid having a short-range order corresponding to an NaCl type of lattice[14] ($r = 3.17 \times 10^{-8}$).

The attempt of some authors to find a correlation between the difference in electronegativity and the width of the forbidden gap in semiconductors is unsuccessful if the whole (not a selection) of the experimental results are taken into account.

It follows from data on the low- and high-frequency dielectric constants of CdTe that the effective charge is close to zero, whereas the width of the forbidden gap ΔE is 1.5 eV, and $\Delta X = 0.55$. With the same value (0.5) for ΔX, however, ΔE for PbTe is 0.63. With CuBr $\Delta X = 1$, while $\Delta E = 5$. In CdS, with the same $\Delta X = 1$, $\Delta E = 2.1$; while in PbS, with $\Delta X = 0.9$, $\Delta E = 1.17$. If CdS and ZnO are compared, the values of ΔE are very similar (2.1 and 2.2 eV), while those of ΔX differ by a factor of 2 (1 and 2). ZnSe and PbS show similar values of ΔX (0.8 and 0.9), while those of ΔE are 2.8 and 1.17. These inconsistencies are not surprising, since electronegativity is not a quantity which can be given a definite physical meaning. The search for a correlation between ΔX and ΔE is therefore without justification.

Few data are available on the determination of effective charges in molecular lattices. An important result was obtained by Yakshin *et al.*[15], who studied the refractions at different wavelengths and the dielectric constants of tetrahalides of Group IV elements — CCl_4, $SiCl_4$, $TiCl_4$, $GeCl_4$, $SnCl_4$, $SiBr_4$, $GeBr_4$, and $SnBr_4$. They determined the total polarisation P and the electron polarisation P_{el}, and hence found the atomic polarisation P_{at}. In the case of an oscillator P_{at} is connected with the effective charge e_1 by the following relation[16]:

$$P_{at} = \frac{Ne_1^2}{9\pi m_1(\nu_1^2 - \nu^2)}, \qquad (10)$$

where ν_1 is the natural vibrational frequency of the effective mass m, and ν the frequency of the deforming field. If f_1 is the corresponding force constant and $\nu_1 = (2\pi)^{-1} \times (f_1/m_1)^{\frac{1}{2}}$, and if $\nu < \nu_1$, then

$$P_{at} = \frac{4\pi}{9}\frac{e_1^2}{f_1}. \qquad (11)$$

For vibrations along a bond of length l, $e = d\mu/dl$. In the molecules HCl, HBr, CO, CO_2, and NH_3, $e_1/e < 0.2$ and $P_{at} \simeq 0.1$ cm³, but in several crystalline substances P_{at} can reach large values. Thus in Magnus' green salt $[Pt(NH_3)_4]\cdot[PtCl_4]$, which contains a Pt–Pt bond of length 3.25 Å, $P_{at} \simeq 55$ cm³ according to Baranova's data[17].

TABLE 6.

Compound	P	P_{el}	P_{at}	e_1/e	ΔX
CCl_4	28.03	25.75	2.28	0.3	0.33
$SiCl_4$	32.00	27.79	4.21	0.286	1.09
$TiCl_4$	40.49	35.51	4.98	0.251	1.51
$GeCl_4$	36.60	30.60	6.00	0.305	0.81
$SnCl_4$	46.83	33.76	13.07	0.351	1.11
$SiBr_4$	45.20	39.19	6.01	0.309	1.00
$GeBr_4$	49.78	42.43	7.35	0.294	0.72
$SnBr_4$	54.94	45.99	8.95	0.268	1.02

For compounds of the type AX_4 theory gives[18]

$$P_{at} = \frac{16\pi N}{9}\frac{\mu^2}{f_\delta} + \frac{16\pi N}{9}\frac{e_1^2}{f}, \qquad (12)$$

where μ is the moment of the bond, f_δ and f are the respective force constants for bending and stretching, and the effective charge is defined as the differential of the dipole moment with respect to bond length. We finally obtain the equation

$$e_1 = \sqrt{\frac{9}{16\pi N}\left(\frac{P_{at}}{\frac{1}{f_\delta}\frac{1}{l^2} + \frac{1}{f}}\right)}. \qquad (13)$$

Table 6 gives values obtained in the above work. The last column gives the electronegativity differences for the corresponding atoms.

It can be seen that the moment of the C–Cl bond in CCl_4 is 0.63 D, which is considerably lower than in CH_3Cl, for example. Although the above results are based on a rough calculation, the observed variation is interesting and instructive. The effective charges fall on passing from CCl_4 to $SiCl_4$ and $TiCl_4$, although ΔX increases. This of course, contradicts the usual ideas on the ionic nature of the bond and on electronegativity, but nevertheless it is quite in order. In contrast to carbon, which contains no d orbitals of similar energy, silicon possesses close-lying $3d$ orbitals. This means that Si can act as an acceptor by virtue of its $3d$ orbitals, owing to which its effective charge may be diminished. This is still more characteristic of Ti, which has three vacant d orbitals. This phenomenon is associated with an important difference between silicon and carbon compounds. Carbon is the only element in the Periodic System in which the valence state comprises four orbitals each containing one electron, and neither vacant orbitals nor orbitals containing an unshared pair of electrons remain. This is thus the classical example of a quadrivalent element, which explains the unique position of carbon among other elements. With silicon a $3d$ orbital lies close to the $3s$ and $3p$ orbitals, resulting in the new valence possibilities reported recently. It will be shown below that Ti possesses a still greater tendency to accept electrons into its vacant orbitals. As can be seen from Table 6, there is no correspondence between the variation of electronegativity and the effective charges in $GeBr_4$ and $SnBr_4$.

5. DIPOLE MOMENTS

Dipole moments are often used in estimating effective charges and electronegativities. The effective charges are sometimes determined from the ratio of the moment of

the bond to the product of the elementary charge and the length of the bond. Theoretically, however, this is incorrect. Dipole moments do not give a direct indication of the magnitude of the effective charge for a number of reasons, primarily because the observed moment includes not only the bond moments but also the moments of the atoms themselves, resulting in particular from their lone pairs of electrons. The N–F bond has a moment of 0.18 D (from data on NF_3), while that of the N–H bond is 1.5 D, although the electronegativity differences are very similar in the two cases (1.03 and 0.97). The moment of the N–F bond itself is evidently considerably larger, but is opposed by the moment of the nitrogen atom due to its $2s^2$ electrons. In general, a single definite dipole moment cannot be assigned to a bond A–B. The dipole moment depends on the valence state, hybridisation, and the other bonds of a given atom. The C–Cl bond has different moments in CCl_4 and in CH_3Cl. This is a further demonstration that a definite electronegativity cannot in general be assigned to an atom irrespective of the bond or of the electronic behaviour of the atom in its given state of hybridisation. The ethynyl halides have the following dipole moments:

$CH{\equiv}CF$ 0.75×10^{-18},
$CH{\equiv}CCl$ 0.44×10^{-18},
$CH{\equiv}CBr$ 0.0.

In these compounds the moments are lower than those of C–X in the sp^3 state of carbon evidently because the halogens are characterised not only by a positive electron affinity but also by their capacity to act as electron donors, as in $PdCl_2$ and other compounds. Thus fluorine would appear to be a strongly electronegative atom, but we must bear in mind its possible electropositive character, exhibited in the donor properties associated with its three lone pairs of electrons. These donor properties are developed still more clearly in chlorine and bromine. If it were possible to isolate ethynyl iodide, the positive end of its dipole might be expected to lie close to the iodine. The large moment of CH_3Cl arises because in this molecule chlorine cannot act as a donor, whereas in ethynyl chloride it may have a partly double-bond character. We are not completely sure of the direction of the moment in the C–H bond (in the sp^3 state). The urge to set up an additive scheme of dipole moments has recently led to an attempt to represent those of C–H bonds as a function of their hybridisation[19]:

CH (sp^3) ~ 0.3D,
CH (sp^2) ~ 0.68,
CH (sp) ~ 1.0,
CH in HCN ~1.13,
CH in CH ≡ CH ~ 1.05 (from infra-red spectra).

In exactly the same way, the following moments have been suggested for C–C bond:

$C^+sp^3 - C^-sp^2$ 0.68,
$C^+sp^2 - C^-sp$ 1.15,
$C^+sp^3 - C^-sp$ 1.48.

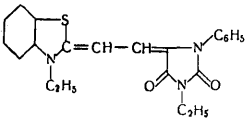
Experiment shows[20], however, that it is impossible by means of these six bond moments to reproduce the dipole moments even of hydrocarbons containing no bonds other than C–C and C–H. Thus for the difference in electronegativity between carbon (2.5) and hydrogen (2.1) the moments can vary from 0.3 to 1.0, and there is no certainty that the more electronegative atom carries the negative charge (in CH_4). Table 7 gives values of the moments of compound of the type XCY_3 obtained experimentally and calculated from the vector sums.

TABLE 7.

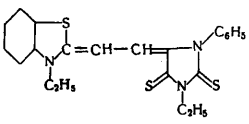
Compound	Experimental moment	Moment from vector sum
CIF_3	0.92	0.22
$CBrF_3$	0.65	0.03
$CClF_3$	0.46	0.05

The deviations from the vector sum evidently depend on the positive double-bond character of the halogens ($I^+ = CF_2F^-$), which increases from chlorine to iodine. This is most clearly shown in the halogenopolynitroalkanes[21]. The moment of nitroform $CH(NO_2)_3$ is 2.71 D. Replacement of the hydrogen by iodine should apparently result in a lower moment, since the halogen usually forms the negative end of the dipole in a C–Hal bond. But the moment of $IC(NO_2)_3$ proves to be 3.79 D, which considerably exceeds that of nitroform. Here the iodine evidently forms the positive end of the dipole owing to its double-bond character and the partly "nitrite" state of the nitro-group. This is confirmed by specific properties of compounds of the type $HalC(NO_2)_3$, such as their ability to hydrolyse with the formation of "hypohalous" acids, to oxidise hydrazine and KI, and to be reduced at a mercury electrode. The ease of these reactions increases from $ClC(NO_2)_3$ through $BrC(NO_2)_3$ to $IC(NO_2)_3$. It follows from these results that in the chlorine derivative the moment of the C–Cl bond is small with the negative charge on the chlorine, in $BrC(NO_2)_3$ the bromine probably already carries a slight positive charge, while in $IC(NO_2)_3$ there is now a considerable positive effective charge on the iodine.

On the usual electronegativity scale oxygen is considerably more electronegative (3.5) than sulphur (2.44). This would appear to be consistent with the fact that sulphur yields sulphonium $-\overset{+}{S}<$ compounds more readily than oxygen gives oxonium derivatives, which (apart from H_3O^+) are very unstable. Thus from the ionisation potential and the electron affinity sulphur should be the more electropositive, but if sulphur and oxygen are conjugated with such a powerful donor atom as nitrogen, the sulphur becomes the more electronegative, since its electron affinity is greater than that of oxygen (47 and 35 kcal). This is evident from the dipole moments of the compounds

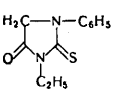


$\mu = 5.54$ D,



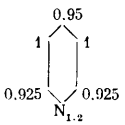
$\mu = 8.83$ D.

These molecules are similar in structure, differing only in the replacement of oxygen by sulphur. Conjugation is achieved in both molecules *via* identical bond systems, and the partly 'onium nitrogen is positive. Conjugation is a decisive factor in these molecules, because



for example, has a considerably lower dipole moment (2.34 D). The two intermediate benzothiazole derivatives in which the five-membered ring contains one oxygen and one sulphur atom have identical moments of 7.35 D. Since the three nitrogen atoms suppress the donor properties of the sulphur atoms, the electron affinity becomes the dominant factor in the latter, leading to a reversal of the electronegativity order.

The question of the significance of electronegativity arises especially in systems having conjugated bonds in which all the electrons must be regarded as in the field of all the nuclei. Five-, six-, and seven-membered rings are known to contain three bonding orbitals for six electrons. That is why the same atom may, depending on the conditions, bear a positive charge in some molecules and a negative charge in others. In the pyridine molecule six electrons move in the field of six nuclei, not counting the lone pair of $2s^2$ electrons on the nitrogen. The electron density is higher on the nitrogen atom, which in fact forms the negative end of the dipole. According to quantum-mechanical calculations the charge distribution is as follows:



The opposite situation occurs in the pyrrole molecule (μ = 1.8 D). Here the six electrons are in the field of five nuclei, but this sextet now includes the unshared electrons of the nitrogen. Hence the latter move only partly in the field of their own nucleus and partly belong to the four other centres. An approximate quantum-mechanical examination shows that the electron density is fairly uniformly distributed. This creates a deficiency of electrons on the nitrogen, which in this molecule forms the positive end of the dipole. The above examples show the possibility of a reversal of the dipole moment and hence of the electronegativity. This is confirmed by experimental data on the dipole moments of pyrrole derivatives and also on the acid–base properties. Whereas pyridine is a base, pyrrole is a weak acid. The basic dissociation constant of the latter is so low that it has not yet proved possible to determine it. Pyridine and pyrrole are examples of compounds in which nitrogen can produce basic and acidic properties. The biological function of nitrogen as an element giving rise to bases and acids may perhaps be associated with this in some cases.

In ordinary binary gaseous molecules of the NaCl type the dipole moment is large and quite close to the product of the charge and the bond length. But even in this case the picture is not really so clear as it appears to be in the primitive view of electronegativity. The dipole moment of CsCl [22] is 7.88 ± 0.17 instead of 11.23 (4.8 × 2.34) D. It is interesting that the bond length is less in CsF (2.34 Å) than in CsH (2.49 Å). It is possible that the CsF molecule has partial double-bond character, which is impossible in caesium hydride.

6. VACANT ORBITALS AND LONE ELECTRON PAIRS

It follows then that the view of a bond as the superposition of one covalent (electron pair in the field of two nuclei) and one ionic state is too rough a simplification. All the valence possibilities must be taken into account in bonds: (1) formation of molecular orbitals by unpaired electrons: (2) utilisation of the vacant orbitals of some atoms and of lone pairs of others; (3) the presence of many-centre orbitals (all the electrons in the field of all the nuclei); (4) the specific character of the given hybridisation; and (5) the participation of *d* orbitals and dative bonds. In conformity with this, the same atom in a given bond can act simultaneously both as a donor and as an acceptor, *i.e.* as both an electropositive and an electronegative atom.

It is useful to compare from this point of view elements of the Second and Third Periods. With the former, having a principal quantum number of 2, *d* orbitals are impossible, or more precisely a transition to 3*d* orbitals is possible only with a very great excitation energy which is not available in chemical compounds. With elements of the Third Period, however, 3*d* orbitals, which do not greatly differ in energy from 3*p* orbitals, are available. Published data show that the electron affinity is greater with elements of the Third than with similar elements of the Second Period [23] (see Table 8). The most reliable of the data in Table 8 are those for C, Si, O, F, Cl, and S.

A consideration of even beryllium on the basis of a superposition of an ordinary covalent bond ($2s2p$) and an ionic bond is clearly inadequate. A very characteristic feature of the chemical behaviour of beryllium is the presence of two vacant *p*-orbitals. Hence the dimerisation of $BeCl_2$, the polymerisation of $Be(CH_3)_2$, etc. In other words, Be is characterised by acceptor properties. Both beryllium and other elements in Group II exhibit acceptor properties with respect to oxygen. The attempt to represent ZnO as a lattice composed of Zn^{2+} and O^{2-}, and ZnS as consisting of Zn^{2+} and S^{2-}, is evidently mistaken [24]. Oxygen has an affinity for one electron of 35 kcal and yields a stable O^- ion. The energy of the oxygen–electron system is represented by the usual type of potential curve with a minimum. But the affinity for a second electron with formation of O^{2-} is characterised by a curve showing merely repulsion at all distances. An endothermic heat of this reaction can be found in the literature (~200 kcal). This is a fictitious quantity, resulting from calculations based on the assumption that in lattices of the MO type the M is a doubly charged positive ion, and the oxygen a doubly charged negative ion. In effect that value of the energy of formation of O^{2-} is calculated which would be necessary for the energy of the hypothetical ionic lattice to agree with the heat of formation of the MO crystal. In other words, an *ad hoc* hypothesis is put forward, an arbitrary calculation is made, then the hypothesis is forgotten, the lattice begins to be regarded as ionic, oxygen with two negative charges begins to be regarded as real, and the affinity of oxygen for two

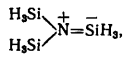
TABLE 8.

Element	Electron affinity, eV	Element	Electron affinity, eV
Li	0.5	Na	0.7
B	0.3	Al	0.4
C	1.13	Si	1.9
N	0.2	P	0.8
O	1.48	S	2.07
F	3.62	Cl	3.82

electrons and the "size of the O^{2-} ion" begin to make their way from book to book as a real affinity and a real ionic dimension. The quantities obtained in this calculation have a considerable scatter. The effective charges (~0.4 for ZnO and 0.96 for ZnS) show that multicharged elementary ions evidently do not exist. The situation is different in complex or polyatomic ions, since the total charge is then dispersed over many atoms (for example $PtCl_4^{2-}$).

Elements of Group III are characterised by acceptor properties due to the presence of a vacant *p* orbital. Hence the dimerisation of $AlCl_3$, in which, in spite of the great electronegativity of chlorine compared with aluminium, the bridge chlorine donates its lone pairs of 3*p* electrons to the vacant 3*p* orbital of aluminium. Compounds of these elements are characterised by three-centre orbitals with an electron deficit, of the type of $Al_2(CH_3)_6$ for example[25,26]. This also explains the specific character of the boron hydrides, in which the coordination number of boron reaches six.

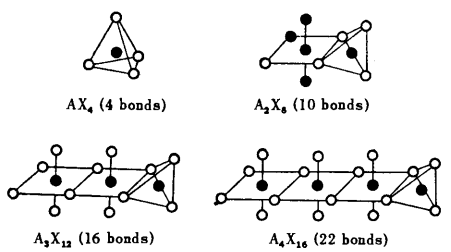
Group IV shows the striking difference in properties between CO_2 and SiO_2. Whereas CO_2 gives a molecular lattice and has a triple point at -56.6°, SiO_2 melts at 1600°–1700°. What is the reason for such a difference between two neighbouring elements in the Group? The important point is that silicon contains a low-lying 3*d* orbital, so that this element can act as an acceptor by virtue of its *d* orbitals, which is impossible for carbon, since with a principal quantum number of 2 the *d* orbitals do not exist, while excitation to 3*s* orbitals requires a very large amount of energy in the case of carbon. In several organosilicon molecules the silicon forms the negative end of the dipole, especially in the case of conjugated systems, when the positive charge may be delocalised, for example in aromatic compounds of silicon[27]. Whereas the C–O–C angle in ethers is 105°, close to the tetrahedral value, the Si–O–Si angle is about 150°, for example in $H_3Si–O–SiH_3$. This is characteristic also of silicates, in which the Si–O–Si angle (for example in SiO_2) is 142° or above§. The $N(CH_3)_3$ molecule is pyramidal, as is to be expected with nitrogen, which forms three bonds with its 2*p*-electrons; the $N(SiH_3)_3$ molecule is planar, for in it we must now reckon with conjugation of the type



corresponding to sp^2 hybridisation of the nitrogen. Hence $N(SiH_3)_3$ is a far weaker base than $N(CH_3)_3$. This ability to act as an acceptor is still more inherent in titanium, which has five vacant *d* and *p* orbitals (in the d^2sp state). This is the reason for the tendency shown by compounds of the type $Si(OR)_4$ and $Ti(OR)_4$ to dimerisation and polymerisation.

§ The fact that the Si — O — Si angle in silicates is considerably greater than the tetrahedral angle (~140°) cannot be explained by the repulsion of Si^{4+} ions, primarily because ions of silicon with four positive charges do not exist in lattices, and also because the tetrahedral angle is preserved in other cases of pure sp^3 hybridisation. Consequently the explanation must not be sought in the hypothesis that the silicon–oxygen chains are readily distorted and supposedly adjust themselves to the cations of a crystal lattice, but in the increased multiplicity of the Si–O bond due to the vacant 3*d* orbitals of the silicon and the donor properties of the oxygen. This is also the reason for the increase in the angle in organosilicon molecules containing Si–O–Si links.

Owing to their vacant orbitals, silicon and titanium are able to raise their coordination number from four to six (transition from a tetrahedron to an octahedron) if their immediate neighbour can donate lone pairs of electrons. On polymerisation the tetrahedra in a compound $A(OR)_4$ are converted into octahedra with a common edge. One tetrahedron remains at the end of the chain, two of its corners at the same time forming an edge of an octahedron. The total number of bonds in *n* isolated molecules is $4n$, whereas on polymerisation $6n-2$ bonds are formed. Thus the number of bonds increases by $2n-2$. Thus two tetrahedral molecules yield an octahedron–tetrahedron, three yield two linked octahedra and a tetrahedron, etc. (see diagram). The physical meaning of such polymerisation [for example in colloidal $Si(OR)_4$] is that the central atom by means of its vacant orbitals forms six instead of four bonds, while the oxygen atoms link two central atoms and one radical by means of their lone pairs. The mean energy of a Ti–Cl bond in the $TiCl_4$ molecule is 102.6 kcal, or 107.2 kcal allowing for the valence state, whereas according to Pauling it should be 85 kcal.[28] This increase in energy, which is not allowed for by Pauling's formula, is explained by the appearance of additional bonds due to the vacant orbitals and lone pairs. Thus although the electronegativity of titanium is nominally lower than that of carbon (1.32 and 2.5), titanium nevertheless attracts electrons more strongly to itself. The reason is that the nominal electronegativity takes no account of the acceptor properties of the element, and therefore cannot characterise it, except in very rare cases. As an example, Table 9 gives several cases of marked discrepancies between experimental bonding energies and those calculated from electronegativities.

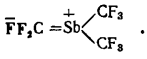


In exactly the same way phosphorus in Group V is less electronegative than nitrogen (2.06 and 3.07), but nitrogen yields only NCl_3, while phosphorus gives PCl_3, PCl_5, and the octahedral ion PCl_6^-: *i.e.* it forms bonds by means of

TABLE 9.

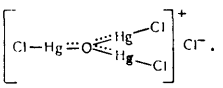
Bond	Energy of bond from electronegativity, kcal	Expt. energy of bond, kcal
NCl	76	115
MnBr	103	58
MnI	79	28
FeCl	82	69
CuF	148	69
HgF	273	140
MnF	224	81

3*d* orbitals. In the $Sb(CH_3)_3$ molecule antimony can exhibit donor properties, but in $Sb(CF_3)_3$ these properties are strongly repressed owing to the state



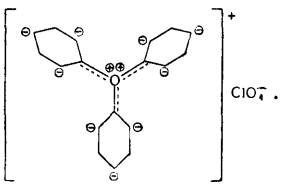
In Group VI of the Periodic System oxygen is regarded as the most electronegative element. Nevertheless, it forms compounds in which it donates its two lone pairs of $2s^2$ and $2p^2$ electrons. It is true that oxonium compounds, in which only one lone pair of electrons is donated, are usually unstable. The only exception is the stable oxonium ion H_3O^+. Products of the addition of acids of the type of HCl to ethers are not oxonium but molecular compounds, owing their existence to a hydrogen bond[29]. The bonding energy then varies from 4 kcal with ordinary ethers [for example $(CH_3)_2O$] to 11 kcal with tetrahydrofuran. Even in the case of three-membered rings, which, as might be expected, are able to exist as positive ions, for example diphenylcyclopropenone, interaction with HCl is confined to the formation of a hydrogen bond[30]. Meerwein compounds of the type R_3OCl are very unstable and are readily hydrolysed. But the situation is quite different when oxygen forms two donor bonds apart from those due to the two unpaired electrons. Utilisation of all its $2s^22p^4$ electrons in bond formation is possible if the neighbouring atoms (1) possess electron affinity, (2) have vacant orbitals, *i.e.* are capable of acting as acceptors, and (3) have charges which can be delocalised, *i.e.* which can stabilise the molecule. Three types of oxonium compounds are then possible[31]. In the *first case* the oxygen forms bonds with four neighbours (sp^3 hybridisation) tetrahedrally, by means of two unpaired electrons and two lone pairs. In the *second case* the oxygen in the sp^2 state has three neighbours in a plane (angle 120°) and forms three σ bonds and one π bond. A cation then results, the odd electron passing to an atom or a group of atoms possessing electron affinity (for example Cl^-, ClO_4^-). Delocalisation of the charge contributes to the stability of the resulting ion. In the *third case* the oxygen is combined with two atoms in the *sp* state (angle 180°) and forms two σ and two π bonds. The first case is represented in the lattices of BeO, PtO, PdO, etc. In BeO the oxygen has tetrahedral coordination with very stable bonds (m.p. 2530°) in which all bonding possibilities are utilised, namely the $2s^2$ electrons of the beryllium, the $2s^2$ and $2p^4$ electrons of the oxygen, and the two vacant orbitals of the beryllium. The same is characteristic of ZnO also. In PtO the oxygen forms an irregular tetrahedron (sp^3), and the platinum a planar rectangle (dsp^2). A tetrahedral configuration is determined not by the "radius" of O^{2-} but by the appropriate hybrid state of the oxygen.

The second case occurs, for example, in the Hg_3OCl_4 lattice (incorrectly written $HgO.2HgCl_2$). The structure of this substance[32,33] is



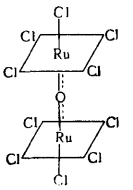
In this compound oxygen forms three coplanar bonds at angles of 120°. Mercury forms two *sp* bonds at an angle of 175°–180° with partial double-bond character delocalised among three atoms, and one chloride ions is outside the complex. Another example of compounds of this type is apparently provided by the triphenyloxonium compounds $[(C_6H_5)_3O]^+ClO_4^-$ prepared by Nesmeyanov and Tolstaya[34].

In contrast to the Meerwein trialkyloxonium compounds, they are extremely stable. Their structure can be represented as follows:



If our hypothesis about this structure is correct, the oxygen forms three bonds in a plane, not making a pyramid as in oxonium compounds (*i.e.* sp^2 hybridisation, not p^3). One negative charge is delocalised over the nine *ortho-* and *para*-positions of the phenyl rings, which should tend to stabilise these substances. Such stabilisation is impossible in Meerwein's trialkyloxonium compounds. Triphenyloxonium compounds should exhibit *ortho–para* orientation. All the $2s^22p^4$ electrons of the oxygen are utilised in the bonds.

The *sp* oxonium state with a coordination number of two and an angle of 180° is achieved in several cases, for example in the binuclear ruthenium complex $[Ru_2Cl_{10}O]^{4-}$. In this compound[35] the two ruthenium atoms are linked by an oxygen bridge:



The ion is diamagnetic, which can be understood when it is remembered that oxygen forms donor bonds with the ruthenium atom and that all the d^5sp^3 orbitals are occupied. In compounds of titanium with an oxygen bridge, the same state is achieved with two σ and two π bonds formed by oxygen at an angle of 180°.

Apart from the above cases of oxonium compounds, in which the oxygen donates two lone pairs, quadrivalent oxygen is theoretically possible as a result of excitation of one paired 2*p* electron to the 3*s* state, when $1s^22s^22p^33s$ oxygen with four unpaired electrons would be obtained. But such excitation requires 207 kcal, so that it is extremely improbable.

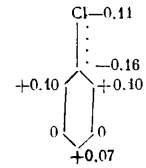
We shall not dwell here on cases in which the coordination number of oxygen is six, for example in lattices of the NaCl type (MgO, CaO, NiO, etc.), for this question will be considered in another paper, on covalent bonds in solids. It may be pointed out only that again there are no grounds for assuming the existence of an ion of atomic oxygen carrying two negative charges. The effective charge on oxygen in such lattices is close to unity, and the oxygen forms delocalised σ bonds.

The possibility of the formation of multiple bonds by oxygen has been shown by Dyatkina *et al.*[36] to be the reason for the existence of inorganic "yls", such as uranyl, neptunyl, plutonyl, osmyl, vanadyl, zirconyl, etc. compounds. The U:O link in uranyl UO_2 is not a double bond but is of greater multiplicity, since the oxygen acts as a donor and the uranium as an acceptor by virtue of its large number of

vacant orbitals. The stability of the uranyl compounds and the variable multiplicity follow from the experimental results, and are explained on the hypothesis of partial transfer of the lone electron pairs of the oxygen to the vacant orbitals of the metal. As a result of its stability, the UO_2 group passes unchanged from one compound to another in a series of reactions. The strengthening of the bond and the increase in multiplicity are accompanied by a decrease in its length, which is 1.710 Å in the UO_2 group. The formation of "yls"is characteristic of metals having vacant orbitals, and able to form acceptor bonds in addition to the usual covalent bonds with oxygen.

On passing from oxygen to sulphur, we must allow for the possibility of bond formation by means of *d* orbitals. Sulphur can therefore be both more electropositive and more electronegative than oxygen. Sulphur is readily converted into the sulphonium state R_3S^+, with a low activation energy[37], by the interaction of R_2S and RCl molecules. But whereas oxonium oxygen, combined with three atoms in the p^3 state, can carry only a positive charge, sulphur can be linked to three atoms and be either positive or negative (if its partner donates a lone pair of electrons to form a bond with the 3*d* orbital of the sulphur). This yields not sulphonium but sulphane $\gtrless\bar{S}-$ compounds[38]. This constitutes an important difference between sulphur in sulphane compounds and oxygen in oxonium compounds.

The elements of Group VII have a considerable electron affinity, forming an inert gas shell s^2p^6. They are regarded as typically electronegative. But even with fluorine donor properties can be developed to a slight extent (in acetyl fluoride for example)¶. With the other halogens (Cl, Br, I) donor properties determine the structure of many compounds. These include all bridge compounds, in which chlorine forms two equivalent bonds ($PdCl_2$, etc.) by means of the unpaired *p* electron and one lone pair of *p* electrons. Thus the "electronegative chlorine" (electronegativity 2.83) is the donor, while the palladium (1.35) is the acceptor. This again shows that the concept of electronegativity, applicable to compounds of the NaCl type, is quite inapplicable to halides of the transition metals. With Br and I the tendency to form donor bonds is considerably more marked than with chlorine. But even the electronegativity of chlorine itself should not be oversimplified, *i.e.* understood solely as a tendency to form a negative ion having an s^2p^6 shell. Chlorine can act as an acceptor by virtue of its vacant *d* orbitals if the other partner exhibits donor properties. The chlorine can then form two bonds (*p* and *d*), one a covalent bond involving the unpaired *p* electron and the other an acceptor bond in a *d* orbital with an effective negative charge. In other words, in conjugated systems chlorine can be bicovalent and negatively charged. A quantum-chemical investigation of this point has recently been made in the cases of vinyl chloride and chlorobenzene[39]. Partial double-bond character and a reduction in energy result from $d_\pi-p_\pi$ hybridisation of the orbitals of the chlorine atom. This compels us to reexamine the problem of dipole moments, energy of conjugation, intensity of ultra-violet spectra, quadrupole coupling constants, etc. With chlorobenzene, therefore, in addition to what has been considered in previous work, we must also take into account the following charge distribution:



This helps us to explain the variation in the relative rates of mononitration of benzene derivatives (C_6H_6 1, $C_6H_5CH_5$ 24.5, C_6H_5F 0.15, C_6H_5Cl 0.033, and C_6H_5Br 0.03). We must in general be cautious in associating the tendency to attract an electron with electronegativity. We come up against this in the so-called hyperconjugation effect. According to this idea, compounds of the type $H_3C-C\equiv X$ show some double bonding between the two carbon atoms (in the sp^3 and *sp* states). This double-bond character is supposed to be due to a positive charge on the hydrogen atoms of the methyl group caused by the electronegativity of the atom or group X. Thus in the case of acetonitrile it is supposed that the double bonding is due to the state $\dot{H}CH_2=C=\bar{N}$. If this is so, it might be expected that the more electronegative is X, the more the electron is drawn away, the greater the hyperconjugation, and the shorter the C–C distance (owing to admixture of the π state). Experiments show, however, that the C–C distance is the same in all derivatives of methylacetylene, independently of their electronegativity. It is identical at 1.46 Å in methylacetylene, dimethylacetylene, prop-1-ynyl iodide and bromide, trifluoromethylacetylene, acetonitrile, malononitrile, trichloroacetonitrile, and trifluoroacetonitrile. Thus the interatomic distance depends on the hybridisation and is insensitive to hyperconjugation, if the latter exists at all in the ground state of the molecule[40]. This question is not yet sufficiently clear. Whether the absence of a relation between double-bond character and electronegativity is a real or an imaginary problem is difficult to say, since as an individual characteristic of an element electronegativity has no clear or fully valid physical meaning. In most cases it is an empirical criterion, being neither a qualitative nor a quantitative characteristic of a chemical bond, as the present paper has tried to show.

¶ Barinskii and Malyukov[41] investigated the X-ray absorption spectrum of sulphur hexafluoride, and found the sulphur to have a negative charge of about -1, so that the fluorine atoms carry appreciable positive charges of about +0.16. This interesting experimental result can be explained only on the assumption that partly unoccupied 3*d* orbitals remain when sulphur forms six bonds, and these are acceptors for the lone electron pairs of the fluorine. These workers found zero charges on sulphur and chlorine in $SOCl_2$ and SO_2Cl_2, and hence also on the oxygen.

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THE CHEMISTRY OF DIBORANE

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INTRODUCTION

The chemistry of diborane and of the higher hydrides of boron was discussed in Stock's monograph [1] published in 1933, and subsequently reviews [2-11] and monographs [12-14] have appeared dealing with certain stages in the development and individual aspects of the chemistry of the boron hydrides. During recent years the chemistry of diborane has been developing very rapidly, and therefore a brief account of the progress made in this field is opportune.

The great theoretical achievement is the formulation of general quantum-chemical principles underlying the so-called "three-centre bonds" which have provided an explanation of the peculiarities of structure of the boron hydrides. The application of physical methods had led to the establishment of the geometrical structure of many interesting functional derivatives of diborane.

Considerable success was achieved in working out methods for obtaining diborane, alkyl- and aryl-diboranes, amine complexes of diborane and its chlorine derivatives, which formed the basis for a more thorough study of the chemical properties both of diborane itself and of its compounds.

Interesting work was carried out in establishing the structure of "diborane diammine", which increased our knowledge about compounds of the boronium type. Further work on the reactions of diborane with phosphorus compounds and especially sulphur compounds revealed new types of derivatives of borine and diborane.

Research on the catalytic effect of alkyldiboranes on the interconversion of organoboron compounds is noteworthy from both theoretical and preparative points of view. During recent years an intensive study has been made of the addition of diborane to unsaturated compounds, which has acquired great importance in the chemistry of organoboron compounds, and also in organic chemistry as a method for the stereospecific hydration of olefines contrary to Markovnikov's rule.

The reactions of diborane and its alkyl, aryl, and alkylthio-derivatives with diene hydrocarbons have been used to develop promising new methods for the synthesis of heterocyclic compounds containing boron in the ring.

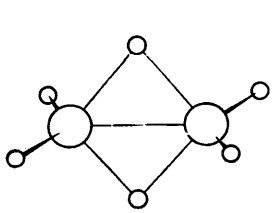
Progress in the chemistry of diborane, by clearing up the urgent problems of complex formation, dimerisation, and disproportionation in electron-deficient compounds, is extremely valuable for the development of the theory of chemical combination and molecular structure.

Diborane and its compounds are also of practical interest. Both diborane itself and several of its derivatives are used as reducing agents, and many compounds of diborane, primarily its nitrogen and phosphorus derivatives, form heat-resistant polymers. Diborane is also of interest in view of its genetic relationship to the higher boron hydrides, which have prospects of employment as rocket fuels.

I. STRUCTURE AND PHYSICAL PROPERTIES OF DIBORANE

The structure of diborane and the higher boron hydrides became the subject of prolonged discussion. The problem arises because they do not fit the usual ideas of the nature of the chemical bond. It is only recently, by careful examination of the experimental data and the development of the concept of a new type of bond, the so-called "three-centre bond", that the problem of the structure of the boron hydrides has been solved.

According to modern views, the 1*s* orbital of hydrogen and four $2sp^3$ orbitals of boron are utilised in diborane. Each of the boron atoms forms two covalent B–H bonds, both the boron atoms and four hydrogen atoms being in the same plane. The two remaining hydrogen atoms are situated at equal distances from this plane on a line perpendicular to it and bisecting the B–B line (see diagram). Each of these two "bridge" hydrogen atoms is joined to both boron atoms by three-centre bonds. Each B–H–B bridge is regarded as a filled three-centre localised bonding orbital, which utilises one hydrogen orbital and one hybrid orbital from each of the boron atoms. The hydrogen atom contributes one electron to this orbital, and each boron atom contributes half an electron [15,16].



Structure of B_2H_6.

Electron-diffraction studies [17] show that the length of a terminal B–H bond in diborane is 1.19 Å, that of a bridge B–H bond 1.33 Å, the distance between the boron atoms 1.77 Å, and the H–B–H angle 121.5°. The frequencies of the stretching vibrations of the terminal B–H bonds lie in the range 2500–2600 cm^{-1} in the infra-red absorption spectra and the Raman spectra, while the vibrational frequencies of the B–H bridge bonds are situated at ~1600 cm^{-1} and ~1800–2000 cm^{-1} (the latter are less intense) in the infra-red absorption spectra, and ~2100 cm^{-1} in the Raman spectra [18-22].

The energy of a terminal boron–hydrogen bond is 93.1 kcal $mole^{-1}$, that of a B–H–B bond 107.2 kcal $mole^{-1}$, and the energy of dissociation of diborane into two borine molecules is 28.5 kcal $mole^{-1}$.[23] The mass spectra of diborane have been investigated [24].

II. METHODS FOR PREPARING DIBORANE AND ITS ALKYL AND ARYL DERIVATIVES

1. Preparation of Diborane

New methods have recently been discovered for obtaining diborane, several of which are very convenient in view of the availability of the starting materials, the rapidity of the process, and the consistently high yields.

One such method, discovered by Schlesinger *et al.* is based on the reaction of boron trichloride with lithium aluminium hydride in ether [25]. It is more convenient to use the ether addition compound of boron trifluoride [26] when the yield of diborane is 70–80%.

$$3LiAlH_4 + 4BX_3 = 3LiX + 3AlX_3 + 2B_2H_6,$$

where X = F, Cl.

Another convenient method for preparing diborane, proposed by Schlesinger and Brown [27,28] is the reaction of the addition complex of ether and boron trifluoride with lithium or sodium borohydride (tetrahydroborate);

$$3MBH_4 + 4BF_3 = 2B_2H_6 + 3MBF_4,$$

where M = Li, Na.

The reaction with lithium borohydride can conveniently be carried out in ethyl ether [29]; when sodium borohydride is used, it is advisable to carry out the process in "diglyme" (the methyl ether of diethylene glycol) [30], when the yield of diborane is 90% based on the above equation. Ethyl ether can be used as solvent instead of diglyme, but the yield of diborane is then ~70% [31]. Boron trichloride also reacts with $NaBH_4$ in diglyme to form diborane, but the yield is decreased in the presence of an excess of BCl_3, and when the reactants are in equimolar proportions diborane is not obtained at all because diborane and BCl_3 are able to form relatively stable addition compounds of ether and chloroborine [30].

Diborane contaminated with SO_2 is obtained by the action of sulphuric acid on sodium borohydride; when the sulphuric acid is replaced by methanesulphonic acid, diborane is obtained in 76% yield free from SO_2.[32]

Another group of methods for obtaining diborane is based on the use of metal hydrides. Lithium hydride as a fine powder suspended in ether reacts on heating with the ether addition compound of boron trifluoride with the evolution of diborane[29]. The process represented by the equation below takes place very slowly and gives low and variable yields of diborane:

$$6LiH + 8BF_3 = B_2H_6 + 6LiBF_4.$$

The influence of temperature[33] and of activators[34] (bromine, iodine) on the course of this reaction has been investigated. The assessment of this method as the simplest and the most economical for obtaining diborane[35] is incorrect.

The reaction between sodium hydride and the ether compound of boron trifluoride in ethyl ether is still less suitable for the preparation of diborane[36]. In diglyme, however, this reaction takes place smoothly[30], and can be recommended as a laboratory preparation.

The photochemical preparation of diborane from BCl_3 and silane in the presence of azomethane has been described[37], and also the reduction of boron halides with calcium hydride[38-40].

2. Preparation of Alkyldiboranes

Schlesinger and his collaborators found that alkyl derivatives of diborane are formed when the latter reacts with trialkylborines. If a mixture of trimethylborine and diborane is left for several hours at room temperature, four methyl derivatives of diborane — methyldiborane, unsymmetrical dimethyldiborane, trimethyldiborane, and tetramethyldiborane — are obtained[41]. When less substituted methyldiboranes are treated with trimethylborine, they are methylated, but even with a considerable excess of trimethylborine no pentamethyldiborane is obtained. Ethyldiborane and unsymmetrical diethyldiborane are obtained by the reaction of triethylborine with diborane in the proportions 1 : 5; excess of triethylborine yields a mixture of tri- and tetra-ethyldiborane[42]. Interaction of diborane and tri-n-propylborine in the proportions 8 : 1 gives n-propyldiborane and unsymmetrical di-n-propyldiborane[42].

Symmetrical dimethyldiborane is not formed directly from trimethylborine and diborane. It can be obtained from monomethyldiborane by treating it with methyl ether[43] or tetrahydrofuran[44] at low temperatures: the methyldiborane is converted into the ether complex of borine and into methylborine, which does not give an ether complex but dimerises:

$$2CH_3B_2H_5 + 2(CH_3)_2O \rightarrow 2(CH_3)_2O \cdot BH_3 + (CH_3BH_2)_2.$$

Symmetrical dimethyldiborane is unstable, being converted on standing into the unsymmetrical isomer.

Solomon *et al.*[45] in a detailed investigation of the properties of ethyldiborane, found that after an hour at 25° half of it has been converted to diborane and symmetrical diethyldiborane. The mechanism of this disproportionation, consisting in the reversible dissociation of diborane and alkyldiboranes, is represented by the following scheme:

$$2C_2H_5B_2H_5 \rightleftharpoons 2C_2H_5BH_2 + 2BH_3$$
$$sym\text{-}(C_2H_5)_2B_2H_4 \quad B_2H_6$$

As usually prepared, unsymmetrical diethyldiborane contains the symmetrical isomer as impurity, from which it cannot be freed by distillation. The pure unsymmetrical diethyldiborane has been isolated using the ability of the symmetrical isomer to react rapidly with diborane. When the latter reacts with a mixture of the diethyldiboranes, the symmetrical isomer is converted into ethyldiborane, which can now be separated by fractionation. Symmetrical diethyldiborane is comparatively stable to heat: it remains unchanged after 24 h at 25°; unsymmetrical diethyldiborane after 16 h at 25° is 30% converted into diborane and different ethyldiboranes, but it does not yield the symmetrical diethyldiborane[45]. These alkyldiboranes were obtained in millimole amounts by a high-vacuum technique, and did not have sufficiently complete physical characterisation. Mikhailov *et al.*[46] synthesised alkyldiboranes in larger amounts by the usual procedures of organic synthesis. By passing diborane into ethereal solutions of tri-n-propylborine and tri-n-butylborine they obtained the comparatively thermally stable tetraalkyldiboranes

$$4BR_3 + B_2H_6 = 3R_2BH \cdot BHR_2,$$

and unsymmetrical di-n-propyldiborane, which is unstable to heating. Determination of the physical constants of these alkyldiboranes enabled the refractions of the terminal and the bridge boron–hydrogen bonds to be calculated as 2.76 and 1.72 cm^3.

Tetrakis(-2-methylpentyl)diborane was obtained by the action of a trialkylamine–borine on tris(-2-methylpentyl). .borine[47].

Alkyldiboranes can be obtained by the action of metal borohydrides (tetrahydroborates) or lithium aluminium hydride on trialkylborines in the presence of hydrogen chloride[48]. Alkyldiboranes of different degrees of substitution can be obtained depending on the proportions of the reactants. The reaction with sodium borohydride takes place at 150°–175° and is represented by the equation

$$NaBH_4 + HCl + 3BR_3 \rightarrow 2R_4B_2H_2 + NaCl + RH.$$

With lithium borohydride the reaction takes place at a lower temperature and has a diff(rent mechanism:

$$2LiBH_4 + 2HCl + 4BR_3 \rightarrow 3R_4B_2H_2 + 2LiCl + 2H_2.$$

Boron trichloride can be used instead of hydrogen chloride, the reaction then being represented by the equation

$$3LiBH_4 + BCl_3 + 2B(CH_3)_3 \rightarrow 3B_2H_4(CH_3)_2 + 3LiCl.$$

Tetraalkyldiboranes can be obtained by the action of lithium aluminium hydride on the dialkylboron chloride in ethereal solution[48]:

$$LiAlH_4 + 4(C_3H_7)_2BCl = 2(C_3H_7)_4B_2H_2 + LiCl + AlCl_3.$$

Diethyldiborane and di-n-propyldiborane are obtained by the action of sodium borohydride on vinyl and allyl bromide respectively[49].

Alkyldiboranes are also obtained by the action of hydrogen under pressure on trialkylborines[50,51].

The vibrational frequencies of the terminal B–H bonds in alkyldiboranes lie within the range 2500–2600 cm^{-1} in the infra-red absorption and Raman spectra, while those of the bridge B–H bonds are in the range 1500–1600 cm^{-1} in the infra-red spectra[52-57].

3. Preparation of Aryldiboranes

In 1929 Pace[58] reported the preparation of phenyldiborane from $C_6H_5BI_2.2HI$ and alcohol, but it proved impossible to repeat his results[59]. Later Hurd[60] showed that hydrolysis of the reaction products obtained from benzene

TABLE 1. Alkyldiboranes and aryldiboranes.

Compound	M.p., °C	B.p., °C	Vapour pressure, mm/°C	References
$CH_3B_2H_5$			55/—78.5	41
$(CH_3)_2BH \cdot BH_3$	—150.2	—2.6	10/—78.5	41,51
$(CH_3BH_2)_2$	—124.9	+4.9	7/—78.5	43
$(CH_3)_2BH \cdot BH_2CH_3$	—122.9	45.5	123/0	41
$[(CH_3)_2BH]_2$	— 72.5	68.6	48/0	41,48,49
$C_2H_5B_2H_5$			7/—78.5	42
$(C_2H_5)_2BH \cdot BH_3$			46/0	42,45
$(C_2H_5BH_2)_2$			36/0	45
$(C_2H_5)_2BH \cdot BH_2C_2H_5$			4/0	42
$[(C_2H_5)_2BH]_2$			0.5/0	42
$n\text{-}C_3H_7B_2H_5$			6.2/—60	42
$(n\text{-}C_3H_7)_2BH \cdot BH_3$		34/32[a]	2.8/0	46
$[(n\text{-}C_3H_7)_2BH]_2$		34/1[b]	21/6	46,48
$[(n\text{-}C_6H_9)_2BH]_2$		41/0.25[c]		46
$(C_6H_5BH_2)_2$	85			53,62
$(p\text{-}ClC_6H_4BH_2)_2$	117			62
$(\alpha\text{-}C_{10}H_7BH_2)_2$	119			62

[a] n_D^{20} 1.4088;

[b] d_4^{20} 0.7388; n_D^{20} 1.4327;

[c] d_4^{20} 0.7647; n_D^{20} 1.4375.

and diborane at 120° and 12 atm yielded phenylboronic acid, but the phenyl derivative of diborane itself was not isolated. Nielsen *et al.*[61] were unsuccessful in preparing phenyldiborane from phenylboron chloride and lithium aluminium hydride in boiling dioxane, since at the given temperature 1,2-diphenyldiborane is converted into triphenylborine and diborane.

It was only in 1958 that Wiberg and his coworkers[59] first obtained an aryl derivative of diborane (1,2-diphenyldiborane) by heating triphenylborine with diborane at 40°–100° and 2–4 atm:

$$2\,(C_6H_5)_3B + 2B_2H_6 \longrightarrow 3\,(C_6H_5BH_2)_2.$$

The same compound was obtained by the reduction of phenylboron dichloride with sodium borohydride in ether.

Mikhailov and Dorokhov[62] showed that 1,2-diaryldiboranes are obtained in high yields by the action of diborane on esters of diarylborinic acids in ether:

$$3Ar_2BOR + 2B_2H_6 = 3\,(ArBH_2)_2 + B\,(OR)_3.$$

This method was used to obtain the 1,2-diphenyl, 1,2-di-*p*-chlorophenyl, and 1,2-di-α-naphthyl derivatives of diborane. 1,2-Diaryldiboranes are obtained in lower but still quite good yields by the action of diborane on arylboronic esters[62]. The properties of the alkyl- and aryl-diboranes are set out in Table 1.

III. CHEMICAL PROPERTIES OF DIBORANE AND ITS ALKYL AND ARYL DERIVATIVES

1. Reactions of Diborane and Its Alkyl and Aryl Derivatives with Nitrogen Compounds

Even at comparatively high temperatures the degree of dissociation of diborane into borine (BH_3) molecules is so low[63] that it cannot be detected experimentally. In chemical reactions, however, diborane behaves as a compound which is easily decomposed into two BH_3 groups. It reacts at low temperatures with substances having lone pairs of electrons, such as amines, ethers, etc. to form coordination compounds of borine.

(a) Reactions of diborane with tertiary amines. Trialkylamine–borines†. Tertiary amines convert diborane into trialkylamine complexes of borine. With trimethylamine the reaction is rapid and quantitative at -110°.[64] The energy of dissociation of trimethylamine–borine $(CH_3)_3N.BH_3$ into its components in the gaseous state is 31.5 kcal mole^{-1},[23] so that formation of the complex involves an increase in energy of 17.3 kcal × × mole^{-1}:

$$(CH_3)_3N + {}^1/_2B_2H_6 = (CH_3)_3N \cdot BH_3.$$

Trialkylamine–borines are prepared by passing diborane into an ethereal solution of the trialkylamine[65]. They can also be conveniently obtained by Schaeffer and Anderson's method[66], based on the reaction in ethereal medium between lithium borohydride and a salt of the tertiary amine. Trimethylamine–borine was obtained in 85% yield in this way. Salts of higher trialkylamines also react smoothly[67]. The primary reaction product is evidently the trialkylammonium borohydride, which evolves hydrogen and is converted to the borine complex:

$$R_3N.HCl + LiBH_4 = [R_3NH]\,BH_4 + LiCl,$$

$$[R_3NH]\,BH_4 = R_3N \cdot BH_3 + H_2.$$

Köster in a short note pointed out the possibility of obtaining trialkylamine–borines by heating a mixture of a trialkylborine and a tertiary amine in the presence of hydrogen under pressure at 220°[68]:

$$R_3N + BR'_3 + 3H_2 = R_3N \cdot BH_3 + 3R'H.$$

Diborane forms complex compounds with pyridine, its homologues, and quinoline. Pyridine–borine is obtained by the action of diborane on pyridine at room temperature[69]. The heat of reaction in nitrobenzene solution was 17.9 kcal × × mole^{-1}:[70]

$${}^1/_2\,B_2H_6 + C_5H_5N\ \text{(in nitrobenzene)} = C_5H_5N \cdot BH_3\ \text{(in nitrobenzene)}.$$

Allowing for the dissociation energy of diborane[23] the change in enthalpy accompanying the reaction

$$BH_3\,(\text{gas}) + C_5H_5N\ \text{(in nitrobenzene)} = C_5H_5N \cdot BH_3\ \text{(in nitrobenzene)},$$

is thus 32.15 kcal. This is very close to the heat of reaction of boron trifluoride with pyridine in nitrobenzene (32.9 kcal) and considerably larger than that of trimethylborine with pyridine (21.4 kcal).[71] Pyridine–borine can be prepared in 80–90% yield by the action of sodium borohydride on pyridine hydrochloride in pyridine solution[72]:

$$C_5H_5N \cdot HCl + NaBH_4 = C_5H_5N \cdot BH_3 + NaCl + H_2.$$

Brown and Domash[70] prepared a series of complex compounds of diborane with homologues of pyridine and measured the heats of reaction. The increased heat of reaction of diborane with 3- and 4-picolines compared with pyridine is consistent with the increase in basicity of these homologues due to the inductive effect of the methyl groups.

† In the naming of the complex compounds of borine and its derivatives with nitrogenous bases, the nomenclature adopted in the American literature should be adhered to. Wiberg's nomenclature, according to which this type of compound is termed a "borazan", cannot be accepted as suitable, since, being based on the purely formal analogy with the alkanes, it does not reflect the complex nature of the B — N bond in such compounds, and it makes the terminology extremely complicated in several cases. Thus the complex of borine with pyridine (pyridine—borine) would be called "*N*-cyclopentatrienylborazan" according to this nomenclature.

The decreased heats of reaction of diborane with 2-alkylpyridines is explained by the effect of steric hindrance, which weakens the donor–acceptor interaction. Steric factors are less evident in complex compounds or borine than in those of trialkylborines or of boron trifluoride [73].

Diborane does not form a complex with trisilylamine [74], which is a weak base.

The properties of the complexes which have been obtained are given in Table 2. For the vapour pressure of trimethylamine–borine see Ref. 75; its dipole moment is 4.62 D, [76,77] while that of pyridine–borine is 5.86 D.[76]

Trialkylamine – alkylborines and trialkylamine – arylborines. Alkyldiboranes react with tertiary amines to form complex compounds of alkylborines. Symmetrical dimethyldiborane and trimethylamine yield trimethylamine–methylborine [43], while tetramethyldiborane with trimethylamine gives trimethylamine–dimethylborine $(CH_3)_3N.BH(CH_3)_2$.[43] Mono- and tri-methyldiborane are converted by trimethylamine into mixtures of the corresponding adducts, which are difficult to separate into their components [43]. The action of trimethylamine and pyridine on solid 1,2-diphenyldiborane in a high vacuum yields the corresponding complex compounds of phenylborine [59].

Hawthorne [79] discovered a very convenient method for preparing trialkylamine–alkylborines, which consists in reducing alkylboronic acid anhydrides with lithium aluminium hydride in the presence of tertiary amines in ether:

$$(RBO)_3 + 3R'_3N \xrightarrow{LiAlH_4} 3R'_3N\cdot BH_2R.$$

By reducing arylboronic esters or the acid anhydrides with lithium aluminium hydride in the presence of pyridine or a tertiary amine in ether Hawthorne [80,81] obtained 24–78% yields of the pyridine and trialkylamine complexes of arylborines:

$$ArB(OR)_2 \xrightarrow[C_5H_5N]{LiAlH_4} ArBH_2\cdot C_5H_5N.$$

By a similar procedure diarylborinic esters yield the pyridine complexes of diarylborines [82]:

$$Ar_2BOR \xrightarrow[C_5H_5N]{LiAlH_4} Ar_2BH.C_5H_5N.$$

TABLE 2. Complexes of borine with tertiary amines.

Compound	M.p., °C	B.p., °C or °C/mm vapour pressure, mm/°C	References
$(CH_3)_3N\cdot BH_3$	95	171	64,66,67,75,77
$(C_2H_5)_3N\cdot BH_3$	— 2	42 /10^{-4}	65,67,68
$(n\text{-}C_3H_7)_3N\cdot BH_3$	18	101 /12	67
$(CH_3)_2C_6H_5N\cdot BH_3$	17.7		65
$CH_3(C_2H_5)_2N\cdot BH_3$	—38		65
$(n\text{-}C_4H_9)_3N\cdot BH_3$	—12	80 /10^{-5}	65,67,68
$(C_2H_5)_2C_4H_9N\cdot BH_3$	—32	125 /14	68
$C_6H_5(CH_3)_2N\cdot BH_3$	35		109
		Vapour pressure	
Pyridine.BH_3[a]	11	2.5/100	69,70,72,78
4-Picoline.BH_3	74	1.2/105	70
3-Picoline.BH_3	10.5	1.1/100	70
2-Picoline.BH_3	51	1.7/100	70
2-Ethylpyridine.BH_3	50	8.6/100	70
2-Isopropylpyridine.BH_3	19	8/80	70
2-t-Butylpyridine.BH_3	25	22/50	70
2,6-Lutidine.BH_3	111	4.9/100	70
Quinoline.BH_3	96		78

[a] n_D^{25} 1.5280.[72]

TABLE 3. Trialkylamine and pyridine complexes of alkyl- and aryl-borines.

Compound	M.p., °C	B.p., °C (extrapolated)	References
$(CH_3)_3N\cdot BH_2CH_3$	0.8	176.4	43
$(CH_3)_3N\cdot BH_2C_3H_7$-n			79
$(CH_3)_3N\cdot BH_2C_3H_7$-iso			79
$(CH_3)_3N\cdot BH_2C_4H_9$-n			79
$(CH_3)_3N\cdot BH_2C_4H_9$-2			79
$(CH_3)_3N\cdot BH(CH_3)_2$	—18	171.4	43
$(CH_3)_3N\cdot BH_2C_6H_5$	69		59,81
$(C_6H_5)_3N\cdot BH_2CH_2C_6H_5$	65		81
$C_5H_5N\cdot BH_2C_3H_7$-iso			80
$C_5H_5N\cdot BH_2C_4H_9$-n			80
$C_5H_5N\cdot BH_2C_6H_5$	83		59,80,81
$C_5H_5N\cdot BH_2C_6H_4Cl$-p	62		80,81
$C_5H_5N\cdot BH_2C_6H_4OCH_3$-p	79		80,81
$C_5H_5N\cdot BH_2C_6H_4OCH_3$-o	56		81
$C_5H_5N\cdot BH_2C_6H_4CH_3$-p	65		80,81
$C_5H_5N\cdot BH_2C_{10}H_7$-α	141		80,81
$C_5H_5N\cdot BH_2CH_2C_6H_5$	106		80
$C_5H_5N\cdot BH(C_6H_5)_2$	109		80,82
$C_5H_5N\cdot BH(C_6H_4Cl\text{-}p)_2$	104		80,82
$C_5H_5N\cdot BH(C_6H_4CH_3\text{-}p)_2$	113		80,82
$C_5H_5N\cdot BH(C_6H_4OCH_3\text{-}p)_2$	110		80,82
$C_5H_5N\cdot BH(C_6H_4Br\text{-}p)_2$	124		80,82

The physical properties of the complexes of the alkyl- and aryl-borines are listed in Table 3.

Properties of trialkylamine – borines and trialkylamine – alkylborines. Trimethylamine–borine reacts slowly with moist air; in the absence of air it is quite stable and withstands being heated at 125° for several hours without appreciable decomposition [43]. Dry hydrogen chloride produces stepwise replacement of hydrogen by chlorine atoms [43]. Hydrolysis of trimethylamine–borine with hydrogen chloride in aqueous and aqueous–dioxane solutions is a first-order reaction with respect to the complex [83], its activation energy being 25.7 kcal mole^{-1}.

The energy of dissociation of trimethylamine–dimethylborine is 23.4 kcal mole^{-1}, whereas the value for the trimethylamine complex of trimethylborine [23] is 17.6 kcal × × mole^{-1}. Thus successive replacement of the hydrogen atoms in borine by methyl groups is accompanied by a decrease in the electron-acceptor properties of the molecule, which is associated with the positive inductive effect of the methyl groups. In conformity with this, the trimethylamine complexes of the methylborines differ in thermal stability [43]. Trimethylamine–methylborine is stable at 100°, but at 200° it undergoes disproportionation according to the equation

$$3(CH_3)_3N\cdot BH_2CH_3 \rightarrow 2(CH_3)_3N\cdot BH_3 + (CH_3)_3N.B(CH_3)_3.$$

Trimethylamine–dimethylborine disproportionates at an appreciable rate even at 70°:

$$2(CH_3)_3N\cdot BH(CH_3)_2 \rightarrow (CH_3)_3N\cdot BH_2CH_3 + (CH_3)_3N + B(CH_3)_3.$$

Trialkylamine–alkylborines react with ammonia in diglyme at 100°–150°, in the presence of aluminium chloride as catalyst, to form *B*-trialkylborazoles [79]:

$$3NH_3 + 3R_3N.BH_2R \xrightarrow{NH_3} (RBNH)_3 + 3R_3N + 6H_2.$$

With phenylenediamine they are smoothly converted into heterocyclic compounds, the dihydrobenzoboradiazoles [79]. Trimethylamine–borine [84] and pyridine–borine [85,86] have been investigated as reducing agents for carbonyl compounds.

The trimethylamine complexes of methylborine and dimethylborine react with dry hydrogen chloride in a similar manner to trimethylamine–borine, but at a greater rate[43].

Hawthorne and Lewis[87] investigated the kinetics of the hydrolysis of pyridine–diphenylborine in acetonitrile solution.

(b) Reactions of diborane with secondary amines. In 1948 Wiberg *et al.*[88] obtained dimethylamine–borine by mixing diborane with the amine:

$$^1/_2B_2H_6 + (CH_3)_2NH = (CH_3)_2NH \cdot BH_3.$$

Dialkylamine–borines are more conveniently obtained by passing diborane into an ether solution of the secondary amine, as did Mikhailov and Dorokhov[89] in the synthesis of diethylamine–borine.

A second method for obtaining dialkylamine–borines is based on the reaction between alkylammonium salts and lithium borohydride discovered by Schaeffer and Anderson[66]. Nöth and Beyer[67] obtained a high yield of dimethylamine–borine by the reaction of dimethylammonium chloride with this reducing agent in ethereal medium at room temperature, in spite of Schaeffer and Anderson's results indicating the formation of dimethylaminoborine by this reaction[66]:

$$(CH_3)_2NH \cdot HCl + LiBH_4 = (CH_3)_2NH \cdot BH_3 + LiCl + H_2.$$

Several other dialkylamine–borines were obtained in yields of 82–98% by this method[67].

At 120°–150° dialkylamine–borines split off hydrogen and are converted into dialkylaminoborines. Wiberg *et al.*[88,90] obtained dimethylaminoborine by heating a mixture of diborane and dimethylamine (1 : 2) at 180°–200°:

$$^1/_2B_2H_6 + (CH_3)_2NH = (CH_3)_2N{-}BH_2 + H_2.$$

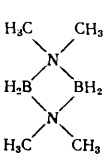
However, the process goes quite smoothly under less severe conditions. Burg and Randolph[91] prepared the same compound in almost quantitative yield by passing diborane into dimethylamine at -42° and then heating the resulting complex in a vacuum at 130°.

At room temperature dimethylaminoborine exists in the form of a dimer, which is 90% dissociated at 105°, the energy of dissocation being 20.7 kcal mole^{-1}. Dimethylaminoborine is comparatively stable to heat: on being heated in a sealed tube at 106° for a week, it undergoes very slight disproportionation into both bisdimethylaminoborine and dimethylaminodiborane[91]:

$$3\,(CH_3)_2NBH_2 \rightleftarrows [(CH_3)_2N]_2BH + (CH_3)_2NB_2H_5.$$

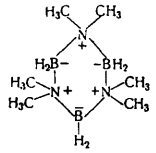
This is a reversible process: when an equimolar mixture of these products is heated at 90° for 12 h, dimethylaminoborine is formed in 90% yield.

The exact structure of the dimer of dimethylaminoborine has not been established, but by analogy with amino- and dimethylamino-diborane it is apparently similar to that of diborane but the bridge hydrogen atoms replaced by dialkylamino-groups combined with the boron atoms by three-centre bonds:



The dimer is stable towards water and hydrogen bromide, with both of which it reacts only on heating[88].

Dimethylaminoborine is able to exist not only as a dimer but also as a trimer, the latter being formed when the dimer is heated with pentaborane–9, B_5H_9, at 110°.[92] Burg, having obtained the trimer in this way, erroneously assigned the formula $[(CH_3)_2N]_3B_3H_4$ to it[93]. X-Ray analysis shows it to have a cyclic structure[94], which is confirmed by nuclear magnetic resonance measurements[92]:



It is stable in moist air, and is not appreciably hydrolysed in moist acetone at room temperature; when heated with methanol at 85° for 26 h it evolves the theoretical quantity of hydrogen.

Dimethylaminodeuteroborine is obtained by heating deuteroborine with $(CH_3)_2ND$.[95]

Not very pure[97] bisdimethylaminoborine[96] is formed when dimethylaminoborine is heated with an equal quantity of dimethylamine (200° for 10 h). To obtain the pure disubstituted derivative[97], it is advisable to heat dimethylaminoborine with a slightly greater quantity of dimethylamine than is required by the equation

$$(CH_3)_2NBH_2 + (CH_3)_2NH = [(CH_3)_2N]_2BH + H_2,$$

at 150° for 12 h.

Dimethylaminoborine is converted into bisdimethylaminoborine also when it is heated with trimethylamine at 140° for 19 h:[97]

$$2\,(CH_3)_2NBH_2 + (CH_3)_3N \rightleftarrows [(CH_3)_2N]_2BH + (CH_3)_3N \cdot BH_3.$$

Formation of an unstable complex of dimethylaminoborine and trimethylamine, $(CH_3)_2NBH_2 \cdot N(CH_3)_3$, was observed in this reaction. Bisdimethylaminoborine was also obtained by the reduction of chlorobisdimethylaminoborine with lithium aluminium hydride[98]:

$$[(CH_3)_2N]_2BCl \xrightarrow{LiAlH_4} [(CH_3)_2N]_2BH,$$

and also by heating dimethylaminoborine with sodium hydride at 100°[97]:

$$2\,(CH_3)_2NBH_2 + NaH \rightarrow [(CH_3)_2N]_2BH + NaBH_4.$$

Bisdimethylaminoborine can be converted to dimethylaminoborine by heating with diborane at 100°:

$$2[(CH_3)_2N]_2BH + B_2H_6 \rightarrow 4\,(CH_3)_2NBH_2.$$

On prolonged heating of diborane with an excess of dimethylamine (1 : 5) at 205°, trisdimethylaminoborine is formed[97], and this reacts with an equimolar quantity of diborane at elevated temperatures to form dimethylaminoborine[97]:

$$2\,[(CH_3)_2N]_3B + 2B_2H_6 \rightarrow 6\,(CH_3)_2NBH_2.$$

With diborane, dimethylaminoborine forms dimethylaminodiborane[91]:

$$2\,(CH_3)_2NBH_2 + B_2H_6 = 2\,(CH_3)_2NB_2H_5.$$

The reaction is carried out either in a sealed tube or in a flow system at 135°, the yield being almost quantitative in both cases. In order to obtain dimethylaminodiborane in greater amounts, diborane is allowed to react with dimethylamine at -42°, the reaction mixture is heated, and diborane is then passed into the resulting crude dimethylaminoborine at 135°. The yield is 75–85%.

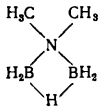
Another method for obtaining dimethylaminodiborane is to heat a mixture of dimethylaminoborine and boron trifluoride at 90°.[91] It is formed just as smoothly, together with a small amount of dimethylaminoborine, when diborane is heated with bisdimethylaminoborine at temperatures close to 100°:

$$2[(CH_3)_2N]_2BH + 3B_2H_6 = 4(CH_3)_2NB_2H_5,$$

or when it is heated with trisdimethylaminoborine[97]:

$$2[(CH_3)_2N]_3B + 5B_2H_6 = 6(CH_3)_2NB_2H_5.$$

The structure of dimethylaminodiborane has been established by electron diffraction[99]. It is equivalent to diborane in which one bridge hydrogen has been replaced by a dimethylamino-group:



The nitrogen atom is at an identical distance of 1.55 Å from each boron atom, while the distance between the boron atoms is 1.92 Å, the B–N–B angle being 76.4 ± 5.5°. For the Raman and infra-red spectra of dimethylaminodiborane, see Ref. 100.

Dimethylaminodiborane reacts with BF_3 at 100° with the formation of diborane and $(CH_3)_2N.BH_2.BF_3$; reaction with BCl_3 yields $(CH_3)_2NB_2H_4Cl$.[91]

There are indications that diethylaminoborine is formed when diethylamine is heated (at 200°–230°) with diborane[88], but the properties of this compound are not stated. Mikhailov and Dorokhov[89] obtained dimeric diethylaminoborine by the pyrolysis of diethylamine–borine at 130°–150° for 7 h, the yield being 89%:

$$2(C_2H_5)_2NH.BH_3 = [(C_2H_5)_2NBH_2]_2 + 2H_2.$$

Bisdiethylaminodiborane is stable at room temperature towards water and alcohols, but it reacts with them at 60° It is capable of adding on to olefinic hydrocarbons in the presence of pyridine at 130° [89]:

$$\tfrac{1}{2}[(C_2H_5)_2NBH_2]_2 + 2R{-}CH{=}CH_2 \rightarrow (R{-}CH_2{-}CH_2)_2B{-}N(C_2H_5)_2,$$

where R = C_2H_5, C_6H_{13}.

Burg and Good[101] investigated the reactions of diborane with cyclic secondary amines. Piperidine forms an unstable piperidine–borine, which changes at 110°–145° into piperidinoborine $C_5H_{10}NBH_2$, and this on heating with diborane (at 85°–110°) gives piperidinodiborane. Pyrrolidine and azetidine behave similarly towards diborane. Aziridine (ethyleneimine) reacts with diborane to form the complex $C_2H_4NH.BH_3$, which is partly converted to ethylaminodiborane with opening of the ring on heating (at 100°) in a current of diborane.

1,2-Dimethyldiborane reacts with dimethylamine in a manner similar to that of diborane. When the components are mixed at -78° a non-volatile methylborine complex is obtained, which on heating is converted to methyl(dimethylamino)borine $(CH_3)_2N.BHCH_3$. In the liquid state this substance is dimeric, but in the gas phase it is almost completely monomeric. Conversion of one form to the other is slow, which enables them both to be isolated in the pure form and their physical properties to be determined.

Methyl(dimethylamino)borine exhibits no tendency to exchange its dimethylamino-group, but at room temperature it disproportionates by exchanging methyl groups for hydrogen atoms, yielding dimethylaminoborine and tetramethylaminoborine:

$$2(CH_3)_2NBHCH_3 \rightleftarrows (CH_3)_2NBH_2 + (CH_3)_2NB(CH_3)_2.$$

The reaction of diethylamine with a solution of 1,2-diphenyldiborane in ether yields diethylamine–phenylborine[89]:

$$(C_6H_5BH_2)_2 + 2(C_2H_5)_2NH \rightarrow 2(C_2H_5)_2NH.BH_2C_6H_5,$$

which on being heated in a vacuum (to 150°) evolves hydrogen and is converted to a mixture of diphenyldiethylaminoborine and diethylaminoborine. The latter is collected, in a trap cooled to -70°, as a mobile liquid which is converted with rise in temperature to crystalline bisdiethylaminodiborane. If the pyrolysis of diethylamine–phenylborine is carried out at atmospheric pressure, it is possible to isolate the intermediate reaction product phenyldiethylaminoborine, which can be reversibly converted to a mixture of diphenyldiethylaminoborine and diethylaminoborine[89]:

$$2(C_2H_5)_2NH.BH_2C_6H_5 \xrightarrow{-H_2} 2C_6H_5B\langle{}^{H}_{N(C_2H_5)_2} \rightleftarrows (C_6H_5)_2BN(C_2H_5)_2 + (C_2H_5)_2NBH_2.$$

The physical properties of the dialkylamine–borines, dialkylaminoborines, alkyl(dialkylamino)borines, and dialkylaminodiboranes are given in Table 4.

The dialkylamine–borines are associated in benzene solution[67]. The dipole moments of the dialkylamine–borines have values of 4.55–4.87 D.[76] For the vapour pressure of dimethylamine–borine, see Ref. 74 and for the infra-red spectra of dimethylaminoborine, see Ref. 102.

TABLE 4. Dialkylamine-borines, dialkylaminoborines, and dialkylamino-*B*-alkylborines.

Compound	M.p., °C	B.p., °C (calc.)	References
$(CH_3)_2NH.BH_3$	37	49/10-2[b]	67,88
$(C_2H_5)_2NH.BH_3$[a]	—20	77/2,5[b]	67,89
$(n\text{-}C_3H_7)_2NH.BH_3$	30	—	67
$(iso\text{-}C_3H_7)_2NH.BH_3$	23	88/1[6]	67
$(n\text{-}C_4H_9)_2NH.BH_3$	15		67
$(iso\text{-}C_4H_9)_2NH.BH_3$	19		67
$C_5H_4NH.BH_3$	42		101
	Vapour pressure, mm/°C		
$[(CH_3)_2NBH_2]_2$	75	9.1/23	88,91
$[(CH_3)_2NBH_2]_3$	97.8		92,93
$(CH_3)_2N.BD_2$	74.5		95
$[(C_2H_5)_2NBH_2]_2$	44		89
$[(C_5H_9N.BH_2]_2$	51.8	186	101
$C_4H_8NBH_2$	34.2	194	101
$C_5H_{10}NBH_2$	110	202	101
$(CH_3)_2NBHCH_3$	—136.2	42	44
		Vapour pressure, mm/°C	
$[(CH_3)_2N.BHCH_3]_2$	melts at room temperature	1.2/0	44
$(H_3Si)_2NBH_2$	—78	7/—78	73
$[(H_3Si)_2NBH]_2$		10/25	73
$(CH_3)_2NB_3H_8$	—54.4	50.3	91,103,104
$(CH_3)_2NB_3D_8$	—57		95
$C_5H_8NB_2H_5$	—45.3	87	101
$C_6H_8NB_2H_5$	—63.6	121.8	101
$C_8H_{10}NB_2H_5$		148	101
		Vapour pressure, mm/°C	
$(H_3Si)_2NB_2H_5$	—68.8	74.5/0	73
$(CH_3NSiH_3)B_2H_5$	—39	81.5/0	73
$[(CH_3)_2N]_2BH$	—57	105.7	96,97

[a] d_4^{20} 0.7568; n_D^{20} 1.4358.

[b] experimental.

(c) Reactions of diborane and of alkyldiboranes with primary amines. Methylamine–borine has been obtained by mixing diborane with methylamine at low temperatures [105,106]. The corresponding ethylamine and n-propylamine compounds are obtained similarly [101].

Nöth and Beyer [67] used Schaeffer and Anderson's reaction [66] for the synthesis of alkylamine–borines, *i.e.* the interaction of alkylammonium salts and lithium borohydride in ether:

$$[RNH_3]Cl + LiBH_4 = RNH_2 \cdot BH_3 + LiCl + H_2.$$

The alkylamine–borines obtained earlier by this method were not isolated, but were heated in the crude form to give *N*-alkylborazoles [106,107]. The alkylamine–borines which have been synthesised [67] are solids with the exception of n-butylamine–borine: methylamine–borine actually has a melting point of 56°, not 10° as stated previously [106]. The stability of the alkylamine–borines to heat varies greatly with the nature of the alkylamine [67]. Thus n-butylamine–borine evolves hydrogen at 10°–15°, whereas t-butylamine–borine decomposes only at 120°–140°.

Several workers [66,105,106] have studied the pyrolysis of methylamine–borine (at ~200°) into *N*-trimethylborazole without isolating the intermediate product, methylaminoborine. Bissot and Parry [108] found that on moderate heating (to 100°) methylamine–borine is smoothly converted to methylaminoborine, which exists as the trimer:

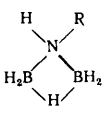
$$3CH_3NH_2 \cdot BH_3 \xrightarrow{100^\circ} (CH_3NHBH_2)_3 + 3H_2.$$

This substance possesses considerable stability, being hydrolysed very slowly by water, and it can be recrystallised from methyl or ethyl alcohol. At 200° the trimer is converted to *N*-trimethylborazole with a yield of 78%. The compound evidently has a cyclic structure with alternating boron and nitrogen atoms, similar to that of trimeric dimethylaminoborine. When diborane is passed into aniline, a crystalline substance is formed, which may perhaps have the structure of diphenylaminoborine [bis(phenylamino)borine ? (Ed. of Translation)] [109].

Alkylamine–borines react with diborane at 90°–100° with the formation of alkylaminodiboranes. The first stage of the reaction is obviously the conversion of the initial complexes to alkylaminoborines, which then add on a borine molecule:

$$RNH_2 \cdot BH_3 \xrightarrow{-H_2} RNH{-}BH_2 \xrightarrow{BH_3} RNH \cdot B_2H_5.$$

Methylamino- [91], ethylamino-, and n-propylamino-diborane [101], have been prepared in this way. Like dimethylaminodiborane and aminodiborane, alkylaminodiboranes evidently have the structure of diborane in which a bridge hydrogen atom has been replaced by an alkylamino-group:



Alkylaminodiboranes are intermediate in stability between aminodiborane (see below) and dimethylaminodiborane. Thus methylaminodiborane is 39% decomposed after 5 h at 90°, and n-propylaminodiborane undergoes a 1.2% change during 4 days at 25°.

With aniline tetraalkyldiboranes form complex compounds which evolve hydrogen at room temperature and are converted into compounds of the phenylaminodialkylborine type [46]:

$$R_4B_2H_2 + 2C_6H_5NH_2 = 2R_2BNHC_6H_5 + 2H_2.$$

The physical properties of the alkylamine–borines and the alkylaminodiboranes are given in Table 5. For the vapour pressure of methylamine–borine, see Ref. 74; the dipole moments of the alkylamine–borines have values of 4.62–5.19 D.[76]

(d) Reactions of diborane with ammonia. In 1923 Stock and Kuss [110] obtained from diborane and ammonia at low temperatures a non-volatile compound, stable at 80°, which had the composition $B_2H_6.2NH_3$. "Diborane diammine" has been assigned the structures (I), [111,112] (II), [113] and (III) [114]:

$$(NH_4)_2B_2H_4 \qquad NH_4[H_3B{:}\ddot{N}{:}BH_3] \qquad [NH_4]^+[H_2BNH_2[BH_4]^-$$
$$\qquad\qquad\qquad\quad \ddot{H}$$
$$\text{(I)} \qquad\qquad \text{(II)} \qquad\qquad\qquad \text{(III)}$$

It has recently been ascertained that the actual structure is (IV): *i.e.* the compound contains a tetrahydroborate (borohydride) anion and a diammineboronium cation:

$$[H_2B(NH_3)_2]^+ BH_4^- . \quad \text{(IV)}$$

Cationic complexes are quite uncharacteristic of boron, and therefore structure (IV) seems unusual. However, compounds of the boronium type have been known for a long time: they were described as early as 1905 by Dilthey [115], who obtained bisacetylacetone and bisbenzoylacetone complexes of boron from the β-diketones and BCl_3.

Schultz and Parry [116] demonstrated the presence of the cation $[H_2B(NH_3)_2]^+$ in "diborane diammine" by preparing diammineboronium salts $[H_2B(NH_3)_2]X$ by the action of ammonium chloride or bromide on the "diammine" in liquid ammonia:

$$[H_2B(NH_3)_2]BH_4 + 2NH_4X = 2[H_2B(NH_3)_2]X + 2H_2,$$

where X = Cl, Br.

X-Ray analysis showed the ionic structure of the salt $[H_2B(NH_3)_2]Cl$; the B–N bonds in it are 1.58 Å in length, and form an almost tetrahedral angle at the boron atom [117].

The salt $[H_2B(NH_3)_2]Br$ reacts with sodium in liquid ammonia with the evolution of one equivalent of hydrogen, as does the "diammine". In both cases the hydrogen comes

TABLE 5. Alkylamine-borines and alkylaminodiboranes.

Compound	M.p., °C	B.p., °C (calc.)	References
$CH_3NH_2 \cdot BH_3$	56		67, 105, 106
$C_2H_5NH_2 \cdot BH_3$	19		67, 91
$n\text{-}C_3H_7NH_2 \cdot BH_3$	45		67, 91
$iso\text{-}C_3H_7NH_2 \cdot BH_3$	65		67
$n\text{-}C_4H_9NH_2 \cdot BH_3$	−48		67
$t\text{-}C_4H_9NH_2 \cdot BH_3$	96		67
$CH_3NH \cdot B_2H_5$		Vapour pressure 47.5 mm/0°C	91
$C_2H_5BHB_2H_5$	−96.4	86.6	101
$n\text{-}C_3H_7NHB_2H_5$	−143*	121	101

* Softening temperature of vitreous mass.

from the ammonia molecules of the boronium cation, which possesses acid properties, as with the ammines and aquo--salts of platinum, cobalt, aluminium, and other metals. The correctness of this conclusion was confirmed by a study of the reaction between sodium and various deutero--derivatives of "diborane diammine" in liquid ammonia[118]. Thus the reaction of a diammineboronium salt and of (IV) with sodium can be represented by the scheme

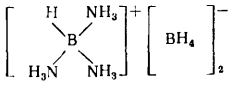
$$[H_2B(NH_3)_2]X + Na \rightarrow NaX + {}^1/_2H_2 + NH_3 + H_2BNH_2,$$

where X = Br, BH_4.

The absence of an ammonium cation from "diborane diammine" is proved by the fact that, unlike ammonium bromide (which reacts rapidly), it does not evolve hydrogen on treatment with sodium borohydride.

The presence of a borohydride ion is confirmed by the formation of sodium borohydride when the "diammine" reacts with sodium, and also by a study of the Raman spectra[119]

The preparation of "diborane diammine" necessitates strict adherence to the reaction conditions: the reactants must be mixed slowly and the excess of ammonia removed at -78°. If, however, the reaction is carried out rapidly or the reaction product is kept at -45° for a long time, a different substance is obtained[120,121], which is apparently the compound (V).[122]



(V)

The behaviour of "diborane diammine" towards ammonium salts in ether is quite different from its behaviour in liquid ammonia, as Shore and Parry[123,124] have shown. Hydrogen is formed in this case too, but a complex, ammine–borine ($H_3N.BH_3$), is obtained instead of a diammineboronium salt. The reaction is accelerated by the presence of a small quantity of ammonia. Hydrogen and ammine–borine are also evolved slowly on the addition of lithium salts to a suspension of "diborane diammine" in ether[125].

A simple method for obtaining ammine–borine, with a yield of ~45%, is based on the reaction between lithium borohydride and ammonium chloride in ether[123,124], the prototype of which is Schaeffer and Anderson's reaction[66] between alkylammonium chlorides and lithium borohydride. "Ammonium borohydride" is obviously formed at first, and then decomposes into hydrogen and ammine–borine:

$$LiBH_4 + NH_4Cl \rightarrow NH_4BH_4 + LiCl,$$
$$NH_4BH_4 \rightarrow H_3N{\cdot}BH_3 + H_2.$$

It is interesting that thermal decomposition of solid ammonium borohydride yields "diborane diammine"[119,126].

Ammine–borine is formed also by the action of ammonia on an ethereal solution of the complex of borine and methyl ether[124]:

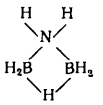
$$(CH_3)_2O{\cdot}BH_3 + NH_3 \rightarrow H_3N{\cdot}BH_3 + (CH_3)_2O.$$

Ammine–borine is a crystalline substance which is slowly hydrolysed by cold water.

Results of X-ray diffraction analysis show the length of the B–N bond in ammine–borine to be 1.56[127] or 1.60 Å[128], close to the B–N length in trimethylamine–borine[129]. The dipole moment of ammine–borine is 4.88 D.[130]

The preparation and properties of ammine–borine provided a direct proof that "diborane diammine" cannot be regarded as a dimer of ammine–borine[131].

Aminodiborane is a byproduct in the preparation of borazole from diborane and ammonia[105]. It is formed in 33% yield when a current of diborane is passed over "diborane diammine" at 88° and atmospheric pressure[132]. It can be stored at room temperature for several days without appreciable decomposition. It melts at -66.5° and boils at 75.2°. The structure of aminodiborane has been established by electron diffraction[99]: it is like that of diborane, with one bridge hydrogen replaced by an amino-group:



(e) Reactions of diborane with hydroxylamine and its methyl derivatives. Diborane and solid hydroxylamine either do not react at temperatures between -186° and -96° or else they do so explosively. In the presence of ethyl ether and with strong cooling the process takes place approximately in conformity with the equation

$$nB_2H_6 + 2\,nNH_2OH \xrightarrow{-112°} 2(H_3B{\cdot}NH_2OH)_n.$$

The reaction product could not be isolated in a pure form, since it was unstable, decomposing with the evolution of hydrogen when the temperature was raised[133]. The product of the addition of *N*-methylhydroxylamine to diborane is also unstable, and was not isolated in a pure form[133]. *NN*-Dimethylhydroxylamine, on the other hand, forms with a borine molecule a molecular compound which withstands being heated to 25°[133].

O-Methyl derivatives of hydroxylamine form still more stable compounds with borine. Thus methoxyamine–borine decomposes explosively on being rapidly heated to 90°, but with slow heating decomposition occurs quietly with the evolution of hydrogen. The use of ether is desirable but not necessary in the preparation of *ON*-dimethylhydroxylamine–borine; this substance decomposes without explosion at 65°. *ONN*-Trimethylhydroxylamine forms an adduct with borine in the absence of solvent; this adduct does not explode on being rapidly heated at 100°, but decomposes slowly at this temperature[134] with the evolution of hydrogen.

(f) Reactions of diborane with nitriles. Diborane and acetonitrile form a solid adduct $CH_3CN.BH_3$[2] having a vapour pressure of 40 mm at 20°; when kept at this temperature for several days, it is converted in 50% yield, to *N*-triethylborazole[135].

The complex of propionitrile with borine $C_2H_5CN.BH_3$ is less stable: it dissociates reversibly at -30°. The heat of dissociation of the solid complex into C_2H_5CN and diborane is 9.8 kcal mole^{-1}, the value for dissociation into the nitrile and BH_3 being 24 kcal mole^{-1}. The compound decomposes at 20° into hydrogen and an unidentified solid. At -10° or 0° the complex is converted to *N*-tri-n-propylborazole in good yield. The formation of *N*-trialkyl derivatives of borazole from complexes of nitriles with borine is represented by the following scheme:

$$RC{\equiv}N{\cdot}BH_3 \rightarrow [RCH{=}NBH_2] \rightarrow [RCH_2N{=}BH] \rightarrow (RCH_2N{-}BH)_3.$$

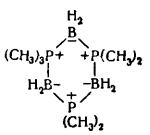
Acrylonitrile and diborane give the addition compound $CH_2:CHCN.BH_3$ at -132°; this decomposes rapidly at 0° without forming a borazole compound. Benzonitrile gives the adduct $C_6H_5CN.BH_3$ with diborane [135].

Diborane forms complexes with silyl cyanides [136]. Trimethylsilyl cyanide–borine decomposes at 100° forming trimethylsilane. It is slowly hydrolysed by water, and reacts with HCl with the evolution of hydrogen; trimethylamine displaces the trimethylsilyl cyanide from the complex.

2. Reactions of Diborane with Phosphorus, Arsenic, and Antimony Compounds

Diborane and phosphine react at 110° to form an unstable compound having the composition $BH_3.PH_3$.[137] The kinetics of this reaction have been studied [138]. Burg and Wagner [139] found greater thermal stability in compounds of borine with methylphosphines, which were obtained by mixing the components at a low temperature. Methylphosphine–borine $CH_3PH_2.BH_3$ loses hydrogen at 100° and is converted to a viscous oil. Dimethylphosphine–borine $(CH_3)_2PH.BH_3$ evolves hydrogen at 150°, the main product being trimeric dimethylphosphinoborine $[(CH_3)_2PBH_2]_3$ together with some tetramer and a polymer. The trimer and the tetramer are chemically inert and heat resistant substances, which are slowly hydrolysed at 300°; [139] the dimer decomposes very slowly at 250°.[140]

According to X-ray studies [141], the trimer of dimethylphosphinoborine has a cyclic structure with alternating BH_2 and $(CH_3)_2P$ groups linked together in the form of a "chair". The P–B bond length is 1.935 Å, and P–C length 1.837 Å:



When dimethylphosphine–borine and ethylmethylphosphine–borine are heated with triethylamine in a vacuum at 200°, polymers are obtained in which the recurrent groups are R_2PBH_2.[142]

Bis(trifluoromethyl)fluorophosphine reacts with diborane forming $[(CF_3)_2PBH_2]_3$, which is also obtained, together with a small amount of the tetramer $[(CF_3)_2PBH_2]_4$, by the interaction of $(CF_3)_2PH$ and diborane. The trimer reacts with hydrochloric acid only at 150°.[143] The cyclic phosphine C_4H_8PH (phospholan) reacts similarly to dialkylphosphines with diborane, forming the complex $C_4H_8PH.BH_3$, which is converted at 200° to $(C_4H_8PBH_2)_3$.[144]

Diborane and phosphorus trifluoride at high pressures give the unstable complex $F_3P.BH_3$.[145]

Recently Burg and Slota [146] have suggested obtaining dialkylphosphinoborines from more readily available phosphorus compounds than dialkylphosphines: heating dimethyl- and diethyl-chlorophosphines with sodium borohydride gave 50–70% yields of the corresponding trimeric dialkylphosphinoborines:

$$(C_2H_5)_2PCl + NaBH_4 \xrightarrow{-NaCl} [(C_2H_5)_2PH\cdot BH_3] \xrightarrow{-H_2} 1/3\,[(C_2H_5)_2PBH_2]_3.$$

The dimethyl trimer was obtained also by the pyrolysis of the complex of borine and dimethylaminodimethylphosphine [146].

TABLE 6. Boron–phosphorus and boron–arsenic compounds.

Compound	M.p., °C	B.p., °C (calc.)	References
	Strongly dissociated at 0°		
$BH_3\cdot PH_3$			137,138
$CH_3PH_2\cdot BH_3$	—49.3	150	139
$(CH_3)_2PH\cdot BH_3$	—22.6	85.5	139,142
$CH_3(C_2H_5)PH\cdot BH_3$	—	—	142
$(CH_3)_3P\cdot BH_3$	103.5	—	139
$(CH_3)_2NP(CH_3)_2\cdot BH_3$	12	—	144
$(CF_3)_2BF\cdot BH_3$	—	—	143
$(CH_3PHBH_3)_x$	—	—	139
$[(CH_3)_2P\cdot BH_2]_3$	86	235	139,144,148
$[(CH_3)_2PBH_2]_4$	161	310	139,148
$[(C_2H_5)_2P\cdot BH_2]_3$		134/1.5	144
$[(CH_3)_2PBH_2]_x$	164—168	—	142
$[CH_3(C_2H_5)PBH_2]_x$	118—126	—	142
$[(CF_3)_2PBH_2]_3$	30.5	177	143
$[(CF_3)_2PBH_2]_4$	—	—	143
$C_4H_8PH\cdot BH_3$	—	—	144
$(C_4H_8P\cdot BH_2)_3$	—	—	144
$F_3P\cdot BH_3$	—116	—61.8	145
$F_3P\cdot BD_3$	—115	—59.8	145
$(C_6H_5)_3PCH_2.BH_3$	192	—	149
$(C_6H_5)_3P\cdot CHCH_3\cdot BH_3$	172	—	149
$(C_6H_5)_3PCHC_6H_5.BH_3$	144	—	149
$CH_3AsH_2\cdot BH_3$	—80	—	150
	Completely dissociated at room temp.		
$(CH_3)_2AsH\cdot BH_3$	—21.5	85.5	150
$(CH_3)_3As\cdot BH_3$	74.5	154	150
$[(CH_3)_2AsBH_2]_x$			
$[(CH_3)_2AsBH_2]_3$	50.6	250	150
$[(CH_3)_2AsBH_2]_4$	150.5	352	150

At -78° diphosphine forms with diborane the complex $P_2H_4.B_2H_6$; at room temperature P_2H_4 and B_2H_6 react slowly with the formation of PH_3, H_2, and a solid having the composition $BPH_{3.5}$.[147] Tetramethyldiphosphine with diborane yields the complex $P_2(CH_3)_4.B_2H_6$, which at 170°–200° is converted to the trimer and the tetramer of dimethylphosphinoborine [148].

Diborane reacts in ethereal solutions with methylenetriphenylphosphorane and its analogues forming methylenetriphenylphosphorane–borine $(C_6H_5)_3PCH_2.BH_3$ and analogous compounds [149].

Arsine and alkylarsines behave similarly to phosphorus compounds towards diborane [150].

The action of sodium borohydride on dimethylantimony bromide yields dimethylstibinoborine, which above 78° decomposes with the evolution of hydrogen [151].

It is interesting that trimethylphosphine forms less stable complexes than does trimethylamine with trimethylborine or boron trifluoride, whereas it acts as a stronger complexing agent than trimethylamine towards borine [143]: $(CH_3)_3N > (CH_3)_3P > (CH_3)_3As$ in relation to $B(CH_3)_3$ and BF_3; $(CH_3)_3P > (CH_3)_3N > (CH_3)_3As > (CH_3)_3Sb$ in relation to BH_3‡. The physical properties of the boron–phosphorus and boron–arsenic compounds are given in Table 6.

3. Reactions of Diborane with Oxygen Compounds

(a) Reactions with ethers, alcohols, etc. Diborane reacts with ethers to form ether complexes of borine $R_2O.BH_3$. The complexes with methyl ether [120,152]

‡ *cf.* F.G.A.Stone, Chem.Rev., 58, 101 (1958) (Ed. of Translation).

(dissociation pressure 18 mm at -78.5°) and with tetrahydrofuran[152,153] (1.6 mm at -78°) have been isolated and described; the existence of a complex of borine with ethyl ether has been demonstrated spectroscopically[154]. The order of stability of these complexes is as follows:

$$\begin{matrix}CH_2{-}CH_2\\ |\quad\quad\\ CH_2{-}CH_2\end{matrix}\!\!>O\cdot BH_3 > (CH_3)_2O\cdot BH_3 > (C_2H_5)_2O\cdot BH_3.$$

The dissociation pressure of the complex of deuteroborine with methyl ether is 32 mm at -78.5° [155].

Alcohols convert diborane into boric esters, but dialkoxyborines are formed when an excess of diborane is used. Only dimethoxyborine[156] (calc. b.p. 26°, m.p. -130.6°) has been studied in detail. In the gas phase this substance is monomeric, its rate of decomposition,

$$6\,(CH_3O)_2BH \rightleftarrows B_2H_6 + 4\,(CH_3O)_3B,$$

being comparatively low and dependent on the vapour pressure; in the liquid state at 0° reaction occurs rapidly. A study has been made of the alcoholysis of diborane and deuteroborine with ordinary and with labelled ethanol[157]. The infra-red spectra of dimethoxyborine[158], diethoxyborine[159], and diisopropoxyborine[160] have been determined. For the reducing properties of diborane, see Refs. 161 and 162.

The mechanism of the hydrolysis of diborane in the gas phase has been investigated[163] and the heat of the reaction determined[164].

The action of n-butyl alcohol on 1,1-di-n-propyldiborane yields n-butyl di-n-propylborinate and n-butyl borate[46].

Mikhailov *et al.*[46] found that the reaction of tetraalkyldiboranes with alcohols is accompanied by disproportionation, so that alkylboronic esters and trialkylborines are obtained in addition to dialkylborinic esters. An analogous disproportionation obviously took place in the experiments of Brown *et al.*[165,166] on the methanolysis of the products obtained by the action of 1 mole of diborane on 4 moles of pent-1-ene in ethereal solution, when the n-pentylboronic ester and tri-n-pentylborine were obtained in addition to the expected ester of di-n-pentylborinic acid. These workers assume that the formation of the above compounds in their experiments is a consequence of equilibrium between tri-n-pentylborine and diborane.

(b) Borine carbonyl $H_3B.CO$. This borine complex, which has been known for a long time, is obtained by the action of an excess of carbon monoxide on diborane under pressure[64]. At room temperature borine carbonyl dissociates into carbon monoxide and diborane. Burg[167] supposed that the equilibrium

$$H_3B\cdot CO \rightleftarrows BH_3 + CO, \qquad (1)$$

is established rapidly, and that the rate-determining stage of the whole process is

$$H_3B\cdot CO + BH_3 \rightarrow B_2H_6 + CO. \qquad (2)$$

Bauer regards this mechanism as incorrect[168]. In his opinion, the kinetics of the process can be satisfactorily interpreted on the assumption that the rate-determining stage is the formation of borine [stage (1)], which is followed by the relatively rapid stages (2) and (3):

$$BH_3 + BH_3 \rightleftarrows B_2H_6. \qquad (3)$$

The energy of the dissociation of borine carbonyl into its components is 18.8 kcal mole^{-1}.[23,169] The carbonyl is also formed, together with B_4H_8CO, by the action of carbon monoxide on pentaborane[170]:

$$B_5H_{11} + 2CO \rightarrow H_3B\cdot CO + B_4H_8CO.$$

4. Reactions of Diborane with Sulphur Compounds

Burg and Wagner[171] showed that at -78° diborane and dimethyl sulphide form the borine complex $(CH_3)_2S.BH_3$. This compound is also obtained by the thermal decomposition of trimethylsulphonium borohydride (tetrahydroborate)[172].

In the dialkyl sulphides the tendency to coordinate increases in the sequence[173]

$$(CH_3)_2S \simeq (C_2H_5)_2S > (CH_2)_4S.$$

It is very interesting that dimethyl sulphide behaves as a stronger base than dimethyl selenide and methyl ether towards borine and trimethylborine[174]:

$$(CH_3)_2S\cdot BH_3 > (CH_3)_2Se\cdot BH_3,\ (CH_3)_2O\cdot BH_3,$$

whereas with boron trifluoride the ether is a stronger complex-forming agent than dimethyl sulphide. With respect to dimethyl sulphide and trimethylphosphine, the acidity of boron compounds falls in the following sequence:

$$BH_3 > BF_3 > B(CH_3)_3.$$

According to Burg and Wagner[171], diborane reacts with methanethiol forming a solid product, which on being heated in a vacuum to about 100° is converted to a complicated mixture of liquid and solid products which are considered to be polymers, $(CH_3SBH_2)_x$, of various degrees of polymerisation. With an excess of trimethylamine the polymer yields the adduct $CH_3SBH_2.N(CH_3)_3$; when a current of diborane is passed over the polymer at 90°, a small yield of unstable methylthiodiborane, $CH_3SB_2H_5$, is obtained.

Mikhailov *et al.*[175-177] found that diborane reacts smoothly with thiols in ether, various alkylthio-derivatives of borine being formed depending on the proportions of the reactants and the nature of the thiols. With methanethiol and ethanethiol the polymeric alkylthioborines are formed independently of the proportions of the reactants. With n-butanethiol diborane gives poly-n-butylthioborine only when the reactants are in the proportions 1 : 2:

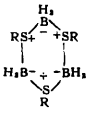
$$xB_2H_6 + 2xRSH \rightarrow 2\,(RSBH_2)_x + 2xH_2.$$

Polyethylthioborine and poly-n-butylthioborine are very thick syrupy liquids, which on standing at room temperature for a day are converted to the trimeric alkylthioborines. The solid polymer of methylthioborine does not undergo such a change spontaneously, but is converted to the trimer in tetrahydrofuran solution:

$$3\,(RSBH_2)_x \rightarrow x\,(RSBH_2)_3,$$

where R = CH_3, C_2H_5, n-C_4H_9.

The trimeric alkylthioborines are very stable towards water, and are difficult to oxidise with hydrogen peroxide, but they are completely destroyed on being heated with alcohols. They probably have a cyclic structure similar to those of the trimers of alkylaminoborines and dimethylphosphinoborine:



Reaction of diborane with an excess of propanethiol and n-butanethiol yields the dialkylthioborines, which are largely dimerised to the tetraalkylthiodiboranes:

$$B_2H_6+4RSH\rightarrow[(RS)_2BH]_2+4H_2.$$

At 100°–150° the alkylthioborine trimers and the tetraalkylthiodiboranes react with thiols forming trialkylthioborates[176,178]:

$$(RSBH_2)_3+6RSH\rightarrow 3B(SR)_3+6H_2.$$

Alkylthioborine polymers react in ether with olefines forming dialkylthioborinic esters:

$$(RSBH_2)_x+2x RCH=CH_2\rightarrow x(RCH_2-CH_2)_2BSR.$$

The reaction is complicated by disproportionation, so that trialkylborines and tetraalkylthiodiboranes are also formed.

In ether solution alkylthioborine polymers readily add on to diene hydrocarbons, forming cyclic compounds containing boron in the ring[179]. 1,3-Dienes yield alkylthio-derivatives of borocyclopentane:

$$(RSBH_2)_x+xC_4H_6\rightarrow xRS-B\begin{matrix}CH_2-CH_2\\ |\\ CH_2-CH_2\end{matrix}$$

while boracyclohexane derivatives can be synthesised from 1,4-dienes:

$$(RSBH_2)_x+xCH_2=CH-CH_2-CH=CH_2\rightarrow xRS-B\begin{matrix}CH_2-CH_2\\ \diagdown\quad\diagup\ CH_2\\ CH_2-CH_2\end{matrix}$$

Since the alkylthio-group attached to the boron atom is highly reactive, 1-alkylthioboracycloalkanes can be sucessfully used for the synthesis of various functional derivatives of cyclic compounds of boron.

Tetrabutylthiodiborane is also able to react with unsaturated compounds[180]. Its addition to hex-1-ene, oct-1-ene, styrene, cyclohexene, and diethylmethylvinylsilane was effected by heating the components in the presence of pyridine at 70°–80°, high yields of n-butyl alkylthioboronates being obtained in all cases other than that of styrene:

$$(n\text{-}C_4H_9S)_2BH+RCH=CH_2\rightarrow RCH_2CH_2B(SC_4H_{9}\text{-}n)_2.$$

The reactions between tetra-n-butylthiodiborane and propene or isobutene are complicated. When the mixture containing propene is heated in the presence of pyridine in an autoclave at 70°–80° and 5–15 atm, n-butyl n-propylthioboronate is formed, together with n-butyl di-n-propylthioborinate and tri-n-butyl thioborate. Isobutene reacts similarly, being converted to a mixture of the isobutylthioboronic and diisobutylthioborinic esters and the thioborate. The formation of dialkylthioborinic esters is explained by the partial conversion under these conditions of tetra-n-butylthiodiborane to the thioborate and n-butylthioborine; it is the latter which forms the corresponding dialkylthioborinic esters with the olefines.

Tetra-n-butylthiodiborane reacts with primary amines (ethylamine, n-butylamine) giving high yields of *N*-trialkylborazoles[180]. A complex of the dialkylthioborine with the amine is evidently formed in the first stage of the process, and this splits off a thiol, being converted to an alkylamino(alkylthio)borine; the latter gives the borazole derivative with the elimination of a further thiol molecule:

$$(n\text{-}C_4H_9S)_2BH+RNH_2\rightarrow(n\text{-}C_4H_9S)_2BH\cdot NH_2R\xrightarrow{-C_4H_9SH}$$

$$\rightarrow(n\text{-}C_4H_9S-BH-NHR]\xrightarrow{-C_4H_9SH}{}^1/_3(HB-NR)_3.$$

Thiols act on tetraalkyldiboranes at room temperature to give 60–83% yields of dialkylthioborinic esters[46,171]:

$$R_4B_2H_2+2R'SH=2R_2BSR'+2H_2.$$

Hawthorne[181] has shown that trimethylamine–borine on being heated with the higher thiols is converted to thioboric esters, while trimethylamine–alkylborines react with thiols at 60°–110° to form alkylthioboronic esters.

With dimethyl disulphide, diborane forms a solid product having the composition $(CH_3SBH_2)_x$;[171] with hydrogen sulphide it gives a vitreous polymer $(HBS)_x$.[171]

Mikhailov and Dorokhov[89] found that dialkylamine–borines and bis(dialkylamino)diboranes react with thiols at 80°–120° to form an interesting new type of compound, the alkylthiodialkylaminoborines, which exist in the monomeric form:

$$R_2NH\cdot BH_3+R'SH=R_2N-BH-SR'+2H_2,$$

$$[R_2NBH_2]_2+2R'SH=2R_2N-BH-SR'+2H_2.$$

When these compounds are heated (60°–70°) with primary amines, they exchange the R_2N and RS groups for alkylamino-groups, thus being converted to the previously unknown bisalkylaminoborines[182]:

$$R_2N-BH-SR'+2R''NH_2=(R''NH)_2BH+R'SH+R_2NH.$$

When these latter compounds are hated above 150°, they eliminate alkylamines and form *N*-trialkylborazoles:

$$3(RNH)_2BH=(HB-NR)_3+3RNH_2.$$

Thiols act on alkylamine–borines giving unstable alkylaminoalkylthioborines, which at 100° eliminate the thiol and condense into *N*-trialkylborazoles[183]:

$$RNH_2\cdot BH_3+R'SH\xrightarrow{-H_2}[RNH-BH-SR']\xrightarrow{-R'SH}(HB-NR)_3.$$

Since the thiol is regenerated during the reaction, *N*-trialkylborazoles can be synthesised from alkylamine–borines with moderate heating (100°) using a small amount of the thiol, which acts as a catalyst for the reaction. The thermal conversion of alkylamine–borines to *N*-trialkylborazoles requires a temperature of 200°–300°.

5. Halogenated Borines

In the synthesis of diborane from BCl_3 and H_2 in an electric discharge, chloroborines are obtained which rapidly disproportionate to B_2H_6 and BCl_3. One of these compounds — chlorodiborane — has been isolated[184]. Dichloroborine, formed in high yield from H_2 and BCl_3 at 400°–450°, can be preserved from further spontaneous changes by cooling to -135°.[185]

Ether complexes of chloroborine, which are quite stable at room temperature, are obtained by the interaction of diborane and boron trichloride in ether[30,186,187]; methyl ether, ethyl ether, diglyme, tetrahydropyran, and tetrahydrofuran can be used as solvents[187]:

$$B_2H_6+BCl_3+3O\begin{matrix}\diagup\\ \diagdown\end{matrix}=3BH_2Cl\cdot O\begin{matrix}\diagup\\ \diagdown\end{matrix}.$$

Equimolar proportions of the reactants yield ether complexes of chloroborine[187] which are liquid at room temperature; proportions of 1:4 give ether complexes of dichloroborines[187].

Nöth and Beyer[188] recommend the preparation of ether complexes of chloroborine by the action of lithium borohydride on an ether solution of BCl_3 or by the action of hydrogen chloride on an ether solution of diborane:

$$BCl_3 + LiBH_4 + 2R_2O = 2BH_2Cl \cdot OR_2 + LiCl,$$

$$2HCl + B_2H_6 + 2R_2O = 2BH_2Cl \cdot OR_2 + 2H_2.$$

Crystalline amine complexes of halogenoborines are also stable, and have recently been obtained by Nöth and Beyer[188] by four methods. The first method consists in the action of a hydrogen halide on an ether solution of an alkylamine complex of borine:

$$R_nNH_{3-n} \cdot BH_3 + HX = R_nNH_{3-n} \cdot BH_2X + H_2,$$

where X = Cl, Br, I. In the second method boron tribromide (or trichloride) acts on trialkylamine–borines:

$$3R_3N \cdot BH_3 + BBr_3 = 3R_3N \cdot BH_2Br + {}^1/_2B_2H_6.$$

By using two moles of BBr_3 in this way, we can also obtain the amine complexes of dibromoborine. The third method is to add a tertiary amine to an ether solution of chloroborine:

$$R_3N + BH_2Cl \cdot OR_2 = R_3N \cdot BH_2Cl + R_2O.$$

Finally, amine complexes of iodoborine can be obtained by the action of iodine on trialkylamine–borines:

$$2(CH_3)_3N \cdot BH_3 + I_2 = 2(CH_3)_3N \cdot BH_2I + H_2.$$

Lynds and Stern found that dichloroborine adds to alkenes at 10°–30° in accordance with Markovnikov's rule, with the formation of alkylboron dichlorides[185], although it had previously been stated that in the presence of ether the reaction results in the production of trialkylborines[187]:

$$BHCl_2 + CH_3CH = CH_2 \rightarrow (CH_3)_2CH - BCl_2.$$

Dichloroborine is capable also of addition to acetylene and butadiene[184].

6. Reactions of Diborane and Tetramethyldiborane with Metals

Diborane does not react with solid alkali metals, but is absorbed by sodium amalgam at room temperature. Stock and his collaborators supposed[110,189,190] that reaction stops after 2–3 days, the compound $Na_2B_2H_6$ being formed. It was later found that sodium is able to absorb a greater amount of diborane than is required to form $Na_2B_2H_6$.[191]

Reaction between diborane and the amalgam is considerably more rapid in the presence of ethyl or n-butyl ether, and is complete in 1–2 days with the absorption of one mole of diborane by one g-atom of sodium[192,193]. The final products of the reaction, which have the empirical composition NaB_2H_6, represent an equimolecular mixture of sodium borohydride and the previously unknown compound NaB_3H_8. The latter substance is stable at 200° and is readily soluble in ether, so that it can be separated from the sodium borohydride:

$$2Na + 2B_2H_6 \rightarrow NaBH_4 + NaB_3H_8.$$

Tetramethyldiborane reacts with sodium in liquid ammonia at -78° to form the salt-like compound $Na_2HB(CH_3)_2$.[194] The reaction with calcium in liquid ammonia leads to the formation of $CaHB(CH_3)_3 \cdot NH_3$.[195]

7. Reactions of Diborane and Alkyldiboranes with Alkoxy- and Alkylthio-Derivatives of Boron

Mikhailov and Vasil'ev investigated the reactions of diborane and tetraalkyldiboranes with boric and organoboric esters[196,197]. In contrast to the reaction of diarylborinic esters with diborane, which yields 1,2-diaryldiboranes and orthoborates[62], dialkylborinic esters react with diborane (2 : 1) to form alkylboronic esters and dialkyldiboranes:

$$2R_2BOR' + B_2H_6 = RB(OR')_2 + 1.5R_2B_2H_4.$$

Since the dialkyldiboranes can equilibrate with dialkylborinic esters, resulting in the formation of alkylboronic esters and tetraalkyldiboranes,

$$4R_2BOR' + R_2B_2H_4 = 2RB(OR')_2 + 2R_4B_2H_2,$$

the action of one mole of diborane on eight moles of the dialkylborinic ester is represented by the equation

$$8R_2BOR' + B_2H_6 = 4RB(OR')_2 + 3R_4B_2H_2.$$

Tetraalkyldiboranes undergo alkyl transfer reactions with borates, slowly at room temperature and rapidly on moderate heating (60°–100°), with the formation of alkylboronic esters and dialkyldiboranes:

$$R_4B_2H_2 + 2B(OR')_3 = 3RB(OR')_2 + {}^1/_2R_2B_2H_4.$$

The process is complicated by the formation of diborane by the partial symmetrical redistribution of the dialkyldiborane and its interaction with the original borate. If the reaction is carried out with the mixture heated to boiling, the diborane being removed from the reaction zone, the reaction between the tetraalkyldiborane and the borate is represented by the equation

$$3R_4B_2H_2 + 8B(OR')_3 = 12RB(OR')_2 + B_2H_6.$$

The ability of alkyldiboranes to undergo alkyl interchange reactions enables them to be used as catalysts for reactions between different boron compounds. Thus in the presence of a catalytic quantity of a tetraalkyldiborane, trialkylborines and borates are smoothly converted at 60°–100° to alkylboronic esters:

$$BR_3 + 2B(OR')_3 \xrightarrow{R_4B_2H_2} 3RB(OR')_2.$$

In the presence of tetraalkyldiboranes good yields of alkylboronic esters are obtained by heating mixtures of a dialkylborinic ester and a borate:

$$R_2BOR' + B(OR')_3 \xrightarrow{R_4B_2H_2} 2RB(OR')_2.$$

An equimolar mixture of a trialkylborine and an alkylboronic ester can be converted to a dialkylborinic ester using a small quantity of a tetraalkyldiborane:

$$BR_3 + RB(OR')_2 \xrightarrow{R_4B_2H_2} 2R_2BOR'.$$

The thio-analogues behave similarly to the borates and alkylboronic and dialkylborinic esters. Thus heating a mixture of a trialkyl thioborate and a trialkylborine in the presence of tetra-n-butyldiborane produces a high yield of an alkylthioboronic ester:

$$BR_3 + 2B(SR')_3 \xrightarrow{R_4B_2H_2} 3RB(SR')_2.$$

8. Reactions of Diborane and Its Alkyl and Aryl Derivatives with Unsaturated Compounds

In 1948 Hurd established that diborane reacts with alkenes to form trialkylborines[60]. By heating ethylene with 2% of diborane in a sealed tube at 100° for 4 h, he obtained a small quantity of triethylborine, which he identified in the mass spectrograph. Diborane adds rather more rapidly to isobutene[60]. In later work a mixture of ethylene and diborane (4.4 : 1) was heated at 60° for 10 days to form triethylborine and a small amount of diethyldiborane[198].

Diborane adds smoothly to alkenes in a circulatory flow system at 230°–250° if its concentration in the gas phase is 3.5–3.8%.[199] The kinetics of the reaction between ethylene and diborane were studied over the range 130°–177° by Whatley and Pease[200]. The kinetics of the reactions of alkenes with aluminium borohydride, as a source of diborane, have also been studied[201,202].

The reactions of diborane with derivatives of ethylene are complicated. The interaction of diborane and fluorinated alkenes involves the formation of boron trifluoride and alkyl fluoroborates; a mixture of diborane and tetrafluoroethylene in certain proportions explodes at 80°–100°;[198,203] the reactions of diborane with acrylonitrile and methyl methacrylate give boron compounds of undetermined structure[204].

In 1957 Brown and Rao[205] discovered that in ethers the addition of diborane to alkenes is very rapid and almost quantitative. "Hydroboronation", as Brown termed the addition of diborane to unsaturated compounds, is carried out by passing a current of diborane into an ether solution of the alkene, the resulting trialkylborine being separated by distillation (or it is oxidised, without separation, to the corresponding alcohol and boric acid). The hydroboronation of ethylene, pent-1-ene, hex-1-ene, hex-2-ene, oct-1-ene, cyclopentene, cyclohexene, and other alkenes, has been accomplished in this way[205,206]. Another procedure is to prepare diborane *in situ* in the reaction vessel containing the alkene in solution. For this purpose, the ether complex of boron trifluoride is added to a solution of the alkene and sodium borohydride in diglyme[206] or to an ether solution of the alkene and lithium borohydride[207]. Alternatively, a suspension of sodium borohydride in tetrahydrofuran or diglyme can be treated with hydrogen chloride, and then the alkene added to the resulting diborane solution[207]. Finally, diborane can be obtained from lithium aluminium hydride and the ether complex of boron trifluoride in ethyl ether[207,208]. The different methods of hydroboronation are described in a review paper by Brown *et al.*[209]

Brown and Rao[210,211] found also that trialkylborines are obtained smoothly by the action on alkenes of a mixture of sodium borohydride and aluminium chloride in diglyme solution:

$$9RCH=CH_2 + 3NaBH_4 + AlCl_3 \rightarrow 3\,(R-CH_2-CH_2)_3B + 3NaCl + AlH_3.$$

The addition of diborane to α-olefines takes place mainly contrary to Markovnikov's rule:

$$3R-CH=CH_2 + {}^1/_2B_2H_6 \rightarrow (R-CH_2-CH_2)_3B,$$

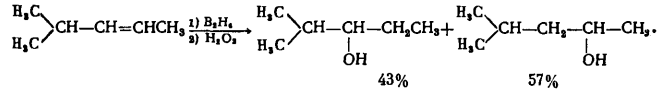
the isomeric compound being formed to only a slight extent. Thus hydroboronation of hex-1-ene with subsequent oxidation of the reaction products yields 94% of hexan-1-ol and 6% of hexan-2-ol:[212]

$$6C_4H_9CH=CH_2 + B_2H_6 \rightarrow (C_4H_9CH_2-CH_2-)_3B + \left(\begin{matrix}C_4H_9\\CH_3\end{matrix}\!\!>\!CH\right)_3B.$$

94% 6%

Branched α-olefines, such as 3-methylbut-1-ene and 3,3-dimethylbut-1-ene, form the corresponding isomeric trialkylborines in the same ratio[212,213]. Phenyl groups adjacent to a double bond change the proportions of the isomers, styrene for example giving 20% of the α- and 80% of the β-isomer. The presence of electronegative substituents in the aromatic ring favours Markovnikov addition still more: *p*-chlorostyrene yields 35% of the α- and 65% of the β-isomer[212,213].

Alkenes with non-terminal double bonds yield almost equal quantities of isomers on hydroboronation. Thus 4-methylpent-2-ene forms a mixture of trialkylborines, oxidation of which yields 43% of 2-methylpentan-3-ol and 57% of 4-methylpentan-2-ol [212,213]:



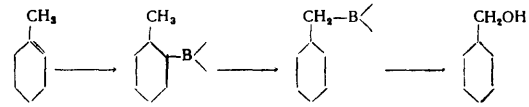
Hex-2-ene gives after oxidation equal quantities of hexan-2-ol and hexan-3-ol [213,214].

Compounds containing a semicyclic double bond are converted to primary alcohols on hydroboronation with subsequent oxidation of the addition products. In this way myrtanol has been obtained fron norpinene, and camphanol from camphenone[215,216].

In spite of its great velocity, hydroboronation is an extremely selective reaction. Treatment of equimolar mixtures of pent-1-ene and pent-2-ene and of hex-1-ene and hex-2-ene with insufficient diborane results in selective conversion of the α-olefines to tri-n-pentylborine and tri-n-hexylborine respectively, while the β-olefines remain unchanged[217].

Brown and Zweifel[218] showed the stereospecificity of hydroboronation in a series of cyclic alkenes, by obtaining the *trans*-2-methylcycloalkanols from 1-methylcyclopentene and 1-methylcyclohexene, and *cis*-1,2-dimethylcyclopentanol from 1,2-dimethylcyclopentene. The hydration of steroids is also stereospecific[208,219]. Cholesterol on hydroboronation followed by oxidation yields as the main product cholestane-3β, 6α-diol and only a small amount of the product of frontal *cis*-addition, coprostane-3β, 6β-diol. Stereospecific *cis*-addition of diborane takes place also with acyclic systems. Thus *trans*-(2-*p*-methoxyphenyl)but-2-ene can be converted to *erythro*-(3-*p*-methoxyphenyl)butan-2-ol, while the *cis*-isomer gives the compound with the *threo*-configuration[220].

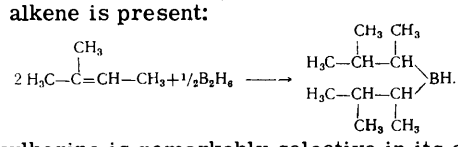
Since trialkylborines with secondary or tertiary alkyl radicals can isomerise on heating to trialkylborines having primary radicals[221], hydroboronation enables alkenes with non-terminal double bonds to be converted to primary alcohols[217,222]. This method also allows cycloalkenes to be converted to alcohols containing the hydroxyl group in the side-chain, so that, for example, cyclohexylmethanol can be prepared from 1-methylcyclohexene[222]:



On the other hand, hydroboronation can be used as a convenient synthetic route for obtaining the thermodynamically less stable alkenes with terminal double bonds from the more stable branched alkenes. This method of "contrathermodynamic" isomerisation of alkenes is based on the fact that trialkylborines on being heated with higher alkenes

undergo transalkylation with the removal of the lower alkene[217,223,224]. The process is thus essentially hydroboronation of an alkene containing the double bond in the middle of the chain, thermal isomerisation of the resulting trialkylborine to a trialkylborine having primary hydrocarbon radicals, and finally displacement of a lower by a higher alkene. For example, 3-ethylpent-2-ene may be hydroboronated, and the reaction product boiled for an hour and then heated with dec-1-ene, the resulting 3-ethylpent--1-ene being distilled off[225].

Not all alkenes are converted by diborane to trialkylborines. In several cases the reaction stops at the dialkylborine stage owing to steric hindrance. Thus Brown and Zweifel[212] found that hydroboronation of 2-methylbut-2-ene at 0° leads to bis(1,2-dimethylpropyl)borine even when an excess of alkene is present:

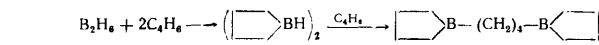


This dialkylborine is remarkably selective in its addition to other unsaturated compounds. The ability of alkenes of different structures to add bis-1,2-dimethylpropylborine diminishes in the following order: hex-1-ene > 3-methylbut-1--ene > 2-methylbut-1-ene > *cis*-hex-2-ene > cyclopentene > *trans*-hex-2-ene > *trans*-4-methylpent-2-ene > > cyclohexene > 1-methylcyclopentene > 2-methylbut-2--ene > 1-methylcyclohexene ≥ 2,3-dimethylbut-2-ene. In many cases the difference in reactivity is so great that bis(1,2--dimethylpropyl)borine can be utilised for the selective hydroboronation of more reactive alkenes mixed with less reactive compounds. In this way pent-1-ene can be practically quantitatively removed from its mixtures with pent-2-ene. Similarly hex-1-ene is quantitatively hydroboronated in the presence of cyclohexene.

A still more marked difference in reactivity towards bis(1,2-dimethylpropyl)borine is observed with *cis-trans*--isomers, which enables the isomers to be separated. Thus treatment with this dialkylborine of commercial pent-2-ene, containing 18% of the *cis*-form, enables *trans*-pent-2-ene of 97% purity to be obtained[226].

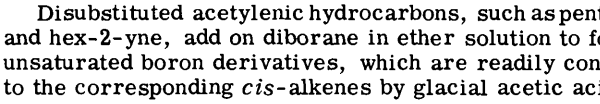
In some cases steric hindrance is so great that the reaction between diborane and the alkene stops at the alkylborine stage. Thus 2,2,5,5-tetramethylhex-3-ene with diborane gives 1-t-butyl-3,3-dimethylbutylborine, $C_{10}H_{21}BH_2$.[227]

Köster found that diborane adds to butadiene with the formation of a bisboracyclopentane, which is converted by an excess of butadiene to 1,4-bisboracyclopentylbutane[228,229]:

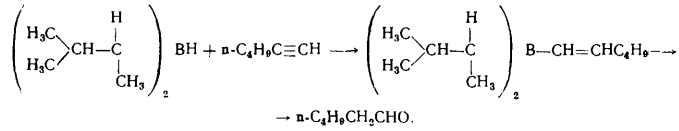


Oxidation of the addition product of diborane and butadiene produces mainly butane-1,4-diol[230]; oxidation of the reaction product from diborane and hexa-1,5-diene gives hexane-1,6-diol[230]. On hydroboronation of cyclopentadiene with subsequent oxidation, a 30% yield of cyclopent-3-enol is obtained[220].

Disubstituted acetylenic hydrocarbons, such as pent-2-yne and hex-2-yne, add on diborane in ether solution to form unsaturated boron derivatives, which are readily converted to the corresponding *cis*-alkenes by glacial acetic acid[231]:



Direct hydroboronation of hex-1-yne cannot be achieved, for about half of the hydrocarbon taken in an experiment does not react with the diborane, while the remainder forms a dialkenyl derivative of borine. However, hex-1-yne does add on bis(1,2-dimethylpropyl)borine; when the addition product is oxidised with hydrogen peroxide, n-hexanal is obtained[231]:



Hydroboronation of 2,2,5,5-tetramethylhex-3-yne with subsequent oxidation of the addition products led to the isolation of 2,2,5,5-tetramethylhexan-3-ol and 2,2,5,5-tetramethylhexane-3,4-diol[227].

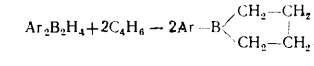
Very little work has yet been done on the reactions of alkene derivatives with diborane. The reaction of vinyl chloride with diborane in methyl ether is complex; a small quantity of a crystalline substance was isolated from the reaction products, and assigned the structure of an ether complex of 2-chloroethylboron dichloride[232]. With allyl chloride, diborane gives a 36% yield of tris(3-chloropropyl)borine and a little bis(3-chloropropyl)boron chloride; hydrolysis of 3-chloropropyl derivatives of boron[233] is accompanied by the formation of cyclopropane.

Seyferth[234,235] investigated the hydroboronation of trimethylvinylsilane with a mixture of sodium borohydride and aluminium chloride, and found that oxidation of the reaction products yielded 1- and 2-trimethylsilylethanol in the ratio 1 : 2.

Tetraalkyldiboranes in ether solution readily add to alkenes forming trialkylborines. Unsymmetrical trialkylborines can be obtained in this way[46].

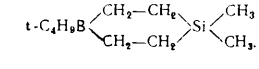
1,2-Diphenyldiborane reacts with alkenes forming phenyldialkylborines, which undergo redistribution even at room temperature into triphenylborine and a trialkylborine[31]:

1,2-Diaryldiboranes add to diene hydrocarbons in benzene solution at -40° with the formation of 1-arylboracyclopentanes[31]:



Hawthorne[236] showed that pyridine–borine adds to alkenes in the presence of diglyme under pressure at 100°. Ashby[237] synthesised trialkylborines by heating alkenes with trialkylamine–borines at 200°. Triethylamine–borine has been used for the hydroboronation of trimethylvinylsilane[235]. A trialkylamine–borine reacts at 100° with butadiene, forming a bisboracyclopentane[229].

Trimethylamine-t-butylborine at 50°–60° adds rapidly to alkenes (ethylene, propene, butene, isobutene) forming unsymmetrical trialkylborines. With butadiene and isoprene it forms 1-t-butylboracyclopentane and 3-methyl--1-t-butylboracyclopentane respectively; reaction between the complex and dimethyldivinylsilane yields 1,1-dimethyl--4-t-butyl-1-sila-4-boracyclohexane[238].



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POLYMERS OF CARBONYL COMPOUNDS

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I. INTRODUCTION

The synthesis of polymers of carbonyl compounds is a comparatively new branch of macromolecular chemistry and technology, which has attracted much attention from research workers during recent years. Polymers of formaldehyde, which can be used in various industries, are especially important. Great interest attaches also to the synthesis of stable polymers of acetaldehyde, especially as acetaldehyde can be obtained by a simple and cheap method, the oxidation of ethylene[1]. Polymers of several other aldehydes are also known, as well as a polymer of acetone.

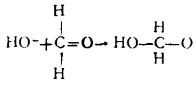
By now a voluminous literature is available on the chemistry and technology of polyformaldehyde, and review papers have been published[2-4], so that in the present survey this polymer will be considered only in relation to other polyaldehydes. The review will be mainly concerned with an examination of published information on the polymerisation of homologues of formaldehyde.

II. PREPARATION AND PROPERTIES OF POLYMERS OF CARBONYL COMPOUNDS

The polymerisation of aldehydes and ketones involves the formation of an acetal chain structure, with alternating carbon and oxygen atoms, independent of the hydrocarbon radical combined with the carbonyl group. Therefore the formation and the properties of these polymers have much in common.

It is believed[3,5,6] that carbonyl compounds polymerise by an ionic mechanism. This is quite likely, since the double bond of the carbonyl group contains a very labile electron pair. Formaldehyde polymerises under the influence of both electrophilic and nucleophilic reagents: *i.e.* polymerisation can take place both by a cationic and an anionic mechanism. This evidently applies also to the polymerisation of acetaldehyde.

The anionic mechanism by which polyformaldehyde is formed is as follows[3]:



Chain propagation:

$$HO-CH_2-O^- + n(CH_2O) \rightarrow HO-(CH_2O)_n-CH_2-O^-.$$

Chain termination:

$$HO-(CH_2O)_n-CH_2O^- + H^+ \rightarrow HO-(CH_2O)_n-CH_2OH.$$

Chain transfer occurs with extraordinary ease during the polymerisation of aldehydes, for example:

$$P-CH_2O-CH_2O^- + H_2O \rightarrow P-CH_2O-CH_2OH + OH^-.$$

The possibility of chain transfer makes extremely severe demands on the purity of the starting materials: even small amounts of chain-transfer agents as impurities may result in the formation of a polymer of low molecular weight.

In order to obtain polymers of high molecular weight, the reaction must be carried out in an anhydrous medium, since the proton produces chain termination, while water molecules are chain-transfer agents[7]. Since aldehydes are readily oxidised, they may contain acids, peracids, and other oxidation products, which are also capable of chain transfer. Thus the molecular weight of polyaldehydes is determined not only by the amount of catalyst but also by the purity of the monomer.

1. Polyformaldehyde

Polymers of formaldehyde have been known since the time of Butlerov, who obtained polyformaldehyde as early as 1859.[8] This history of polyformaldehyde, from the mechanically fragile polymer of low molecular weight to the commercial thermoplastic (Delrin), has been described in detail in the review by Schweitzer *et al.*[3]

The influence of the quantity of monomer, solvent, initiator, stabiliser, temperature, and rate of addition of monomer on the course of the polymerisation of formaldehyde has been described[9]. Since the molecular weight of formaldehyde polymers depends on the amount of impurity in the monomer, great attention has been paid in the literature to the preparation of pure dry formaldehyde[2]. Most of the proposed methods are based on the preparation of formaldehyde by decomposing its polymers of low molecular weight, which are very readily available.

The du Pont Corporation in the USA[10] has suggested a method for obtaining polyformaldehyde of high molecular weight by heating trioxan [paraformaldehyde] with AlF_3, BiF_3, SbF_3, etc.

Physical properties of polyformaldehyde[4,11-16]. Polyformaldehyde is an opaque white material, m.p. 180°, which can easily be dyed any colour. Its physical properties have been described in detail by Gogdall and Hardesty[14], according to whom it possesses great strength, which is virtually unaffected up to 120° and is not diminished by moisture; the modulus of elasticity also possesses great stability.

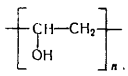
The creep of the material is greater than with amorphous polymers (polystyrene) but less than with crystalline polymers such as polyethylene and polyamides. A distinctive feature of polyformaldehyde is its dimensional stability.

Polyformaldehyde is more durable than ordinary thermoplastics (other than 6,6-nylon). It possesses excellent frictional and electrical properties. Its disadvantage is lack of resistance to acids and alkalis. In spite of this, rigidity and strength, low creep, high tenacity, abrasion resistance, elasticity, dimensional stability, and other properties, make polyformaldehyde one of the most valuable of thermoplastic materials.

2. Polyacetaldehyde

Acetaldehyde is not so readily polymerised as is formaldehyde. Methods of four types are available for polymerisation of acetaldehyde: (*a*) crystallisation polymerisation, (*b*) polymerisation by means of heterogeneous catalysts, (*c*) polymerisation by means of stereospecific catalysts, and (*d*) polymerisation induced by radiation.

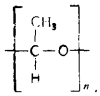
A paper has recently been published[17] on the formation of a polymer of acetaldehyde of the type of poly(vinyl alcohol):



This will be discussed in detail below.

Each type of polymerisation will be examined separately.

(*a*) Crystallisation polymerisation. Polyacetaldehyde was first obtained by this method, applied at the freezing point of the monomer, by Travers[18] and by Letort[19] in 1936. Staudinger suggested for the new polymer a structure based on a methyloxymethylene unit. This suggestion was later confirmed[20,21] by an investigation of the infra-red spectra, and at the present time the following structure is generally accepted for the polymer chain:



According to the most recent work, the molecular weight of the polymer is $(1-2.5) \times 10^6$.

A detailed investigation of the polymerisation of acetaldehyde was begun in 1943, a great contribution having been made by Letort and his coworkers, who worked out a technique for preparing the polymer[22,23]. At first the process seemed very simple: it was sufficient to freeze and unfreeze acetaldehyde several times, when formation of the polymer took place. Polymerisation seemed to be independent of the purity of the acetaldehyde, of the presence of water, air, etc. These workers concluded that the only factor influencing the polymerisation was the rate of crystallisation.

Later[24] they made a more detailed study of this question, and discovered that polymerisation occurs at the interface between the liquid monomer and the crystal. Letort[25] and Rigby and Danby[26] reported that the rate of polymerisation is greatly dependent on the temperature: polymerisation does not occur above the melting point of acetaldehyde (−123.5°), and is very slow below this temperature (see Fig. 1).

Bevington and Norrish[27], in contrast to the above workers, achieved reproducible results by maintaining a high degree of purity during an experiment. They found that the smallest amount of impurity has a great effect on the polymerisation: 0.5 mole % of water, alcohol, or acetone considerably decreases the yield of polymer; the reaction depends on the duration of the experiment, and on water, oxygen, etc. sorbed on the walls of the vessel.

These workers made a more detailed study of the properties of polyacetaldehyde. In contrast to polyformaldehyde, it is soluble in acetone, butyl acetate, ether, acetic acid, carbon tetrachloride, and ethyl alcohol; it swells in benzene, but is insoluble in water and petroleum ether. Polymeric acetaldehyde is a rubber, but it has no great mechanical strength or thermal stability. At room temperature the polymer slowly decomposes, forming acetaldehyde; the process of depolymerisation is accelerated by the presence of acetic acid.

The question of the effect of initiators on the polymerisation of acetaldehyde, left open by these authors, is answered in later papers by Letort *et al.*[28-30] After working with acetaldehyde of the greatest possible purity, they reached a conclusion opposite to that in the earlier work[22,23]. Crystallisation is a necessary but not a sufficient condition for polymer formation, since no polymer is formed in the absence of oxygen. If, however, a measured quantity of air or oxygen is introduced into the reaction mixture, and the latter exposed to ultra-violet radiation, the yield of polymer is markedly increased. Hence these workers reached the quite correct conclusion that the reaction is accelerated by oxidation products of acetaldehyde — acetyl peroxide or peracetic acid.

Special experiments showed the initiator to be peracetic acid formed by the oxidation of acetaldehyde. A more detailed study of the polymerisation established the following facts.

1. The presence of peracetic acid is necessary for the polymer to be formed during crystallisation of the monomer.

2. The duration of polymerisation P affects the yield and molecular weight of the polymer. At high rates of crystallisation ($P \leq 8$ min) the yield increases rapidly with increase in P, reaching a maximum (35%) when $P = 8$ min (Fig. 2). With $13 < P < 38$ min the yield increases linearly with increase in P, but above 38 min it suddenly drops to 6%.

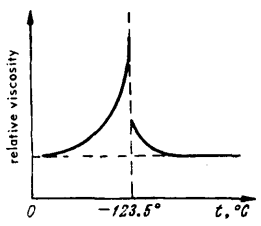


Fig. 1. Dependence of the viscosity of polymer on the temperature of polymerisation.

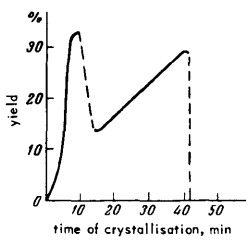


Fig. 2. Dependence of the yield of polymer on the duration of crystallisation.

3. The concentration of peroxide and the number of crystal nuclei also influence the yield and molecular weight of the polymer.

Letort and his collaborators discovered[31,32] a further extremely important fact: the presence of a single initiator is insufficient for the successful polymerisation of acetaldehyde, a cocatalyst — water or ethyl alcohol — being necessary. Fig. 3 gives an idea of the effect of water on the polymerisation: in very small quantities, 15–60 moles per 10^6 moles of acetaldehyde (0.002 wt.%), water exerts an extremely favourable effect on the yield of the polymer; in greater amounts, it begins to act as an inhibitor. It was also found that a mixture of peracetic acid and water produces the maximum effect when equimolar proportions of the components are present.

No exact idea of the mechanism of polymerisation can be obtained from these experimental results. In Letort's view the necessity of introducing a peroxide initiator (peracetic acid) and the inhibiting effect of water indicate a radical mechanism; the phenomenon of cocatalysis provides a weighty argument in support of an ionic mechanism, as does also the fact that several other acids[33], but not acetyl peroxide, can be employed instead of peracetic acid. All the organic acids used and the mineral acids cause polymerisation. In the latter case the yield is considerable, but the degree of polymerisation is low. Lewis acids, especially BF_3, are very active polymerisation catalysts. Ammonium salts of mineral acids also have an initiating effect, but neutral salts (for example NaCl) do not initiate polymerisation.

The method of crystallisation polymerisation is characterised by comparatively low yields of the polymer (of the order of 15%) and very high demands made on the purity of the materials and the experimental technique. The temperature, absence of impurities (air, water, etc.), and the duration and number of crystal nuclei must be controlled most accurately; the method requires exact adjustment of the low temperature (–123.5°, neither above nor below) and regulation of traces of water (up to 0.001%). If the experimental conditions are not adhered to, it is impossible to obtain reproducible results.

In 1959 Letort[34] published yet another paper on the synthesis of polyacetaldehyde, in the presence of ammonium persulphate and BF_3. Contrary to the earlier hypothesis of the necessity for crystallisation, it was discovered that the reaction can also take place above the melting point of acetaldehyde, at -80° or -65°; the presence of traces of water as cocatalyst is still necessary. The yield of the polymer is 30–50%.

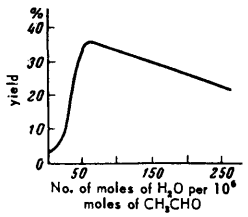


Fig. 3. Effect of water on the yield of polymer.

The main requirement of the method is the very exact measurement of small quantities (of the order of 10^{-4}%) of the catalyst and cocatalyst.

(*b*) Polymerisation of acetaldehyde using heterogeneous catalysts. The work of Furukawa *et al.*[35,36] provided a more practicable and cheaper method for obtaining acetaldehyde polymers at a higher temperature (-70° instead of -123.5°). The reaction was carried out in the presence of aluminium oxide, prepared by hydrolysis of the isopropoxide; before the experimental the aluminium oxide was heated in a current of dry air at 600° for 15 h (see Table 1).

Table 1 shows that the degree of dehydration of the aluminium oxide has a great effect on the reaction: ignition at 200° and at 1150° yields an inactive oxide, the best results being obtained with the oxide heated at 500°–600°. The reaction is also influenced by the temperature of polymerisation: at -10° or 15° no polymer is formed; at -184° a polymer is formed with a high molecular weight, but in low yield.

The resulting polymer is a non-sticky, highly elastic material which is soluble in most solvents — acetone, ether, butyl acetate, carbon tetrachloride, ethyl alcohol, and benzene — and insoluble in water, petroleum ether, and carbon disulphide. The infra-red spectrum indicates that the polymer obtained by means of aluminium oxide consists of the same structural units as Letort's polymer.

Experiment showed that basic substances (KOH, triethylamine, ammonia) inhibit the polymerisation.

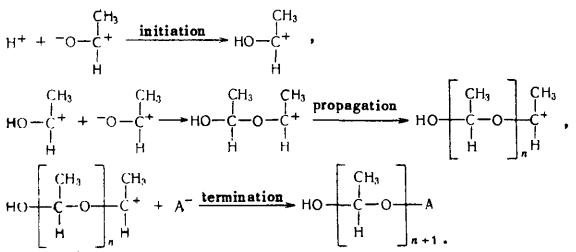
TABLE 1. Synthesis of polyacetaldehyde on aluminium oxide.

Aluminium oxide			Polymerisation		Polymer		
origin	ignited at, °C	water content, %	temp., °C	time, h	yield, %	η [d]	degree of polymerisation
Aluminium isopropoxide	—	—	— 70	43	0		
A[a]	200	20.3	— 70	43	0		
A	400	3.6	— 70	43	49	7.07	50 000
A	600	1.4	— 70	43	55	7.17	52 000
A	800	0.5	— 70	43	91	5.40	33 000
A	1000	0.2	— 70	43	76	6.65	40 000
A	1150[c]	0.0	— 70	43	8	0.03	
B[a]	not ignited[b]	13.5	— 70	65	23	3.88	17 500
B	600	1.6	— 70	65	66	2.40	9 400
B	1000	0.2	— 70	43	57	4.30	23 000
B	600[e]	1.6	— 70	55	63	4.07	21 000
B	600	1.6	— 70	20	0		
B	600[f]	1.6	—184	1.5	34	4.35	23 500
C			—184	1.5	9	5.60	35 000

Note. A[a] — oxide prepared by decomposition of aluminium isopropoxide; B[a] — commercial aluminium oxide (8–14 mesh); [b] commercial aluminium oxide used without being ignited; [c] no water present at 1150°; [d] in ethyl methyl ketone at 27.6°; [e] the monomer was distilled onto aluminium oxide under nitrogen at 1 atm; [f] aluminium oxide cooled with liquid air, and acetaldehyde distilled into it for 1½ h, the reaction mixture then being heated to room temperature and the polymer separated in the usual way; C in absence of aluminium oxide (acetaldehyde was condensed in liquid air in a tube for 1½ h).

Oxides other than alumina were tested, and it was found that CrO_3 and MoO_3 give high polymers in low yields; Be_2O_3, P_2O_5, MgO, ThO_2, and aluminosilicates form some polymer of low molecular weight; and SiO_2, CuO, TiO_2, ZrO_2, V_2O_5, ZnO, Fe_2O_3, MnO, CaO, BaO, PtO_2, PdO, and Ni_2O_3 yield no polymer. Hence it was concluded that aluminium oxide is exceptionally active in the polymerisation of acetaldehyde.

The reaction mechanism suggested by Furukawa for the polymerisation of acetaldehyde on aluminium oxide is as follows:



Later the polymerisation of acetaldehyde on Al_2O_3–SiO_2, ThO_2 [37] was reported, as well as polymerisation in the presence of aluminium oxide activated with diethylzinc,[38] which will be discussed in detail below.

In 1959 the production of a stable elastic polymer of acetaldehyde was described[39]; the new polymer was quite cheap, being half the price of acrylonitrile and butadiene–styrene rubbers; it was better than the latter in thermal stability. There was also a report[39] of the synthesis of a rubberlike polymer of acetaldehyde by the du Pont Corporation. This rubber could be vulcanised by irradiation and other methods without the use of sulphur.

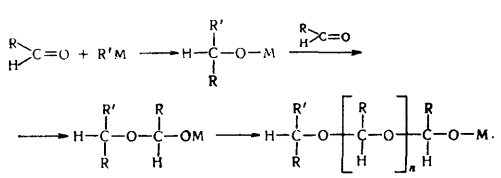
This practically exhausts the information available on the synthesis of elastic polyacetaldehyde.

(*c*) Stereospecific polymerisation of acetaldehyde. Until recently only elastic acetaldehyde polymers of irregular structure were known, although the possibility of obtaining polymers of regular structure is suggested by the molecular structure of the monomer.

In 1960 Natta[40] and Furukawa[41] and their collaborators discovered that acetaldehyde and its homologues form insoluble solid polymers in the presence of organometallic catalysts (metals of Groups II and III) at low temperatures. The polyacetaldehyde obtained in this way is a white thermoplastic resin. It is a solid, and, in contrast to the amorphous polymer, is insoluble in the usual organic solvents at their boiling points.

Apart from this information, which appeared in 1960, no other data have been published on the properties of plastic polyacetaldehyde, although work on these lines is evidently continuing.

The suggested reaction mechanism is



A crystalline, isotactic chain structure was suggested for these polymers on the basis of the infra-red spectra and X-ray data.

Recently Furukawa *et al.*[38] have synthesised polyacetaldehyde by the method described previously[41], using aluminium oxide activated with diethylzinc as catalyst. A block polymer was obtained, differing from ordinary polyacetaldehyde. It is a solid, sparingly soluble in methanol and soluble in chloroform. It was concluded from an examination of the infra-red spectra that it consisted of polymeric chains of acetaldehyde which were partly amorphous and partly crystalline.

From a detailed X-ray structure analysis of isotactic polyacetaldehyde, Natta *et al.*[42] concluded that the unit cell contains 16 monomeric units. It is similar in structure, not to polypropylene as was to be expected, but to polyvinylcyclohexane. The oxygen atoms in the polymer are shielded by the methyl groups, resulting in complete insolubility of isotactic polyacetaldehyde in the usual organic solvents.

(*d*) Polymerisation of acetaldehyde under the influence of ionising radiation. The possibility of obtaining polyacetaldehyde by this method was reported in 1960 by Chachaty[43]. Polymerisation was carried out in liquid and solid phases exposed to γ-radiation. With polymerisation in the liquid phase (-80°) an induction period is observed, and then reaction proceeds at a constant rate up to 20% conversion, after which the velocity of polymerisation increases rapidly. The polymer obtained is amorphous and rubberlike, similar to that of Letort and Furukawa, soluble in organic solvents, and unstable to heat; the molecular weight of the polymers lies between 5×10^5 and 1.5×10^6.

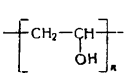
A radical mechanism for the polymerisation of acetaldehyde under the conditions investigated was suggested on the basis of the data obtained, although no final conclusion was reached.

In this way the range of catalysts for the polymerisation of acetaldehyde was extended, and it was established that acetaldehyde, like formaldehyde, can be polymerised by both anionic and cationic mechanisms. A radical method is also possible.

Copolymers of acetaldehyde with other aldehydes and monomers have been little discussed in the literature. At the plenary session of the International Symposium on Macromolecular Chemistry held in Moscow in 1960, Mark[7] mentioned that work was being carried out on the copolymerisation of acetaldehyde with formaldehyde and with acetone; great interest is aroused by work on the copolymerisation of acetaldehyde with acrolein at the carbonyl double bond. The resulting copolymers, owing to the presence of double bonds in the side-chains, would be capable of vulcanisation by the usual methods.

Chachaty[43] describes an acetaldehyde–formaldehyde copolymer obtained by γ-irradiation. It contains 20–50% of formaldehyde, and is a rubberlike elastic material which is more stable than polyacetaldehyde. The other properties of the copolymer are not described.

Polymers obtained by the above methods have a polyoxymethylene structure. The probability of the existence of an enol form of acetaldehyde, $CH_2:CHOH$, under certain conditions would make it possible for polymerisation to occur at the vinyl bond with formation of a poly(vinyl alcohol) type of polymer:



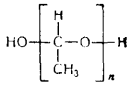
Imoto[17] obtained a polymer having the structure (according to its infra-red spectrum) of partly dehydrated poly(vinyl alcohol):

$$CH_3-(CH(OH)-CH_2)_n-CH=CH-(CH(OH)-CH_2)_m-(CH=CH)_k-CHO$$

Polymerisation was carried out in the presence of triethylamine at 40°–100° and 300–1200 atm, the molecular weight of the polymer being 1100. According to Imoto, polymers of higher molecular weight can be obtained by using still higher pressures.

The possibility of obtaining poly(vinyl alcohol) from such a readily available monomer as acetaldehyde is very promising, since this polymer has recently attracted a great deal of attention from chemists and technologists. Work on these lines is in its initial stages, and no other results have been published, so that we shall consider below only aldehyde polymers formed by reaction at the carbonyl double bond (acetal resins).

Various methods of investigation have shown[21,44] that polyacetaldehyde obtained in different ways has the same structure, which has been represented by the following formula:



(*e*) Physical properties of acetaldehyde polymers. The physical properties of polyacetaldehyde depend solely on the molecular structure of the polymer. Polymers of irregular chain structure, obtained in different ways, have identical properties. They form a rubberlike elastic material, yielding films which do not lose their elasticity at low temperatures. The polymer is soluble in many organic solvents (acetone, alcohol, ether, etc.), and can be precipitated from them with water or petroleum ether. Several physical properties of this polymer have been described by Bovey and Wands[45].

Apart from these very incomplete data, no information has been published on modification of the properties of the polyacetaldehyde rubber, on the properties obtained with fillers and after vulcanisation. No definite conclusion can be reached, therefore, as to its range of usefulness. This is probably a matter for the future, since work on the synthesis of elastic polyacetaldehyde is evidently continuing (in France, Italy, the USA, and Japan).

Published information on the properties of the crystalline, regular polyacetaldehyde is still scantier. In contrast to the amorphous polymer, it is a plastic white material, melting at 165°,[46] and insoluble in boiling solvents such as alcohol, ether, acetone, etc.

Thus, depending on the conditions of polymerisation and the spatial structure of the chain, two quite different types of polymer, based on acetaldehyde, can be obtained [without counting the polymer obtained by Imoto and having a poly(vinyl alcohol) structure]: (1) amorphous, atactic polymers, which are rubberlike elastic materials; and (2) crystalline, isotactic polymers, which are plastic and resinlike.

3. Polymers of Higher Aldehydes

Attempts have also been made to obtain polymers of higher aldehydes, and, as in the polymerisation of acetaldehyde, two types of polymers — amorphous and crystalline — have been obtained. Amorphous, atactic polymers have been obtained at high pressures (several thousand atmospheres) from propionaldehyde[21], n-butyraldehyde and isobutyraldehyde[47–54], n-valeraldehyde, and n-hexanal[47].

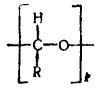
In a more detailed investigation of the polymerisation of n-butyraldehyde Gonikberg *et al.*[54] found that the polymer is formed only at pressures exceeding 5000 atm. Conant and Peterson[49], while investigating the polymerisation of n-butyraldehyde, were the first to observe an increase in reaction velocity in the presence of oxygen or benzoyl peroxide, the type of polymer obtained also being affected. This was an unusual observation, since it was regarded as established that carbonyl compounds polymerise by an ionic mechanism.

Zhulin and Gonikberg[52,53], who studied in greater detail the mechanism of the polymerisation of butyraldehyde under high pressures, observed that aldol condensation of the original aldehyde takes place in the presence of amines, whereas in the presence of acids parabutyraldehyde is formed. Water and alcohols produce a marked decrease in the molecular weight of the polymer, evidently owing to chain transfer.

These workers also confirmed Conant and Peterson's results: benzoyl peroxide catalyses the polymerisation of butyraldehyde, although the resulting polymer has a somewhat lower molecular weight than in the absence of a peroxide catalyst. Quinol inhibits polymerisation. In their opinion, these facts show that butyraldehyde polymerises by a radical-chain mechanism under the conditions studied.

Polymers of the higher aldehydes, like those of formaldehyde and acetaldehyde, are depolymerised to the monomers; acids and alkalis catalyse this reaction, and increase in temperature also substantially accelerates the decomposition. The introduction of inhibitors (for example, quinol) delays depolymerisation.

Novak and Whalley[21,47] used infra-red spectroscopy to make a thorough investigation of the molecular structure of polyaldehydes, which they found to consist of substituted polyoxymethylene chains terminating in hydroxyl groups:



where R = C_nH_{2n+1} and k = 1–6. No data have been published on the physical and mechanical properties of these polymers.

Crystalline polymers of higher aldehydes (propionaldehyde, butyraldehyde, etc.) were obtained only in 1960.[40,41,46] Polymerisation was carried out at low temperatures in the presence of organometallic catalysts, the yield of polymers being 10–20%. The polymers apparently have an isotactic structure, and differ markedly in properties from their amorphous analogues; they are solids, insoluble in the usual organic solvents. No data are given for other properties of the polymers obtained.

4. Polymers of Halogenated Aldehydes

It has long been known that chloroacetaldehyde and dichloroacetaldehyde form trimers and polymers[55–57]. Pure, dry chloroacetaldehyde yields on standing[58] a white, crystalline polymer, insoluble in water, alcohol, ether, and

chloroform. When heated above 120° the polymer decomposes to the monomer. The polymer of dichloroacetaldehyde is also formed spontaneously[58] as a block of soft, transparent material; the polymer is insoluble in water and alcohol, but soluble in acetone, from which it can be precipitated by methanol as a white solid which decomposes on being heated. The X-ray diffraction patterns showed both polymers to be crystalline. Their properties have not been described.

Polymers of trichloroacetaldehyde are known too[59-65]. They are formed when an amine — pyridine, trimethylamine, or quinoline — is added to anhydrous[63,64] chloral; polymeric chloral can also be obtained by the action of sulphuric acid on anhydrous chloral or chloral hydrate[61,62].

The polymer is a white solid, insoluble in all the organic solvents used other than pyridine and dimethylformamide. Later work by Novak and Whalley[65] showed that addition of the latter solvents to polychloral is accompanied not by dissolution but by degradation of the polymer. They showed by a detailed investigation of the infra-red spectra and X-ray diffraction patterns of polymeric chloral obtained in different ways — in the presence of sulphuric acid, pyridine, etc. — that, like other polyaldehydes, it is analogous to polyformaldehyde with hydroxyl groups at the ends of the chain.

Also like other polyaldehydes, polychloral is depolymerised at 140°–200° with formation of the monomer. The rate of thermal degradation is greatly dependent on the method of preparation. This effect is believed to be associated with the presence of traces of the acid or basic catalyst. X-Ray diffraction data showed that the crystallinity of the polymers also depends on the method of polymerisation.

Recently Furukawa *et al.*[41,59] have obtained a resinlike crystalline polymer from chloral (in the presence of an organometallic catalyst at a low temperature), which they suppose to have an isotactic structure, although they do not describes its properties. The literature contains no data on polymers of other chlorinated aldehydes.

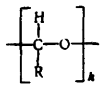
The polymerisation of fluorinated aldehydes of the aliphatic series has also been investigated during the past decade. This is a new field in the chemistry of polyaldehydes, since monomeric fluoroaldehydes were first obtained only in 1950[66].

Very scanty data are available in the literature on the preparation and properties of polymers of fluorinated aldehydes. In 1950 Schechter[66] first prepared a polymer of the first representative of this series — trifluoroacetaldehyde — and since then papers have been published[67-69] on polymers of pentafluoropropionaldehyde and heptafluorobutyraldehyde.

The polymers are obtained as a result of spontaneous[66,67,70] radical or ionic polymerisation. It is possible that the spontaneous polymerisation is caused by traces of some impurity. Acetyl peroxide, benzoyl peroxide, cumene hydroperoxide, and sodium persulphate can be employed as initators for the radical polymeristion of perfluoroaldehydes[70]. Radical polymerisation can be carried out at room temperature, being slowed down by a fall in temperature and accelerated by a rise. Polymerisation takes place also in the air, but is faster in its absence. All fluoroaldehydes readily form hydrates in the presence of water, so that polymerisation should be carried out in anhydrous media.

The higher fluoroaldehydes polymerise more slowly than trifluoroacetaldehyde, and the order of effectiveness of the catalysts is different. Heptafluorobutyraldehyde polymerises rapidly by an ionic mechanism, in the presence of sulphuric acid or acetic anhydride. A peroxide initiator is less effective. The opposite holds for the polymerisation of trifluoroacetaldehyde.

The usual polyaldehyde structure, *i.e.* a substituted polyoxymethylene chain, has been suggested for the polymeric fluoroaldehydes:



where R = C_nF_{2n+1} and k = 1–3.

Properties of polymeric fluoroaldehydes[70]. Polymeric fluoroaldehydes are transparent resinous materials which are insoluble in the usual organic solvents. They possess a unique and valuable combination of properties: they contain more than 50% of fluorine, and hence do not burn, they possess exceptional resistance to the action of various corrosive agents, and are resistant both to hydrocarbon and to aqueous solvents.

The resistance of these polymers to the action of fuming nitric acid even at elevated temperatures is of especial interest. Thus the polymer of trifluoroacetaldehyde lost only 0.8% of its weight after being boiled in fuming nitric acid for 6 h. The polymers are resistant to cold concentrated sulphuric acid, but are dissolved on boiling. Those of trifluoroacetaldehyde are also very resistant to the action of alkalis at room and elevated temperatures. Fluoroaldehyde polymers neither melt nor soften on being heated without the application of pressure; at high temperatures they, like other polyaldehydes, decompose to the monomers.

It can be seen from these facts how extensive and important are the practical potentialities for the employment of these polymers, especially under corrosive conditions at high temperatures.

5. Polyacroleins

Among polymers of unsaturated aldehydes, only polymeric acrolein has been described in detail in the literature, and this has already been known for more than a century. It was first mentioned in 1843, when Redtenbacher[71] found that acrolein passes spontaneously into an insoluble white solid. He suggested that the acrolein had polymerised, and termed the product "bisacryl".

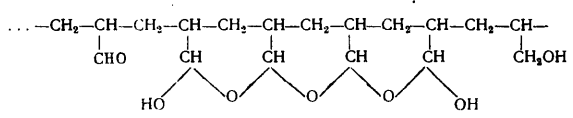
Subsequently Moureu and Dufraisse[72] discovered that the process is accelerated by light and by oxygen; quinol, catechol, and organometallic compounds inhibit the polymerisation of acrolein. It can take place by anionic, cationic, and radical mechanisms, and also in the presence of redox systems[73]. In many cases polymerisation is very rapid, even at low temperatures[74]. Techniques for the polymerisation of acrolein have been described in detail[75-80].

Physicochemical properties. Polyacroleins exist as powders, which are sparingly soluble in organic solvents, and which at 200°–220° sinter to a yellow or

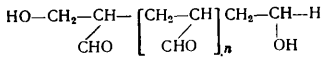
brown mass. The physicochemical properties of polyacrolein are greatly dependent on the mode of polymerisation. Polymer samples obtained in different ways differ in solubility, thermal stability, viscosity, etc., but no explanation of these differences is given in the literature.

The structure of the polyacroleins is not sufficiently understood, although a considerable number of papers have been published on this problem[74,76,77,81]. It has been established (by oxime formation) that these polymers contain carbonyl groups. The formation of hemiacetals, bisulphite derivatives, hydrazones, and phenylhydrazones has been described, as well as the Cannizzaro reaction. The spectra show the presence of an ether link. Although polyacroleins obtained in different ways differ in properties, their spectra show no substantial differences.

The following formula agrees well with the spectroscopic data and the chemical properties of the polyacroleins:

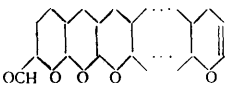


The formula below has been suggested[82,83] for acrolein polymers obtained by the use of organic bases:



where $n = 0-5$.

Scherlin[84] and his collaborators propose a polycyclic structure, formed by a process of continuous diene synthesis, for the polyacrolein (bisacryl) obtained by heating:



Other structures have also been suggested to represent polymeric acrolein[85], but none can be regarded as having been rigorously proved.

It is evident from this brief survey that the polymerisation of acrolein has not been investigated in detail, although several workers (for example Schulz and his collaborators) are carrying out intensive research in this field. The conditions under which the polymerisation of acrolein could be made to occur solely at the vinyl or solely at the carbonyl double bond, which would be of the greatest interest, are unknown.

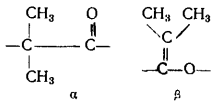
Mark[7] reported that work was being done on the preparation of rubberlike copolymers of acrolein and acetaldehyde. Owing to the presence of a double bond, such copolymers would be capable of vulcanisation with sulphur. No other data have been published on the polymerisation of acrolein at the carbonyl bond.

Polymers of methacryldehyde have also been described[86]. No polymers of other unsaturated aldehydes have been reported.

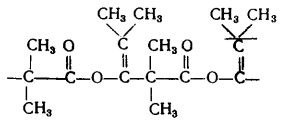
6. Polymers of Ketones

Kargin *et al.*[87] have recently described the preparation of polymers of acetone. Polymerisation was carried out by the simultaneous condensation of molecular beams of the monomer and the initiator (metallic magnesium) on a strongly cooled wall. A layer of condensate consisting of a vitrified molecular mixture of acetone and magnesium was deposited on the wall. If the temperature of the latter was allowed to rise, conditions were created, at the instant of the phase transition, which were kinetically favourable to polymerisation. This resulted in the formation of a polymer of acetone as an elastic white mass soluble in acetone (specific viscosity 0.6 at a concentration of 0.5 g per 100 ml of acetone). At room temperature this polymer is depolymerised; even the most stable specimens in the absence of oxygen and moisture can exist for at most 10–12 h.

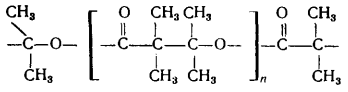
In 1960 Natta *et al.* reported the preparation of a polymer of dimethylketen[88] and of its copolymers with acetone and with acetophenone[89]. In the presence of aluminium bromide or triethylaluminium, dimethylketen gives a regular polymer or, more precisely, a copolymer derived from the two double bonds in the monomer:



Thus, the polymer has the following structure:



The dimethylketen–acetone copolymer is formed by polymerisation of the former at the C=C double bond, and of the latter at the carbonyl double bond:



A similar product is obtained by the copolymeristion of dimethylketen with acetophenone.

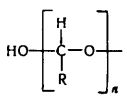
No other information on the polymerisation of ketones is available in the literature.

III. MOLECULAR STRUCTURE OF CARBONYL POLYMERS

A quite large literature exists on this question, concerned mainly with polyformaldehyde[4,12,90,91]. Koch and Lindvig[4] made a detailed study of the structure of this compound, and found that the molecules have a linear chain structure, no branching being detected. The molecular weight distribution is similar to that of polymers having a narrow distribution (for example 6,6-nylon).

Novak and Whalley[21,47,58,65,90] have published a series of papers on the infra-red spectra of polymeric aldehydes. They studied the spectra of polymers of formaldehyde, acetaldehyde, propionaldehyde, n- and iso-butyraldehyde

and -valeraldehyde, n-heptanal, and mono-, di-, and tri--chloroacetaldehyde. The spectra of polymers prepared in different ways were found to have an identical structure (Furukawa[36] reached a similar conclusion on comparing the spectra of polyacetaldehyde obtained by different methods). The band around 3440 cm^{-1} forms an exception, having different intensities in different specimens, and being completely absent in some of them. This frequency was assigned to stretching vibrations of the terminal OH group. The variation in its intensity is obviously associated with the different molecular weights of the polymer specimens. On the basis of their investigations, Novak and Whalley ascribe to polyaldehydes a substituted polyoxymethylene structure:



where R is a radical containing 0–7 carbon atoms or a halogenated radical.

The exact molecular structure of polymeric acrolein has not been established; there is evidence that polymerisation involves rupture of both double bonds, resulting in a cross--linked structure.

IV. DEGRADATION AND STABILISATION OF POLYALDEHYDES

A characteristic property of polyaldehydes is their degradation by heat, acids, bases, etc. The causes of and the laws governing the degradation and stabilisation of polyaldehydes are considered individually, since this problem is of great importance for the practical application of these polymers.

Whereas with carbon-chain and many heterochain polymers an increase in thermal stability merely extends their possible fields of application, polymers of carbonyl compounds cannot be of any practical use without being stabilised. Polyformaldehyde, first obtained as long as a century ago, has begun to be employed as a constructional material only during recent years, when it has proved possible to increase its thermal stability considerably.

With the high polymers of other carbonyl compounds which have been obtained the problem of stabilisation still remains unsolved, so that they cannot yet be utilised. Therefore a solution to the problem of the stabilisation of such polymers is important not only from the theoretical but also from the practical point of view.

We shall examine the published data available on the degradation and stabilisation of polymers of carbonyl compounds.

1. Polyformaldehyde

This polymer is formed from the monomer at temperatures not exceeding 110°. The maximum temperature of polymerisation is considerably lower with solutions of formaldehyde in organic solvents. In methylene chloride it is 30° for a 0.06 M concentration and 0° at 0.04 M.[92]

The rate of degradation of polyformaldehyde depends on many factors. According to results obtained by Schweitzer *et al.*[3], polymers of improved thermal stability can be obtained by using special methods of polymerisation. This is explained by a smaller number of weak links in the polymer, but no convincing arguments in support of this explanation are given.

Such special methods for the polymerisation of formaldehyde are described in a series of patents[2]. The resulting polyformaldehyde possesses a high molecular weight, which, however, does not explain its increased thermal stability, since the product of the spontaneous polymerisation of liquid formaldehyde has low thermal stability in spite of a high molecular weight[3].

The patent literature lists several compounds which have been proposed as stabilisers for polyformaldehyde. They can be divided into four groups: (1) substituted hydrazines and hydrazides; (2) secondary and tertiary aromatic amines; (3) substituted phenols and naphthols; and (4) urea, thiourea, and their derivatives.

These substances were used before to increase the resistance to "aging" of other polymers, since they are antioxidants, *i.e.* they retard chain oxidations which take place by a radical mechanism.

Polyamides[94] and sulphonamides[95] have recently been suggested for the stabilisation of polyformaldehyde. Polymers possessing basic properties also act as stabilisers[96]. Considerably greater stabilisation is achieved by replacing the terminal OH groups of the polyoxymethylene glycol by $OCOCH_3$ or OCH_3 groups. Staudinger himself observed a considerable increase in the heat resistance of the diacetates and the dimethyl ethers compared with the original glycols[97], but the products which he investigated were not of very high molecular weight.

The acetylation of polyformaldehyde has been described in detail in the patent literature[23]. The acetylated polymer is considerably more stable (by a factor of about 10) than the original. It can be worked by the usual methods employed with thermoplastic materials, in particular by pressure casting.

Polyformaldehyde is degraded also by exposure to ultra--violet radiation. The usual additives, which strongly absorb short-wave radiation, such as hydroxybenzophenone derivatives[98], have been proposed to retard the photodegradation of polyformaldehyde.

Staudinger suggested a mechanism for the degradation of polyformaldehyde in acid and alkaline media. Rupture of the main chain takes place in the presence of acids, whereas alkalis react with the terminal OH groups, after which monomeric formaldehyde molecules are split off one by one from the polymer chain[97]. Later, several suggestions were made in the patent literature concerning the mechanism of the thermal degradation of polyformaldehyde. However, these are in the nature of hypotheses, since they are not supported by experimental data. The subject was greatly clarified by a paper by Kern and Cherdron[99], showing that five reactions leading to the separation of monomer occur during thermal degradation: (1) depolymerisation, starting at the end-groups of the macromolecule; (2) oxidative cleavage; (3) cleavage by secondary oxidation products; (4) thermal decomposition; and (5) hydrolysis and acid catalysed hydrolysis.

Depolymerisation, beginning at the terminal groups, occurs according to the scheme:

$$—O—CH_2—O—CH_2—OH \rightarrow —O—CH_2—OH + CH_2O \rightarrow \text{etc.}$$

The reaction is of first order with respect to the polymer. The low thermal stability of polyoxymethylene glycols is due mainly to the occurrence of this reaction. Above 160° it is accompanied by cleavage of the polymer chain by oxygen, which also forms compounds which accelerate the decomposition (probably HCOOH).

The inherent strength of the macromolecular chain is characterised by the temperature of purely thermal decomposition, which with the dimethyl ethers of polyoxymethylene glycols is above 270°, the decomposition being a first-order reaction. Addition of acidic substances considerably accelerates the decomposition of polyformaldehyde.

Kern and Cherdron feel that a combination of methods should be used to increase the thermal stability of the oxymethylene polymer: (*a*) protection of the end-groups; (*b*) addition of antioxidants which are not acidic in nature; and (*c*) addition of substances to combine chemically with the formaldehyde evolved during degradation. They consider protection of the end-groups to be the most important. This is reasonable, since it is this type of degradation which determines the thermal stability of polyformaldehyde.

2. Polyacetaldehyde

Right at the start of work on the synthesis of polyacetaldehyde it became evident that this polymer decomposes at room temperature and above, forming the monomer[18]. The first semiquantitative estimate of its rate of degradation was given by Letort[23]: after 40 days at room temperature in air the polymer had lost 9% of its weight.

Later Rigby and Danby[26] reported that the most stable specimens of polyacetaldehyde rubber which they had synthesised were converted to a liquid after two weeks at room temperature. According to their results, depolymerisation does not take place below -9° with the most stable specimens, or below -20° with the least stable. They were unable to determine the temperature coefficient of the rate of decomposition because of the poor reproducibility of the results.

All papers on the synthesis of polyacetaldehyde indicate that the polymer is formed only below -30°. Comparison of these results with those of Rigby and Danby[26] yields a rough estimate of the limiting temperature for the polymerisation of acetaldehyde, *i.e.* between -20° and +30°.

Like Rigby, Bevington and Norrish[27] were unable to obtain reproducible results for the kinetics of the decomposition of polyacetaldehyde. In their view its stability is intermediate between those of polyformaldehyde and of polymers of the higher aldehydes obtained under high pressures. Investigating depolymerisation in air from loss in weight, they were the first to note the autocatalytic character of the reaction. They were also the first to point out the catalytic action of acetic acid, which has been demonstrated by direct experiment. In view of this, Bevington and Norrish explain the difference in stability between different specimens of polyacetaldehyde by the presence of different amounts of acetic acid, formed when acetaldehyde is oxidised by the air.

TABLE 2.

Weight loss of polymer after 3 min		Dependence of weight loss and viscosity on time of pyrolysis at 110°		
temp., °C	weight loss, %	time, h	weight loss, %	η
40	0.23	0	0	3.9
60	0.18	0.5	3.75	1.4
80	0.64	1.0	8.43	1.1
100	1.60	1.75	16.9	0.9
110	3.76	2.0	25.5	0.7
120	8.38			

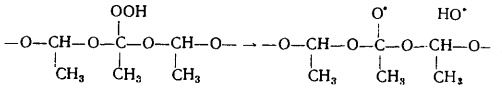
The degradation of polyacetaldehyde was studied subsequently by Bovey and Wands[45], who used specimens of polyacetaldehyde rubber, stabilised with 2-naphthylamine, which they had obtained from Letort. Their results are summarised below (see Table 2).

The data in Table 2 indicate that degradation of polyacetaldehyde is markedly accelerated with rise in temperature above 100°, and that during degradation the molecular weight drops sharply even when the loss in weight is small. Furthermore, infra-red spectroscopy has shown only acetaldehyde to be present among the degradation products. Application of Grassie and Melville's method[100] to the results indicated that, at the start of decomposition, every cleavage of the polymer chain was accompanied by 159 eliminations of a monomer unit. This quantity increases as the process continues, reaching a steady value of about 400.

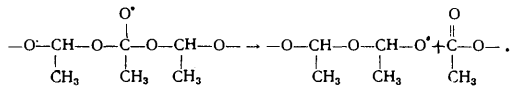
Smets and Delzenn reported during 1956–1957 [101,102] that the polyacetaldehyde chain cleaves in two ways, by heterolytic and by homolytic cleavage. In both cases this is followed by rapid depolymerisation to acetaldehyde.

The instability of polyacetaldehyde in neutral solutions is explained by homolytic decomposition of hydroperoxide side-groups (one group per 1000–4000 acetaldehyde units) with subsequent chain cleavage and depolymerisation[101].

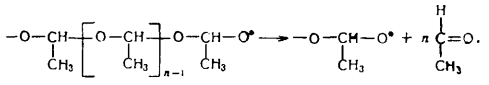
1. Decomposition of the hydroperoxide group:



2. Homolytic cleavage of the chain:



3. Depolymerisation:

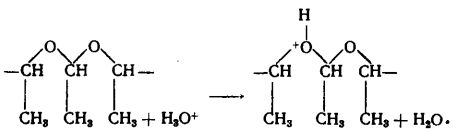


The usual activation energy for processes 1 and 2 is 29 kcal mole^{-1}, and the total activation energy for depolymerisation 18.8 kcal mole^{-1}. The process is inhibited by quinol and by dinitrobenzene.

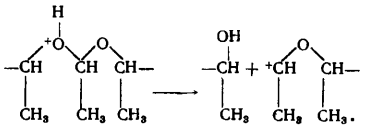
In the presence of acetic acid the rate of decomposition of polyacetaldehyde is increased by a factor of about 700 compared with the spontaneous process. By analogy with

acetals of low molecular weight, Smets and Delzenn suggested the following mechanism for the acid hydrolysis of polyacetaldehyde[102].

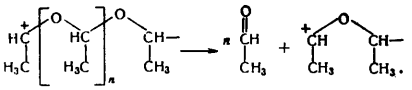
1. Addition of a proton to the acetal:



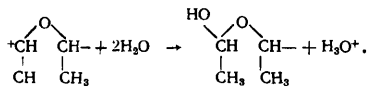
2. Heterolytic fission:



3. Depolymerisation of the carbonium ion:



4. Nucleophilic substitution of the carbonium ion:



An important point is that the H_3O^+ ion can break the polymer chain at any position. The activation energy for the acid hydrolysis of polyacetaldehyde is 20.4 kcal mole^{-1}, which agrees well with the value of 20.5 kcal mole^{-1} for diethylacetal. The small activation energy for depolymerisation, only 2.4 kcal mole^{-1}, is characteristic of ionic processes. The ionic character of depolymerisation follows also from its insensitivity to the presence of inhibitors of radical processes. Kinetic measurements made by these workers support their hypothetical mechanism for the decomposition. Thus the rate of cleavage and the rate of depolymerisation vary linearly with the concentration of acid in the solution, while the rate of formation of acetaldehyde in each experiment remains constant even when the extent of reaction is considerable.

No papers have been published recently on the degradation and stabilisation of polyacetaldehyde. There is only an isolated report that a polyacetaldehyde has been prepared in the University of Kyoto which is more heat resistant† than butadiene–styrene rubber[39]. The same report states that a similar polymer has been obtained by the du Pont Corporation.

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Research on the polymers of carbonyl compounds, which was only started comparatively recently (the main literature has appeared during 1955–1960), is being intensively pursued at the present time. Previously known polymers are being studied more thoroughly, and the preparation of polymers of several new carbonyl compounds is being investigated. Thus during 1959–1960 three new methods have been found for the polymerisation of acetaldehyde, the possibility of obtaining stereoregular polymers of aldehydes has been discovered, and polymers of acetone, dimethylketen, etc. have been obtained.

All this suggests that polymers of carbonyl compounds will, in the not very distant future, be of practical as well as academic interest. This will necessitate the solution of the most important problem of the chemistry of the aldehyde polymers — to find sufficiently reliable methods for their stabilisation.

† The report does not make it clear whether this refers to heat resistance or to thermal stability.

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ROTATORY DISPERSION AND ITS APPLICATION IN ORGANIC CHEMISTRY

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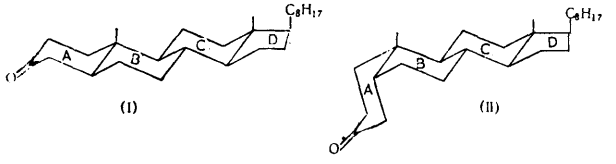
I. INTRODUCTION

Recent years have seen the application of new physical methods in organic chemistry. Microwave spectroscopy, nuclear magnetic resonance, electron paramagnetic resonance, and other modern research methods have proved powerful tools in the hands of organic chemists. None of these methods, however, is very suitable for the study of problems connected with the spatial structure of molecules, especially questions of the relative and absolute configuration of organic compounds, which are of particular importance in the chemistry of natural products. Many stereochemical problems could be solved by X-ray, electron, and neutron diffraction methods, but unfortunately these procedures are frequently inapplicable because of the very nature of organic compounds. The most convenient method for the solution of problems of spatial structure would, of course, be the use of a physical phenomenon directly linked with the structure of the molecule and greatly dependent on the slightest changes in its configuration. Such a phenomenon has long been known to chemists. It is the variation in the optical activity of substances with change in the wavelength of the polarised light, *i.e.* the dispersion of the rotation of the plane of polarisation or the "rotatory dispersion".

Considering the conformations of molecules of cholestan-3-one (I) (*trans*-linking of rings A and B) and coprostan-3-one (II) (*cis*-linking of rings A and B), we can see that the environments of the keto-groups in the molecules are quite different.



It is quite evident that the rotatory dispersion (which is associated with the symmetry of the molecule) will also be completely different (see Section III). Consequently, even slight variations in the conformation of the molecule will greatly affect its symmetry, leading to a marked change in the rotatory dispersion curve, which thus becomes characteristic of the spatial arrangement of groups in the molecule. The practical value and the quite extraordinary sensitivity of rotatory dispersion as a method for studying the spatial structure of organic compounds were thoroughly investigated at the start of the present century in the work of Chugaev (for a detailed survey see Ref.1) and several others (for review see Ref.2). However, the lack of ultra-violet spectropolarimeters was a great obstacle. It is only during the past few years that suitable instruments have become available[3-6].

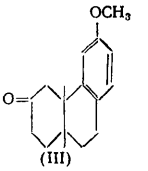
Since no reviews of this subject have been published in Russian, it appeared useful to examine some general aspects of the method of rotatory dispersion, and to cite individual examples to illustrate the possibilities of its application. Therefore the present review does not claim to be a complete account of the available facts, but is intended merely to direct attention to the main achievements of this new research method.

II. OPTICAL ROTATORY DISPERSION AND THE COTTON EFFECT

Refractive indices are known to increase markedly with decrease in wavelength. Furthermore, the refractive index of a substance measured in a region of the spectrum in which the latter has an absorption band exhibits a characteristic anomalous behaviour, as shown in Fig.1.

Since the rotation of the plane of polarisation of light in an optically active substance is caused by the difference in refractive index between the right-hand and left-hand components of linearly polarised light, this phenomenon should obviously be governed by the same fundamental laws as the refractive index. Indeed, as early as 1821 Biot[7] had derived an empirical rule to represent the dependence of the specific rotation $[\alpha]$ on wavelength: $[\alpha] = A/\lambda^2$, where A is a constant characteristic of a given substance. It follows from this formula that, as with the refractive index, the specific rotation should increase on passing into the ultra-violet region of the spectrum.

The most striking example in support of this rule is provided by the behaviour of the tricyclic ketone (III) obtained from morphine[8]:



Over the range 700–500 mμ it was found to have no appreciable activity, whereas at 310 mμ its rotation reached +1172°.

The variation in rotation with the wavelength of the polarised light will also be analogous to that of the refractive index. An anomalous change in rotation occurs within

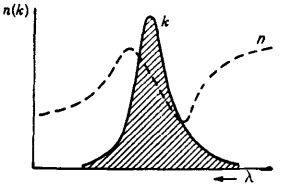


Fig.1. Change in refractive index in the vicinity of an absorption band: n — refractive index; k — absorption coefficient.

an absorption band of an optically active substance. This was first discovered in 1896 by Cotton[9], and is known as the Cotton effect†. An absorption band in the spectrum of a substance is caused by energy losses due to excitation of a chromophoric group and the conjugated system as a whole. This is associated with the transition of electrons from one orbital to another, or from one state to another. This will, of course, change the nature of the interaction between the chromophore and the remainder of the molecule. And this change will primarily affect the symmetry (or dissymmetry) of the molecule, a direct consequence of which will be a marked distortion of the rotatory dispersion curve.

Thus the Cotton effect is in its very nature extremely sensitive to any variation in molecular structure, and it is for this reason that the rotatory dispersion curve is just as characteristic of a given substance as, for example, the characteristic infra-red vibrations of a functional group.

Fig. 2 shows typical curves for the variation of the absorption coefficient (log k) and molecular rotation $[M]$ with wavelength[10].

The Cotton effect can be either positive (+) or negative (-). A positive rotation on the long-wave side of an absorption band (Fig. 3A) indicates a positive Cotton effect, and a minus sign for the rotation on the long-wave side (Fig. 3B) implies a negative Cotton effect. In general, a change in the sign of rotation need not necessarily occur within an absorption band, but the anomalous character of the curve is still maintained.

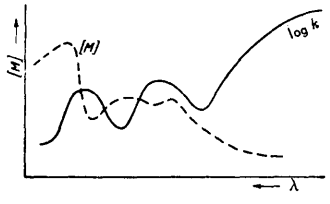


Fig. 2. Variation of absorption log k and molecular rotation $[M]$ with wavelength.

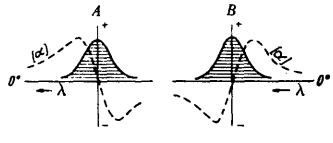


Fig. 3. Shape of curves for positive (A) and negative (B) Cotton effect.

† The concept of the "Cotton effect" includes also the problems of circular dichroism, but, although this is connected with the matter under discussion, it does not need to be dealt with here, since it is not required for the subsequent exposition.

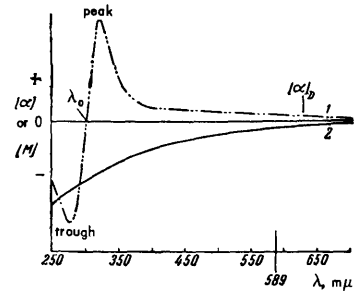


Fig. 4. 1) Anomalous curve (positive Cotton effect); 2) smooth curve.

Some substances do not exhibit the Cotton effect in the region of the spectrum accessible to measurement (usually the near ultra-violet), and a smooth dispersion curve (Fig. 4) is then obtained. This too can be utilised for the determination of molecular structure.

On the suggestion of Djerassi and Klyne[11], to avoid confusion, the maximum of the curve representing the Cotton effect is termed a "peak" (Gipfel, sommet, pik), and the minimum a "trough" (Tal, creux, trog). Such a terminology is appropriate, since the concepts of "maximum" and "minimum" already have a definite meaning in ultra-violet spectroscopy, and the terms "pik" and "trog" themselves have long been used in Russian (in geography and geology). The distance between them is called the "amplitude", and is characteristic of each type of molecular structure. If the curve shows additional peaks and troughs within an absorption band, it is said to be a complex Cotton-effect curve.

III. MAIN REGULARITIES OF ROTATORY DISPERSION AND THE "OCTANT RULE"

Since the Cotton effect is exhibited only within (or close to) an absorption band, its investigation requires that the substance should have a group which absorbs in the part of the spectrum selected. Such groups are termed, by analogy with dyes, chromophoric groups.

The chromophore is in most cases the carbonyl group, but other chromophoric groups can be used, containing, for example, sulphur (xanthates, dithiourethanes, thiones)[12-16], nitrogen (nitroalkanes, nitriles, azides, etc.)[17-21], halogens[22-25], aromatic rings[17,18,26,27], and also such uncommon groups as diselenide[28] and dipyrrolylmethyl[29]. Rotatory dispersion has been most thoroughly studied in the near ultra-violet (down to ~230–250 mμ), because organic chemists deal largely with colourless substances having absorption bands in the ultra-violet. Furthermore, it is possible in this region to work with very small amounts of material (of the order 0.1–1 mg), since, as already mentioned, the rotation increases markedly on passing into the ultra-violet region of the spectrum.

Although 150 years have elapsed since the discovery of the phenomenon of optical activity by Arago (1811), and a comprehensive study has been made of the phenomenon, especially with the aim of finding a relation between the

structure of optically active substances and the nature of the rotation, no rigorous or sufficiently general theory has yet emerged. On the basis of a huge amount of experimental data, it has been possible to establish only a multitude of empirical rules, which, although having no theoretical foundation, have proved useful for elucidating and systematising most of the observed facts. These rules have been carefully tested by Djerassi and his coworkers on more than 2000 optically active substances[28,30,31]. Some of the most general of these empirical rules are given below.

1. Kuhn[32] discovered experimentally and explained theoretically a rule forming the basis of the method, according to which weak absorption bands produce a marked change in rotation, *i.e.* a strong Cotton effect. It is for this reason that aldehydes and ketones have been investigated for the most part, as they have a characteristic band of very low extinction in the ultra-violet (λ_{max} 280–300 mμ, $\epsilon_{max} \sim 50$).

2. Chugaev's proximity rule[33-38]: (*a*) substances of similar structure undergo identical changes in rotation with changes in structure; (*b*) an identical change in structure produces a smaller change in rotation, the farther it is from the chromophoric group and from the asymmetric atom.

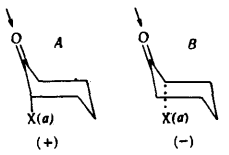
These two rules are the most general.

3. Change in the mode of linking of the rings (*cis* or *trans*) in steroid ketones and their bicyclic analogues involves a change in the sign of the Cotton effect (see Fig. 5). The presence of various other substituents (hydroxyl, ether group, lactone, acyl, etc.) or even of a double bond can be ignored, provided that they do not affect the conformation of the molecule. The only exceptions are other ketone or aldehyde groups[37].

4. Angular substituents do not appreciably affect the shape of the curve representing the Cotton effect[38,39].

5. The axial "halogeno-ketone rule" enables us to determine the sign of the Cotton effect in halogenated cyclic ketones[40,41]: introduction of a halogen atom (other than fluorine) into the axial position α to the keto-group reverses the sign of the Cotton effect and greatly increases the amplitude.

The sign of the Cotton effect can be determined by looking at the molecule from the point of view of the keto-group:



With cyclohexane in the "chair" form, for example, the Cotton effect will be positive if the axial halogen atom is located to the right of the observer (*A*), and negative if the halogen atom is to the left (*B*). The rule is applicable also to polycyclic systems. Equatorial halogen atoms do not influence the sign of the Cotton effect[42].

6. The sign of the Cotton effect changes on passing from five- to six-membered rings, and from six- to seven-membered rings.

7. "The 4,4-dimethyl effect"[37]. Introduction of two methyl groups into the 4-position of 3-keto-steroid and related systems causes a reversal in the sign of the Cotton effect. Introduction of only one methyl group produces no change at all. This phenomenon is not caused by 1,3-diaxial interaction between axial methyl groups attached to C_4 and C_{10}.

8. "The octant rule"[31]. Consideration of a vast quantity of experimental results has enabled a quite simple rule — the so-called "octant rule" — to be derived, enabling us to predict the nature of the curve representing the Cotton effect from the spatial structure of the molecule. Since all the remaining rules are merely particular cases deriving from this rule, and since, moreover, the determination of absolute configuration is based on it, we must consider it in greater detail (see Fig. 6).

If the cyclohexanone molecule is intersected by three mutually perpendicular planes, in such a way that plane *A* passes through the O, C_1, and C_4 atoms, plane *B* through C_1, C_2, and C_6, and plane *C* between the O and C_1 atoms,

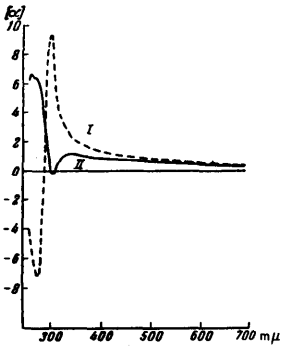


Fig. 5. Rotatory dispersion of: I) cholestan-3-one; II) coprostan-3-one.

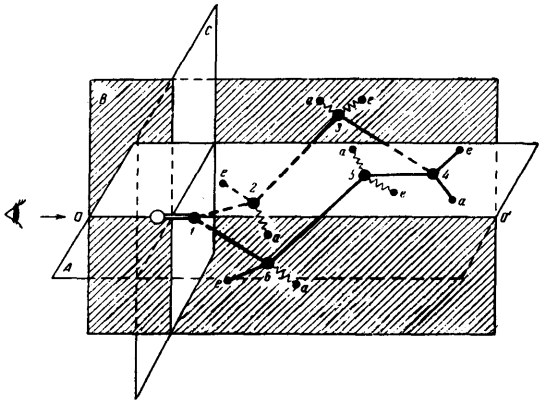


Fig. 6. Diagram illustrating the "octant rule".

the whole molecule will be divided into eight parts or octants. It is then seen that the C_3 and C_5 atoms lie outside the planes, equatorial (*e*) substituents attached to C_2 and C_6 lie in plane *B*, and both equatorial (*e*) and axial (*a*) substituents attached to C_4 lie in plane *A*.

The octant rule states: (1) To a first approximation, no substituent lying in one of the planes has any effect on the form of the curve representing the Cotton effect. (2) All carbon atoms and other groups located in the octants *II* (far upper left, looking at the molecule along the axis *OO'*), *IV* (near lower left), *V* (near upper right), and *VII* (far lower right) change the rotation to more positive values (make a positive contribution to the Cotton effect). With cyclohexanone, this type of change will be produced by axial and equatorial substituents attached to C_3 and by axial substituents attached to C_6. (3) Carbon atoms and other substituents situated in the remaining octants (*I*, *III*, *VI*, and *VIII*) change the rotation to more negative values (make a negative contribution to the Cotton effect). Such an effect will be exerted in cyclohexanone by axial and equatorial substituents attached to C_5 and by axial substituents attached to C_2. (4) The magnitude of the positive or negative contribution to the Cotton effect depends in general on the size of the substituents, since it determines the extent to which the symmetry of the molecule is destroyed. Thus 3-methyl--5-t-butylcyclohexanone, for example, should exhibit a negative Cotton effect, while interchange of the substituents should make it positive, since the t-butyl group is larger than the methyl group.

Fig. 6 can be represented schematically by a so-called "octant diagram" (Fig. 7) if we look at the molecule along

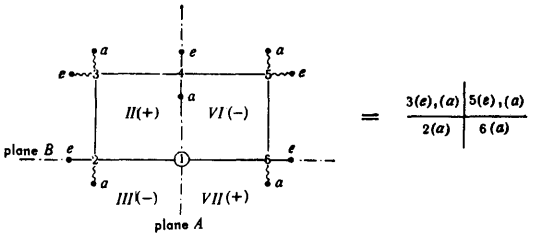


Fig. 7. Simplified diagram of octant rule.

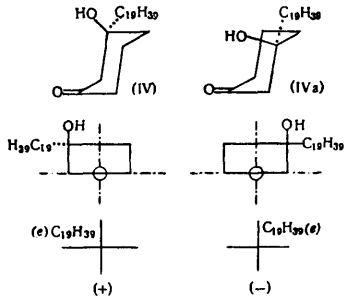


Fig. 8. Determination of the configuration of 3-hydroxy-3-nonadecylcyclohexanone.

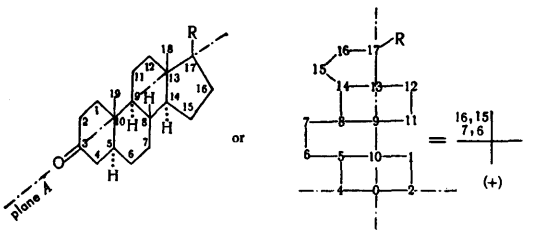


Fig. 9. Octant diagram for 3-oxo-5α-steroids.

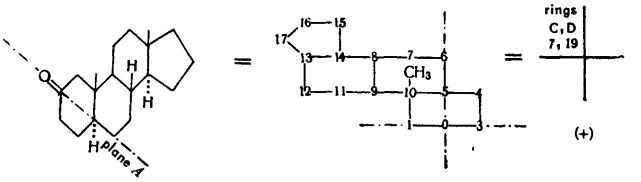


Fig. 10. Octant diagram for 2-oxo-5α-steroids.

TABLE. [31] Cotton effect in 5α-steroid ketones.

Position of oxo-groups	Arrangement of substituents (octant diagram)		Cotton effect: predicted	Cotton effect: found
2	7, 19, rings C and D		+++	+121
3	16,15,7,6		+	+ 65
4		19, rings C and D	— —	— 94
6	19	12, 18, ring D	— —	— 76
7	16,15	2,3	—	— 16
11	16,18	6 2	+	+ 16
12	2,3,4,5,6	18, side-chain	++	+ 42

Note. The bold type denotes atoms located in the near octants (I, IV, V, and VIII).

the axis *OO'* and ignore the near octants (the Roman numerals in Fig. 7 denote the numbers of the octants).

We shall discuss a few cases of the application of this rule.

1. In the 3-hydroxy-3-nonadecylcyclohexanone molecule (IV) the nonadecyl group is considerably larger than the hydroxyl group, so that, according to the conformational rules, it should occupy the equatorial position. Hence the absolute configuration (IV) can be readily established from an examination of the Cotton effect curves (Fig. 8).

If the compound does have configuration (IV), its Cotton effect should be positive (both substituents situated in

octant *II*). If, however, the absolute configuration of this molecule is represented by (IVa), the Cotton effect will be negative (both substituents located in octant *VI*). It has been shown experimentally[28] that 3-hydroxy-3-nonadecylcyclohexanone has a positive Cotton effect, and hence its absolute configuration corresponds to formula (IV).

2. Similar reasoning can be applied to more complex molecules. If 5α-steroids (with *trans*-linking of rings A and B) are examined on the basis of the octant rule, the diagram obtained for 3-oxo-5α-steroids shows that they should possess a positive Cotton effect (see Fig. 9).

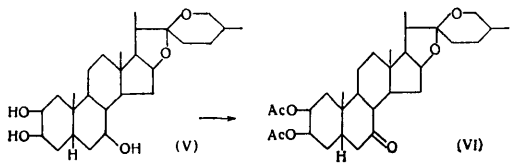
Fig. 10 shows the octant diagram for 2-oxo-5α-steroids, according to which they too should possess a positive Cotton effect, as is actually observed. A detailed study of the Cotton effect in other 5α-steroids also confirmed the correctness of the octant rule. Several of the results obtained are given in the Table.

IV. SOME APPLICATIONS OF ROTATORY DISPERSION

It is clear from the above account that the new method of investigation can be employed in all cases entailing determination of the spatial structure of molecules, which is a most important problem of modern organic chemistry. Among a large amount of experimental work involving the application of rotatory dispersion, only those cases will be considered below which illustrate particularly clearly the inherent potentialities of this new method.

1. Orientation of a Hydroxyl Group in Trihydroxymetagenin (V)[43]

The structure of this sapogenin has been almost completely established by chemical methods, apart from the position of one hydroxyl group. In order to solve this problem, the triol (V) was oxidised to the keto-diol derivative (VI), and the rotatory dispersion curve of the latter was determined.

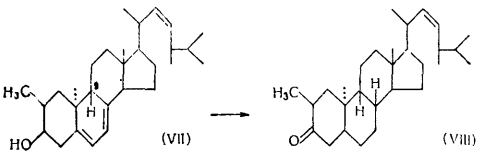


The curve was found to differ from all known curves for the Cotton effect obtained with oxosapogenins[44], but corresponded fully to the curve characteristic of 7-oxosteroids with *cis*-linkage of the A and B rings. Hence this hydroxyl group in trihydroxymetagenin (V) is attached to C_7, which was subsequently confirmed by chemical means.

2. Use of Rotatory Dispersion in Solving Stereochemical Problems

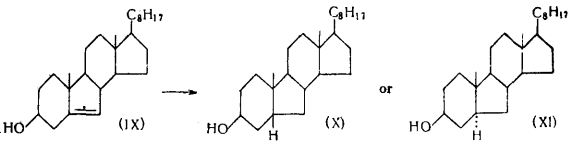
Determination of absolute configuration and its relation to optical rotation forms one of the most important tasks of theoretical chemistry. However, its solution has encountered immense difficulties. It was only in 1958 that the relation between the left-hand rotation of α-quartz and its structure (right-hand spiral in the crystal lattice) was finally established with certainty[45]. Several examples have shown that measurement of the rotatory dispersion often enables such problems to be solved quite reliably.

(*a*) Stereochemistry of the C_9 atom in lumisterol (VII).[46,47] In order to establish the stereochemistry of the C_9 atom, lumisterol (VII) was converted to the cyclic ketone (VIII):



The curve for the Cotton effect in this ketone is the mirror image of that for coprostan-3-one (II) (see Fig. 1), which corresponds to the 8β,9β-configuration in (VIII), and hence the 9β-configuration in lumisterol itself (VII). This conclusion was subsequently confirmed by chemical methods.

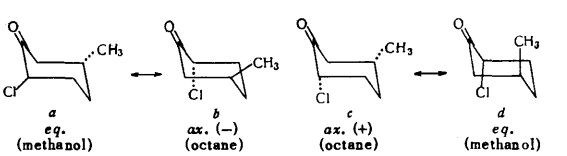
(*b*) Stereochemistry of the link between six- and five-membered rings in B-norcholestanol (X)[48] [This section has been modified to accord with the sources quoted (Ed. of Translation)]. B-Norcholestanol, formed by the hydrogenation of (IX), can posses one of the two possible configurations (X) or (XI) with *cis*- or *trans*-linkage of the A and B rings:



In order to solve this problem, the hydrogenated product was oxidised to the ketone, whose rotatory dispersion curve is given in Fig. 11. This shows that the ketone has a *cis*-linkage of the A and B rings, and hence that B-norcholestanol itself has the same configuration (X), although all the early chemical and spectroscopic data had indicated[49] the presence of a *trans*-linkage.

A later, more rigorous investigation[50] confirmed Djerassi's results. The reason for the error was that the earlier workers had applied to B-norsteroids chemical and spectroscopic rules obtained with steroids having a six-membered B ring.

(*c*) Determination of the configuration of 2-chloro-5-methylcyclohexanone. This compound (XII) can exist in four different chair conformations:



It had previously been found[51] that conformations having the chlorine atom in the axial position (*i.e. b* or *c*) predominate

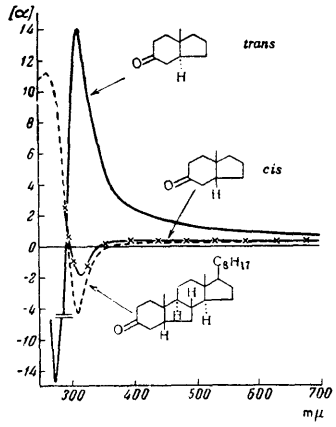


Fig.11. Confirmation of the configuration of B-norcholesterol.

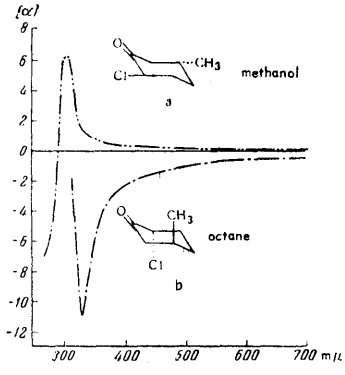


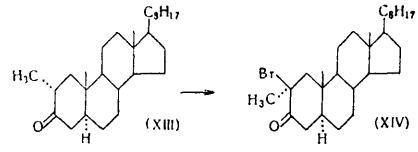
Fig.12. Change in the conformation of 2-chloro-5-methylcyclohexanone.

in non-polar solvents (for example, in octane), whereas the equatorial forms (*a* or *d*) predominate in polar solvents (for example, in methanol). However, it was impossible by means of spectroscopy to decide to which series (*cis* or *trans*) these conformations belong.

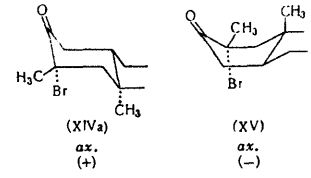
It is readily seen from the "halogeno-ketone rule" (Section III) that, of the two forms with the chlorine atom in the axial position, only one (*b*) will possess a negative Cotton effect, whereas the other (*c*) should show a positive effect. Hence if a negative Cotton effect is observed in octane, and a positive effect in methanol, 2-chloro-5-methylcyclohexanone (XII) will belong to the *trans*-series, whereas if the Cotton effect has the opposite signs, the compound will have the *cis*-configuration. An experimental check (Fig.12) showed that the change in the form of the curves corresponds to the first case, and hence that 2-chloro-5-methylcyclohexanone has the *trans*-configuration[52].

The change in sign of the Cotton effect with the polarity of the solvent provides a confirmation of the conformational mobility of cyclohexane systems.

(*d*) Proof of the boat form of the A ring in 2α-methylcholestan-3-one. On the basis of the ultra-violet and infra-red spectra, it had been accepted[53] that the product formed by bromination of 2α-methylcholestan-3-one (XIII) has the structure 2β-bromo-2α-methylcholestan-3-one (XIV):



Since it has been proved that the bromine occupies an axial position in this molecule, its configuration could be confirmed by the "halogeno-ketone rule" (Section III), according to which XIV should have a positive Cotton effect (bromine atom on the right):

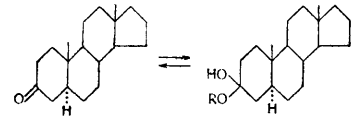


The compound was found, however, to exhibit a negative Cotton effect. As can be seen from the conformational formulae, this is possible only if the A ring has the boat form (XV). This result shows that the A ring in steroids exists in some cases in the boat form and not in the chair form, as had been assumed.

3. Rotatory Dispersion Study of the Formation of Ketone Acetals and Hemiacetals

It has been shown earlier[54] that, when an acid is added to an alcoholic solution of a ketone, an equilibrium is established between the ketone and a hemiacetal (or an acetal). Since this involves the disappearance of the chromophoric group, and thereby the conversion of the anomalous curve representing the Cotton effect to a smooth curve, this phenomenon can be utilised for the study of structural and steric problems. The following empirical rules have been established[55] with polycyclic ketones as examples.

(*a*) The changes in amplitude and shape of the curve representing the Cotton effect are very sensitive to steric factors. Replacement of methanol by ethanol, for example, produces a marked shift in the equilibrium towards hemiacetal formation, while replacement of methanol by propan-2-ol completely suppresses the formation of a hemiacetal:

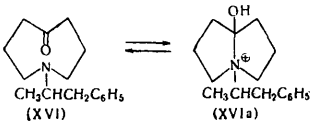


(*b*) Hemiacetals are formed more readily by six-membered ring ketones than by those with a five-membered ring.

(*c*) The presence of substituents in the vicinity of the keto-group impedes this process.

(*d*) If the resulting acetal can undergo 1,3-diaxial interaction with an angular methyl group, acetalisation does not take place. This provides a ready means for distinguishing 2- and 3-oxo-5α-steroids, since the former do not yield hemiacetals, and hence the form of the Cotton effect curve is not changed on addition of acid to their alcoholic solutions.

Study of the rotatory dispersion curves during acetal formation has provided solutions to several difficult problems associated with the structure of a number of organic compounds. Thus the possibility of transannular interaction within the eight-membered cyclic ketone (XVI) has been demonstrated by means of this method. It has been established[56] that, on addition of acid to this ketone, its characteristic negative Cotton effect curve is converted to a smooth positive dispersion curve. This means that the chromophoric group has disappeared, which can be readily explained by interaction of the keto-group with the nitrogen atom (XVIa):



This method has been used to determine the position of the hydroxyl group in two macrolides (methymycin and neomethymycin). The problem was solved[57,58] with their dehydro-derivatives (XVII) and (XVIII). Dehydromethynolide (XVII) was found on addition of acid to give only a smooth dispersion curve (Fig. 13) instead of the characteristic Cotton effect curve, which indicates its ability to form a cyclic hemiacetal. The Cotton effect curve of the second product — dehydroneomethynolide (XVIII) — undergoes no change under these conditions, and hence the hydroxyl group in (XVIII) must be so situated that intramolecular hemiacetal formation cannot take place.

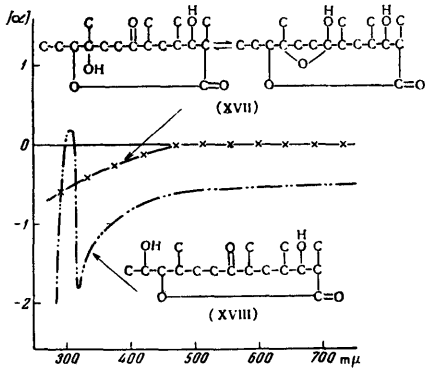


Fig. 13. Demonstration of the position of the hydroxyl group in methymycin and neomethymycin.

4. Employment of Smooth Rotatory Dispersion Curves in Some Structural and Stereochemical Problems

A smooth dispersion curve does not, of course, enable us to settle fine points of structural chemistry, and therefore the opportunities for its employment are for the present limited. Nevertheless, it is more useful for structure determination than the usual measurement of optical activity in the visible region (~500–700 mμ). It must also be remembered that a smooth rotatory dispersion curve may become anomalous in another region of the spectrum.

(*a*) Difference in the curves for cholestene isomers[59]. All cholestene (XIX) isomers have a smooth dispersion curve in the measurable region. Fig. 14 shows, however, that the curve for each isomer differs from those for the others, and this can be used for the identification both of the isomers themselves and of compounds of analogous structure, such as the pentacyclic terpenes.

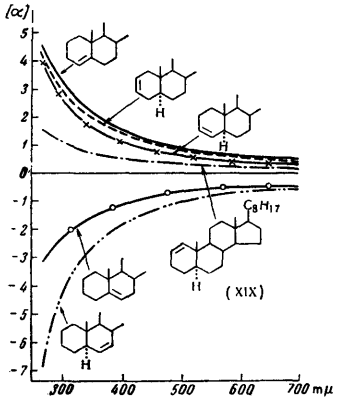


Fig. 14. Rotatory dispersion of cholestene isomers.

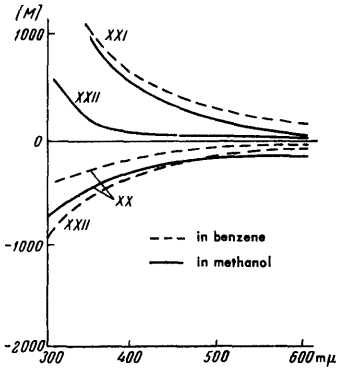
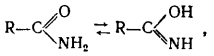
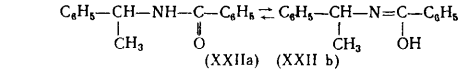


Fig. 15. Use of rotatory dispersion to prove the occurrence of tautomerism in amides.

(*b*) Study of tautomerism [60,61]. In order to demonstrate the tautomerism of amides

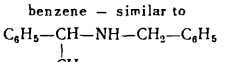


a study was made of the rotatory dispersion curves of α-methyldibenzylamine (XX), *N*-benzylidene-α-methylbenzylamine (XXI), and *N*-(α-methylbenzyl)benzamide (XXII) in methanol and in benzene (Fig.15). It was found that the curves for (XX) and (XXI) changed little on passing from benzene to methanolic solutions, but with (XXII) the curve in benzene was similar to that for (XX), while the curve in methanol resembled that for (XXI).



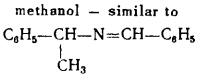
(XXIIa) (XXII b)

benzene – similar to



(XX)

methanol – similar to



(XXI)

The conclusion was drawn that *N*-(α-methylbenzene)benzamide (XXII) occurs in the amide form (XXIIa) in benzene, and in the imide form (XXIIb) in methanol. This was subsequently confirmed by a study of the crystalline forms of XXII.

The smooth rotatory dispersion curve is widely employed also for investigating the structure of proteins, polypeptides, and other substances of high molecular weight (see, for example, Ref.62), but these questions are beyond the scope of the present paper.

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It is evident even from the few examples discussed above that study of rotatory dispersion and the Cotton effect open up very great possibilities in the stereochemistry of complicated molecules. At the present time, when this method is still only in its initial stages, it is difficult to predict its future development. It is quite clear, however, that it will soon become just as irreplaceable a tool in the hands of the organic chemist as infra-red and ultra-violet spectroscopy have become.

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PROGRESS IN THE ANALYSIS OF INORGANIC AND ORGANIC COMPOUNDS IN NON-AQUEOUS SOLUTIONS

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N.A.Kazaryan, and N.Sh.Aldarova

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I. INTRODUCTION

Until recently, chemists used chiefly chemical and physicochemical methods of analysis in the study of matter, based on reactions in aqueous solutions. As a result, while physical chemists up to the end of the 19th century studied the properties of aqueous solutions, analytical chemists developed methods of analysis in such solutions. At the present time all the theories, definitions and chemical and physicochemical methods of analysis in analytical chemistry are based on principles developed for aqueous solutions.

The rapid increase in the production of monomeric and polymeric organic compounds led to considerable interest in the analytical chemistry of non-aqueous solutions since analytical methods developed for aqueous solutions are inapplicable to such compounds. This is indicated by the ever-increasing number of original and review articles and monographs published in different countries on problems associated with the theory of non-aqueous solutions and their practical application[1-26].

The idea of using non-aqueous solutions for analytical purposes has recently attracted the attention not only of analytical chemists, but also of many physical and organic chemists[27-53].

In non-aqueous solutions it is possible to determine various compounds by alkalimetric and acidimetric titration[54-80]. On the basis of the specific properties shown by salts in non-aqueous solutions, it is possible to titrate non-aqueous salt solutions successfully by the precipitation method, making use of the insolubility, in non-aqueous solvents, of certain salts which are soluble in water[81-83]. Since the solvents influence redox potentials, it is possible to titrate non-aqueous solutions by oxidimetric methods[84-96]. The use of non-aqueous solutions for analytical purposes can also be extended to complexometric, photometric, chromatographic, electrochemical, and other analytical methods[97-114].

In view of the vast amount of published work on all these methods, we shall in the present review consider only acid-base titration methods in non-aqueous solutions, of greatest theoretical and practical interest.

The use of non-aqueous solvents makes it possible to extend considerably the possibilities of acid-base titration. Methods of non-aqueous titration are of great importance in the study of inorganic substances and particularly for the analysis of monomeric and polymeric organic compounds. The application of non-aqueous solutions in analysis is extremely promising, since it shows a number of advantages over aqueous solutions[15,17].

Considerable progress has now been made in the analysis of inorganic and organic compounds, and of organic derivatives of the elements, in non-aqueous solutions. It is sufficient to point out that only by acid–base titration in non-aqueous media is it possible to determine compounds irrespective of their pK, isomers, chemical compounds of the same homologous series, substances which have nothing in common with our usual ideas of acids and bases, multicomponent mixtures of various compounds, etc. This progress is due chiefly to the development of the chemical theory of solutions, whose foundations were laid by the Russian school of D.I.Mendeleev[17,20,26,115-130].

II. FUNDAMENTALS OF THE THEORY OF NON-AQUEOUS SOLUTIONS

Detailed studies of solutions of various substances in liquid inorganic and organic solvents and in liquefied gases have shown that acids and bases exist not only in aqueous solution, in which there is a dynamic equilibrium between hydrogen and hydroxide ions, but also in non-aqueous solutions, in which this equilibrium is not present [7,9,15,17,20,26,130-132].

Study of the solutions shows that the individual character of the solvent strongly influences the state of ions in solution. This effect is indicated, for example, by data on the electrical conductivity of salts which, although showing equal degrees of dissociation in aqueous solutions, behave differently in solvents of different chemical character with similar values of the dielectric constant, for example in methanol, acetonitrile, and nitromethane [117,118,124-126,133].

The solvent also influences the direction of the reaction. For example, the reaction

$$H_2S + I_2 \rightleftarrows 2HI + S,$$

proceeds from left to right in aqueous solution and from right to left in the vapour phase, but does not take place at all in non-aqueous solvents [for example in CCl_4, $(C_2H_5)_2O$, etc.].

Very often the influence of the solvent on a chemical reaction arises through formation of a substance which is insoluble in it, which displaces the equilibrium towards the formation of the substance. Thus, for example, copper nitrate and sulphuric acid in anhydrous acetic acid react to yield a precipitate of copper sulphate [9,134,135]:

$$Cu(NO_3)_2 + H_2SO_4 \xrightarrow[CH_3COOH]{} \downarrow CuSO_4 + 2HNO_3.$$

In liquid ammonia the reaction of silver chloride with barium nitrate yields a precipitate of $BaCl_2$:

$$2AgCl + Ba(NO_3)_2 \xrightarrow[NH_3]{} \downarrow BaCl_2 + 2AgNO_3.$$

To chemists these reactions are unusual, as is the behaviour of certain electrolytes in non-aqueous solutions, for example that of urea, which is a weak base in water, an acid in liquid ammonia, and a strong base in anhydrous acetic acid. Ethyl alcohol, which is an indifferent (neutral) substance in aqueous solution, shows clearly-defined basic character in liquid hydrogen fluoride and can be titrated with strong acids in the same way as caustic soda in aqueous solution. This is because liquid hydrogen fluoride has a marked influence on the solute and as a result of its marked protogenic nature readily gives up protons even to those substances from which water removes protons. Thus alcohols, and even phenols, which react as acids in water, behave as bases in liquid hydrogen fluoride:

$$ROH + HF \longrightarrow [ROH_2]^+ + F^-.$$

Liquid hydrogen fluoride reacts similarly even with acetic and formic acids, acetates, nitrates, and other compounds, which behave as bases in this medium:

$$CH_3COOH + HF \rightleftarrows [CH_3COOH_2]^+ + F^-,$$
$$HCOOH + HF \rightleftarrows [HCOOH_2]^+ + F^-,$$
$$CH_3COOK + 2HF \rightleftarrows K^+ + [CH_3COOH_2]^+ + 2F^-,$$
$$KNO_3 + 2HF \rightleftarrows K^+ + [H_2NO_3]^+ + 2F^-.$$

The different action shown by different solvents on electrolytes has been studied by many workers [26,130] and was noted by Walden [124-126]. The action of many solvents on a solute is analogous to the action of water. Thus Jander and Kraffczyk [136] concluded that the reaction of ethyl ether as solvent is analogous to that of water:

$$HOH \rightleftarrows H^+ + OH^-,$$
$$C_2H_5OC_2H_5 \rightleftarrows C_2H_5^+ + OC_2H_5^-.$$

Thus the reaction

$$C_2H_5Br + LiOC_2H_5 \longrightarrow C_2H_5OC_2H_5 + LiBr,$$

can be regarded as a neutralisation involving the formation of a molecule of ether (the solvent) and salt.

The reaction of aluminium bromide with ethyl ether

$$AlBr_3 + C_2H_5^+OC_2H_5^- \rightarrow C_2H_5^+ + [AlBr_3 \cdot OC_2H_5]^-,$$

can be regarded as the reaction of a Lewis acid with a base.

Janz and Danyluk [137], who studied the ionisation of HCl in acetonitrile, represented the reactions as follows:

$$CH_3CN + HX \rightleftarrows CH_3CN \cdot HX, \quad (1)$$
$$CH_3CN \cdot HX \rightleftarrows CH_3CNH^+X^-, \quad (2)$$
$$CH_3CNH^+X^- \rightleftarrows CH_3CNH^+ + X^- \text{ (solv.)}, \quad (3)$$
$$HX + X^- \text{ (solv.)} \rightleftarrows HX_2^- \text{ (solv.)}. \quad (4)$$

The overall reaction is

$$CH_3CN + 2HX \rightleftarrows CH_3CNH^+ + HX_2^- \text{ (solv.)};$$

from Eqns. (1) and (2)

$$CH_3C{\equiv}NH^+X^- \rightleftarrows CH_3C^+{=}NH \cdot X^-,$$
$$CH_3C^+{=}NH \cdot X^- + HX \rightleftarrows CH_3\overset{X}{\overset{|}{C}}{=}NH_2^+X^-,$$
$$CH_3\overset{X}{\overset{|}{C}}{=}NH_2^+X^- \rightleftarrows CH_3\overset{X}{\overset{|}{C}}{=}NH_2^+ + X^- \text{ (solv.)}.$$

A detailed study of the influence of acidic solvents on the properties of electrolytes and the theory of the problem have been described by Shkodin [130].

According to Izmailov [26], the observed interactions of an electrolyte KA with a solvent M can be represented as a series of coupled dynamic equilibria:

1. Formation of solvates:

$$KA + nM \rightleftarrows KAM_n$$

with instability constant

$$K^*_{inst} = \frac{a^*_{KA}}{a^*_{KAM_n}}. \quad (1)$$

The asterisk denotes that the activities refer to infinite dilution of the solution, and n is the number of molecules of solvent.

2. Dissociation of the solvated product with the formation of solvated ions:

$$KAM_n + mM \rightleftarrows K^+(\text{solv.}) + A^-(\text{solv.}),$$

$$K^*_{diss} = \frac{a^*_{K^+(solv)}\, a^*_{A^-(solv)}}{a^*_{KAM_n}}, \quad (2)$$

where m is the number of molecules of solvent.

3. The formation (particularly in solvents with a low dielectric constant) of ion pairs:

$$K^+(\text{solv.}) + A^-(\text{solv.}) \rightleftarrows K^+(\text{solv.})\, A^-(\text{solv.}),$$

$$K^{-1}_{ass} = \frac{a^*_{K^+(solv)}\, a^*_{A^-(solv)}}{a^*_{K^+(solv)\, A^-(solv)}}. \quad (3)$$

Bruckenstein[138], who studied the state of electrolytes in anhydrous acetic acid, concluded that even the strongest electrolytes are very slightly dissociated and exist only in the form of ion pairs, and that in a medium with a very low dielectric constant triple and quadruple ions are formed, complicating the quantitative treatment of the processes taking place in the solution. For solvents whose dielectric constant differs from that of acetic acid[6,18] the picture is different.

The ratio of the activities of the different products of these reactions depends on the properties and concentration of the solute and solvent.

The dissociation constant measured by ordinary methods, K_{ord}, expressing the ratio of the activity product of the free ions to the total activity of undissociated electrolyte species,

$$K_{ord} = \frac{a^*_{K^+(solv)}\, a^*_{A^-(solv)}}{\Sigma a^*_{undiss}}, \qquad (4)$$

can be written

$$K_{ord} = \frac{K_{diss}}{1 + K^*_{inst} + K_{conv}}, \qquad (5)$$

where K_{conv} is a conversion constant taking account of the conversion of the undissociated addition product to an ion pair:

$$KAM_n + x\,M \rightleftarrows K^+(solv.)\,A^-(solv.) + y\,M,$$

$$x + y = m,$$

$$K_{conv} = \frac{a^*_{K^+(solv)\,A^-(solv)}}{a^*_{KAM_n}}. \qquad (6)$$

Different processes may predominate, depending on the nature of the solute and the properties of the medium, so that Eqn. (5) may assume a number of particular forms. For example, the acid-base equilibria anhydrous acetic acid, which has marked protogenic character and low dielectric constant (ϵ = 6.16), are expressed by the following scheme[138-141]:

$$HX \underset{(I)}{\rightleftarrows} H^+X^- \underset{(II)}{\rightleftarrows} H^+ + X^-.$$

The equilibrium constant of reaction (I), referred to by Izmailov as the conversion constant K_{conv} and by Kolthoff as the ionisation constant K_i,

$$K_i = \frac{(H^+X^-)}{[HX]},$$

is related to K_{diss} and K_{ass} by the expression

$$K_{conv} = K_i = K_{diss}K_{ass},$$

or

$$K_{diss} = K_{conv}K^{-1}_{ass} = K_iK^{-1}_{ass}.$$

The equilibrium constant of reaction (II), referred to by Kolthoff as K_d, expresses the dissociation of the ion pairs and is equivalent to the reciprocal of the association constant K^{-1}_{ass}, *i.e.*

$$K_d = \frac{[H^+][X^-]}{[H^+X^-]}. \qquad (7)$$

Kolthoff represents the state of equilibrium established between the ions and undissociated molecules HX and H^+X^- as follows:

$$K_{HX} = \frac{[H^+][X^-]}{[HX] + [H^+X^-]}$$

or

$$K_{HX} = \frac{K_i\,K_d}{1 + K_i}. \qquad (8)$$

Eqn. (8) is a particular case of Eqn. (5) with the condition $K^*_{inst} \ll 1$. Substituting activities for equilibrium concentrations in Kolthoff's equation (8) and expressing the equilibrium constants by Izmailov's method, we obtain

$$K_{ord} = \frac{K_{conv}K^{-1}_{ass}}{1 + K_{conv}} = \frac{K_{diss}}{1 + K_{conv}},$$

since

$$K_i = K_{conv};\ K_d = K^{-1}_{ass}.$$

Thus Kolthoff's equation is a particular case of Izmailov's equation.

Analogously it can be shown that the equilibrium schemes and equations of other authors (Ref. 26, p. 603) (Berg and Patterson[142], Smith and Elliot[143], Halban[144], Correy[145], Sadek and Fuoss[146], and others) are particular cases of the general equilibrium scheme put forward by Izmailov:

$$KA + (n+m)\,M \overset{K^*_{inst}}{\rightleftarrows} KAM_n + m\,M \overset{K_{diss}}{\rightleftarrows} K^+(solv.) + A^-(solv.),$$

$$\uparrow\downarrow K^{-1}_{ass}$$

$$x\,M \overset{K_{conv}}{\rightleftarrows} K^+(solv.)\,A^-(solv.) + y\,M.$$

Izmailov's theory is applicable to acids, bases, and salts in non-aqueous solutions and has been described in detail[20,26,147-150].

The modern theory of non-aqueous solutions, according to which the same substance, under the influence of the solvent, may be a strong or weak electrolyte and alter its acidity, basicity, solubility, and other properties, is derived from the above ideas and is based on a quantitative consideration of the affinity between the ions of the dissociating substance *in vacuo* and the energy of their solvation and of the solvation of the solvent molecules.

The dependence of the strength of the electrolyte on the properties of the substance and the solvent is expressed quantitatively by the equation

$$K_{ord} = K_{exp}\frac{\Sigma A_x - A_{mol}}{RT}, \qquad \dagger\ (9)$$

where K is the dissociation constant of the electrolyte *in vacuo*, ΣA_x the total energy of solvation of the ions, and A_{mol} the energy of solvation of the molecules.

By making a detailed analysis of Enq. (9) and introducing the theory developed by Bernal and Fowler[151] and Mishchenko and Sukhotin[152] to define the energy of solvation of ions, Izmailov deduces particular cases[20] of the general equation (9) for salts, acids, and bases and the ionic product of the solvent. From the equations which he gives it follows that:

1. The strength of any acid increases with increase in the basicity of the solvent and the energy of solvation of the lyonium and lyate ions; this energy increases with increase in the dielectric constant of the solvent and the dipole moment of its molecules. The solvent influences not only the absolute strength of acids but also their relative strengths. A differentiating action with respect to acids is particularly characteristic of solvents with a low dielectric constant (Table 1).

2. The strength of any base increases with increase in the acidity of the solvent and the energy of solvation of the

† It appears that this equation should read $K_{ord} = K\exp\left(\frac{\Sigma A_x - A_{mol}}{RT}\right)$ (Ed. of Translation).

TABLE 1. Dependence of the strength of hydrochloric and benzoic acids on the nature of the solvent.

Solvent	Dielectric constant	The logarithm of the reciprocal of the autoprotolysis constant pK_i^*	$pK_{ord(b)}$ (benzoic acid)	$-\log \frac{K_i^*}{K_{ord(b)}}$	$pK_{ord(h)}$ (hydrochloric acid)	$-\log \frac{K_i^*}{K_{ord(h)}}$
Water	78.5	14.0	4.02	9.89	0.80	13.2
Liquid ammonia	21.0	33.7	3.82	29.88	2.90	30.8
50% acetone	24.0	20.3	9.80	10.50	2.47	17.83
Acetone	19.1	—	11.95	—	4.00	—
Ethanol	24.0	19.1	10.13	9.13	1.95	17.35
Anhydrous acetic acid	6.1	14.5	—	—	9.10	5.35

Note. $K_{ord(b)}$ and $K_{ord(h)}$ are the dissociation constants of benzoic and hydrochloric acids respectively.

ions. A differentiating action with respect to bases is also particularly characteristic of solvents with a low dielectric constant (Table 2).

Titration of acids. The influence of different solvents alters not only the absolute strength of acids, but also their relative strengths. This applies particularly to acids of different character, soluble in solvents of low dielectric constant [153-187]. The accuracy of the titration of individual acids and bases is determined by the ratio of the autoprotolysis constant K_i of the solvent to the dissociation constant K_{ord} of the acid or base being titrated, K_i/K_{ord}

The accuracy of the differentiating titration of acid or base mixtures is determined by the ratio of the strengths of the individual components of the mixtures being titrated:

$$K_{ord(II)}/K_{ord(I)}. \qquad (10)$$

The differentiating action of acid solvents on inorganic acids is shown only when the solvent has a low dielectric constant [188]. In acid solvents it is possible to determine separately the concentration of strong acids in mixtures with organic (weak) acids [189]. Even the strongest organic acids are not titrated in protogenic solvents, since the pK values of organic acids are numerically much greater than 10. For example, pK for trichloroacetic acid — the strongest organic acid — is 11.64 (Table 3) [13]. The strongest acid in acetic and formic acids is perchloric acid (Table 3), so that best results in protogenic solvents are given by perchloric acid as titrant.

TABLE 2.

Base	H_2O, $pK_i^* = 14$		CH_3COOH, $pK_i^* = 14.45$		HCOOH, $pK_i^* = 5.7$	
	$pK_{ord(base)}$	$-\log \frac{K_i^*}{K_{ord(base)}}$	$pK_{ord(base)}$	$-\log \frac{K_i^*}{K_{ord(base)}}$	$pK_{ord(base)}$	$-\log \frac{K_i^*}{K_{ord(base)}}$
Diethylamine	2.9	11.1	—	—	0.74	5.0
Urea	13.82	0.18	10.24	4.2	1.25	4.50
Pyridine	8.69	5.31	6.1	8.35	0.95	5.3
Benzidine	9.03	3.97	—	—	0.75	5.0
Aniline	9.4	4.6	—	—	0.44	5.31
α-Naphthylamine	10.8	3.2	—	—	0.88	4.89
Triphenylamine	—	—	5.38	9.07	—	—

Note. $K_{ord(base)}$ is the dissociation constant of the base.

TABLE 3. pK values for some strong acids in different solvents.

Acid	Solvent		
	H_2O	CH_3COOH	HCOOH
Perchloric	—	5.80	0.28
Hydochloric	—	8.85	0.89
Sulphuric	1.92(K_2)	8.20	0.58
Trichloroacetic	0.89	11.64	—

In the titration of acid mixtures, in addition to the value of the ratio $K_{ord(II)}/K_{ord(I)}$, the ratio of their initial concentrations C_1 and C_2 is of great importance. According to Komar', [190] the distribution of alkali between two acids present in a titration mixture may be expressed by the equation

$$\frac{K_1}{K_2} = \frac{\alpha}{(1-\alpha)^2}\left[\frac{C_2}{C_1} - (1-\alpha)\right],$$

where K_1 and K_2 are the dissociation constants of the acids, and α the distribution coefficient of the alkali between the acids. It is possible by solving this equation, to calculate theoretically the ratio C_2/C_1 at which differentiating titration of the acids is possible.

For the accurate separate titration of a mixture of acids when $C_1/C_2 = 0.01$, it is necessary that $K_1/K_2 \geqslant 10^6$, but the ratios of the constants of, for example, sulphuric and lactic acids and sulphuric and citric acids in water are, respectively:

$$\frac{K_{sulphuric}}{K_{lactic}} = \frac{1.2 \times 10^{-2}}{1.4 \times 10^{-4}} = 85.7,$$

$$\frac{K_{sulphuric}}{K_{citric}} = \frac{1.2 \times 10^{-2}}{8.7 \times 10^{-4}} = 13.8.$$

These data show that for this ratio of the constant the separate titration of these acids in aqueous medium is impossible with $C_1/C_2 = 0.01$. This applies to an even greater extent at less favourable ratios of C_1 and C_2, *i.e.* when the concentration of the weaker acid is much greater than that of the stronger acid. Such titrations are possible, however, for mixtures of strong and weak acids in non-aqueous solutions [191].

The use of protogenic solvents in analytical chemistry has extensive possibilities in the analysis of individual acids and bases and their mixtures, including acids and bases whose pK values are > 10.

The processes taking place in the titration of weak acids by bases in protophilic solvents can be represented by the following equations:

$$HCON(CH_3)_2 + HX \rightleftarrows [HC\overset{+}{O}NH(CH_3)_2]^+ + X^-,$$

$$(C_2H_5)_4NOH \rightleftarrows [(C_2H_5)_4N]^+ + OH^-,$$

$$[HC\overset{+}{O}NH(CH_3)_2]^+ + OH^- \rightarrow HCON(CH_3)_2 + H_2O,$$

$$\overline{(C_2H_5)_4NOH + HX \rightarrow (C_2H_5)_4NX + H_2O}.$$

Titration of bases. The strength of bases increases with increase in the acidity of the solvents and the energy of solvation of the ions. A differentiating action

TABLE 4. pK values for some bases in different solvents.

Base	Solvent		
	H_2O	CH_3COOH	HCOOH
Pyridine	8.69	5.96	0.45
α-Naphthylamine	10.08	6.40	0.88
Caffeine	13.39	—	0.78
Urea	13.82	9.8	1.25

with respect to bases is observed particularly for solvents with a low dielectric constant and low acidity [192-200].

In protogenic solvents (for example CH_3COOH) even weak bases with p$K > 10$ are titrated as strong bases. Since the value of $K_{i(CH_3COOH)}$ (2.5×10^{-13}) [*cf.* Table 2, 3.5×10^{-15}? (Ed. of Translation)] is close to that of $K_{i(H_2O)}$, the possibility of titrating bases results from the marked increase in the dissociation constant of bases in protogenic solvents.

In acid solvents reactions leading to the formation of the ions of the base proceed nearly to completion, the degree of completeness being greater, the greater the protogenic properties and dielectric constant of the solvent. For example, in formic acid, which has more marked protogenic properties and a higher dielectric constant than acetic acid, electrolytes exhibit a more marked basic character. Table 4 gives pK values for some bases in acetic and formic acids; data for aqueous solutions are also given for comparison [13]. Table 4 shows that some very weak bases, which cannot be titrated in water or in anhydrous acetic acid, can be titrated quantitatively as strong bases in a solution of anhydrous formic acid.

Acidic solvents, due to their pronounced protogenic properties, have a levelling effect on the strength of bases; this property is particularly characteristic of formic acid, first studied in this connection by Hammett and Dietz [201] and studied in detail later by Shkodin and others [13,130,202-204]. One advantage of formic acid as solvent is that in this acid it is possible to titrate extremely weak bases which cannot be titrated in acetic acid [202,203].

The processes taking place during the titration of weak bases, in protogenic solvents, by perchloric acid dissolved in anhydrous acetic acid, can be represented by the following equations:

$$C_5H_5N + HCOOH \rightleftarrows C_5H_5NH^+ + HCOO^-,$$
$$HClO_4 + CH_3OOH \rightleftarrows CH_3COOH_2^+ + ClO_4^-,$$
$$CH_3COOH_2^+ + HCOO^- \rightleftarrows CH_3COOH + HCOOH,$$
$$C_5H_5NH^+ + ClO_4^- \rightleftarrows C_5H_5NHClO_4,$$
$$C_5H_5N + HClO_4 \rightarrow C_5H_5NHClO_4.$$

The fundamental theory of acid-base titrations in non-aqueous media has been described in a number of papers [205-236].

The above review shows the vast possibilities of non-aqueous solutions in analytical chemistry, which are assisting in the development of new, highly-sensitive, rapid, and accurate methods of analysis.

III. SOLVENTS USED IN NON-AQUEOUS TITRATION

1. Solvents for Compounds Titrated as Bases

Conant *et al.* [237-239] first used anhydrous acetic acid as solvent for the titration of weak bases with perchloric acid. Marcunas and Riddick [240,241] showed that many amines, salts of organic acids, choline salts of carboxylic acids, salts of organic bases, oxazolines, amino-alcohols, etc. can be determined in acetic acid. Salts without basic properties are converted to acetates, which can be titrated as bases [242-244]. Titration in anhydrous acetic acid is now widely used to determine a variety of organic substances [245-267]. Pifer *et al.* [268] and Poulos [269] established that the addition of hydrocarbons or their halogeno-derivatives, dioxane, and other solvents to acetic acid facilitates the dissolution of organic compounds and makes the end-point of the titration sharper. Mixtures of acetic acid with chloroform [270,271], benzene [272], nitromethane [256], nitrobenzene [273], and acetonitrile [256], have been used as solvents.

Titration in acetic acid has a number of disadvantages however [274]. Pifer and Wollish's studies [275] showed that the water content of the acetic acid should not exceed 1%. The addition of acetic anhydride eliminates the influence of water and increases the potential jump. Acetic acid can also be dehydrated with triacetyl borate [276]. A number of authors [277,278] have shown that complete removal of water from the acetic acid makes the end-point of the titration much sharper. Many weak bases, which cannot be titrated in acetic acid, can be titrated in a mixture of acetic acid and acetic anhydride [250,279,280]. Some authors have used pure acetic anhydride instead of acetic acid and its mixtures with acetic anhydride [271,279-283]. A method has been developed for the micro- and ultramicro-titration of organic compounds in acetic acid [259,260,271].

Hammett [201,284] and others [285] found that formic acid can also be used for titrating very weak bases: aniline, urea, etc., and the acid has been used for this purpose by Shkodin, Izmailov, Dzyuba, and others [202,203,286]. In formic acid, which is a more acidic solvent than acetic acid, it is possible to titrate weak bases which cannot be titrated in acetic acid. Mixtures of formic acid with acetic acid [285], nitromethane [287], and dioxane [288] have also been used for titrations. The addition of dioxane improves the conductometric titration of weak bases.

A number of workers have titrated bases in propionic [289-294], butyric [295], chloroacetic [188,296,297], trichloroacetic [188], and trifluoroacetic [298,299] acids.

Indian workers [7,300-308] have used glycol solvents. Glycols have also been used as solvents for the titration of bases by other workers [309-311].

Vorländer and others have titrated bases in benzene, chloroform, and carbon tetrachloride [263,269,312-319]. Mixtures of benzene with dioxane have been used as solvents, as well as cyclohexane, ethyl acetate, chlorobenzene, n-heptane, nitrobenzene, nitromethane, ethyl ether, petroleum ether, and other solvents [200,256,263,277,319-325].

Fritz [326] found that anhydrous dioxane is a good solvent for the titration of bases, and this was confirmed by other authors [268,269,327]. Mixtures of dioxane, benzene, and toluene with acetic anhydride have also been used as media for the titration of bases [328].

Solvents with strong acidic properties cannot be used for the differentiating titration of mixtures of bases, due to the levelling action of these solvents on the bases. Solvents with neutral or amphoteric properties have no levelling action on bases, and can be used for the differentiating titration of mixtures of bases which cannot be titrated in water and acidic solvents because their dissociation constants are too similar. Fritz[329] and others[256,321] used acetonitrile as solvent for the differentiating titration of amine mixtures. Chatten[330] titrated bases in a phenol–chloroform–acetonitrile medium.

Acetone[331-333] and methyl isobutyl ketone[334] have been used for the differentiating titration of mixtures of organic bases.

We have studied the differentiating action of acetone, methyl ethyl ketone (MEK), and methyl butyl ketone (MBK) in the titration of mixtures of organic bases[335], and found that MEK is one of the best differentiating solvents. The differentiating titration of multicomponent mixtures of organic bases is possible in MEK.[336,337]

Pyridine[338] and other solvents[323,339-341] have also been used for the titration of organic bases.

2. Solvents for Compounds Titrated as Acids

Inert solvents such as benzene, chloroform, toluene, carbon tetrachloride, and their mixtures were used initially for the titration of acids[342-347], and are still receiving attention[348,349].

Fairly sharp end-points are observed in the titration of acids in alcohols[237]. Acids can be titrated in methyl, ethyl, propyl, isopropyl, butyl, pentyl, isopentyl, benzyl, and other alcohols, and also in mixtures of alcohols with benzene, chloroform, carbon tetrachloride, dioxane, anisole, acetone, and pyridine[350-389]. In 1951 Fritz[390] introduced benzene–methanol mixtures for non-aqueous titration, and these mixtures have since been used by other workers[391-398].

Of the basic solvents, liquid ammonia has the greatest solvent power for organic substances. Reviews on acid–base titration in liquid ammonia have appeared[9,131]. Methods of titration in liquid ammonia have also been described[399,400], but these have limited applications.

Moss *et al.*[401] used anhydrous ethylenediamine (EDA) for the titration of phenols and other weak acids. In EDA it is possible to titrate certain nitro-compounds, which behave as acids[402]. Other authors have also titrated weak acids in EDA.[383,403-411] Many acidic substances have been titrated in butylamine[390,396,404,412,413] and also in ethylamine, diethylamine, and triethylamine[414].

Pyridine[375,391,412,415-424] and piperidine[334] are often used as a medium for the titration of different acidic substances. Marcunas and Cundiff[389,425] found that pyridine is the most suitable solvent for the titration of mixtures of strong acids.

Fritz[404,426,427] suggested the use of dimethylformamide (DMF) as solvent for the titration of acids. Very many compounds of acidic character can be titrated in this medium[408,418,424,428-435]. Diethylamine, diethylformamide, and other amides have also been used for the titration of acidic substances[433,436]. Shkodin and others have used acetic and formic acids as solvents for the titration of mixtures of strong acids[2,191,204,437-439]. Acids have also been titrated in butyric, monochloroacetic, and trichloroacetic acids[130,188,295].

Acids have been titrated in mixtures of ethylene glycol with isopropyl alcohol, acetone, and chloroform[301,440-442], and also in ethers[443,444], dioxane[445-447], and acetonitrile[347,389,448-450].

A number of ketones have been used for the titration of acidic substances. Cray[451] first carried out titrations in acetone. Izmailov and others made use of the differentiating action of ketones (acetone, MEK, methyl propyl ketone) for the titration of acid mixtures[376]. Other authors have also titrated acids in ketones[423,452-457]. Alcohols, ethers, hydrocarbons, and other solvents have been added to acetone to facilitate the dissolution of organic acids[458]. Bruss and Wyld[334] suggested the use of methyl isobutyl ketone for the titration of mixtures of strong, weak, and very weak acids. Cundiff and Marcunas[389,425] showed that methyl isobutyl ketone cannot be used for the titration of mixtures containing strong acids.

We have titrated various organic and inorganic acids in MEK.[459]. It was established that MEK exhibits good differentiating properties with respect to both strong and weak acid mixtures. In this respect MEK is superior to acetone and MBK. Strong acid mixtures cannot be titrated in acetone, and in MBK the salt formed during the titration is often precipitated[460]. Compounds of acidic character have also been titrated in various other solvents[436,453,461-463]

IV. TITRANTS

Titrants of acidic character. A solution of hydrogen chloride in benzene was first used for the titration of bases in non-aqueous media[464]. Subsequently it was established that $HClO_4$ is the strongest acid in non-aqueous solvents: $K_{HClO_4} = 1.6 \times 10^{-4}$ and $K_{HCl} = 1.4 \times 10^{-7}$.[465] [*cf.* Table 3, (Ed. of Translation)] Solutions of perchloric acid in acetic acid are now chiefly used for the titration of bases[253-256,466-479]. Solutions of hydrogen chloride in organic solvents have also been used[249,480-482]. For titration in glycols, glycol solutions of $HClO_4$ and HCl are employed[7,308,309].

Pifer and Wollish[275] found that the end-point is sharper when solutions of $HClO_4$ in dioxane are used. Solutions of $HClO_4$ in dioxane are often used for the titration of bases in inert and differentiating solvents[321,327,329,483]. Solutions of $HClO_4$ are also prepared in acetonitrile[329], nitromethane[484], dioxane–formic acid mixtures[288], and propionic acid[293,294].

We have successfully used a solution of $HClO_4$ in MEK.[336,337] Titration in MEK with a solution of $HClO_4$ in the same solvent gives sharper end-points than $HClO_4$ solutions in anhydrous acetic acid and dioxane.

Udovenko and Vvedenskaya[332] used solutions of H_2SO_4, HNO_3, and β-naphthalenesulphonic acid for titrations in acetone; H_2SO_4 and HNO_3 solutions have also been used by other workers[485,486].

Sulphonic acids have been widely used for the titration of bases, *e.g.* *p*-toluenesulphonic acid[321,487-489]. Hall[321] used perfluorobutyric and methanesulphonic acids. In non-aqueous solvents, the strength of benzenesulphonic acid is comparable to that of sulphuric acid[490]. The strengths of methanesulphonic, ethanesulphonic, benzenesulphonic, and naphthalene-2-sulphonic acids in acetic acid are lower than that of perchloric acid, but the sulphonic acids do not form precipitates and gels during the titration[491,492]. Solutions of diphenyl phosphate and periodic and salicylic acids have also been used as titrants[311,489,493].

Solutions of perchloric acid and other acids in non-aqueous media are usually standardised with sodium carbonate[468,471,472], diphenylguanidine[326,496], potassium hydrogen phthalate[241,497,498], 4-aminopyridine[499], and potassium tetraborate[500].

Titrants of basic character. Potassium and sodium methoxides and ethoxides, and potassium, sodium, and lithium butoxides and amyloxides [342-345,387] were used initially for the titration of acids in non-aqueous media. Many workers have used these titrants[391-393,436,501]. Rubidium and caesium methoxides have also been used for the high-frequency titration of acids[502].

Stronger basic titrants include sodium aminoethoxide in EDA,[401,411] sodium triphenylmethane in an ether–benzene mixture[503], and lithium aluminium hydride and lithium aluminium amide in tetrahydrofuran[504-507]. A solution of sodamide in liquid ammonia has been used as titrant in this solvent[399]. Acids have also been titrated with solutions of pyridine, piperidine, and aniline[204,415,439,440,508], various amines, morpholine, nitron, and dimethylaminoantipyrine[375,402,415,434,441,450,508], alcoholic or ethereal alkali solutions[136,372,384,421,440,441,509], and sodium, potassium, and lithium acetates in anhydrous acetic acid[188,189,191,279,437,441,510,511].

Deal and Wyld[408] titrated mixtures of strong and weak acids with a solution of tetrabutylammonium hydroxide (TBAH) in aqueous isopropyl alcohol. Harlow *et al.*[407] used TBAH dissolved in absolute isopropyl alcohol. Cundiff and Marcunas[418] used a benzene–methanol solution of TBAH. Quaternary ammonium hydroxides have been widely used in analysis[334,374,375,391,425,452,454,456,458,512,513].

We have used a benzene–methanol solution of tetraethylammonium hydroxide (TEAH) for the titration of multicomponent mixtures of compounds exhibiting acidic character in non-aqueous media[459,460]. The titration curves show sharp end-points. Salts of TEAH and inorganic and organic acids are readily soluble in organic solvents.

Benzoic acid is generally used to standardise solutions of the above titrants[7,17,459]. Sulphamic acid has been used to standardise CH_3OLi solutions[514].

V. METHODS OF TITRATING BASIC SUBSTANCES IN NON-AQUEOUS MEDIA

1. Visual and Potentiometric Methods

Primary, secondary, and tertiary aliphatic and aromatic amines. The majority of organic bases can be titrated in non-aqueous solvents. Primary, secondary, and tertiary amines are titrated in anhydrous acetic acid[240,263,468,471,515-517], propionic acid[518], glycols[7,309], and other solvents[263,329,519]. Hall[321] titrated about 70 individual mono- and di-amines in non-aqueous solvents. Micro-[520] and ultramicro-methods[260] have also been used for the determination of amines.

Bloomrich and Bandel[468] developed a method for determining tertiary amines in mixtures with primary and secondary amines by titration in an acetic acid–acetic anhydride medium. Wagner *et al.* extended this method to the determination of mixtures of primary, secondary, and tertiary aliphatic amines[521,522]. The total amine content is first determined by titration. A known quantity of the specimen being studied is then treated with acetic anhydride, after which the tertiary amine is titrated. A third titration gives the sum of the secondary and tertiary amines after treatment of the mixture with salicylaldehyde, which converts the primary amines to Schiff's bases. The glycol titration method has also been used for the quantitative determination of mixtures of primary, secondary, and tertiary aromatic amines[310].

Johnson and Funk[523] have described a modification of the method of Wagner *et al.* Salicylaldehyde in pyridine is added to the amine mixture, after which the excess salicylaldehyde is titrated with sodium methoxide. The primary amine content is found by difference. Critchfield and Johnson[327], in the determination of mixtures of primary, secondary, and tertiary amines, converted the primary amines to the weakly basic imine, by treating the amine mixture with salicylaldehyde, and determined the total content of secondary and tertiary amines. Dioxane was then added to the mixture and the imine was titrated. Primary aliphatic amines have also been determined by titration of the excess 2,4-pentadione which had not reacted with the amine[524].

Kubias[481] developed a method for the analysis of mono-, di-, and tri-ethanolamines. The triethanolamine content was determined by titrating the mixture after treatment with acetic anhydride. The mono- and di-ethanolamines were determined iodometrically, by oxidising them with periodate and titrating the liberated iodine with Na_3AsO_3 solution. Gal'pern and Bezinger[525] developed a method for analysing a mixture of primary, secondary, and tertiary aliphatic amines by titration in glacial acetic acid. The method is based on the quantitative reaction of primary amines with phthalic anhydride, and of the primary and secondary amines with acetic anhydride.

Many Schiff's bases have been titrated in acetic acid[526]. The differentiating titration of amines and Schiff's bases is possible in chloroform and acetonitrile. Primary amides of the sulphonamide series can be titrated in acetic acid[471].

Organic bases containing heterocyclic nitrogen. Many organic bases containing heterocyclic nitrogen have been titrated in non-aqueous solvents. These bases include purines, pyridine, pyridone, thiazole, pyrazolones, quinoline, hydrazones, hydrazides, oxazolines, their derivatives, 5-acetamidomethyl-4-amino-2-methylpyrimidine, aminopyrine, and other compounds[240,241,249,253,277,278,473,476,527-534].

Mizukami and Hirai[535] have developed a method for the separate determination of the hydrazide of isonicotinic acid and sulphoisoxazole. The mixture of these compounds in acetic acid is treated with acetic anhydride; the acetate of the isonicotinic acid hydrazide dissolves in the acid and is titrated with perchloric acid in a mixture of acetic acid and acetic anhydride.

Lieber *et al.*[477] have developed a method for determining the acidic and basic forms of substituted 5-amino-1,2,3-triazoles. The acidic forms are determined by titrating with a benzene-methanol solution of sodium methoxide in dimethylformamide. The basic forms dissolved in acetic acid are titrated with $HClO_4$ solution. The method is applicable to the separate determination of the acidic and basic forms in a mixture.

Hennart and Merlin[294] have titrated benzoimidazole and ethyl-2-benzoimidazole with an alkyl group in the 2- or 5-position, in anhydrous propionic acid.

Alkaloids. A number of authors have used non-aqueous solvents for the titration of many alkaloids which are weak bases: theobromine, caffeine, quinine, brucine, and others[247,262,263,473,536,537]. The titration of the alkaloids is carried out in acetic acid, and also in chloroform, carbon tetrachloride, and their mixtures[268,312-317,538]. The glycol titration method has also been applied to the analysis of strychnine, brucine, narcotine, narceine, papaverine, thebaine, and others[7,301,307,539].

Other organic bases. The nitro-derivatives of aromatic amines exhibit very weak basic properties, even in strongly protogenic solvents. In pyridine these compounds exhibit acidic properties and can be titrated quantitatively with a benzene–methanol solution of triethyl-n-butylammonium hydroxide. Fritz[338] used this method to determine the nitro-derivatives of amines, substituted in the 2,4- or 2,4,6- [2,6- or 4,6? (Ed. of Translation)] positions with two NO_2 groups or one NO_2 group and one or several Cl atoms, diphenylamine derivatives containing NO_2 in position 4, and also trinitrotoluene and trinitrobenzene. Quantitative determination of certain mixtures of nitro-compounds is also possible.

Wimer[282] developed a potentiometric method for titrating different substituted and unsubstituted amides in acetic anhydride. Under these conditions the sparingly soluble diamides of dibasic acids (with the exception of malonamides and tetra-substituted phenylamides), *N*-phenyl- and α-phenyl-substituted amides, and unsaturated amides, with a double bond conjugated with the carbonyl group, are not titrated. The method is applicable to the determination of amide–amine mixtures. The authors also titrated aliphatic, aromatic, and heterocyclic sulphoxides in acetic anhydride.

Certain amides have been titrated in acetic acid[257,540].

Salts of organic acids or bases. Many alkali metal salts of carboxylic acids are readily soluble in acetic acid and can be titrated as bases[240,241,247-249,268,471,541]. The addition of acetic anhydride increases the accuracy of the determination. Titration of salts is also possible in propionic acid[518]. The glycol titration method is applicable to the determination of a large number of salts of monobasic acids and also to the determination of the acetates of all the alkali and alkaline earth metals and a number of other metals[7,301,302,308].

Salts of organic acids and bases are titrated in formic acid[201,203], acetone[331,465,542], butanol[543], and methanol[544]. The differentiating titration of salt mixtures is also possible[545].

Pifer and Wollish[243,275] have developed a method for converting the salts of hydrohalic acids to the acetates, which are titrated in acetic acid as bases. This method is based on the reaction of the salts with mercuric acetate, according to the equation

$$2KA + Hg(CH_3COO)_2 \rightarrow 2CH_3COOK + HgA_2.$$

Pifer and Wollish[242] have titrated a large number of salts of hydrohalic acids, heterocyclic compounds, vitamins, and quaternary ammonium salts. This method has also been used by other authors for the determination of the hydrochlorides of various amines, the hydrohalides of antihistamine bases, certain narcotic and antibiotic salts, and halide complexes[278,546-548]. Anastasi[252] has determined proguanide (paludrine hydrochloride) by potentiometric titration in an acetic acid–acetic anhydride medium in the presence of mercuric acetate. Gyenes[475] has determined salts of tertiary amines in the presence of salts of acetylated amines with the aid of an acetylating mixture of acetic anhydride and mercuric acetate, dissolved in acetic acid.

Bayer[549] has used mercuric acetate for the analysis of organic bases containing sulphur. The method was tested for the determination of $CS(NH_2)_2$ and thiosinamine. Hennart and Merlin[293] determined amine halides by titration in propionic acid. The amine halides are dissolved in propionic acid, mercuric propionate solution is added, and the liberated propionate is titrated with perchloric acid.

Belcher and Berger[259,260] developed a method for the ultramicrotitration of the sodium salts of carboxylic acids, amine hydrohalides, and quaternary ammonium salts. A method has been developed for determining the sparingly soluble salts of phenothiazine bases in acetic acid, acetic anhydride, acetone, nitrobenzene, and acetonitrile[283]. Best results are obtained by titration in acetone and acetonitrile. Salts have also been titrated in non-aqueous solvents by other workers[281,550-555].

Inorganic salts. Many inorganic salts can be titrated in acetic and propionic acids[208,293]. Pifer and Wollish[243] have applied their method for the analysis of organic bases in acetic acid to the analysis of inorganic salts. Many salts of Na, Al, Co, Fe, Pb, Mg, Mn, K, Ag, Sr, Zn, and other metals have been titrated by this method.

Salts of many metals have been determined in glycols[7]. The metals are precipitated as the oxides, hydroxides, carbonates, or salts of a weak organic acid, after which the precipitate is dissolved in acetic acid. The solution is evaporated and the acetate dissolved in the glycol solvent and titrated.

Differentiating titration of bases. Fritz[329] carried out differentiating titration of mixtures of aliphatic and aromatic amines in acetonitrile, which has no levelling action on bases. He carried out differentiating titration of mixtures of di-n-butylamine + pyridine, aniline + *o*-chloroaniline, β-phenylethylamine + aniline, pyridine + caffeine, and aniline + sulphothiazole. The presence of small quantities of water in the solvent decreases considerably the sharpness of the end-point. Schiff's bases and the original amines can be titrated separately in acetonitrile[526].

Pifer *et al.*[556] have carried out differentiating titration of potassium and ammonium acetates, in a mixture with the acetates of a number of other metals, in an acetic acid–chloroform medium. These authors established that differentiating titration of mixtures of potassium and ammonium acetates with n-butylamine or pyridine is possible. Certain alkaloid mixtures, for example codeine and caffeine, have been determined in nitromethane[484]. Differentiating titration of mixtures of bases has also been carried out in ethylene glycol–phenol, methyl isobutyl ketone, and benzene–methanol[334,557,558].

We have carried out differentiating titration of two-, three-, and four-component mixtures of organic bases in MEK:[335-337] tetraethylammonium hydroxide + piperidine, piperidine + acridine, tetraethylammonium hydroxide + triethylamine + pyridine, tetraethylammonium hydroxide + + triethylamine + *m*-tolylenediamine, and tetraethylammonium hydroxide + triethylamine + pyridine + *m*-tolylenediamine.

Acids titrated as bases. Some organic acids exhibit basic properties in acidic solvents. Thus pyridinecarboxylic acids and their derivatives are titrated as bases

in acetic acid[249,470]. A number of amino-acids also exhibit basic properties in acetic acid[246,486,559-561]. The back--titration method gives best results in certain cases, however. The amino-acids are treated with an acetic acid solution of perchloric acid and the excess of the latter is titrated with an acetic acid solution of guanidine acetate or sodium acetate[9,245]. The basic groups of amino-acids have also been titrated in ethyl alcohol[364,365].

Some amino-acids also exhibit basic properties in glycols[7,307]. These include glycine, asparagine, aminosalicylic acid, *p*- and *o*-aminophenols, and others. Anthranilic and hippuric acids exhibit acidic properties in glycol solvents and cannot be titrated as bases.

2. Conductometric Method

The conductometric method has been used for the titration of substances of basic character in non-aqueous media[320,346,562]. Udovenko and Vvedenskaya[332,492] have carried out the conductometric titration of anabasine, lupine, and other alkaloids. McCurdy *et al.*[288] have described a method for the conductometric titration of weak organic bases in a dioxane–formic acid medium. The titration of binary mixtures of bases has also been carried out.

Van Meurs and van Dahmen[322] have studied the influence of the composition, solvating power, and dielectric constant of the solvents, the temperature of the solution, the anion of the titrant (for example $HClO_4$ and HCl), the number of NH_2 groups in the molecules of nitrogen-containing bases, and the distance between them on the results of the conductometric titration of mono- and di-acidic bases and their mixtures in non-aqueous media.

Amino-acids have been titrated as bases by a conductometric method in trifluoroacetic acid[299].

3. High-Frequency Method

Many organic bases which can be titrated in non-aqueous media by visual, potentiometric, and conductometric methods, can be titrated successfully by the high-frequency method. Thus Wagner and Kauffman[563] have titrated aniline, *p*-toluidine, pyridine, and other bases in acetic acid. The high-frequency and potentiometric curves showed good agreement. Sharp end-points could not be obtained for *p*-nitroaniline (K_{H_2O} 1×10^{-12}), *o*-nitroaniline (K_{H_2O} 1.5×10^{-14}), and urea (K_{H_2O} 1.5×10^{-14}).

Ishidate and Masui[564] have titrated a number of alkaloids and weak organic bases in aqueous alcohol solutions. They established that in acetic acid the method is applicable to the analysis of bases with K_{diss} greater than 10^{-9} and alkaloids with $K = 10^{-10}$.[565] Lippincott and Timnick[566] have titrated aniline, its derivatives, and amino-acids in acetic acid. The differentiating titration of two-component mixtures was achieved.

Riolo *et al.*[567] have developed a high-frequency method for the titration of phenazine, hydrooxyphenazine, benzo[*a*]-phenazine, and benzo[*a*]phenazine-1,2-*N*-monoxide in acetic acid. In mixtures of acetic acid and dioxane the authors were able to carry out differentiating titration of mixtures of triethanolamine with quinoline or pyridine, and of triethanolamine in the presence of quinaldine, acridine, and 2-picoline[568]. The high-frequency method in acetic acid as solvent has been used for the analysis of phenylhydrazine, brucine, phenanthroline, *p*-toluidine, and a number of amines. Compounds containing imino- and hydroxyamino--groups, and urea and thiourea could not be titrated[420].

4. Photometric method

The photometric method has been used for the titration of weak organic bases in acetic acid[474,569]. Later Connors and Higuchi[258] put forward an improved method for the titration of weak bases in acetic acid. The titration of acetamide, urea, dimethylpyrone, thiourea, caffeine, antipyrene, and triphenylguanidine has been studied. The quantitative determination of the individual compounds and mixtures (antipyrene + triphenylguanidine, urea + antipyrene) has been carried out.

Hummelstedt and Hume[570] have carried out photometric titration of weak bases in acetic acid and acetonitrile. Two- and three-component mixtures have been titrated in acetic acid. In acetonitrile it is possible to titrate even four-component mixtures (di-n-butylamine + *N,N*-diethylaniline + aniline + *o*-chloroaniline). It has been established that differentiating photometric titration is possible if the p*K* values of the bases differ by 1.5 or more. The photometric method has proved very successful for the differentiating determination of mixtures of components with similar basic strengths.

VI. METHODS OF TITRATING ACIDIC SUBSTANCES IN NON-AQUEOUS MEDIA

The first analytical determination of the higher aliphatic acids in inert solvents was carried out by Folin *et al.*[342-345]. The practical application of non-aqueous solvents for the titration of weak acids began with the studies of Moss *et al.*[401], who used an EDA medium for the titration of phenols, carboxylic acids, and their derivatives, which cannot be titrated in aqueous media.

1. Visual and Potentiometric Methods

Carboxylic acids. Many workers have titrated mono-, di-, and tri-basic carboxylic acids and their derivatives in non-aqueous media[390,395,400,571,572]. Deal and Wyld[408] have titrated *o*-, *m*-, and *p*-phthalic acids in dimethylformamide. Cundiff and Marcunas[418] have titrated hydroxybenzoic acids in pyridine. They found that *m*- and *p*-hydroxybenzoic acids behave as dibasic acids, whereas *o*-hydroxybenzoic acid behaves as a monobasic acid. In the titration of maleic, succinic, *o*-phthalic, oxalic, malonic, malic, and fumaric acids in pyridine, they obtained curves with two inflections. The titration curves for ethylenediaminetetraacetic acid in dimethylformamide and of citric acid in pyridine show three inflections. The authors used pyridine as solvent for the titration of a number of amino--acids (alanine, leucine, threonine, asparagine, etc.), and also acetic, benzoic, salicylic, and nicotinic acids.

Harlow *et al.*[349,370] titrated dibasic carboxylic acids in aqueous isopropyl alcohol, benzene, toluene, and gasoline. Fritz and Yamamura[452,453] titrated carboxylic acids in acetone. They found that unsubstituted carboxylic acids have approximately identical strengths, and that the presence of halogens at the carbon atoms, like the presence of one or more nitro-groups in the benzene ring, increases

the strength of aromatic acids. Van Dahmen[573] studied the titration of aliphatic and aromatic carboxylic acids in pyridine and acetone, and established that each carboxyl group in maleic and fumaric acids has a different strength.

We have titrated carboxylic acids in MEK.[459] The titration curves for the dibasic malic, malonic, succinic, phthalic, oxalic, and maleic acids showed two inflections. The tribasic citric acid gives a titration curve with three inflections. Carboxylic acids have also been titrated in non-aqueous solvents by other workers[376,407,416,423,456,458,461].

Phenols and their derivatives have been titrated successfully in EDA and DMF.[401,404] Substituted phenols containing formyl, keto, ether, or nitro groups in the *o*- and *p*-positions are stronger acids than unsubstituted phenols and can be titrated in DMF. Alkyl- and aryl-substituted phenols are titrated in EDA.

Deal and Wyld[408] titrated mono- and di-hydric phenols and polyphenols. The best results were obtained in DMF. Polyphenolic compounds containing two or more phenolic groups and joined by the carbon atoms in the *o*-position (*o*,*o*'-dihydroxydiphenylmethane) are much more strongly acidic than phenol itself. The titration curves for these compounds show only one inflection. The titration curves for compounds joined in the *p*-position (*p*,*p*'-dihydroxydiphenyldimethylmethane) show two inflections.

Cundiff and Marcunas[418] titrated phenol in pyridine, DMF, acetonitrile, and a mixture of benzene and isopropyl alcohol. Di- and tri-hydric phenols were titrated as monobasic acids. Fritz and Yamamura[452,453] titrated 18 phenol derivatives in acetone. The results show that functional groups increase the acidity of phenols in the order:

$$-NO_2 > -C\begin{matrix}O\\H\end{matrix} > -C\begin{matrix}O\\R\end{matrix} > Cl,\ Br,\ I > -C_6H_5.$$

A group in the *o*- or *p*-position increases the acidity of phenol more than one in the *m*-position.

Streuli *et al.*[416,574] studied the acidity of phenols in pyridine and found that phenols and bisphenols have a higher acidity, that of the *o*-compound being greater than that of the *m*- and *p*-compounds. Only one hydroxy-group in the bisphenols is titrated. Alkylphenols and alkylthiophenols have been titrated in pyridine[573]. Phenols can also be titrated in DMF by a micromethod[424].

We have shown that phenol, *o*-, *m*-, and *p*-cresols, resorcinol, catechol, and α- and β-naphthols show fairly strong acidic properties in MEK and can be titrated as monobasic acids[459,575]. A number of other authors have titrated phenols in non-aqueous media[396,407,430,576,577].

Our studies[578,579] of the properties of *o*-, *m*-, and *p*-nitrophenols, 2,4-, 2,5-, and 2,6-dinitrophenols, and picric acid in MEK show that the mononitrophenols are stronger acids than phenol itself. The strength of dinitrophenol is comparable to that of carboxylic acids, and that of trinitrophenol (picric acid) is the same as that of hydrochloric acid. Others have also titrated individual nitrophenols in non-aqueous media[418,452,456,577].

Derivatives of barbituric acid. Titration in non-aqueous media has found wide application in the determination of derivatives of barbituric acid. The titration is carried out in butylamine, pyridine, DMF, and mixtures of benzene with isopropyl alcohol and chloroform[385,412,435,576,580].

Enols, imides, amides, and other compounds. Enols, imides, and a number of amides exhibit acidic properties in non-aqueous solvents, and this makes it possible to titrate them as acids. Fritz[390,427,452,453] titrated many enols and imides in butylamine, benzene–methanol mixtures, EDA, DMF, and acetone. Certain thiols, which exhibit acidic properties in butylamine, have also been titrated. Enols, imides, and thiols are also titrated in pyridine[418].

The SO_2NH group exhibits fairly strong acidic properties in DMF. Weaker sulphonamides are not titrated in DMF, but they can be titrated in butylamine[581]. Sulphonamides can also be titrated in other solvents[393,452,453,576] Acetamide, benzamide, and acylamino-acids can also be titrated in liquid ammonia[399].

Salts of ammonia, aliphatic amines, and other organic bases can be titrated as acids in DMF and EDA. Sharp end-points are obtained[426].

Brockmann and Meyer[402] titrated certain aromatic compounds which behave as acids in EDA. Thus *m*-dinitrobenzene is titrated as a dibasic acid, and picric acid as a tribasic acid. The authors considered that the substances formed during the titration were addition compounds of the bases and nitro-compounds.

A number of esters have been titrated in non-aqueous solvents[405,427,582-584]. The hydrazide of isonicotinic acid, which is titrated as a base in acetic acid, can be titrated as an acid in dimethylaniline[585]. The titration of benzotriazoles in DMF has been described[586].

Even such weakly acidic substances as alcohols can be titrated in non-aqueous solvents[504,505,587], *i.e.* benzene. This method has been used to titrate not only alcohols, but also certain hydrocarbons. It does not, however, distinguish different functional groups [ketones, aldehydes, ethers (esters), lactones, or alcohols].

Deal and Wyld[408] used EDA and DMF for the titration of dialkyl and trialkyl phosphates, which exhibit weak acidic properties in these media. A number of other organic compounds have been titrated as acids in non-aqueous solvents[458,503,588-590].

Acid anhydrides and acid chlorides. A combination of aqueous and non-aqueous titrations has been used to determine mixtures of anhydrides and acids. The total acid and anhydride content was determined by aqueous titration. In alcohol, the acid is titrated as a dibasic acid, and the anhydride reacts with the alcohol to form the ester, which is titrated simultaneously as a monobasic acid[591]. Anhydrides and acid chlorides in benzene–methanol media behave like monobasic carboxylic acids[390].

Siggia *et al.*[592] applied Malm and Nadeau's method for the determination of acetic anhydride in acetylating mixture[593] to mixtures of other carboxylic acids and their anhydrides. The method has been used to determine propionic, maleic, phthalic, camphoric, and butyric anhydrides in the presence of the corresponding acids. Free maleic and phthalic acids and their anhydrides have been determined by titration in acetone and MEK with solutions of tertiary amines, with which the anhydrides do not react[434].

Johnson *et al.*[594] developed a direct method for determining anhydrides in the presence of carboxylic acids by titration with morpholine solution. The anhydrides of *N*-carboxy-α-amino-acids have been titrated in non-aqueous solvents[595,596].

Patchornik and Rogozinski[375] developed an interesting method for determining anhydrides and acid chlorides in the presence of inorganic and organic acids. The inorganic acid is determined by titration in dioxane. The solution is then heated with ethyl alcohol and the acid chloride is determined by titrating the hydrochloric acid liberated. The organic acid content is found by difference after determination of the total acidity. In the analysis of a mixture of anhydride and organic acid the specimen is titrated in dioxane with an alcoholic solution of sodium methoxide the anhydride being titrated as a monobasic acid. Another portion of the solution is treated with pyridine and titrated with trimethylbenzylammonium hydroxide solution in the presence of thymol blue; in this case the anhydride is titrated as a dibasic acid. The results of the two titrations are used to calculate the concentration of acid and anhydride. Anhydrides in the presence of acids have also been titrated by other workers[597,598].

Per-acids. Wolf[599] has carried out the separate determination of perbenzoic acid in the presence of benzoic acid in benzene. Martin[410] titrated per-acids, primary and secondary hydroperoxides, and hydrogen peroxide in EDA. Mixtures of certain peroxides, for example H_2O_2 and ethyl hydroperoxide, have also been titrated.

Inorganic acids. H_2SO_4,[439,440,450,455,600] HCl,[334,450,454] $HClO_4$,[334,439,510] HNO_3,[334,600] H_3PO_4,[418,440,600] and other acids[7] have been titrated in non-aqueous solvents.

In the titration of H_2SO_4 in certain solvents the titration curve shows two inflections, corresponding to the first and second stages of the dissociation of H_2SO_4.[301,418,455] The curve for the titration of H_3PO_4 in pyridine shows three inflections[418].

2. Differentiating Titration of Acid Mixtures

Non-aqueous solvents can be used to carry out differentiating titration of mixtures of acids whose pK values in aqueous medium differ by at least 2–3 units, or, in some cases, by only 1 unit. It is possible to carry out differentiating titration of multicomponent mixtures of strong inorganic acids, mixtures of inorganic and carboxylic acids, various mixtures of carboxylic acids with one another and with phenols. In some cases the method of high-frequency titration makes it possible to distinguish isomers, for example m-, p-, and o-cresols. Differentiating titrations were first carried out by Lavine and Toennies[449], who titrated a mixture of acetic and perchloric acids in acetonitrile.

Mixtures of strong acids. Izmailov *et al.*[376] titrated mixtures of HCl with mono-, di-, and tri-chloroacetic acids in ketones and alcohols, and showed that the components of the mixture of HCl with monochloroacetic acid, and of HCl with dichloroacetic acid, can be titrated separately in either acetone or MEK. In the titration in acetone of HCl and trichloroacetic acid, which have similar strengths, the first inflection, corresponding to the neutralisation of HCl, is less distinct than in MEK and methyl propyl ketone. Shkodin and Izmailov[189] have titrated mixtures of strong acids in anhydrous acetic acid and concluded that the strongest acid in acetic acid is $HClO_4$, which can be titrated in mixtures with H_2SO_4, HCl, and HNO_3. p-Toluenesulphonic acid is titrated separately in mixtures with HNO_3 but not in mixtures with H_2SO_4 or HCl; HNO_3 cannot be titrated separately in the presence of H_2SO_4 and HCl. The authors found that in acetic acid carboxylic acids exhibit very weak acidic properties and are not titrated, so that it is possible to determine traces of H_2SO_4 in carboxylic acids in an acetic acid–acetic anhydride medium. The method has been used to determine traces of H_2SO_4 in citric, malic, and lactic acids[191,438].

Mixtures of H_2SO_4 with HCl, HNO_3, and p-toluenesulphonic acid have been titrated in acetonitrile[450]. Mixtures of $HClO_4$ with H_2SO_4 and HNO_3, and of HCl with H_2SO_4 and HNO_3, have been titrated in methyl isobutyl ketone[334]. Mixtures of H_2SO_4 with acetic and p-toluenesulphonic acids have been titrated in pyridine[370]. Cundiff and Marcunas[389,425,600] have studied the titration of mixtures containing strong acids, in acetone, isopropyl alcohol, methyl isobutyl ketone, DMF, acetonitrile, and pyridine. They found that mixtures containing strong acids can be determined quantitatively with sufficient accuracy only in pyridine.

Das and Mukhergee[440] published an interesting paper on the analysis of acid mixtures containing sulphuric acid, by titration in a 2 : 1 ethylene glycol–acetone medium. The method was used to determine mixtures of H_2SO_4 with HNO_3, HCl, $HClO_4$, H_3PO_4, p-toluenesulphonic, salicylic, and acetic acids. Titration of some three-component acid mixtures is also possible, for example H_2SO_4 + p-toluenesulphonic acid + acetic acid, H_3PO_4 + H_2SO_4 + salicylic acid, and H_2SO_4 + $HClO_4$ + H_3PO_4. Kalidas and Das[441] titrated strong acids ($HClO_4$, HNO_3, CCl_3COOH) and certain mixtures of acids (H_2SO_4 + phthalic acid; trichloroacetic acid + + monochloroacetic acid) in ethylene glycol. Components of mixtures of H_2SO_4 with H_3PO_4, $HClO_4$, HNO_3, p-toluenesulphonic and benzenesulphonic acids have been titrated separately in methanol[601].

Mixtures of weak acids. One of the most important advantages of non-aqueous solvents is that in these solvents it is possible to carry out differentiating titration of mixtures of various weak acids[348,360–362,432], particularly mixtures of carboxylic acids and phenols[391,407,408,602,603].

Fritz and Yamamura[452,453] titrated two-component mixtures of phenol and its nitro- and halogeno-derivatives, sulphonamide mixtures, mixtures of phenol derivatives with enols and imides, and mixtures of certain carboxylic acid derivatives. For example, dichloroacetic acid can be titrated in mixtures with acetic acid, but not in mixtures with monochloroacetic acid. The authors have titrated the three-component mixture 2,4-dinitrophenol + o-nitrophenol + + methyl salicylate.

The separate determination of components in mixtures of terephthalic and p-toluic acids in pyridine and in a 1 : 4 pyridine–chloroform medium has been described[421,422]. The first inflection corresponded to the neutralisation of terephthalic acid and the second to the neutralisation of p-toluic acid.

We have carried out differentiating titration of mixtures of carboxylic acids and of phenols with carboxylic acids in MEK.[459,460] In this medium it is possible to titrate separately components of mixtures of benzoic acid with malic or malonic acids, and mixtures of phenol with benzoic or oxalic acids. Two-component mixtures of mononitrophenol with di- or tri-nitrophenols, mixtures of di- and tri-nitrophenols, and three-component mixtures of mono-, di-, and tri-nitrophenols have also been titrated[578,579].

Shain and Svoboda[456] have carried out potentiometric titration of mixtures of weak acids in acetone. They established that differentiating titration is possible in the case of

mixtures of two acids, one of which has a strength equal to or greater than that of acetic acid, and the other a strength equal to or less than that of nitrophenols. In pyridine it is possible to titrate mixtures of cyanamide and dicyanamide, catechol and hydroquinone, and 2,4,6-trichlorophenol and *p*-chlorophenol[574].

Mixtures of strong, weak, and very weak acids. In differentiating solvents it is possible to titrate multicomponent mixtures of acids of different character and strength. In ketones it is possible to carry out differentiating titration of mixtures of strong mineral acids, weak carboxylic acids, and very weak acids of the phenol type. Thus a mixture of hydrochloric acid, acetic acid, and phenol can be titrated in DMF.[408]

Cundiff and Marcunas[418] titrated three-component mixtures of strong, weak, and very weak acids in pyridine. Mixtures of *p*-toluenesulphonic acid + benzoic acid + phenol, hydrochloric acid + acetic acid + *p*-cresol, and nitric acid + + malic acid + *p*-cresol have been titrated. The last mixture gives a curve with distinct inflections corresponding to the neutralisation of nitric acid, *p*-cresol, and the two stages of the dissociation of malic acid. The titration curve for a mixture of the four acids nitric, malic, acetic, and phenol shows five inflections. Bruss and Wyld[334] carried out differentiating titration of a mixture of five acids — perchloric, hydrochloric, salicylic, acetic, and phenol — in methyl isobutyl ketone. We have successfully titrated multicomponent mixtures of acids containing 5–6 acids in MEK.[460,575]

3. Conductometric Method

The conductometric method was first used for the titration of acids in benzene by LaMer and Downes[346]. Strong acids[437,511], carboxylic acids and phenols[604,605], and sulphonamides[606] have been titrated by the conductometric method in non-aqueous media.

Van Meurs and van Dahmen[398,607,608] studied the conductometric titration of carboxylic acids, phenols, and their mixtures, in pyridine, DMF, and their mixtures with benzene and xylene. Monobasic aliphatic acids (formic, acetic, and caproic) and aromatic acids (benzoic, salicylic, and *p*-hydroxybenzoic), dibasic aliphatic acids (oxalic, malonic, succinic, adipic, fumaric, maleic, and tartaric) and aromatic acids (phthalic, isophthalic, and terephthalic), and a number of phenols (phenol, cresol, xylenol, and *o*- and *p*-nitrophenols) have been titrated. The conditions for the titration of mixtures of carboxylic acids with one another and with phenol have been studied[391]. For mixtures of monobasic acids with dibasic acids, the best results were obtained by titration in pyridine and a 1 : 3 DMF–benzene mixture. Two-component mixtures of dibasic acids were titrated in pyridine and DMF.

Bruss and Harlow[609] studied the conductometric titration of phenol and its chloro, nitro, dialkyl, and trialkyl derivatives in benzene, toluene, xylene, carbon tetrachloride, pyridine, alcohols, and ketones.

The conductometric titration of aromatic mono- and di-carboxylic acids, mono- and di-hydric phenols, enols, and amides in pyridine, ethylamine, diethylamine, and triethylamine has been studied[414].

4. High-Frequency Method

Ishidate and Masui[392,610] have carried out high-frequency titration of weak inorganic and organic acids in a benzene–methanol medium. Boric acid is titrated with the addition of several drops of ethylene glycol. Dibasic organic acids whose molecules have 1–2 C atoms between the carboxyl groups show very characteristic titration curves. The anhydrides of carboxylic acids are titrated as dibasic acids.

Masui[611] titrated long-chain carboxylic acids (9–18 C atoms) and studied the high-frequency titration curves for dicarboxylic acids in non-aqueous solvents[612,613].

Lippmaa[436] studied the high-frequency titration of acidic groups in basic solvents. The best results were obtained by titration in a mixture of diethylamine, diethylformamide, pyridine, and a small quantity of thymol. Diethylformamide is added to increase the dielectric constant, since that of diethylamine is low. Pyridine is added to increase the solvent power. Thymol improves the equivalence point of the titration of carboxylic acids and polyhydric phenols. The author showed that the method can be used for the titration of individual phenols, enols, and carboxylic acids. The best results were obtained in the titration of monohydric phenols.

High-frequency titration in non-aqueous media makes it possible to analyse certain mixtures of isomers. Thus Karrman and Johansson[397,614] carried out high-frequency titration of phenols and mixtures containing phenols, in a benzene–methanol medium. Phenol, *o*-, *m*-, and *p*-cresols, α- and β-naphthols, catechol, resorcinol, hydroquinone, pyrogallol, and phloroglucinol have been titrated. Each component gives an inflection on the titration curve of mixtures of phenols. Mixtures of *o*- and *m*-cresols, *o*- and *p*-cresols, *o*-, *m*-, and *p*-cresols, and α- and β-naphthols have been titrated.

Riolo and Notarianni[615] studied the high-frequency titration of organic and inorganic acids in a benzene–methanol medium and in pyridine. Monobasic acids (dichloroacetic, bromoacetic, mandelic, benzoic, and acetic), dibasic acids (sulphuric, fumaric, malonic, succinic, and maleic), tribasic acids (citric and phosphoric), and acid mixtures (benzoic + *p*-toluenesulphonic, fumaric + *p*-toluenesulphonic, and maleic + acetic) have been titrated. In the titration of citric acid the inflections are more distinct in pyridine than in the benzene–methanol medium. Jamieson[616] titrated mono-, di-, and tri-hydric phenols, enols, and imides in ethyl alcohol. The high-frequency method has also been used by other authors[420,428].

5. Photometric Method

McKinney *et al.*[617] titrated phenols in butylamine photometrically. Satisfactory results were obtained both for the individual compounds and for their two-component mixtures with one another and with a strong acid. Hummelstedt and Hume[618] titrated phenol and its derivatives in isopropyl alcohol. They were able to carry out differentiating titration of two-, three-, and four-component mixtures of phenols, including mixtures of phenol with *o*-chlorophenol, 2,4,6-trichlorophenol with 2,4-dichlorophenol, *p*-nitrophenol with the *m*-isomer, etc.

VII. PRACTICAL IMPORTANCE OF NON-AQUEOUS TITRATIONS

The titration of organic compounds in non-aqueous media has been widely applied in research and industrial laboratories for the analysis of various industrial materials. Thus the acidic impurities in coal and petroleum products, fats, oils, and asphalt are determined by titration in alcohols, hydrocarbons, and other solvents[272,351-359,371,384,386,387,619-624]. The basic impurities in hydrocarbons and oil and coal products are determined in anhydrous acetic acid[272,472,515,625-626]. Minczewski *et al.*[270] used acetic acid as solvent to determine pyridine bases and ammonia in coal tar products. They also determined guanidine nitrate in the technical product containing ammonium nitrate and dicyanamide[255].

The determination of phenols in coal and its products[270,409,512], lignins[372,429,629,630], oils[631], resins and bitumins[396] has been described. The aliphatic acids in drying oils are determined by high-frequency titration in an alcohol–benzene medium.

Titration in non-aqueous solvents has been used to determine sulphuric and other acids in mixtures used for acetylation, sulphochlorination, and nitration[279,454,510]. Gribova and Levin[455] developed a method for titrating sulphuric acid and sulphonic acids in acetonitrile and acetone. The method is applicable to the determination of sulphuric, anthraquinone sulphonic, anthraquinonedisulphonic, naphthalenesulphonic, and benzenesulphonic acids for the control of the various stages of industrial sulphonation processes. The same authors[333] developed a method for analysing industrial mixtures of cyclo- and dicyclo-hexylamines and aniline, based on two titrations in acetone. The first titration makes it possible to determine the aniline content and the sum of the cyclo- and dicyclo-hexylamines, and the second titration, after preliminary titration with salicylaldehyde, makes it possible to determine the dicyclohexylamine content. The cyclohexylamine content is found by difference.

Titration in non-aqueous media is frequently employed for the analysis of pharmaceutical products[242,248-250,256,275,419,473,633-655]. Much work in this field has been carried out by Izmailov, Shkodin, Dzyuba, and others. They have used non-aqueous solvents to determine alkaloids, their salts, and the salts of organic bases and organic acids, used in pharmaceutical products[12,379,542,656-658]. These products are analysed in acetic acid[659-673], hydrocarbons[674-676], pyridine, acetone, EDA[677-683], and other solvents[684-695].

Sarson[696] used non-aqueous titration for the analysis of explosives. Nitro-compounds are titrated as acids in DMF and methyl isobutyl ketone, and differentiating titration of mono-, di-, and tri-nitrotoluene was described. Hexahydro-1,3,5-trinitro-*s*-triazine in explosives has been titrated[697].

Analysis in non-aqueous media has been widely used for the determination of a number of monomeric and polymeric organic compounds[698-705]. Streuli[287] has determined the basic copolymers of acrylonitrile. The copolymers are dissolved in a mixture of nitromethane and formic acid and the amines and salts of amines and quaternary ammonium bases are titrated. Halides are converted to the acetates by adding mercuric acetate. To determine salts of heterocyclic amines, the polymers are dissolved in DMF. Owens and Maute[706] have titrated the organic acids and bases present in acrylonitrile. To determine weak bases, acetic acid is added to the acrylonitrile, and to determine strong bases and acids, a mixture of ethylene glycol and isopropyl alcohol is used. Non-aqueous solvents have been used in the analysis of polymerisation accelerators[707] and the determination of the concentrations of vinylpyridine, acrylonitrile, and acrylic acid in elastomers[708].

Sergienko *et al.*[378,709] studied high-molecular-weight petroleum compounds. They used a mixture of benzene and alcohol to determine the acid numbers and saponification numbers of petroleum resins. Kirrmann and Daune-Dubois[431] determined the concentration of carboxylic acids and phthalates in polycondensation resins.

Titration in non-aqueous media is used to determine various functional groups in organic and macromolecular compounds: the carboxyl group in polyesters[501,710], the carboxyl and amino-groups in polyamides[699,711,712], the basic group in gelatin[713], and the benzoyl[714] and carbonyl groups[715-718] in other monomeric and polymeric compounds. Epoxy-compounds are also analysed in non-aqueous solvents[719-723].

Kreshkov and Drozdov have developed methods for the analysis of monomeric and polymeric organosilicon compounds, which exhibit acidic or basic properties in non-aqueous solvents[508,724-727]. The analysis of individual products is based on the potentiometric or visual titration in acetonitrile. Differentiating titration of two- and three-component mixtures is possible by a conductometric method in an acetonitrile–ethyl alcohol medium. A method has been developed for the analysis of nitrogen-containing organosilicon compounds with the nitrogen directly attached to the silicon atom, and with nitrogen in the organic radical. Other workers have titrated organosilicon compounds in non-aqueous media[728,729].

Ershov and others[373,730,731] developed high-frequency methods for the analysis of the raw materials, intermediates, and finished products of the plastics industry. Phenol in solutions of synthetic resins and plasticisers, acetic acid in acetylcellulose, 1,3,5-xylenol in the technical product, etc. have been determined.

Analysis in non-aqueous solvents is also used for organic acids and their salts in chrome liquors[732], foodstuffs[733,734], water-insoluble emulsions[735], tobacco[736,737], clays[738,739], wool, wax[395], agricultural chemicals[740], soaps[7], and other substances[741-743].

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ORIENTATION IN DIENE SYNTHESIS AND ITS DEPENDENCE ON STRUCTURE

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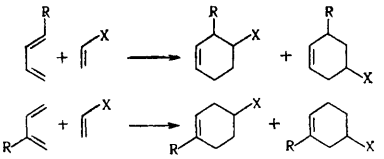
1. INTRODUCTION

In any practical application of diene synthesis — from the preparation of the simplest cyclohexane derivatives to the building up of complicated steriod systems — the mutual orientation of diene and dienophile during the reaction is of paramount significance. One of the most important aspects of this question — structural directivity — is shown in the condensation of unsymmetrical dienes and dienophiles. As can be seen from the scheme below, two pairs of structural isomers — *ortho*† and *meta* with 1-substituted dienes, and *para* and *meta* with 2-substituted dienes — can theoretically be formed.



Available experimental data show that in the first case *ortho*-adducts predominate, and in the second *para*-adducts: *i.e.* the reaction exhibits quite definite structural selectivity.

The study of this dependence of orientation on structure has passed through several stages. For about twenty years after the reaction was discovered it was assumed that diene synthesis takes place without structural ambiguity, only one of the two theoretically possible isomers being formed in any particular case. During 1948–1949 it proved possible to isolate a second structural isomer from among the reaction products obtained with penta-1,3-diene and with isoprene; this result was later extended to dienes having other types of substituents, such as C_6H_5, Cl, CH_3O, etc. Finally, much attention has been paid recently to determining the way in which the proportions of structural isomers depend on the structure of the reactants and the reaction conditions.

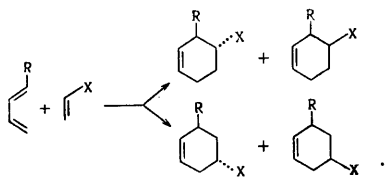
Most of the experimental results on structural directivity have accumulated during the past 8–10 years, and have not been covered by reviews on diene synthesis[1-4]. The present survey, which covers the literature up to the beginning of 1961, represents an attempt to fill this gap. In view of the very large number of diene condensations which have been carried out between unsymmetrical reactants, only work in which the structure of at least one of the isomers has been *proved* is included in the review.

† The terms *ortho*, *meta*, and *para* are now generally accepted for the structurally isomeric adducts of diene synthesis, although strictly they are applicable only to benzene derivatives.

2. 1-SUBSTITUTED DIENES

1-Substituted dienes can exist in the form of two geometrical isomers, corresponding to the *cis*- and *trans*--positions of the substituent. Dienes having the substituent in the *cis*-position are extremely difficult to condense even with the most active dienophiles. Thus the *cis*-1-substituted butadiene derivatives in which the substituent is the methoxycarbonyl[5,6], phenyl[7,8], chloro[9], and cyano[10] group hardly condense at all with maleic anhydride, while *cis*--penta-1,3-diene reacts with it only under very severe conditions[11]. All the condensations described in this section therefore relate solely to the *trans*-isomers of the dienes.

Formation of both *ortho*- and *meta*-adducts is possible in the condensation of *trans*-1-substituted dienes with unsymmetrical dienophiles. Each of them can in turn exist in the form of two geometrical isomers with the substituents in the *cis*- and *trans*-positions, which makes direct separation of the reaction products considerably more difficult.



In this and subsequent sections the published data will be discussed according to the types of substituents in the diene.

The structure of the adducts from condensations of *1-alkylbutadienes* is usually determined by dehydrogenation to the aromatic compounds, which are then converted to known products by various methods (hydrolysis, oxidation, etc.). The proportions of the structural isomers are estimated by fractional crystallisation either of the adducts themselves or of their dehydrogenation products, but this method gives only a semi-quantitative idea of the composition of the mixture.

The early work had already shown that in a large number of cases the main product of the reaction is the *ortho*--isomer. This isomer was obtained in the condensation of penta-1,3-diene with acrylic acid and its derivatives (esters and the nitrile)[12-17], citraconic anhydride[18], and acrolein[12,16,17,19,20]. Condensations of the same diene with acetylenic dienophille — propiolic acid[21,22] and aldehyde[23], ethynyl methyl ketone[24] — also yielded the *ortho*-adducts.

The formation of a *mixture* of structural isomers was established in 1940 in the condensation of penta-1,3-diene with toluquinone[25]. Somewhat later it proved possible to demonstrate the presence of the *meta*-isomer in a mixture of adducts of the same diene with acrylonitrile[26]. The *meta*-isomers were then isolated in the reaction of penta--1,3-diene with acrylic, methacrylic, and 2-isopropylacrylic esters, and also with styrene and acrolein (see Table 1).

Other 1-alkylbutadienes studied were the isopropyl, butyl, and t-butyl compounds, which have been condensed with acrylic acid and esters of α-substituted acrylic acids[27-29]. Both *ortho*- and *meta*-isomers were isolated in all cases, and their relative proportions determined.

1-Phenylbutadiene forms *ortho*-adducts when condensed with acrylic acid and its derivatives[30-36], and also with propiolic[35] and itaconic[37] acids, citraconic anhydride[37], acrolein[30-32,38], and methyl vinyl ketone[36,39]. The presence of *meta*-isomers was demonstrated only in the condensation of this diene with methyl acrylate, methyl methacrylate, and also styrene[40].

TABLE 1. Condensation of 1-substituted dienes with unsymmetrical dienophiles.

Diene $CH_2=CHCH=CH$ (R)	Dienophile $CH_2=C(R_1)R_2$ R_1	R_2	Reaction conditions, t, °C/h	Yield of adducts, %	*ortho*/*meta* ratio	References
CH_3	CHO	H	—	—	6 : 1	57
CH_3	CHO	H	—	—	8 : 1	58
CH_3	CN	H	100/24	56	7.3 : 1	26
CH_3	CN	H	100/12	30	10 : 1	59
CH_3	CO_2CH_3	H	230/2	82	5.2 : 1	59
CH_3	CO_2CH_3	H	200/2	85	6.8 : 1	28
CH_3	CO_2CH_3	CH_3	200/3	52	10.5 : 1	59
CH_3	CO_2CH_3	CH_3	200/2	68	5 : 1	28
CH_3	$CO_2C_2H_5$	iso-C_3H_7	200/15	33	2.5 : 1	28
CH_3	C_6H_5	H	200/2	41	6 : 1	59
iso-C_3H_7	CO_2CH_3	H	200/5	60	5 : 1	28
iso-C_3H_7	CO_2CH_3	CH_3	200/5	52	3.1 : 1	28
iso-C_3H_7	$CO_2C_2H_5$	iso-C_3H_7	200/10	32	2.4 : 1	28
n-C_4H_9	CO_2CH_3	H	200/5	74	5.1 : 1	28
t-C_4H_9	CO_2CH_3	H	160/5	60	3 : 1	27
t-C_4H_9	CO_2CH_3	H	200/5	76	4.1 : 1	28
t-C_4H_9	CO_2CH_3	CH_3	200/5	75	2.6 : 1	28
t-C_4H_9	$CO_2C_2H_5$	iso-C_3H_7	200/10	19	0.9 : 1	28
$OCOCH_3$	citraconic anhydride		100/4	59	1.5 : 1	47
$OCOCH_3$	xyloquinone		100/3	55	1.5 : 1	48
OCH_3	xyloquinone		110/1	62	10 : 1	48
C_6H_5	CO_2CH_3	H	150/3	61	39 : 1	40
C_6H_5	CO_2CH_3	CH_3	150/3	38	13 : 1	40
C_6H_5	C_6H_5	H	150/50	33	8.1 : 1	40
CO_2H	CO_2H	H	150/6	86	8.8 : 1	56
CO_2H	C_6H_5	H	150/6	58	5.7 : 1	56

Derivatives of 1-phenylbutadiene containing various substituents in the benzene ring have also been subjected to diene synthesis. The reactions of 1-*p*-bromophenyl- and 1-*p*-nitrophenyl-butadiene with acrylic acid, propiolic acid, and acrolein yielded only the *ortho*-isomers[41,42]. Condensation of 1-*o*-nitrophenylbutadiene with acrylic acid and acrolein also gave only one structural isomer, the *ortho*--orientation of the substituents in which was proved by conversion of the compounds to phenanthridine[43].

Condensation of *1-acetoxybutadiene* with acrylic acid[44] and with acrolein[45] yields only the *ortho*-adducts, whose structure was proved by conversion to 2-oxocyclohexanecarboxylic acid, whereas its reaction with 5-hydroxy-1,4--naphthaquinone yields a mixture of the two structural isomers[46]. The reactions of 1-acetoxybutadiene with citraconic anhydride[47] and xyloquinone[48] result in the formation of a mixture of *ortho*- and *meta*-isomers in which there is a slight preponderance of the former. The difference between acrylic acid and acrolein on the one hand and citraconic anhydride and xyloquinone on the other, revealed by this work, can be explained by the fact that the methyl group, being the only unsymmetrical feature in the latter two dienophiles, has little influence on the relative proportions of the structural isomers. Another factor is evidently the comparatively weak orienting effect of the acetoxy--group in the diene. In this connection it is interesting that the condensation of 1-methoxy- and 1-ethoxy-butadiene with xyloquinone shows a far more marked structural selectivity. In the former case only ~10% of the *meta*--adduct could be isolated, and in the latter the *ortho*-adduct alone was obtained[48].

Investigation of the adducts of *1-diethylaminobutadiene* is made quite difficult by their ready deamination even during the diene condensation itself[49]. However, by carrying out the reaction under mild conditions (in benzene solution at room temperature), it proved possible to obtain adducts in which the amino-group was preserved. Condensation of 1-diethylaminobutadiene with ethyl acrylate, acrylonitrile, and acrolein under these conditions[50] led to the formation of the *ortho*-isomers, the structure of which was proved by hydrogenation to known compounds.

Condensation of *1-cyanobutadiene* with methyl and ethyl acrylates resulted in the isolation of the *ortho*-isomers alone, which were converted to phthalic acid by dehydrogenation with *N*-bromosuccinimide followed by hydrolysis[51].

The *ortho*-adducts were isolated in the condensation of *butadiene-1-carboxylic acid* with acrylic acid[52] and with 1-vinylnaphthalene[53]. The same isomer was obtained by the interaction of butadiene-1-carbonyl chloride and acryloyl chloride[52]. When, however, the reaction was carried out between the anions of these acids (between salts of the acids in aqueous solution), roughly equal amounts of *ortho*- and *meta*-isomers were isolated[54]. This result was explained by repulsion between ions having like charges, and also by a decrease in orienting power on passing from COOH to COO^-. It has recently been shown that small amounts of the *meta*-isomer are present also in the condensation of butadiene-1-carboxylic acid with acrylic acid and with styrene[55,56].

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Examination of published data on the condensation of 1-substituted dienes with unsymmetrical dienophiles shows that in all cases the *ortho*-isomers preponderate in the resulting mixtures of adducts. This has been established both with ethylenic and acetylenic dienophiles and with unsymmetrical quinones. The preferential formation of the *ortho*-isomers has been demonstrated for the following substituents: in the diene — R (alkyl), C_6H_5, $C_6H_4NO_2$, C_6H_4Br, CN, COOH, OR, CH_3COO, and $N(C_2H_5)_2$; and in the dienophile — COOH, COCl, $CONH_2$, CHO, CN, COR, and C_6H_5. Nevertheless, in some condensations it was possible to isolate the *meta*-isomers from the mixture of adducts, and to prove their structure (see Table 1).

The introduction of different substituents into the diene and the dienophile influences the relative proportions of the structural isomers in different ways. The more one isomer preponderates in the mixture of adducts formed, the greater the "orienting power" of the substituents is taken to be. The data in Table 1 show that, with a phenyl substituent in the 1-position of the diene, the *ortho*-isomer is formed almost exclusively, while on passing to carboxyl and methyl the amount of this isomer in the mixture successively decreases. Therefore these substituents can be arranged in the sequence $C_6H_5 > COOH > CH_3$ according to their orienting power. On condensation with xyloquinone 1-acetoxybutadiene forms considerably less of the *ortho*-isomer than does 1-methoxybutadiene, so that $CH_3O > > CH_3COO$ in orienting power.

These sequences in order of orienting power, derived purely empirically, are determined by a complex interaction between electronic and steric effects of the substituents in the diene and the dienophile, and it is in general extremely difficult to separate these effects. However,

TABLE 2. Ratio of *ortho*-to *meta*-isomers in condensations of 1-alkylbutadiences (at 200°)[29].

Diene	Dienophile: $CH_2=C(H)COOCH_3$	Dienophile: $CH_2=C(CH_3)COOCH_3$	Dienophile: $CH_2=C(CH(CH_3)_2)COOC_2H_5$
$CH=CHCH=CH_2$, CH_3	6.8 : 1	4.9 : 1	2.5 : 1
$CH=CHCH=CH_2$, $CH(CH_3)_2$	5.0 : 1	3.1 : 1	2.4 : 1
$CH=CH-CH=CH_2$, C_4H_9	5.1 : 1	—	—
$CH=CHCH=CH_2$, $C(CH_3)_3$	4.1 : 1	2.6 : 1	0.9 : 1

the role of the steric factor can be quite clearly demonstrated by comparing the condensation of dienes and dienophiles containing alkyl substituents which differ greatly in bulk. The data in Table 2 show that, in condensations of 1-alkylbutadienes with esters of substituted acrylic acids, the change from methyl to t-butyl in the diene and from hydrogen to isopropyl in the dienophile results in an increased content of the *meta*-isomer in the mixture of adducts. This phenomenon must be explained by steric effects, since increase in the steric repulsion of the substituents with increase in their volume should yield a higher proportion of the *meta*-isomers, whose formation takes place in this case *via* sterically less hindered transition complexes[60,61].

Comparison of the condensation of penta-1,3-diene with acrolein and methyl acrylate (Table 1) at different temperatures suggests that structural directivity is influenced by the temperature of the reaction. This hypothesis has recently been verified with the latter dienophile[28]. The ratio of *ortho*- to *meta*-isomer was found to be 18 : 1 when reaction took place at 20°, 6.8 : 1 at 200°, and only 3.7 : 1 at 400°. Thus the proportion of the *meta*-isomer in the mixture of adducts increases as the temperature of the reaction rises. If we neglect the difference in steric effects in the formation of the structural isomers, this temperature dependence of orientation could be explained by the activation energy in the formation of the *ortho*-isomer being in this case 1.5 kcal $mole^{-1}$ lower than with the *meta*-isomer[61].

3. 2-SUBSTITUTED DIENES

As stated in the Introduction, condensation of 2-substituted dienes with unsymmetrical dienophiles can result in *para*- and *meta*-adducts. Up to the present time, structural directivity has been investigated in more than a hundred examples of such condensations, although in most cases it has proved possible to isolate and characterise only the *para*-adduct.

Diene condensations involving *isoprene* have been studied especially thoroughly owing to its ready availability. The *para*-isomer has been isolated from the reaction products and its structure proved in condensations with acrylic acid and its derivatives[13,62-65], and also acrolein[19,62,63], 2-ethylacrolein[66], and chloromethyl vinyl ketone[67]. The *para*-adduct alone was obtained in the condensation of isoprene with ethylenesulphonyl chloride[68], 2-vinylpyridine[69], and *p*-nitrophenylmaleic anhydride[70]. Acetylenic dienophiles

react similarly to the ethylenic compounds with isoprene: thus *para*-adducts are formed by propiolic acid and its derivatives[22,65], propynal[23], and ethynyl methyl ketone[24].

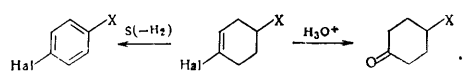
Nevertheless, in several cases it has proved possible to observe *meta*-isomers among the adducts, sometimes in considerable quantities. Thus isoprene forms ~ 20% of the *meta*-isomer with acrylonitrile[71] and methyl acrylate[62], and up to 40% with ethyl methacrylate[72]. Mixtures of the two isomers were also obtained in the condensation of isoprene with acrolein[57], esters of 2-substituted acrylic acids[59,73], styrene[69], 1-naphthylmaleic anhydride[74], and 2-methoxy-5-methylbenzoquinone[14].

Structural directivity has been studied in the condensations of other 2-alkylbutadienes, namely the ethyl, propyl, isopropyl, and t-butyl compounds. Their condensation with acrylic acid[27], esters of 2-substituted acrylic acids[75], and also phenylmaleic[76] and naphthylmaleic[74] anhydrides resulted in the formation of mixtures of the two structural isomers (see Table 3); with *p*-nitrophenylmaleic anhydride[70], however, only the *para*-adducts could be isolated. The condensation of myrcene with acrylic acid and its nitrile[77-79] and also with acrolein and methacrolein[78] led to the formation of mixtures of adducts having the same ratio, 4 : 1, of *para*- to *meta*-isomers; but condensation with vinyl acetate[80] gave only the *para*-adduct.

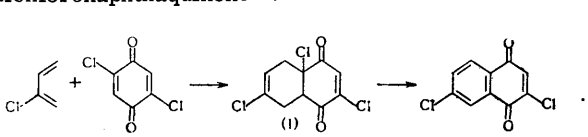
2-Phenylbutadiene yielded only *para*-adducts in most of its diene condensations. The *para*-structure has been proved for adducts of this diene with acrylic acid[81], methyl acrylate[82], acrolein[81,82], styrene[55,81], and phenylacetylene[82]. Nevertheless, it has proved possible to isolate up to 20% of the *meta*-isomer from the mixtures of adducts formed by 2-phenylbutadiene with dienophiles of the type of acrylic acid (see Table 3)[55,82].

Exclusive formation of the *para*-isomers has been noted in the condensation of 2-*p*-methoxyphenylbutadiene with acrylic acid, methyl methacrylate, and methyl vinyl ketone[83,84].

Proof of the structure of the adducts formed by *2-halogenobutadienes* with unsymmetrical dienophiles was based either on their dehydrogenation to known halogenated aromatic compounds[85,86] or on their hydrolysis with concentrated sulphuric acid to the corresponding ketones[40,87]:



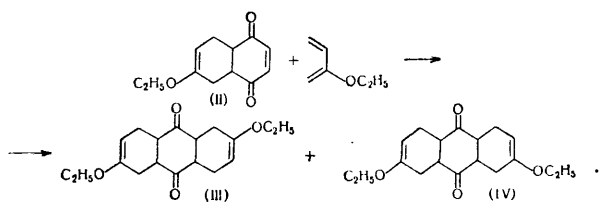
The formation of *para*-adducts has been demonstrated in the condensation of chloroprene with acrylic acid and various of its derivatives[85,86,88], ethyl ethylenesulphonate[89], acrolein[90], and 2-methylpropenyl vinyl ketone[87]. Among acetylenic dienophiles which form *para*-adducts with chloroprene are propynal[91], ethynyl methyl ketone[90], and propiolic acid[22] and its nitrile[65]. Only the *para*-adduct (I) could be isolated after condensation of chloroprene with 2,5-dichlorobenzoquinone, its dehydrogenation yielding 2,7-dichloronaphthaquinone[92]:



The *para*-orientation of the substituents has been proved also for the adducts of other 2-halogenated butadienes — bromoprene and fluoroprene — with propynal[91], and also for the condensate of fluoroprene with ethynyl methyl ketone[93]. The *meta*-isomers could be isolated only from the condensation of chloroprene with acrylic acid and with styrene[55,94].

2-Methoxybutadiene and *2-ethoxybutadiene* form adducts which are readily hydrolysable ethers of enols, and therefore the usual method for determining their structure is to hydrolyse them to known substituted cyclohexanones.

In general only *para*-adducts could be isolated from condensations of 2-alkoxybutadienes with acetylenic and ethylenic dienophiles, for example with esters of acrylic acid and its homologues[83,86,95,96], acrylonitrile[97], dimethyl mesaconate[98], and citraconic anhydride[98]. Reactions with carbonyl compounds — acrolein[99,100], propynal[91], and methyl vinyl[101], ethynyl methyl[102], and 2-methylpropenyl vinyl[87] ketones‡ — also resulted in the *para*-adducts. The *meta*-isomers could be isolated only from the condensation of 2-alkoxybutadienes with acrylic acid, styrene[55,94], and a few cycloalkenones[103,104]. There are indications that 2-alkoxybutadienes form mixtures of structural isomers also with toluquinone, thymoquinone[105], and 5-methoxy-1,4-naphthaquinone[106]. An interesting condensation is that of the monoadduct (II) of 2-ethoxybutadiene and benzoquinone with a second molecule of the diene, which yields a mixture of the isomers (III) and (IV) in the ratio 7 : 1.[107] Thus even an unsymmetrical feature which is remote from the reactive centres and is not conjugated with them can have a strong influence on the diene synthesis orientation:



Structural orientation in the reactions of 2-cyanobutadiene with methyl vinyl ketone and with acrylonitrile was studied[108]. In both cases the *para*-isomer alone was obtained, its structure being proved by conversion to terephthalic acid.

From the above survey of the literature it is evident that structural directivity in the condensation of 2-substituted dienes with unsymmetrical dienophiles has been studied with a great variety of substituents in the reactant molecules. Thus the dienes contained the substituents R (alkyls), C_6H_5, $CH_3OC_6H_4$, F, Cl, Br, OR, HCOO, and CN; and the dienophiles COOH, COCl, $CONH_2$, COR, CHO, CN, SO_2Cl, CH_3COO, C_6H_5, 1-naphthyl, and 2-pyridyl. In all these condensations the main reaction product proved to be the *para*-isomer. In several cases, however, the presence among the adducts of a certain amount of the *meta*-isomer could be established, and its structure proved (see Table 3).

It follows from Table 3 that the presence of the *meta*-isomer has been proved with almost all types of substituents in the diene. For the condensation of 2-substituted dienes with acrylic acid, we can arrange the substituents in the diene in the following sequence according to orienting

‡ The *para*-adduct alone was isolated from the condensation of 2-formyloxybutadiene with this dienophile[87].

TABLE 3. Condensations of 2-substituted dienes with unsymmetrical dienophiles.

Diene $CH_2=CRCH=CH_2$	Dienophile $CH_2=C(R_1)(R_2)$		Reaction conditions, t, °C/h	Yield of adducts, %	*para*/*meta* ratio	References
R	R_1	R_2				
CH_3	CHO	H	—	—	5.8 : 1	57
CH_3	CHO	H	200/2	88	1.8 : 1	73
CH_3	$COCH_3$	H	130/3	62	*	62
CH_3	$COCH_3$	H	200/5	81	2.3 : 1	109
CH_3	CN	H	200/2	89	2.2 : 1	73
CH_3	CO_2H	H	200/2	80	1.9 : 1	73
CH_3	CO_2CH_3	H	130/3	73	4.7 : 1	62
CH_3	CO_2CH_3	H	100/10	70	7.3 : 1	59
CH_3	CO_2CH_3	H	200/2	84	2 : 1	73
CH_3	CO_2CH_3	CH_3	220/2	70	9 : 1	59
CH_3	CO_2CH_3	CH_3	200/2	66	2.5 : 1	73
CH_3	$CO_2C_2H_5$	CH_3	200/12	95	1.4 : 1	72
CH_3	$CO_2C_2H_5$	C_2H_5	200/60	61	*	66
CH_3	$CO_2C_2H_5$	iso-C_3H_7	200/15	43	4.2 : 1	73
CH_3	C_6H_5	H	160/24	20	*	69
CH_3	C_6H_5	H	200/10	31	3.5 : 1	109
CH_3	NO_2	H	150/5	47	3.7 : 1	109
CH_3	phenylmaleic anhydride		80	74	12.4 : 1	76
C_2H_5	phenylmaleic anhydride		80	61	6 : 1	76
n-C_3H_7	CO_2CH_3	H	200/2	81	2.4 : 1	75
n-C_3H_7	CO_2CH_3	CH_3	200/2	65	3.4 : 1	75
iso-C_3H_7	CO_2CH_3	H	200/5	65	3 : 1	75
iso-C_3H_7	CO_2CH_3	CH_3	200/5	43	7.3 : 1	75
iso-C_3H_7	$CO_2C_2H_5$	iso-C_3H_7	200/10	31	14 : 1	75
iso-C_3H_7	phenylmaleic anhydride		80	59	8.6 : 1	76
t-C_4H_9	CO_2H	H	150/10	45	*	27
t-C_4H_9	CO_2CH_3	H	200/5	47	3.5 : 1	75
t-C_4H_9	CO_2CH_3	CH_3	200/5	36	10 : 1	75
iso-C_6H_{11}**	CO_2H	H	—	—	4 : 1	77
iso-C_6H_{11}	CHO	H	110/4	72	4 : 1	78
iso-C_6H_{11}	CHO	CH_3	160/6	73	4 : 1	78
C_6H_{11}	CN	H	135/18	90	4 : 1	78
C_6H_5	CO_2H	H	140	77	2.5 : 1	82
C_6H_5	COH_2	H	80	20	7 : 1	82
C_6H_5	CN	H	80/12	33	4 : 1	82
C_6H_5	CO_2CH_3	H	150/5	73	4.5 : 1	40
C_6H_5	CO_2CH_3	CH_3	150/5	51	14 : 1	40
Cl	CO_2H	H	150/5	85	9.3 : 1	94
Cl	C_6H_5	H	150/12	20	14 : 1	94
CH_3	CO_2H	H	150/10	72	8 : 1	94
CH_3O	C_6H_5	H	150/10	59	12 : 1	94

* Traces of the *meta*-isomer.

** $CH_2CH_2CH=C(CH_3)_2$

power: Cl > CH_3O > C_6H_5 > CH_3. Comparison of the condensation at 200° of isoprene with dienophiles of the type CH_2 : CHX enables us to arrange the substituents according to their orienting power when present in the dienophile NO_2 > C_6H_5 > COOH, CH_3COO, CH_3CO, CN, CHO.

Comparison of Tables 1 and 3 reveals a more marked structural selectivity in the condensations of 1-substituted than in those of 2-substituted dienes. Thus a given substituent exerts a greater orienting power in the 1- than in the 2-position.

In condensations of 2-alkylbutadienes with unsymmetrical dienophiles, formation of the transition complex corresponding to the *meta*-adduct is sterically the more difficult[60,61]. If the steric factor is important, the amount of *meta*-isomer in the mixture of adducts should diminish with increasing bulk of the substituents in the dienophile and in the 2-position of the diene. This argument is fully supported by the data in Table 4, relating to the condensation of 2-alkylbutadienes with esters of 2-substituted acrylic acids.

According to modern views, diene synthesis takes place *via* a cyclic transition state which is stereochemically similar to the adduct, the diene and dienophile molecules arranging themselves in parallel planes[110-120]. On the

TABLE 4. Ratio of *para*-to *meta*-isomers in condensations of 2-alkylbutadienes (at 200°)[29].

Diene	Dienophile: H $CH_2=C(H)-COOCH_3$	Dienophile: CH_3 $CH_2=C(CH_3)-COOCH_3$	Dienophile: $CH(CH_3)_2$ $CH_2=C(CH(CH_3)_2)-COOC_2H_5$
$CH_2=C(CH_3)-CH=CH_2$	2 : 1	2.5 : 1	4.2 : 1
$CH_2=C(C_6H_7)-CH=CH_2$	2.4 : 1	3.4 : 1	—
$CH_2=C(CH(CH_3)_2)-CH=CH_2$	3 : 1	7.3 : 1	14 : 1
$CH_2=C(C(CH_3)_3)-CH=CH_2$	3.5 : 1	10 : 1	20 : 1

basis of this model of the transition state, rough estimates were made of the steric hindrance in diene synthesis as measured by the linear overlap of the van der Waals radii of the substituents in the diene and in the dienophile[61]. The results are compared in the diagram with experimental data on the relative proportions of the structural isomers (Tables 2 and 4).

The diagram shows very good agreement between the increase in steric hindrance to the formation of a structural isomer and the diminution in its content in the mixture of adducts. Thus steric effects are of great importance in diene condensations involving alkylbutadienes. Nevertheless, it must be noted that, in condensations of 1-alkylbutadienes with unsymmetrical dienophiles, the *ortho*-isomers predominate in the adduct mixtures, and steric hindrance must be overcome in their formation. Therefore the steric factor, in spite of the important part which it plays, cannot be regarded as paramount for structural directivity in diene synthesis.

Condensations of isoprene and of 2-isopropyl-, 2-t-butyl-, and 2-phenyl-butadiene[40,61,73] have been used as examples in studying the temperature dependence of structural directivity in the reactions of 2-substituted dienes.

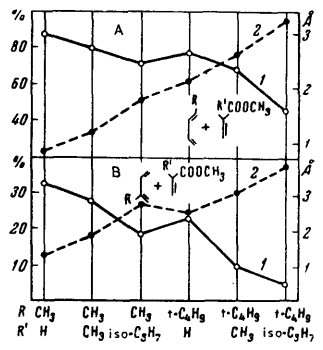
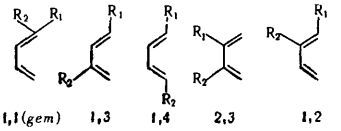


Fig. A: 1) % of *ortho*-isomer in mixture of adducts; 2) steric hindrance to the formation of the *ortho*-isomer.
Fig. B: 1) % of *meta*-isomer in mixture of adducts; 2) steric hindrance to the formation of the *meta*-isomer.

In all cases the amount of the *meta*-isomer was found to increase with rise in temperature: *i.e.* the composition of the adduct mixtures tended to even out, as with the 1-substituted dienes. Thus the following values were obtained for the *para* : *meta* ratio in the condensation of isoprene with methyl acrylate: 5.4 : 1 at 20°, 2.0 : 1 at 200°, and 1.4 : 1 at 400°.[73] This variation in composition of the adduct mixture with temperature can be explained (as with the condensations of penta-1,3-diene) by assuming that the activation energy of formation is about 1 kcal mole^{-1} smaller for the *para*- than for the *meta*-isomer[61].

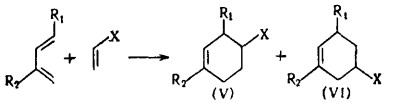
4. DISUBSTITUTED DIENES

Disubstituted dienes exist as five structural isomers, the arrangement of the substituents in which influences the structural orientation of diene synthesis in different ways.



Unfortunately, it is impossible to assess exactly the effect of geminal substitution on structural orientation, since *1,1-disubstituted dienes* undergo diene synthesis only after preliminary isomerisation into the 1,3-disubstituted dienes. Thus 1,1-dimethylbutadiene reacts with dienophiles only after isomerisation into 1,3-dimethylbutadiene, and 2,5-dimethylhexa-2,4-diene only after conversion to the corresponding 1,3-diene[121-123].

With *1,3-disubstituted dienes* each substituent may be expected to enhance the effect of the other, not to compete with it, since the substituent in the 1-position of the diene is *ortho*-directing, while that in the 2-position is *para*--directing. In fact, 1,3-dimethylbutadiene[12,17] and 1-methyl-3-isohexenylbutadiene[124-127] form only adducts of type (V) with acrylic acid and its derivatives:

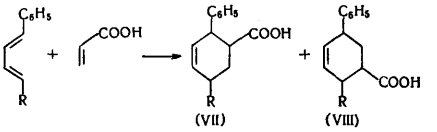


The same applies to the reactions of acrylic acid with 1-methyl-3-phenyl- and 3-methyl-1-phenyl-butadienes[128]. It is only quite recently that it has proved possible to isolate ~ 5% of isomer (VI) in the condensation of 1,3-dimethylbutadiene with methyl acrylate, methyl methacrylate, and acrylonitrile[129].

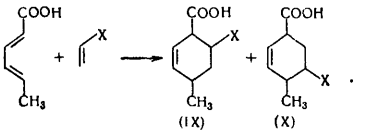
The study of structural orientation in the condensations of other types of disubstituted butadienes is of the greatest interest. The reactions of 1,4-disubstituted dienes with unsymmetrical dienophiles enable us to compare the orienting power of different substituents in the 1-position of the diene. Condensations of 2,3-disubstituted dienes make it possible to assess the orienting power of substituents in the 2-position. Finally, condensations of 1,2-disubstituted dienes permit comparison of the orienting power of substituents in the 1- and 2-positions of the diene.

Of course, when different substituents are present in the 1- and 4-positions of a diene, the adduct which is formed preferentially will be that in which the dienophile substituent is *ortho* to the most strongly orienting substituent in the diene§.

Condensation of 1-methyl-4-phenylbutadiene with acrylic acid[135] yielded adducts (VII) and (VIII) (R = CH_3) in the ratio 9 : 1, whereas reaction of 4-phenylbutadiene-1-carboxylic acid with acrylic acid[135] gave only adduct (VII) (R = COOH). Thus the phenyl group in the 1-position has a far stronger orienting effect than have methyl and carboxyl.



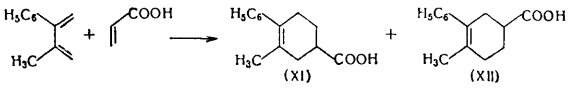
The orienting power of the methyl and carboxyl substituents can be compared by studying the diene condensations of sorbic acid:



Reaction of the chlorides and ethyl esters of sorbic and acrylic acids[136,137] yielded only the *ortho*-methyl isomer (X), whereas condensation with phenyl vinyl ketone resulted in the *ortho*-carboxy-isomer (IX)[138]. Alder *et al.*[135], who have studied this question most thoroughly, have shown that condensation of sorbic and acrylic acids produces a mixture of structural isomers with a slight preponderance of adduct (X). On the other hand, condensation with substituted styrenes[139], 1-vinylnaphthalene[53], indene[140], 1,2-dihydronaphthalene[140], and 1,2-dihydro-7-methoxynaphthalene[141] gave only adducts of type (IX) with *ortho*-orientation to the carboxyl. Reaction of methyl sorbate with styrene[123] yields a mixture of the two structural isomers, also with adduct (IX) preponderant.

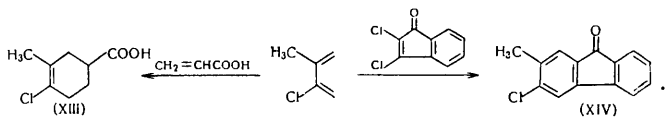
Thus adduct (X) predominates in the condensation of sorbic acid with acrylic acid, but adduct (IX) in its condensation with styrene. It is evident that methyl and carboxyl substituents in the diene are very similar in orienting power, and the nature of the substituent in the dienophile, which is in general less important, can substantially change the pattern of structural directivity.

Diene condensations of *2,3-disubstituted dienes* have been little studied. Reaction of 2-methyl-3-phenylbutadiene with acrylic and propiolic acids[142] gave a mixture of adducts with a slight preponderance of isomer (XI), in which phenyl exerts the main directing influence:



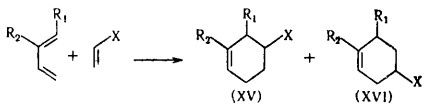
§ The data cited here relate solely to the *trans-trans*-isomers of 1,4-disubstituted dienes, since *cis-cis*-isomers of these dienes do not react at all by the mechanism of diene synthesis, while *cis--trans*-isomers either do not undergo reaction or else react with great difficulty[130-134].

Condensation of 2-chloro-3-methylbutadiene with acrylic acid[142] yielded almost exclusively adduct (XIII), in which the chlorine has determined the orientation. An analogous situation was observed in the reaction of this diene with dichloroindenone, which resulted in adduct (XIV)[143]. Thus chlorine exerts a far stronger orienting effect than does the methyl group:



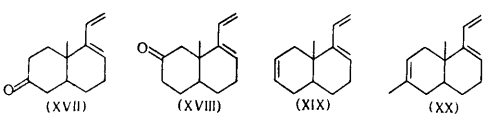
(XIII) (XIV)

In *1,2-disubstituted dienes* preferential orientation with respect to the substituent in the 1-position should lead to formation of adduct (XV), whereas the substituent in the 2-position will tend to favour formation of adduct (XVI). If the substituents R_1 and R_2 are identical, the latter, which is more remote from the reaction centre, has less influence on the orientation of the dienophile, as was to be expected. Thus condensation of 1,2-dimethylbutadiene with acrylonitrile and with methyl methacrylate[59] gives a (XV) : (XVI) ratio of about 6 : 1, whereas condensation of 1,2-diphenylbutadiene with acrylic acid[144] yields solely the isomer (XV).



(XV) (XVI)

1,2-Disubstituted dienes include also the vinylcycloalkenes in which the substituents R_1 and R_2 form part of a ring system. Only adducts of type (XV) could be isolated in most of the condensations which have been carried out with vinylcyclohexene[145-147], as well as in the dimerisation of styrene[148]. Condensation of the bicyclic dienes (XVII)–(XX) and of 1-vinylnaphthalene with citraconic anhydride and various cyclic ketones has been studied[53,149-154] in connection with the synthesis of polycyclic compounds related to the steroids, and here too only isomers of type (XV) were obtained. It was only in the condensation of vinylcyclohexene with acrylonitrile[59], propiolic acid[155], citraconic anhydride[156], and dimethyl mesaconate[157] that the (XVI) isomer could be isolated (5–15%) and its structure determined. Thus in cyclic dienes too a substituent in the 2-position of a diene system has a weaker orienting effect than a substituent in the 1-position.



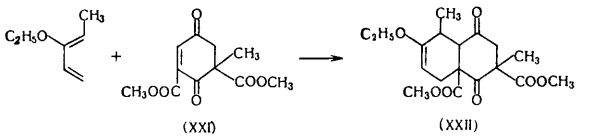
(XVII) (XVIII) (XIX) (XX)

Two possibilities arise if the substituents in positions 1 and 2 are different.

1. The substituent in position 1 is more strongly orienting than the substituent in position 2. In this case the structural directivity will be governed by the substituent in the 1-position, which should lead to exclusive formation of adducts of type (XV). In fact such adducts were alone obtained in the condensation with acrylic and propiolic acids of 1-phenylbutadienes substituted in the 2-position by methyl, ethyl, and methoxycarbonyl groups respectively[144].

2. The substituent in position 1 of the diene has a weaker orienting power than the substituent in position 2. In this case competition from the 2-substituent is quite strong, so that the reaction yields a mixture of the two isomers.

Thus in the condensation of 1-methyl-2-phenylbutadiene with acrylic acid[144] the ratio of (XV) to (XVI) is 4 : 1, and in the reaction of 2-chloro-1-ethyl(and methyl)butadienes with propiolic acid[158] the ratio is 3 : 1. A mixture of structural isomers, in which adducts of type (XV) usually slightly preponderate, is formed also in the condensation of 6-methoxy-1-vinyloctalin with citraconic anhydride and various cycloalkenones[159-165]. Condensation of 2-ethoxy-1-methylbutadiene with compound (XXI)¶ gives only adduct (XXII), in which the methoxycarbonyl is *para* to the ethoxy-group[166]. It is evident that, even in the 2-position, the ethoxy-group exerts a stronger orienting effect than the methyl group in the 1-position:

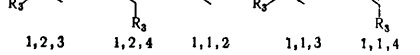


(XXI) (XXII)

Collation of the data for the condensation of 1,4-, 2,3-, and 1,2-disubstituted dienes enables us to derive the following sequence of substituents based on their orienting power when present in the diene: Cl, RO, C_6H_5 > COOH > > CH_3. Comparison with the data in Sections 2 and 3 makes it obvious that the sequence of substituents according to their orienting power in the diene is roughly the same for mono- and di-substituted dienes.

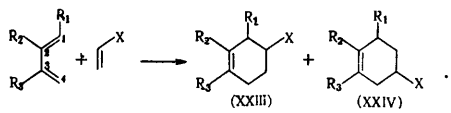
5. TRISUBSTITUTED DIENES

Three substituents in a diene molecule can be arranged in five different ways, resulting in the existence of five structural isomers:



1,2,3 1,2,4 1,1,2 1,1,3 1,1,4

Data on the structural directivity of diene synthesis with disubstituted dienes can serve as a basis for explaining the structure of adducts obtained in the condensation of more highly substituted dienes. An example is provided by the condensation of *1,2,3-trisubstituted dienes*, in which two adducts, (XXIII) and (XXIV), can be formed, with the dienophile substituent oriented *ortho* to positions 1 or 4 of the diene system:



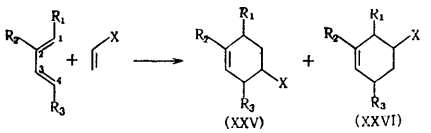
(XXIII) (XXIV)

The substituent from the dienophile will be directed to the 1-position (isomer XXIII) by substituents R_1 and R_3, and to the 4-position (isomer XXIV) only by substituent R_2. Since substituents in a diene system are considerably less strongly orienting when in positions 2 and 3 than in 1 and 4, almost exclusive formation of the (XXIII) isomer can be expected in condensations of 1,2,3-trisubstituted dienes.

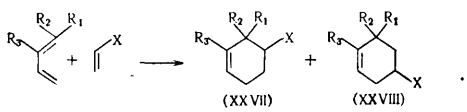
¶ A mixture of the two structural isomers is obtained also in the condensation of this diene with toluquinone[167].

This conclusion has been confirmed in a study of the condensation of 1,2,3-trimethylbutadiene with acrylonitrile and with crotonaldehyde: in neither case did the content of the (XXIV) isomer exceed 5–7% of the mixture of adducts[168]. An analogous pattern should obviously be observed in condensations involving cyclic dienes having this type of substitution. The reactions of 1-isopropenylcyclohexene with citraconic anhydride[169] and of 1-α-acetoxyvinylcyclohexene with derivatives of acrylic acid, with citraconic anhydride, and with 2,6-xyloquinone[170-176] did actually result exclusively in (XXIII) adducts with "contiguous" substituents. Dimerisation of atropic acid[177] and its nitrile[178] also yields adducts of type (XXIII).

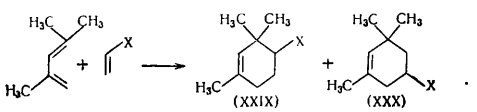
In the reactions of *1,2,4-trisubstituted dienes* the dienophile substituent is directed to the 4-position of the diene system (adduct XXV) by substituents R_2 and R_3, and to the 1-position (adduct XXVI) only by R_1. Hence preferential formation of the first isomer is to be expected, as has been confirmed in a study of the condensation of alloocimene[179] and of 1-β-acetoxyvinylcyclohexene[180,181] with acrylic acid and its derivatives:



1,1,2-Trisubstituted dienes undergo only partial diene synthesis without isomerisation into 2-substituted and 1,2,3-trisubstituted[168,182] dienes. The simplest representative of this group — 1,1,2-trimethylbutadiene — forms adducts of type (XXVII) in diene condensations with unsymmetrical dienophiles[121,123,168]. Similar structural directivity was shown in the condensation of 2-isopropyl-1,1-dimethylbutadiene with acrylonitrile[182]. In several papers, however, adducts of 1,1,2-trimethylbutadiene with crotonaldehyde and but-2-ynal have been assigned structure (XXVIII)[183-188]:



1,1,3-Trisubstituted dienes have been studied only in the case of the diene condensations of 1,1,3-trimethylbutadiene, which undergoes diene synthesis without isomerisation, since migration of the double bonds along the carbon skeleton does not change the substitution pattern[123]. All three substituents in dienes of this type orient the dienophile in the same direction, and therefore almost exclusive formation of adducts of type (XXIX) is to be expected from their condensations.

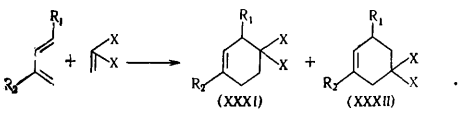


And indeed 1,1,3-trimethylbutadiene does form adducts of type (XXIX) with acrolein[189,190], crotonaldehyde[191], but-2-ynal[192], hept-2-ynal[192], acrylic acid[12], and propiolic[193] and methylenemalonic[194] esters. Adduct (XXX) could be isolated only from the condensation of this diene with acrylonitrile[195], and then in amount not exceeding 3–5% of the adduct mixture.

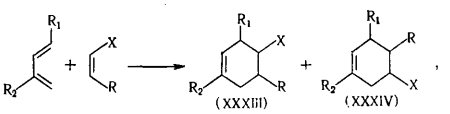
The structural directivity in the condensation of *1,1,4-trisubstituted dienes* has not been investigated, although it has been shown that 1,1,4-trimethylbutadiene can undergo partial diene synthesis without isomerisation[122].

6. DISUBSTITUTED DIENOPHILES

Only a very small number of 1,1-disubstituted dienophiles have been studied†. Thus condensation of diethyl methylenemalonate with isoprene[194], 2-phenylbutadiene[196], and penta-1,3-diene[16,194] produces only the (XXXI) isomer (where X = C_2H_5COO). The same isomer (X = CN) is formed also in the reaction of 2-phenylbutadiene with the corresponding dinitrile (vinylidene dicyanide)[197]. Thus the reactions of 1,1-disubstituted dienophiles are quite analogous to those of monosubstituted dienophiles both with 1-substituted and with 2-substituted dienes.



The condensations of *1,2-disubstituted dienophiles* with unsymmetrical dienes enable us to study the orienting effects of different substituents in the dienophile. The weakest orienting effect in the dienophile is evidently exerted by an alkyl substituent. Thus the condensation of isoprene[112], penta-1,3-diene[12,59], and vinylcyclohexene[146] with crotonic acid results in mixtures of adducts having a marked preponderance of the (XXXIII) isomer, in which the carboxyl exerts the main orienting influence:



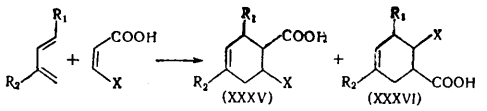
where X = COOH, CHO, NO_2, C_6H_5; R = CH_3, C_2H_5, C_3H_7.

The same isomer is formed in the reaction of 2-ethoxybutadiene with 3-ethylacrylic acid[83], and also in the condensation of penta-1,3-diene[21], 2-ethoxybutadiene[198], and vinylcyclohexene[155] with but-2-ynoic acid. The condensation of penta-1,3-diene[17,191] and 2-isopropylbutadiene[168] with crotonaldehyde and that of isoprene[199], 2-methoxybutadiene[95,103,104], and vinylcyclohexene[200,201] with unsaturated cyclic ketones also give adducts of type (XXXIII). Finally, this adduct (X = NO_2) is formed in the condensation of penta-1,3-diene with nitropentene[202]. Thus the carboxyl, carbonyl, and nitro groups are more strongly orienting than are alkyl groups in the dienophile. No data are available for a direct comparison of the orienting effects of phenyl and alkyl groups, but in view of the fact that the condensation of indene with isoprene gives predominantly, and that with penta-1,3-diene solely, adducts of type (XXXIII)[203], it can be concluded that phenyl also is more strongly orienting than are alkyl groups.

Several instances are available for comparing the orienting effect of the carboxyl group with those of other groups.

† The effect of an alkyl group in the 1-position of a dienophile has been considered above in discussing the role of the steric factor in structural directivity.

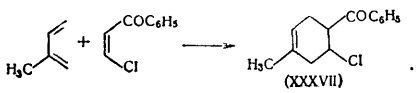
Condensation of isoprene and of 1-phenylbutadiene with 4,4,4-trifluorocrotonic acid[204] results in the formation of adducts of type (XXXV) with orientation with respect to the carboxyl group.



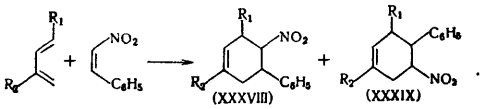
where X = CF_3, C_6H_5, CH_3CO.

This type of isomer is the main product in the reaction of various dienes with cinnamic acid[128,205-207] and its analogues — 2,6-dimethoxy-4-n-pentylcinnamic[208] and *o*-nitrocinnamic[209] acids — and also with phenylpropiolic acid[21], cinnamaldehyde[206], and methyl styryl ketone[207]. Nevertheless, the condensation of 3-acetylacrylic acid with 2-phenylbutadiene[83], 2-*p*-methoxyphenylbutadiene[210], and 1-vinylnaphthalene[159] resulted in mixtures of isomers consisting mainly of the (XXXVI) adduct. Hence it can be concluded that the carboxyl group is more strongly orienting than trifluoromethyl and phenyl in the dienophile, but less strongly orienting than the acetyl group.

Diene condensation of isoprene with 2-chlorovinyl phenyl ketone[211] yields adduct (XXXVII), and therefore the keto--group is more strongly orienting than chlorine:



Finally, the phenyl and nitro groups can be compared by examining the condensation of unsymmetrical dienes with β-nitrostyrene‡. Condensation of isoprene, penta-1,3--diene, and 2-ethoxybutadiene with this dienophile results in the formation of mixtures of adducts containing mainly the (XXXVIII) isomer, in which orientation is determined chiefly by the nitro-group[202,212]. The corresponding isomer was obtained in the condensation of isoprene with 4-methoxy-β-nitrostyrene[69] and of 2-ethoxybutadiene with 2,4-dimethoxy-β-nitrostyrene[69].

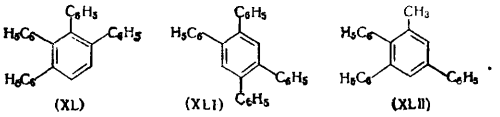


Published data enable us to arrange substituents in the following sequences according to their orienting power in a dienophile: COR, NO_2 > COOH > CF_3, C_6H_5 > CH_3; COR > Cl. These series are derived from a study of disubstituted dienophiles, in which the substituents act on one another through the double bond. The structural directivity is then characteristic not so much of the sum of or the difference between the effects of the individual substituents as of the molecule as a whole. Discrepancies can therefore arise in deductions made from studies of monosubstituted and of disubstituted dienophiles. Thus whereas in monosubstituted dienophiles phenyl proves to have a stronger orienting effect than carboxyl (see Sections 2 and 3), in the disubstituted dienophile containing both of these groups (cinnamic acid) it is the carboxyl which, in contrast, exerts the main orienting effect.

‡ Product orientation in the condensation of isoprene with 1--nitro-3,3,3-trichloropropene has also been studied,[213] but the proportions of the resulting structural isomers were not determined.

7. CYCLIC DIENES

In comparison with acyclic dienes, those compounds in which the two double bonds are located in the same ring exhibit several peculiarities with respect to structural directivity. We can take as an example the condensations undergone by substituted cyclopentadienones. Whereas the reactions of 1,2,3- and 1,2,4-triphenylcyclopentadienones with phenylacetylene[214] result in the formation of adducts (XL) and (XLI) in conformity with the rules of orientation derived above for trisubstituted acyclic dienes, the condensation of 1-methyl-2,3-diphenylcyclopentadienone with this dienophile[215] apparently gives adduct (XLII), in violation of these rules.



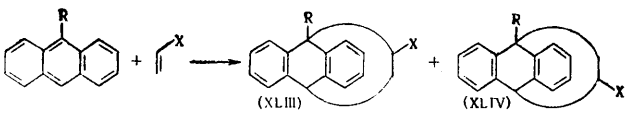
Structural directivity is almost completely absent in the condensation of 1,5,5-trimethylcyclopentadiene[216] and of 2,6,6-trimethylcyclohexa-2,4-dienone[217] with vinyl acetate, for the two structural isomers are formed in about equal amounts.

An especially thorough study has been made of structural directivity in the condensations undergone by 9-substituted anthracenes. Since these compounds are formally analogous to 1-substituted butadienes, their reactions with unsymmetrical dienophiles can lead to the formation of isomers having *"ortho"* (XLIII) or *"meta"* (XLIV) orientation. The results obtained were quite unexpected. It was found that completely different ratios of the structural isomers could be obtained even when the substituents in the reactants had very similar electronic and steric characteristics. The data in Table 5 show that these ratios vary from exclusive

TABLE 5. Condensation of 9-substituted anthracenes with unsymmetrical dienophiles.

Diene R	Dienophile X	Reaction conditions, *t*, °C/h	Yield of adducts, %	Ratio (XLIII)/(XLIV)	References
CN	COOH	140/2	21	(XLIII) alone	218
CN	$COOCH_3$	140/21	38	ditto	218
CN	$CONH_2$	130/16	25	»	218
CHO	COOH	130/24	62	»	219
CHO	CN	130/24	78	»	219
CHO	CH_2OH	200/12	63	»	219
$CH(OCH_3)_2$	$COOCH_3$	120/17	60	2.8 : 1	220
CN	CH_2OH	175/16	50	2.1 : 1	220
$CONH_2$	COOH	125/3	20	2 : 1	221
$CONH_2$	CH_2OH	170/17	62	2 : 1	221
NO_2	$CONH_2$	160/48	39	1.7 : 1	221
NO_2	CN	135/24	—	1.3 : 1	221
NO_2	COOH	150/20	93	(XLIII) < (XLIV)	221
CN	CN	200/22	51	1 : 1.8	218
NO_2	COCl	135/24	78	1 : 5.5	221
COOH	COOH	150/9	20	(XLIV) alone	54
COO	COO	230/36	75	ditto	54
NO_2	$COOCH_3$	135/24	60	»	221
NO_2	CH_2OH	190/20	6	»	221

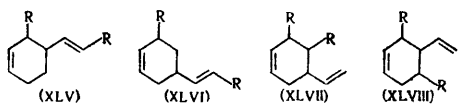
formation of the *ortho*-isomer (XLIII) to complete predominance of the *meta*-isomer (XLIV). This phenomenon has not yet been satisfactorily explained, and is at variance with all other data on structural directivity.



The comparatively few data available on structural directivity in condensations of cyclic dienes do not permit any generalisations to be made. The results which have been obtained clearly make it necessary to approach cautiously the question of extending to cyclic compounds the conclusions reached with acyclic dienes.

8. DIMERISATION OF MONOSUBSTITUTED DIENES

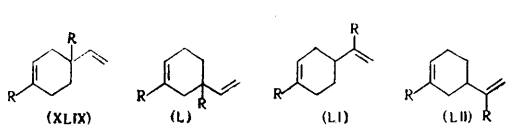
The dimerisation of diene compounds with formation of a six-membered ring is considered as a particular case of diene synthesis. It must be borne in mind that dimers containing four- and eight-membered rings can also be formed [222-225]. A brief account will be given in the present section of the most important work on the dependence of product orientation on structure in the dimerisation of monosubstituted dienes.



In most work on the dimerisation of *1-substituted dienes*, of the four theoretically possible structural isomers (XLV)–(XLVIII) containing a six-membered ring, only the dimer (XLV), resulting from the reaction at the unsubstituted vinyl group of the diene, could be obtained.

Thus this type of isomer has been obtained in the dimerisation of 1-phenylbutadiene [226], 1-cyanobutadiene [227,228], butadiene-1-carboxylic acid [229], and hexa-1,3,5-triene [230]. It was shown [231] in 1955, however, that the dimerisation of penta-1,3-diene at 140°–240° yields, practically independently of the temperature, a mixture of dimers containing about 90% of (XLV), 4–5% of (XLVI), and 1–2% each of (XLVII) and (XLVIII). Thus in this case all the possible structural isomers could be isolated, the ratio of *ortho*- to *meta*-dimers being about 13 : 1.

The dimerisation of *2-substituted dienes* also can result in four isomers, (XLIX)–(LII), containing a six-membered ring. For a long time it was assumed that only the *para*-dimers (XLIX) and (LI) were formed in the reaction.

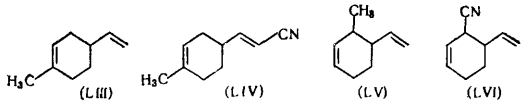


This conclusion was based on a study of the dimerisation of 2-methoxy- and 2-formyloxy-butadienes [dimer (LI) was isolated] [232], 2-neopentylbutadiene (LI) [233], chloroprene [(XLIX) and (LI)] [234], 2-phenylbutadiene [(XLIX) and (LI)] [81,235], 2-cyanobutadiene (XLIX) [236,237], and butadiene-2-carboxylic acid (XLIX) [238]. Nevertheless, it was believed that isoprene forms a mixture of *para*- and *meta*-dimers in which the *meta*-isomer predominates in some cases [239-242]. It is interesting that only the *meta*-dimer of type (L) was isolated also in the dimerisation of isopropenylacetylene [2-methylbut-1-en-3-yne] [243].

These views have been substantially amended recently. Thus in the dimerisation of isoprene (at 100°–300°) it has proved possible to isolate all the theoretically possible dimers, rise in temperature being found to increase the content of dimers (XLIX) and (LI) and decrease that of (L) and (LII) in the mixture. The *meta*-isomer (L) predominated in the first fraction at low temperatures, and the *para*-isomer (XLIX) at high temperatures [244,245]. The preferential formation of *meta*-dimers and the reversal of structural directivity with rise in temperature distinguish the dimerisation of isoprene from that of all other dienes. This difference may be associated with peculiarities in the mechanism of the dimerisation of isoprene [246].

The dimerisation of chloroprene at 20° [247] resulted in the formation of roughly equal fractions comprising dimers (LI) + (LII) and (XLIX) + (L) respectively. The *para*-dimer (XLIX) predominated in the latter, and the *meta*-dimer (LII) in the former. In contrast to the low-temperature dimerisation of isoprene, the total content of the *meta*-isomer in the mixture of dimers did not exceed one-third.

In reactions between two different dienes it has proved possible in some cases to determine the structure of the compounds which are formed preferentially. Thus the reaction of isoprene with butadiene [248,249] and with 1-cyanobutadiene [250] yielded mixtures of reaction products in which (LIII) and (LIV) respectively, with *para*-orientation of the substituents, were the main products. The reaction of penta-1,3-diene [249] and of 1-cyanobutadiene [251] with butadiene resulted mainly in the formation of isomers (LV) and (LVI), with *ortho*-orientation of the substituents. It is interesting that butadiene is in both cases involved in the reaction principally as the dienophile.

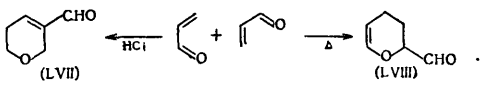


Thus structural directivity in the dimerisation of diene compounds follows basically the same rules as in other diene condensations in which they are involved. Dimerisation of 1-substituted dienes yields mainly *ortho*-dimers, whereas that of 2-substituted dienes gives the *para*-dimers. The behaviour of isoprene (and to a less extent of chloroprene), however, differs markedly from that of the other dienes whose dimerisation has been investigated.

9. DIENES AND DIENOPHILES CONTAINING HETEROATOMS

Besides the "classic" diene synthesis, *i.e.* the condensation of dienes and dienophiles having double bonds between carbon atoms, the formation of six-membered heterocycles from unsaturated compounds containing heteroatoms is also often included in this group of reactions (see Hahn's review [252]). At the present time there is no generally accepted view as to how closely the mechanism of such heterocyclisation reactions approaches that of the "classic"

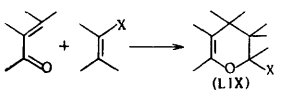
diene synthesis. Condensations involving compounds containing the strongly polar C=O, C=N, C≡N, or N=O bonds could be reasonably regarded as taking place by an ionic mechanism. But evidently this is not so. In the dimerisation of acrolein under the influence of traces of hydrochloric acid, for example, which undoubtedly takes place by an ionic mechanism, dimer (LVII) is formed; nevertheless, thermal reaction yields dimer (LVIII)[253]. The thermal cleavage of dihydropyran at 540° into ethylene and acrolein is a homogeneous reaction which is completely analogous to the retrodiene decomposition of cyclohexene into ethylene and butadiene[254].



(LVII) (LVIII)

This all suggests that the mechanism of such thermal reactions is similar to that of diene synthesis. We must therefore examine the main results obtained on structural directivity in this field.

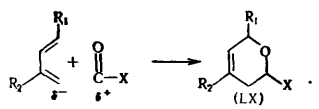
Study of the reactions of unsaturated aldehydes and ketones with unsymmetrical dienophiles shows that, when either electron-donor or electron-acceptor substituents are present in the dienophile, only adducts of type (LIX) are formed[210,255-257]. Compounds of the same type have been obtained by the dimerisation of unsaturated aldehydes and ketones[258,259]:



(LIX)

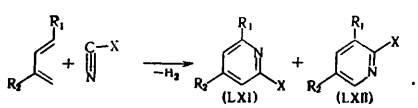
where X = OR, SR, CH_3COO, COR, COOR, CN, CH_2OH, C_6H_5, and C_1-C_6 alkyl.

Structural directivity in the condensation of dienes with aldehydes was studied in the reactions of isoprene with chloral[260] and of 1,3-dimethylbutadiene with formaldehyde[261]. It was proved in both cases that adducts of type (LX) were formed with orientation according to the polarity of the reactant molecules:



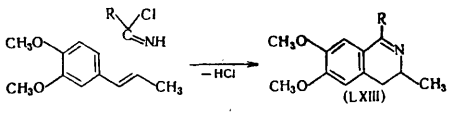
(LX)

The structure of the adducts was established also in the condensation of unsymmetrical dienes with cyanogen[262], acetonitrile[263], and benzonitrile[264], which were accompanied by dehydrogenation of the adducts to pyridine derivatives. The reactions involving isoprene and 1,3-dimethylbutadiene resulted in the (LXI) isomer; but the condensation of chloroprene with cyanogen produced a mixture of adducts in which the other isomer [(LXII), with X = CN] predominated:



(LXI) (LXII)

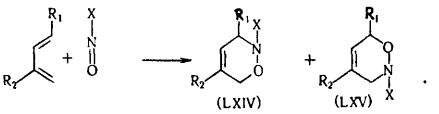
Condensation of isosafrole and methylisoeugenol with imino-chlorides gives adducts of type (LXIII)[265,266]:



(LXIII)

where R = H, CH_3, C_6H_5.

Reaction of dienes with nitroso-compounds can give adducts (LXIV) and (LXV). With adducts of chloroprene where X = cyclohexyl and 1-cyanocyclohexyl[267,268], and also with adducts of penta-1,3-diene in which X = C_6H_5,[269] the (LXIV) isomer has been shown to predominate in the mixture. Since in the N=O bond the oxygen atom is negatively charged, structural isomers of type (LXIV) are formed in these cases in opposition to the polarity of the reactants:



(LXIV) (LXV)

The above results lead to the conclusion that, in diene condensations involving heterodienes and heterodienophiles, the orientation is independent of the polarity of either the diene or the dienophile component.

10. STRUCTURAL DIRECTIVITY AND MECHANISM OF DIENE SYNTHESIS

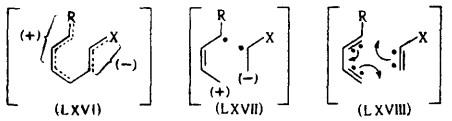
The mechanism of diene synthesis was recently reviewed by Syrkin and Moiseev[270], so that we need not discuss here the immense literature on this problem, but can confine ourselves to an examination, on the basis of the different reaction mechanisms, of the rules of structural directivity in this reaction.

The mechanisms which have been suggested for diene synthesis can be divided into two large groups — heterolytic and homolytic — according to the type of transition states which are postulated. The factors which influence structural directivity are governed primarily by the type of electron transfer, and are relatively independent of whether the reaction takes place in two stages, with the intermediate formation of kinetically independent reactive species, or in one stage *via* a cyclic transition complex. We can therefore consider one-stage and two-stage reaction mechanisms together.

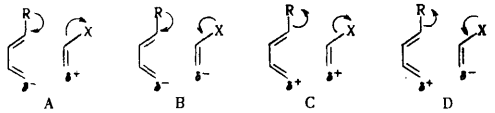
A special position is occupied by the proposed mechanism of diene synthesis which postulates complete delocalisation of electrons in the intermediate complex[270,271]. However, this mechanism explains structural directivity by the preferential orientation of diene and dienophile according to their polarity, *i.e.* in a manner analogous to a heterolytic mechanism, and therefore it will not be considered separately.

From 1932 onwards[272] several versions of a *heterolytic mechanism* of diene synthesis were put forward. It was assumed in most cases that the diene, as a nucleophilic reagent, attacks the double bond of the dienophile to form an intermediate ion (LXVI), which is then cyclised to the final reaction product[273-278]. Another view[279,280] was that

both diene and dienophile are converted before the reaction to dipolar ions, which react by a quadrupole mechanism to form the adduct. Woodward's scheme[118,119], according to which reaction takes place *via* the intermediate formation of a radical-ion complex (LXVII), linked by ionic forces, can also be regarded as a variant of an ionic mechanism. Finally, heterolytic displacement of electrons takes place also in "cyclic electron transfer" (LXVIII), which has recently been suggested as the mechanism of diene synthesis[281].



According to all these versions, structural directivity is governed by the presence in diene and dienophile molecules of fractional charges arising under the influence of substituents. Diene and dienophile molecules of different polarity can theoretically be combined in four ways (A–D), which are illustrated for the case of 1-substituted dienes:



It is obvious that, if the mode of reaction is determined by the polarity of the reactants, the *ortho–para*-isomers should be obtained preferentially in cases A and D (with opposite polarities of diene and dienophile), whereas the *meta*-isomers should predominate in cases B and C, with the reactants of like polarity. Examination of the literature for Sections 2 and 3 shows that most of the diene condensations which have been studied relate to case A, with an electron-donor substituent in the diene and an electron-acceptor substituent in the dienophile. In condensations of this type the structural directivity agrees with the polarity of the reactants, and this was previously regarded as providing confirmation of a heterolytic mechanism. However, quite a large number of diene condensations are now known in which formation of the adduct takes place in opposition to the polarity of the reactants. In addition to the condensations of heterodienes and heterodienophiles discussed in Section 9, the following reactions can be noted, in which *ortho–para*-isomers are formed instead of the *meta*-isomers (see Sections 2 and 3).

Reactions of type B (electron-donor substituents in diene and dienophile) include the condensations of penta-1,3-diene, isoprene, 1- and 2-phenylbutadienes, and 2-methoxybutadiene with styrene, of myrcene with vinyl acetate, and of 2-phenylbutadiene with phenylacetylene.

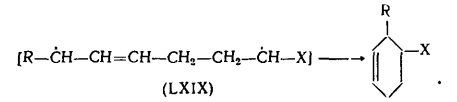
Reactions of type C (electron-acceptor substituents in diene and dienophile) include as examples the condensation of 1-*p*-nitrophenylbutadiene, 1-*p*-bromophenylbutadiene, 1-*o*-nitrophenylbutadiene, and butadiene-1-carboxylic acid with acrylic acid, of 1-cyanobutadiene with methyl acrylate, and of 2-cyanobutadiene with acrylonitrile and methyl vinyl ketone.

The formation of *ortho*-isomers in type C reactions of 1-substituted dienes has been explained[270] by deactivation of the double bond directly adjacent to the substituent in the diene. This makes the terminal C=C bond more reactive, and the reaction leading to the *ortho*-isomer becomes more advantageous. However, these ideas are obviously inapplicable to type C reactions of 2-substituted dienes and to all type B condensations, so that they are unable to explain deviations from the polar reaction scheme. It must therefore be concluded that *the polarity of the reactant molecules is not the decisive factor in the structural directivity of diene synthesis*.

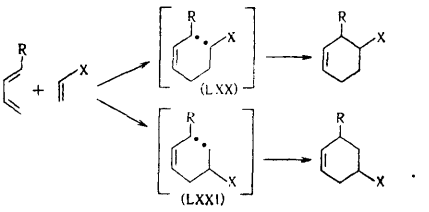
With this fact established we can discuss also the part played in structural directivity by "prereaction" interaction between the reactants. In many cases the diene synthesis is known to be preceded by the formation of a "prereaction" molecular complex between diene and dienophile[282,283]. Such complexes arise as a result of donor–acceptor interaction between the molecules[245], their formation involving unactivated molecules, which will doubtless be oriented in conformity with their polarity in the ground state. Since the structural directivity of diene synthesis does not conform with the polarity of the reactants, it cannot be determined by the orientation of the molecules in the "prereaction" molecular complex.

Thus a heterolytic mechanism cannot explain the structural directivity of diene synthesis. This conclusion, as well as kinetic[275] and energetic[270] data, shows that diene synthesis cannot take place *via* the formation of ionic intermediate states: the reaction is primarily, although not entirely, a homolytic process.

Most variants of the *homolytic mechanism* suggest that reaction takes place in one stage and that the transition state is an open-chain biradical (LXIX)[246,259,284,285]. Another view[286] is that diene synthesis takes place in two stages — formation of a biradical (LXIX) and its cyclisation to the end-product with a low activation energy. A "latent-radical" reaction mechanism has also been suggested, which presupposes homolytic displacement of electrons within a cyclic transition complex[61,287]:



A homolytic mechanism shows better agreement with the experimental data on structural directivity than does a heterolytic mechanism, since a characteristic feature of radical processes is that the mode of the reaction is practically independent of the polarity of the reactants. According to modern views, radical reactions involve the intermediate formation of the most stable radicals[288,289], tertiary radicals being more stable than secondary, and the latter in turn more stable than primary radicals. An explanation of the structural directivity of diene synthesis has been suggested on the basis of this principle[257,290]. Thus in the condensation of a 1-substituted diene with an unsymmetrical dienophile, the *ortho*-isomer is formed *via* a bisecondary biradical (LXX), whereas the *meta*-isomer involves a primary–secondary biradical (LXXI).



Since on the above basis radical (LXX) is more stable than (LXXI), the main product should be the *ortho*-isomer

regardless of the polarity of the substituents, as is actually observed. In the condensations of 2-substituted dienes, however, both structural isomers are formed *via* primary–secondary biradicals, and arbitrary assumptions must be made in order to explain the structural directivity; the same applies to condensations of disubstituted dienes and dienophiles.

Apart from this purely qualitative treatment, the concept of radical attack at the atom having the greatest free valence number, which has proved valuable with radical reactions in the aromatic series[291,292], can also be used in explaining the structural directivity of diene synthesis. Existing calculations[293] indicate that with styrene 2-vinylbutadiene should form mainly the *para*-isomer, whereas hexatriene with styrene should yield mainly the *meta*-isomer. This obviously contradicts experimental data on structural directivity. Thus a detailed interpretation of the effect of substituents on the proportions of structural isomers which is based on a radical mechanism encounters great obstacles, caused mainly by our inadequate knowledge of the relative stabilities of radicals. Nevertheless, the fundamental compatibility of a homolytic reaction mechanism with structural directivity is of very great significance.

The experimental study of structural directivity in diene synthesis has already reached a level which permits the investigator to foretell accurately, on the basis of empirical rules, which structural isomer will be the main product of a given reaction. The theoretical interpretation of the phenomena of structural directivity, however, lags far behind the accumulated experimental results. As follows from the above account, the structural directivity of diene synthesis has not yet found a comprehensive explanation on the basis of any particular reaction mechanism. Progress in this direction will evidently be associated primarily with the development of ideas on the mechanism of diene synthesis, which is a very peculiar reaction, combining features of both ionic and radical processes.

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CYCLISATION REACTIONS BASED ON ACRYLONITRILE

P. F. Butskus

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Both acrylonitrile itself and the cyanoethylated compounds synthesised with its help[1-4] are widely employed for obtaining both simple and complex ring systems. Almost all the investigations in this field have been published during the past fifteen years. The starting materials for these reactions are in most cases readily available.

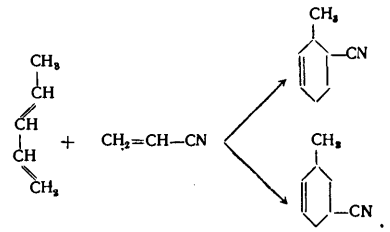
The use of acrylonitrile and cyanoethylated compounds in reactions involving ring formation is of interest from the point of view of both theory and preparative work, as it enables various cyclic systems to be synthesised, including those containing the cyanoethyl group, that either cannot be obtained by other methods or else can be so obtained only in poor yields.

1. ACRYLONITRILE IN DIENE SYNTHESIS

Acrylonitrile acts as a dienophile in reactions involving the Diels-Alder diene synthesis.

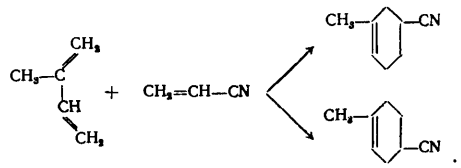
Condensation of butadiene with acrylonitrile results in the formation of cyclohex-3-enyl cyanide[1,3,5-12], although under some conditions it is assumed that 2-vinyldihydropyridine is formed as well[12].

Two structural isomers can theoretically be formed in condensations of 1-substituted dienes with acrylonitrile. It was considered for a long time that such reactions yield exclusively the *ortho*-isomer. In 1947, however, Frank *et al.*[13] demonstrated the presence of a small quantity of the *meta*-isomer in the mixture of adducts obtained by the condensation of penta-1,3-diene with acrylonitrile. The structural orientation of diene synthesis was subsequently studied in detail by Nazarov and his coworkers[14,15], who showed that the condensation of 1-substituted dienes with acrylonitrile yields a mixture of the two possible adducts containing 85–95% of the *ortho*-isomer and 5–15% of the *meta*-isomer. For example, in the case of penta-1,3-diene the reaction proceeds as follows:

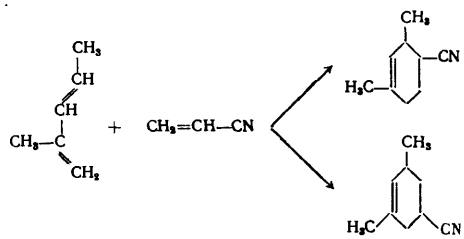


Other workers have also investigated[5,16-21] the interaction of penta-1,3-diene with acrylonitrile.

In the condensation of 2-substituted dienes with acrylonitrile, the orienting effect of the substituent in the diene molecule results in preferential formation of *para*-adducts[14,15]. In the case of isoprene[16,17,22-24] the process takes place according to the scheme

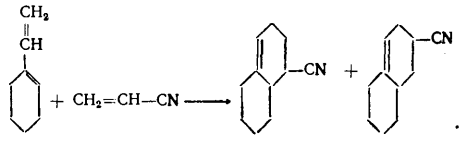


The interaction of 1,2-dimethylbutadiene (3-methylpenta-1,3-diene) with acrylonitile gives mainly 2,3-dimethylcyclohex-3-enyl cyanide and a small quantity of 4,5-dimethylcyclohex-3-enyl cyanide[14]. Reaction of 1,3-dimethylbutadiene (2-methylpenta-1,3-diene) with acrylonitrile produces mainly 2,4-dimethylcyclohex-3-enyl cyanide and also a small amount of the "symmetrical" isomer[15]:

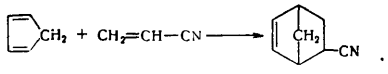


Heating diethyl *trans–trans*-muconate with acrylonitrile in the presence of quinol at 160°–170° for 30 h gives a 64%

yield of diethyl 2-cyanocyclohex-5-ene-1,4-dicarboxylate[25,26]. The reaction of vinylcyclohexene with acrylonitrile can be represented as follows[14]:



Cyclopentadiene[1,9,27,28], tetraphenylcyclopentadiene[29], and cyclohexa-1,3-diene[27,28] give the corresponding bicyclic systems with acrylonitrile, for example:



Interaction of acrylonitrile with 1,1-bicyclohexenyl results in the formation of 9-cyanododecahydrophenanthrene[30].

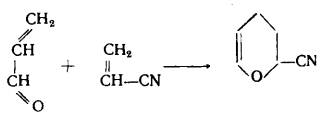
Anthracene is not cyanoethylated by acrylonitrile, but forms a diene synthesis adduct with it[31-34].

9-Anthraldehyde[35], 9-cyanoanthracene[36], and 9-nitroanthracene react similarly[37]. Diene synthesis products have been obtained also by the interaction of acrylonitrile with chloroprene[6,11,38], bromoprene[6], fluoroprene[39], 2-methoxy-,[40] 2-ethoxy-,[11,40] 2-cyano-,[41] 1-phenyl-,[42,43] 2-phenyl-,[44] and 1-*p*-nitrophenyl-butadienes[45], and with the following di- and tri-substituted butadienes: 2-chloro--3-methyl[46], 1,1-dimethyl[47], 2,3-dimethyl[5], 1,4-bisdimethylamino[48], 1,1,2-trimethyl[49], 1,1,3-trimethyl[49-51], 1,2,3-trimethyl[52], and 2-isopropyl-1,1-dimethyl[49,53]. The reaction of acrylonitrile with the following compounds has also been investigated: hexa-2,4-diene[5,54], hexachlorocyclopentadiene[55], 6,6-dimethyl-[9,56] and 6,6-diphenyl--fulvenes[57], alloocimene[58,59], myrcene[58,60], α- and β--pyronens[61], L-pimaric acid[62], some unsaturated aliphatic acids and their esters[63,64], cyclooctatetraene[65], bicycloheptadiene[66], 1,3-diphenyl-[67] and 1,3-di-1-naphthylisobenzofurans[68], and other compounds containing a system of conjugated double bonds[1,3,5,8,9,65,69-73].

In the case of the condensation of 2-isopropyl-1,1-dimethylbutadiene with acrylonitrile the normal product of diene synthesis is accompanied by the corresponding adduct of the isomeric 2-isopropyl-1,3-dimethylbutadiene[53]. When 1,1-dimethylbutadiene is heated with acrylonitrile in a solvent at 200° for 4 h, the adduct corresponding to 1,3-dimethylbutadiene is obtained in ~ 20% yield[47].

cis-1-Cyanobutadiene does not react with acrylonitrile; the *trans*-isomer apparently gives an adduct, but the latter has now been isolated in a pure form[74].

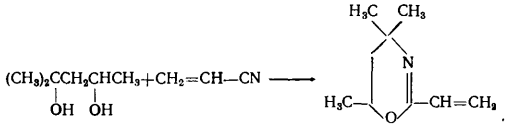
The reaction of acrylonitrile with acrolein also constitutes a diene synthesis[75]:



Experiments on the preparation of Diels-Alder reaction products from acrylonitrile and 3,5-dimethylpyrazole, 2,4-dimethylthiazole, and *N*-methylimidazole[76], as well as tetramethylfuran[77], had no success[76]. Attempts to carry out a diene synthesis between acrylonitrile as the diene and quinone as the dienophile were likewise unsuccessful[78].

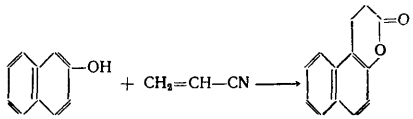
2. ACRYLONITRILE IN OTHER REACTIONS INVOLVING RING FORMATION

Acrylonitrile reacts with several glycols in the presence of concentrated sulphuric acid to give heterocycles containing a vinyl group in the side chain[79-82], for example:

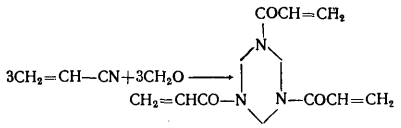


With mercapto-alcohols acrylonitrile similarly forms thiazolines and dihydrothiazines[83].

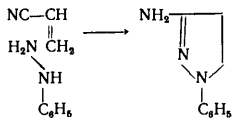
Condensation of acrylonitrile with 2-naphthol in the presence of zinc chloride and hydrogen chloride yielded the lactone of 3-(2-hydroxynaphth-1-yl)propionic acid[84]:



Formaldehyde (and also trioxymethylene) form 1,3,5-triacryloylhexahydro-1,3,5-triazine with acrylonitrile in the presence of concentrated sulphuric acid[1,3,85-87]:

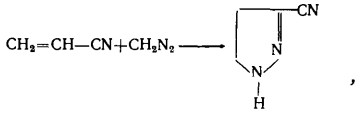


Duffin and Kendall[88] obtained from acrylonitrile and phenylhydrazine a 74% yield of 3-amino-1-phenylpyrazoline:

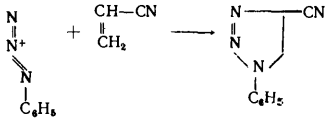


This reaction also takes place with other arylhydrazines.

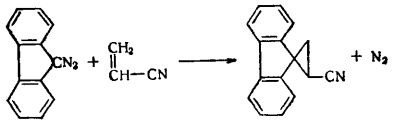
Although some investigators[89] were unable to isolate the reaction products from acrylonitrile and diazomethane in a pure form, Gurvich and Terent'ev[90] obtained a 94% yield of 3-cyanopyrazoline from these starting materials:



and from acrylonitrile and diazoacetic ester they obtained ethyl 5-cyanopyrazoline-3-carboxylate. They also showed that acrylonitrile reacts with phenyl azide at room temperature to form 4-cyano-1-phenyltriazoline in 91% yield:



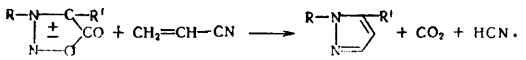
With 9-diazofluorene nitrogen is evolved and a three-membered ring is formed[91,92]:



Interaction between acrylonitrile and diazoacetone is supposed to involve the formation of a pyrazoline ring[93].

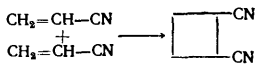
According to Pietra's results[94] the action of acrylonitrile on benzamidine results in the formation of 3,4,5,6-tetrahydro-4-imino-2-phenylpyrimidine. The reaction between acrylonitrile and diazonium salts can be used in the synthesis of 3-arylpiperidines[95] and 3,4-diarylpiperidines[96]; with benzonitrile oxide acrylonitrile gives isoxazoline derivatives[97]. Reaction of acrylonitrile with 2-amino-4-hydroxypteridines in aqueous pyridine yields the corresponding tricyclic systems[98]. Acrylonitrile has been used as starting material for the synthesis of *N*-substituted derivatives of 4-hydroxpiperidine[99] and the betel nut alkaloid arecoline[100,101]. The interaction of acrylonitrile with tetrafluoroethylene[102-104] and with allenes[69,105-109] has also been investigated, derivatives of cyclobutane and Δ9-octahydronaphthalene being obtained in the latter case. Acrylonitrile[110-113] and its addition product with hydrogen chloride[114-120] have also been used to obtain other cyclic systems.

On being heated with acrylonitrile, sydnones undergo cleavage with evolution of CO_2 and HCN and formation of pyrazole derivatives[121]:



Thus 3-phenylsydnone and excess of acrylonitrile yielded on heating 1-phenylpyrazole in ~ 80% yield. The reaction evidently takes place *via* the intermediate formation of nitriles of substituted pyrazolinecarboxylic acids.

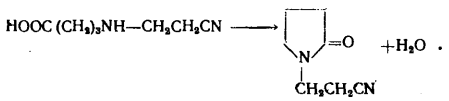
When a benzene solution of acrylonitrile is heated at 280° for 2 h, a 5% yield is obtained of a mixture of *cis*- and *trans*-1,2-dicyanocyclobutane[122]:



Pyridine can be detected in the residue from the distillation of technical acrylonitrile. However, attempts to dimerise acrylonitrile with the aim of preparing pyridine and its derivatives proved unsuccessful[78].

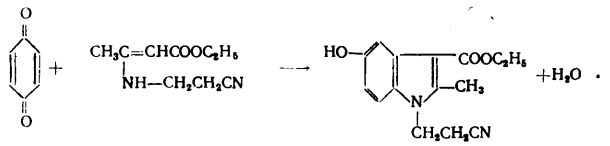
3. CYCLISATION OF CYANOETHYLATED COMPOUNDS PRESERVING THE 2-CYANOETHYL GROUP

Heating *N*-(2′-cyanoethyl)-4-aminobutyric acid leads to the formation of *N*-(2′-cyanoethyl)pyrrolid-2-one[123]:



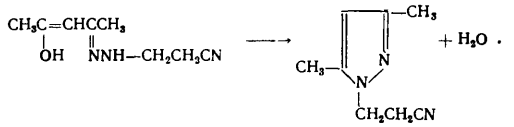
Similarly, the cyanoethylation products of glutamic acid[124,125] and of δ- and ε-amino-acids[126] yield the corresponding *N*-cyanoethylated lactams.

Ethyl *N*-(2′-cyanoethyl)-3-aminocrotonate forms with *p*-benzoquinone ethyl 1-(2′-cyanoethyl)-5-hydroxy-2-methylindole-3-carboxylate[127]:

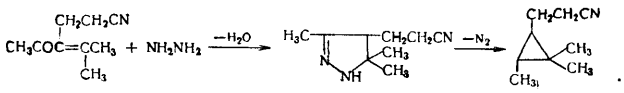


Reaction of cyanoethylated phenylhydrazine with cyclopentanone, cyclohexanone, and cycloheptanone yielded *N*-cyanoethylated indole with five-, six-, and seven-membered rings respectively fused in the 2,3-position[128].

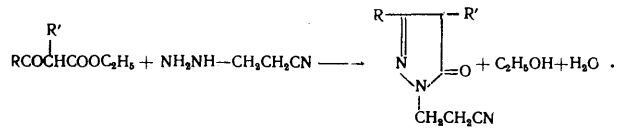
The monohydrazone obtained from monocyanoethylated hydrazine and acetylacetone cyclises into *N*-cyanoethylated 3,5-dimethylpyrazole[76]:



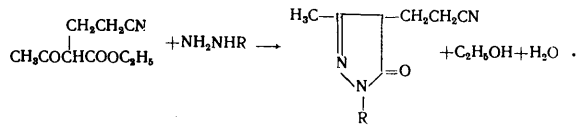
The action of monocyanoethylated hydrazine on mesityl oxide and other αβ-unsaturated ketones gives the corresponding *N*-cyanoethylated pyrazolines[129]. Monocyanoethylation products of mesityl oxide are readily converted by hydrazine hydrate to 4-(2′-cyanoethyl)-3,5,5-trimethylpyrazoline, which under the conditions of a Woolf–Kishner reaction yields 1-(2′-cyanoethyl)-2,2,3-trimethylcyclopropane[130]:



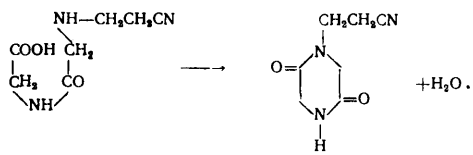
Kost *et al.*[131] have shown that the interaction of monocyanoethylhydrazine with esters of various β-keto-acids gives good yields (65–95%) of the corresponding 1-(2′-cyanoethyl)-3,4-dialkylpyrazol-5-ones:



The patent literature[132,133] contains an indication that it is possible to obtain 1-(2′-cyanoethyl)-3-methyl- and 1-(2′-cyanoethyl)-3-phenyl-pyrazol-5-ones by this method. Pyrazolones having the β-cyanoethyl group in position 4 are synthesised from monocyanoethylated acetoacetic ester and the corresponding hydrazines[131]:

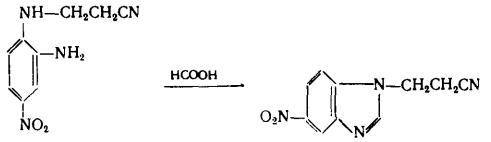


Cyclisation of *N*-2-cyanoethylglycylglycine in ethylene glycol gives 1-(2′-cyanoethyl)-2,5-dioxopiperazine[134]:

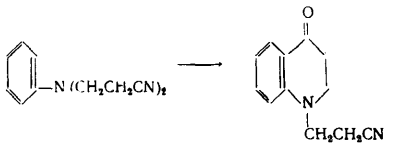


The same cyclic product is obtained under similar conditions from *NN*-di-(2-cyanoethyl)glycylglycine[134]. Esters of *N*-2-cyanoethyl-α-amino-acids on being heated form 1,4-di-(2′-cyanoethyl)-2,5-dioxopiperazines[134,135]. Attempts to prepare the latter by heating certain *N*-mono-2-cyanoethyl- and *NN*-di-(2-cyanoethyl)-α-amino-acids in ethylene glycol were unsuccessful, since under these conditions decyanoethylation takes place as well cyclisation[134]. Several derivatives of *C*-cyanoethylated 2,5-dioxopiperazine also can be obtained by reductive cyclisation[136].

2-(2′-Cyanoethyl)amino-5-nitroaniline reacts with acetic anhydride or formic acid to give the corresponding *N*-2-cyanoethylbenzoimidazole derivatives[137], for example:



When *NN*-biscyanoethylated aromatic amines are heated in chlorobenzene in the presence of aluminium chloride and a small amount of concentrated hydrochloric acid, 1-(2′-cyanoethyl)-1,2,3,4-tetrahydro-4-oxoquinolines are obtained together with other cyclisation products[138-141], for example:

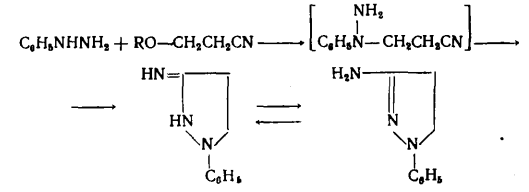


Other compounds which have been used to obtain various cyanoethylated cyclic systems are 3-aminopropionitrile[137,142-146], cyanoethylhydrazine[146], di-2-cyanoethylamine[142], *N*-2-cyanoethylanthranilic acid[147], tetra-2-cyanoethyl-*p*-phenylenediamine[140], *N*-2-cyanoethyl-*N*-phenylthiourea[3], *NN*-biscyanoethylated monoamides of dibasic acids and of some of their derivatives[148,149], *N*-2-cyanoethylisatin[150], and other cyanoethylated compounds[151]. According to the patent literature[152,153], several cyclic tetramers, pentamers, hexamers, and heptamers can be obtained from *Si*-cyanoethylated compounds.

4. CYCLISATION OF CYANOETHYLATED COMPOUNDS INVOLVING THE 2-CYANOETHYL GROUP

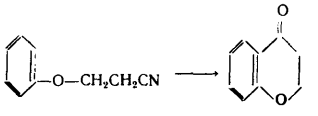
(*a*) *O*-Cyanoethylated Compounds

Kost and Ershov[118] have shown that ethylene cyanohydrin and 3-alkoxypropionitriles react with phenylhydrazine in the presence of sodium ethoxide to form 3-amino-1-phenylpyrazoline:



3-Alkoxypropionitriles have been empolyed for the synthesis of lactones[154], oxalactones[155], pyrimidines[156-164], and thiazolines[165]. The reaction between acrylonitrile and salicylaldehyde gives both the cyanoethylation product and cyclisation products (3-cyano-4-hydroxychroman and 3-cyanobenzopyran)[166,167].

Chromanone and its derivatives have been obtained by the cyclisation of 3-aryloxpropionitriles[166,169-171], for example:



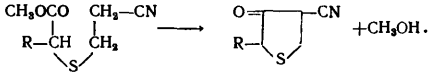
2-Cyanoethyl ethers of 2-naphthol and its derivatives are cyclised in a similar manner[169,172]. The yield of chromanone is 87.5%. The cyclisation of 3-aryloxypropionitriles to chromanones can be effected *via* an intermediate stage of hydrolysis[173,174]. Cyclisation of bis-2-cyanoethyl ethers of dihydric phenols[166,175] and of the bis-2-carboxyethyl ethers[176] obtained from them yields the corresponding bicyclic and tricyclic systems.

Ring formation also takes place when resorcinol reacts with 2-cyanoethyl *p*-toluenesulphonate[177].

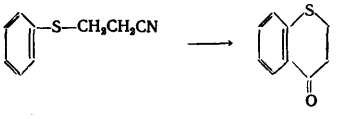
Attempts to synthesise dehydromorpholines from 2-cyanoethyl ethers of acetylenic alcohols, *via* a stage of keto-amide formation and subsequent treatment with sodium hypobromite, were unsuccessful. Dehydromorpholines can be obtained from these starting materials by forming successively the corresponding keto-esters, hydrazone-hydrazides, keto-azides, and finally the keto-urethanes, which are hydrolysed with calcium hydroxide[178].

(*b*) *S*-Cyanoethylated Compounds

The patent literature mentions[179] the formation of 5-substituted derivatives of 3-cyano-4-oxothiolane by the cyclisation, under the influence of sodium ethoxide, of esters of *S*-cyanoethylated α-mercapto-carboxylic acids:



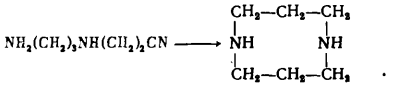
The cyclisation of 3-arylthiopropionitriles is represented as follows[169,172]:



3-Alkyl-6-oxo-2-thiotetrahydro-1,3-thiazines were obtained from cyanoethylated *N*-alkylated dithiocarbamic acids[180] and their hydrolysis products[181].

(*c*) *N*-Cyanoethylated Compounds

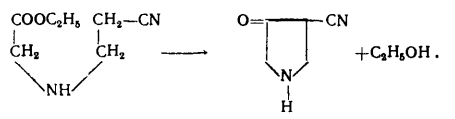
Several *N*-cyanoethylated compounds undergo cyclisation on reduction. Thus an 82% yield of 1,5-diazacyclooctane is obtained when *N*-2-cyanoethyltrimethylenediamine is reduced with sodium in butanol[182]:



When di-(2-cyanoethyl)methylamine is hydrogenated in the presence of nickel and ammonia, 1-methyl-1,5-diazacyclooctane is formed as a side-product[183]. Hydrogenation of 3-acylaminopropionitriles yields acyl derivatives of trimethylenediamine, which on distillation cyclise to form a tetrahydropyrimidine ring[3]. Ring formation takes place in the reduction of *N*-2-cyanoethylsuccinimide[3].

Some *N*-cyanoethylated compounds cyclise under the influence of strongly alkaline reagents. Thus di-(2-cyanoethyl)amine is converted to 3-cyano-4-oxopiperidine by the action of metallic sodium[185]. The biscyanoethylation product of methylamine is cyclised in a similar way[186].

In 1952 Cocker *et al.* [187] reported that heating the ethyl ester of *N*-2-cyanoethylglycine in benzene in the presence of sodium ethoxide leads to the formation of 3-cyano-4-oxopyrrolidine:



However, these workers did not investigate the structure of the reaction product, but confined themselves merely to the analytical data. Nevertheless, 1,4-di-(2′-cyanoethyl)-2,5-dioxopiperazine [135], which is obtained when the same ester is heated in the absence of solvent and alkaline reagent, has the same melting point and gives the same analysis as the 3-cyano-4-oxopyrrolidine obtained by the Irish workers.

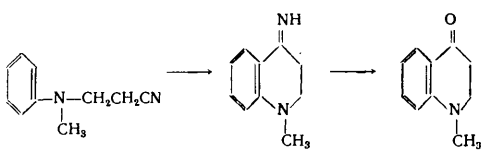
The ethyl ester of *N*-2-cyanoethylsarcosine cyclises in a similar way in the presence of alkaline reagents, forming 3-cyano-1-methyl-4-oxopyrrolidine [186].

Kost and Ershov [118] have shown that 3-dialkylaminopropionitriles react with phenylhydrazine in the presence of sodium ethoxide to form 3-amino-1-phenylpyrazoline. *p*-Tolylhydrazine reacts similarly to phenylhydrazine [188].

According to Pietra [94] *N*-2-cyanoethyl-*N*-phenylhydrazine under the influence of heat or dilute alkalis cyclises into the corresponding amine, whose structure was confirmed by its hydrolysis to 3-oxo-1-phenylpyrazolidine. *N*-2-Cyanoethyl-*NN*′-diphenylhydrazine does not give the corresponding pyrazolidine under similar conditions. Other workers showed later [189] that *N*-2-cyanoethyl-*N*′-phenylhydrazine can be cyclised to 3-amino-2-phenylpyrazoline or 3-amino-2-phenylpyrazole depending on the conditions.

According to the patent literature [190], the nitrosation of 3-arylaminopropionitriles followed by their reduction with zinc in acetic acid gives 1-arylpyrazolidine derivatives.

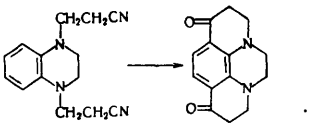
Several quinoline derivatives have been obtained by the cyclisation of *N*-monocyanoethylated aromatic amines in the presence of aluminium chloride. In particular, the cyclisation of *N*-2-cyanoethyl-*N*-methylaniline yielded 1-methyl-4-oxo-1,2,3,4-tetrahydroquinoline [1,3,168,191]:



Heating *NN*-biscyanoethylated aromatic amines in chlorobenzene in the presence of aluminium chloride and a small amount of concentrated hydrochloric acid results in the formation of 1-(2′-cyanoethyl)-4-oxo-1,2,3,4-tetrahydroquinolines or 1,6-dioxojulolidines [138-141,192-194].

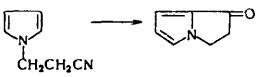
Ring formation has been effected with the products of the *NN*-biscyanoethylation of aniline, *m*- and *p*-chloroanilines, *p*-bromoaniline, *m*- and *p*-toluidines, *p*-anisidine (in this case the reaction is sometimes accompanied by demethylation), *p*-aminobiphenyl, and 2-naphthylamine, and also with the tetrakiscyanoethylation product of *p*-phenylenediamine.

Heating 1,4-biscyanoethyl-1,2,3,4-tetrahydroquinoxaline in chlorobenzene in the presence of aluminium chloride and concentrated hydrochloric acid at 140°–160° gives a 63% yield of a dioxodiazadecahydropyrene [195]:



N-2-Cyanoethylindoline has also been subjected to the action of aluminium chloride and concentrated hydrochloric acid [196,197].

N-2-Cyanoethylpyrrole is cyclised under the influence of hydrogen chloride and zinc chloride [198]:

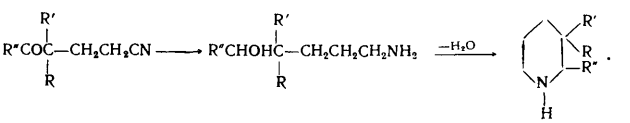


The cyclisation of 1-(2′-cyanoethyl)-1,2,3,4-tetrahydroquinoline [193,199] and of *N*-2-cyanoethylcarbazole [199,200] has also been investigated. Heating *N*-2-cyanoethylanthranilic acid with acetic anhydride in the presence of potassium acetate did not result in ring formation [147].

In some cases the cyclisation of *N*-cyanoethylated compounds passes through an intermediate stage involving hydrolysis, esterification, reduction, or the formation of imino-ethers. Products of the hydrolysis of *N*-cyanoethylated aromatic amines [191-193,201-203] *N*-cyanoethylated anthranilic acid [147,203], *N*-2-cyanoethylindoline [196], 1-(2′-cyanoethyl)-1,2,3,4-tetrahydroquinoline [193], *N*-2-cyanoethylphenoxazine [204], *N*-2-cyanoethylphenothiazine [205,206] and its derivatives [206,207], *N*-2-cyanoethylphenoselenazine [208], and 1-(2′-cyanoethyl)-2-chlorophenoselenazine [208] have undergone such cyclisation. Ring formation has been carried out also with products of the esterification of di-(2-cyanoethyl)methylamine [100,101], *N*-2-cyanoethylanthranilic acid [209], and *N*-2-cyanoethylphenothiazine derivatives [207], and reduction products of 3-aminopropionitrile and its *N*-substituted derivatives [210,211], and also some imino-ether products [212,213]. Other cases and examples of the application of *N*-cyanoethylated compounds for the synthesis of cyclic systems have also been studied [3,212,214-222].

(*d*) *C*-Cyanoethylated Compounds

The principal method for obtaining ring systems from *C*-cyanoethylated compounds is reductive cyclisation. Reduction of the monocyanoethylation product of benzyl cyanide by Vyshnegradskii's procedure gives a 59% yield of 3-phenylpiperidine [96]. Products of the monocyanoethylation of nitrocyclohexane [223] and of the biscyanoethylation of benzyl cyanide [224,225] have also been cyclised. Terent'ev and Gurvich [226-229] showed that homologues of piperidine are formed by the reduction of monocyanoethylated ketones under the conditions of the Vyshnegradskii reaction:



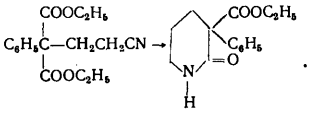
Acetone, diisopropyl ketone, and isopropyl phenyl ketone were used as starting materials. Appreciable quantities

of the corresponding amino-alcohols could be isolated in addition to the piperidine homologues. Reductive cyclisation of monocyanoethylated cylohexanone with metallic sodium in butyl alcohol results in the formation of *trans*--decahydroquinoline. Ketonic cleavage of the cyanoethylation products of acetoacetic ester and its homologues followed by cyclisation under the conditions of the Vyshnegradskii reaction yielded the corresponding piperidines [230].

Kost *et al.* [231] prepared a series of 2-oxopiperidines by the reaction of monocyanoethylated ketones with formic acid and sodium formate. Yur'ev *et al.* [232] used the same method to convert 2-(4'-cyano-2,2-dimethyl-1-oxobutyl)-selenole† to 3,3-dimethyl-6-oxo-2-(selenol-2'-yl)piperidine. The reduction of monocyanoethylated cyclohexanone under these conditions gives *trans*-octahydro-2-oxoquinoline in 72% yield [231].

Catalytic hydrogenation of succinonitrile (the product resulting from the cyanoethylation of hydrocyanic acid) produces pyrrolidine [233,234]. 2-Oxopyrrolidine also has been obtained from this dinitrile [235]. Reductive cyclisation of 2-ethoxycarbonyl-2-phenylglutaronitrile over palladised charcoal (in absolute ethyl alcohol in the cold) yields 3-ethoxycarbonyl-3-phenylpiperidine [116,117].

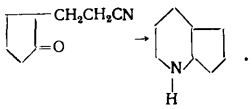
Hydrogenation of the cyanoethylation product of phenylmalonic ester in acetic acid over platinum oxide gives a 70% yield of ethyl 2-oxo-3-phenylnipecotate [236]:



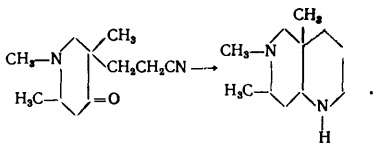
2-(2'-Cyanoethyl)-2-phenylcyclohexanone, on hydrogenation in the presence of the same catalyst in absolute ethyl alcohol, is converted into decahydro-10-phenylquinoline [115].

Hydrogenation of 4-ethoxycarbonyl-4-(pyrid-2'-yl)-butyronitrile in acid medium in the presence of platinum gives 1-ethoxycarbonylquinolizidine and 2-oxo-3-(piperid--2'-yl)piperidine [237]. 2-(Pyrid-2'-yl)propionitrile gives a 43% yield of indolizidine under similar conditions.

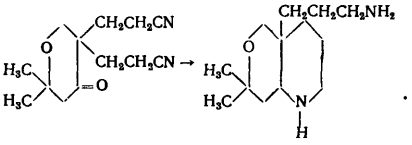
Nickel is often used as a catalyst in reductive cyclisations. That of cyanoethylated nitro-compounds in the presence of Raney nickel yields substituted pyrrolidines and oxopyrrolidines [238,239]. The product obtained by the monocyanoethylation of cyclopentanone gives a 76% yield of 2,3-cyclopentanopiperidine [240]:



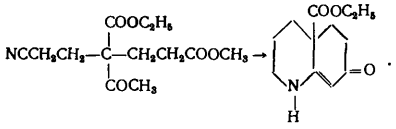
Products of the monocyanoethylation of several substituted cyclopentanones undergo analogous ring formation [241]. Nazarov *et al.* [242] showed that decahydroquinolines are obtained by reduction in the presence of Raney nickel of mono- and bis-cyanoethylated cyclohexanone. They established that the products of the monocyanoethylation of 1,2,5-trimethyl-, 2,5-dimethyl-1-ethyl-, and 1,2,3,6--tetramethyl-4-oxopiperidines on hydrogenation in the presence of nickel in an autoclave at 100° undergo cyclisation to form bicyclic compounds containing two nitrogen heteroatoms and an angular methyl group, for example:



The products of the monocyanoethylation of 2,4-dimethylcyclopentanone and 2,4-dimethylcyclopentanone are cyclised in a similar manner. Under the same conditions monocyanoethylated decahydro-1,2-dimethyl-4-oxoquinoline gives an 81% yield of a tricyclic compound containing two nitrogen heteroatoms and a fused ring in the angular position. The same workers report that reduction of the biscyanoethylation product of 2,2-dimethyl-4-oxotetrahydropyran gives a 66% yield of a bicyclic compound containing a pyran and a piperidine ring fused together:



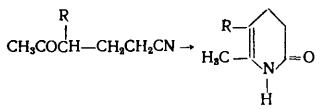
The octahydroquinoline system, with a fully reduced piperidine ring, is obtained from the following cyanoketo--ester [243]:



The same system is formed by reducing the monocyanoethylation product of isophorone in the presence of nickel [244]. This method has been used to obtain the corresponding piperidines from products of the cyanoethylation of aldehydes [245], ketones [246-248], derivatives of benzyl cyanide [249], malonic ester [250], acetoacetic ester and its homologues [248,251-253], and also esters of other keto-acids [248-251]. Products of the cyanoethylation of malonic ester [254-256], its acetamido [257-259], dodecyl [247], and phenoxy [256] derivatives, and also other cyanoethylated esters [260] have yielded the corresponding 2-oxopiperidines.

The reductive cyclisation of *C*-cyanoethylated compounds has also been carried out with iron in hydrochloric acid, zinc dust in the presence of ammonium chloride [239], and lithium aluminium hydride [261].

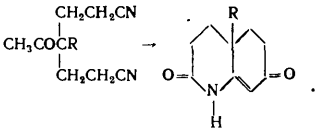
Shusherina *et al.* [262] have shown that cyclisation of the monocyanoethylation products of ethyl methyl, butyl methyl, isobutyl methyl, and methyl pentyl ketones under the influence of hydrogen chloride gives 25–60% yields of 5,6-dialkyl-3,4-dihydropyrid-2-ones:



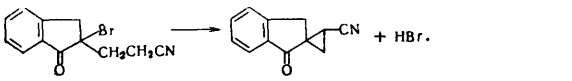
Products of the biscyanoethylation of ethyl methyl ketone, benzyl methyl ketone, and acetoacetic ester, as well as

† "Selenophen" in the original paper (Ed. of Translation).

triscyanoethylated acetone, on being heated with 40–80% sulphuric acid form the corresponding octahydro-2,7-dioxoquinolines in yields of 42–68% [263]:



Under the influence of bases 2-bromo-2-cyanoethylindanone gives a cyano-ketone having the following structure [264]:

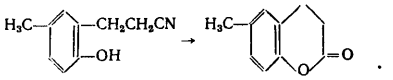


The latter compound is also formed directly from acrylonitrile and 2-bromoindanone.

Ziegler cyclisation of *o*-di(2-cyanoethyl)benzene yields the bicyclic benzocycloheptane system. Whereas American workers [265] obtained the corresponding cyano-ketone by this reaction, Chizhov [266] was able to stop the process at the stage of the formation of 6-cyano-7-iminobenzocycloheptane.

The biscyanoethylation product of fluorene yielded corresponding spirocompounds [267].

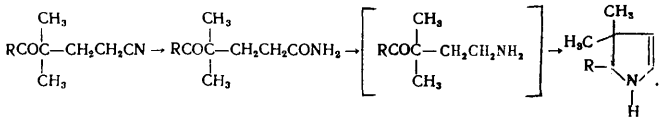
Cyclisation of the *C*-cyanoethylation products of monohydric and polyhydric phenols leads to the formation of dihydrocoumarin and its derivatives [1,3,84,114,119,120,268-272], for example:



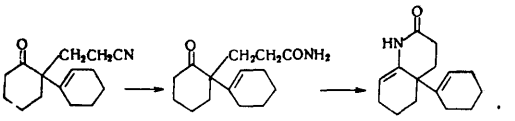
9-Cyanoethylfluoren-9-ol undergoes an analogous cyclisation [273].

Hydrolysis of the monocyanoethylation product of benzyl cyanide gives the corresponding acid, isolated as the anhydride [274], while products of the biscyanoethylation of the same nitrile [225,274,275], and of cyanoacetic and malonic acids [276], yield the corresponding acid imides on acid hydrolysis.

In some cases the cyclisation of *C*-cyanoethylated compounds passes through an intermediate stage of hydrolysis. Thus hydrolysis of the monocyanoethylation products of diisopropyl ketone and isobutyrophenone to the amides by Radzishevskii's method followed by Hofmann rearrangement leads to the formation of 4,4-dimethyl-5-isopropyl-2--pyrroline (yield 70%) and 4,4-dimethyl-5-phenyl-2-pyrroline (yield 58%) [277]:

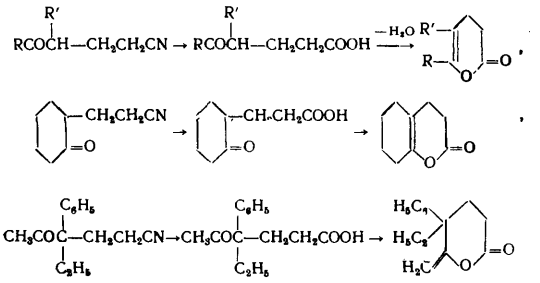


The corresponding amide could not be isolated in the case of monocyanoethylated butyrophenone. Hydrolysis with hydrogen peroxide gave an oil, which on vacuum distillation was converted to an unsaturated lactam [278]. A cyclic system having the following structure [279] has been synthesised from 2-cyanoethyl-2-cyclohexenylcyclohexanone, the corresponding amide being obtained as an intermediate stage:



Hydrolysis of the mono- and bis-cyanoethylation products of some nitro-compounds with concentrated hydrochloric acid gives γ-lactones [280]. Saturated δ-lactones can be obtained from monocyanoethylated aldehydes by reaction of the latter with organomagnesium compounds followed by alkaline hydrolysis [281,282].

A convenient method for the synthesis of unsaturated δ-lactones is saponification of monocyanoethylated ketones to δ-keto-acids with subsequent lactonisation of the latter [244,278,283-296]:



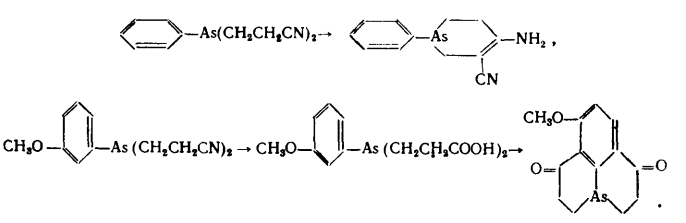
The following have been used as the initial ketones: acetone, ethyl methyl, methyl propyl, butyl methyl, methyl pentyl, isopropyl methyl, and diisopropyl ketones, acetophenone, cyclopentanone, cyclohexanone, α- and β-tetralones, indanone, methyl *p*-tolyl and benzyl methyl ketones, propiophenone, isophorone, and other ketones. The yields of δ-keto-acids are 75–100%. Lactonisation usually takes place when the δ-keto-acids are heated with acetyl chloride or acetic anhydride. The above method can be used for the synthesis of steroids and allied substances [295,296].

Other work has also been published on the cyclisation of *C*-cyanoethylated compounds passing through an intermediate hydrolysis stage [225,273,275,276,297-312].

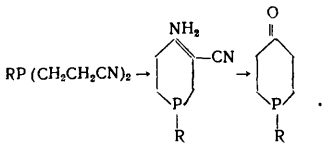
In some cases cyclisation passes through an intermediate esterification stage [222,267,299,300,304,313-325]. Other cases are also known of the employment of *C*-cyanoethylated compounds for the synthesis of cyclic systems [1,3,222,230,248,274,282,326-344].

(*e*) *As*- and *P*-Cyanoethylated Compounds

Among products of the mono- and bis-cyanoethylation of arsines, cyclic systems have been obtained containing an arsenic atom in the ring [345,346], for example:



Several cyclic compounds have been synthesised from biscyanoethylated phosphines[345]:



Other attempts to cyclise cyanoethylation products of arsines[192,347] and phosphines[347] were unsuccessful.

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Fresh work has been published very recently on the use both of acrylonitrile itself and of cyanoethylated compounds synthesised with its aid, to obtain simple and complex ring systems[348-369].

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MICROBIOLOGICAL REACTIONS OF STEROIDS

L. M. Kogan

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I. INTRODUCTION

Hardly anyone has to be convinced nowadays of the importance of microorganisms for the development and sustenance of life on earth. Nor do chemists have to be told of the significance of microbiological processes in present-day industry. The mere mention of antibiotics is sufficient.

The present review deals with an extremely narrow field of the metabolic activity of microorganisms, which has, nonetheless, attracted the attention of chemists all over the world.

This review of the reactions of steroids induced by microorganisms is not exhaustive. Its purpose is to emphasize the possibilities for the cooperation of chemists and microbiologists, without going into too many details.

Transformation of a substrate is caused by enzymes produced by the metabolic activity of a microorganism. Microbiological reactions such as alcoholic and lactic fermentation have been in use since time immemorial. The correlation of these processes with the metabolic activity of living organisms was first observed by Schwann in the thirties of the last century. Pasteur termed the microbiological reactions accompanied by gas evolution as "fermentations", but this term was later extended to other microbiological processes.

The capacity of certain microorganisms to induce various transformations in steroids was noticed more than 20 years ago. The earliest work, by Mamoli and Vercellone[1,2,3], dealt with the hydrogenation of an oxo-group conjugated with a double bond, or with the dehydrogenation of a secondary hydroxyl group. In 1948 Kramli and Horvath[4] first succeeded in introducing a hydroxyl group into a steroid molecule by a microbiological method. It was not, however, until after Peterson[5] had obtained 10% 11α-hydroxyprogesterone (I) by incubating progesterone (II) with a *Rhizopus nigricans* culture that microbiological transformations of steroids awakened widespread interest.

Microbiological steroid reactions are extremely diverse in character. They include introduction of hydroxyl groups, formation of oxo-groups, formation and cleavage of epoxides, hydrogenation, dehydrogenation, etc. In spite of this diversity, techniques employed in carrying out microbiological reactions are fairly uniform. In experiments where a large quantity of the substance is either not required or is not available trial runs are carried out in flasks mounted on agitators, several flasks being usually set up in series. Most often 750–1000 ml flasks are used with 100–200 mg steroid. For steroid amounts of the order of 1–2 g glass fermenters of 10–20 litre capacity are used, provided with stirrers, thermometers, devices for filling, emptying, and sampling, heat-exchange elements, and, when needed, with an air bubbler. In industry and in pilot plants steel apparatus is usually employed, fitted with similar devices.

The procedure used in the glass fermenter is essentially the same as that used in flasks or the steel apparatus (this does not mean, however, that the reaction in the flask can completely model that in the fermenter). The fully equipped fermenter is sterilised, and filled with a sterile culture medium, which has been inoculated by the microorganism under sterile conditions. Special attention must be paid to the observance of strictly sterile conditions throughout all the operations. Depending on the experiment, sterilisation is carried out in an autoclave at 110°–120°, by working in boxes illuminated with bactericidal lamps, or by carrying out filling, sampling, etc. in the flame of a gas burner. After the addition of the inoculated culture medium (usually transferred by means of compressed air), a definite period of time is required for the development of the culture (from several hours to several days). The steroid is introduced in solution in an organic solvent, *e.g.* acetone, alcohol, propylene glycol, or dimethylformamide. A suspension of the steroid, obtained by precipitation with water of an ethanol or acetone solution, is sometimes advantageous as far as the yields are concerned. Reaction is carried out at a temperature requisite for the normal growth and metabolic activity of the microorganism, mostly at 24°–33°. The course of the reaction is followed by assay using either paper chromatography or microbiological methods. "Thin layer chromatography", on an adsorbent on glass plates, without a binding agent, is widely used in following the course of microbiological reactions of steroids[6,7]. By this method steroids can be separated and detected in 30–45 min, in contrast to several hours needed by paper chromatography.

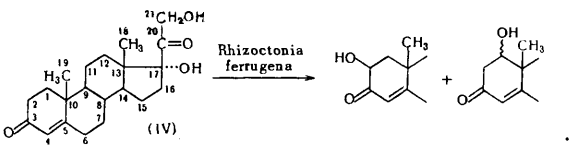
At the end of the process the reaction mixture is extracted by an organic solvent immiscible with water, usually chloroform, dichloroethane, ethyl acetate, methylene chloride, and sometimes ether. In some cases only the filtered reaction liquid need be extracted. For complete separation of steroids, extraction is sometimes preceded by homogenisation of the reaction mixture. The extract is concentrated *in vacuo* and the steroid isolated from it either by crystallisation or chromatography.

According to a recent paper, microbiological steroid reactions can be carried out by passing the steroid solution through a layer of the microorganism culture on a carrier[8]. This method has possibilities as a continuous industrial process.

II. VARIOUS TYPES OF MICROBIOLOGICAL STEROID REACTIONS

1. Introduction of a Hydroxyl Group

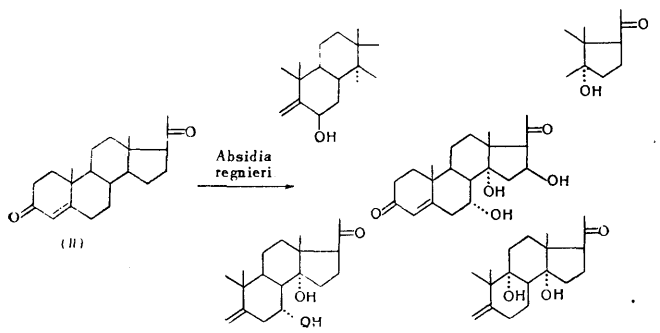
Introduction of a hydroxyl group at carbons 1 and 2 of the steroid molecule was carried out on various steroid substrates, *e.g.* androstenedione[9] (III), Reichstein's substance S [10] (IV), 9α-fluorohydrocortisone[11] (V), and other steroids, by incubation with microorganisms such as *Streptomyces*, *Penicillium*, *Rhizoctonia*, and *Sclerotinia*.



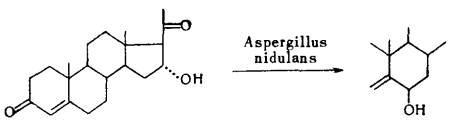
(IV)

In all cases examined both 1α- and 2β-isomers were obtained. The yield of the 1- and 2-hydroxy derivatives rarely exceeds 10%. Hydroxylation in the 1- and 2-positions is usually complicated by various side-reactions, which make difficult the isolation and purification of the reaction products. Most often 1- and 2-hydroxylations proceed concomitantly with hydroxylations at C_{11} and C_{15}, and with the reduction of the oxo-group at C_{20}.[12]

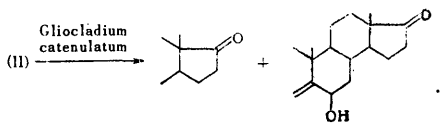
Hydroxylation in the 6β-position, mostly induced by fungi, is also seldom completely selective. For example, incubation of progesterone (II) with *Absidia regnieri* culture[13] yields five products:



6β-Monohydroxylation only occurs if the other possible position for the hydroxyl group is already taken[14]:



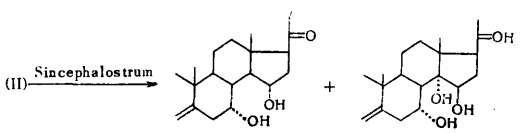
Peterson[16] reported a case where the 6β-hydroxylation was accompanied by oxidative degradation of the side-chain:



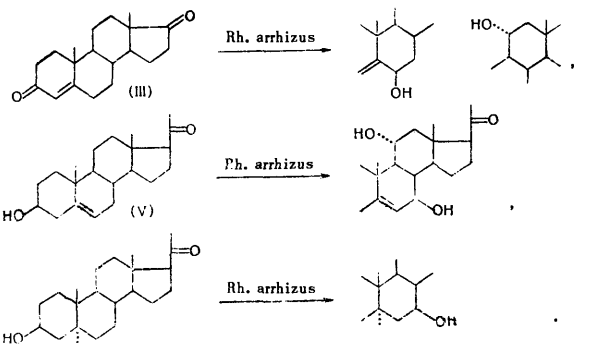
The preparation of 30% 6β,17α,21-trihydroxypregn-4--ene-3,20-dione by incubation of Reichstein's substance S (IV) with *Bacillus cereus* has recently been reported[15].

For all substrates undergoing 6β-hydroxylation the presence of the 4-ene-3-oxo-grouping is a characteristic feature, the nature of the side-chain at C_{17} not being of decisive importance. 6β-Hydroxy-derivatives were also obtained from compounds such as progesterone (II) and androstenedione (III).[13,16]

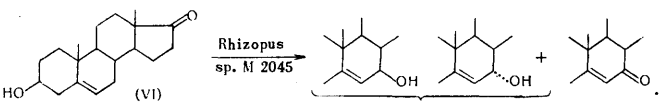
Microorganisms which induce 7α-hydroxylation are *Cephalosporium*[17], *Helmintosporium*[18], *Proactinomyces*[19], and *Sincephalostrum*[20].



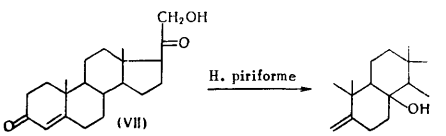
The course of hydroxylation is in certain cases predetermined by the structure of rings A and B of the steroid nucleus. Thus, the mould *Rhizopus arrhizus*, which induces 11α- and 6β-hydroxylations in 4-ene-3-oxo-steroids, *e.g.* androstenedione (III),[21] hydroxylates pregnenolone (V) in positions 7β and 11α, and compounds of the allopregnane series in the 7β-position[22,23]:



On incubation of 3β-hydroxyandrost-5-en-17-one (VI) with a species of *Rhizopus* (M2045), Dodson[24] isolated from the reaction products a molecular compound of the 7α- and 7β-hydroxy-derivatives:

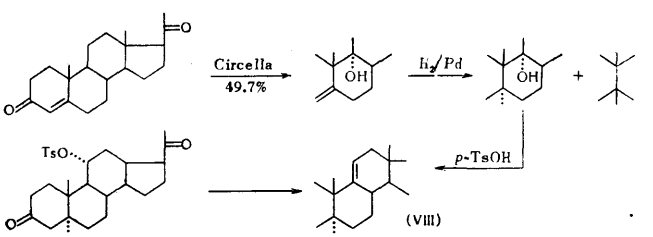


A tertiary hydroxyl group was introduced at C_8 of deoxycorticosterone (VIII) by the action of *Helicostylum piriforme*[21]:



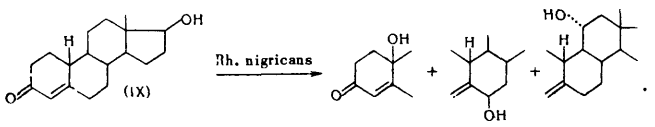
8-Hydroxylation can be carried out by microorganisms such as *Curvularia pallescens*[25], *Mucor parasiticus*[26], etc.

Schubert and collaborators[27] obtained 9α-hydroxyprogesterone using a *Circella* culture. Its structure was established by subsequent hydrogenation and dehydration into the known pregn-9(11)-ene-3,20-dione (VIII):



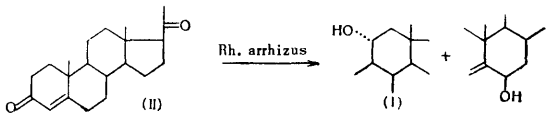
Hydroxylation of the tertiary carbon atom in the 10-position occurs on incubation of 19-nortestosterone (IX) with a

species of *Rh.nigricans*, the microorganism which usually hydroxylates the 11α- and 6β-positions[28]:

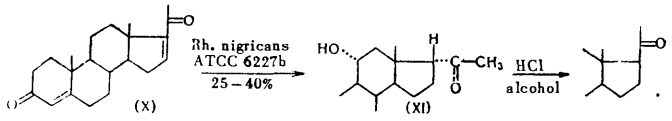


Djerassi's group[29], however, reported 11α-monohydroxylation of 19-norprogesterone in 70% yield by means of a species of *Rh.nigricans*.

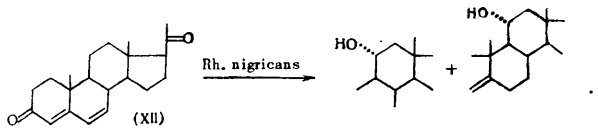
The microbiological preparation of 11α-hydroxyprogesterone (I) in 1952 by Peterson opened up a simple way for the introduction of an oxygen-containing functional group at the 11-position of steroids. This is of great importance for preparing corticosteroids difficult to obtain by chemical methods.



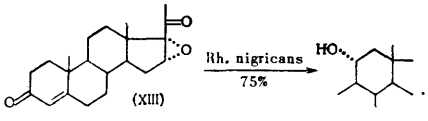
Incubation of progesterone with *Rh.nigricans* gave 95% of 11α-hydroxyprogesterone[30]. This oxidation, however, does not always proceed unidirectionally, 11α-hydroxylation often being accompanied by 6β-,[15,31] 17α-,[32,33] and 21-hydroxylations[34]. Incubation of Δ[16]-dehydroprogesterone (X) with *Rh.nigricans* gave 11α-hydroxy-17-isoprogesterone (XI):[35]



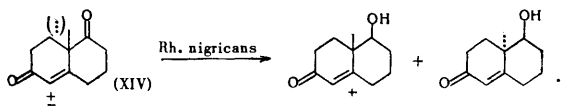
On incubation of Δ[6]-dehydroprogesterone (XII) with a species of *Rh.nigricans*, partial hydrogenation of the Δ[6]-double bond took place[36]:



Hydroxylation of pregnane-3,20-dione and allopregnane-3,20-dione with *Rh.nigricans* gave the corresponding 11α-hydroxy-derivatives in 40% and 25% yields, respectively[37]. Ercoli[38] and Peterson[39] and their collaborators carried out the fermentative hydroxylation of 16α,17α-epoxyprogesterone (XIII) in 75% yield:

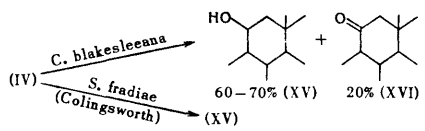


Hydroxylation of steroids by *Rh.nigricans* is an excellent example of the combination of specificity and diversity of action of microorganisms. Incubation with *Rh.nigricans* induces primarily hydroxylation in position 11 of steroid substrates such as progesterone (II), Δ[6]-dehydroprogesterone (XII), 16α,17α-epoxyprogesterone (XIII), etc. But 11α-hydroxylase is not the only enzyme formed by *Rh.nigricans*. Prolog and Acklin[40] showed that *Rh.nigricans* can reduce substrates such as Δ[4]-methyloctaline-3,8-dione (XIV):



It has been reported[41] that during the incubation of 4-methyltestosterone the methyl group in position 4 hinders the introduction of the hydroxyl group at carbon 6, with the result that 7β- and 11α-hydroxy-derivatives are chiefly formed, with very small amounts of 7α- and 6β-hydroxy-derivatives. Simultaneous formation of 11α- and 15β-hydroxy-derivatives has been described by Muir and Dodson[42]. Meister and Weintraub[43] obtained both 11α-hydroxytestosterone and testosterone with *Sporotrichum epigaem*. 11α-Hydroxylation has been effected by incubating steroids with *Condiobolus sp.*, *Basidiobolus ranarum*[44], and *Metarrhizium anisopliae*[45].

Even more important is the introduction of the 11β-hydroxy-group into the steroid molecule, since it is known to be responsible for the physiological activity of corticosteroids (hydrocortisone, corticosterone). Colingsworth and his collaborators[46] were the first to carry out this hydroxylation, although with very small yield:

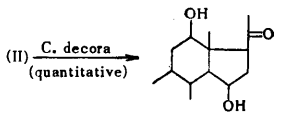


Shull and Kita[47] obtained 41%, and Dulaney[48] 50% of hydrocortisone (XV) by incubating Reichstein's substance S (IV) with *Curvularia lunata*. Connel[49] increased the yield of hydrocortisone to 60–70% by incubating compound S with *Cunninghamella blakesleeana*, obtaining at the same time 20% of cortisone (XVI).

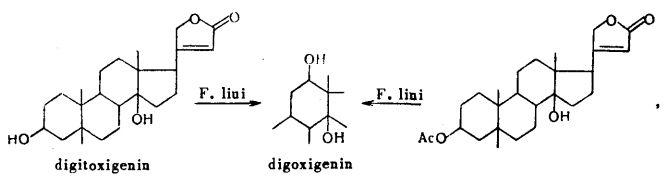
It has been shown that the yield of hydrocortisone can be increased by changing the culture medium, *e.g.* by adding trioleates[50], phenol[49], and other substances.

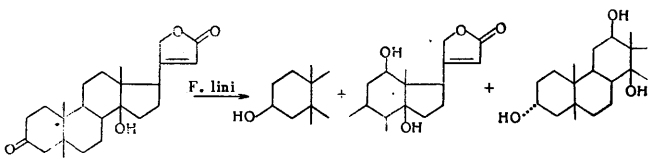
A number of communications appeared on the 11β-hydroxylation by means of other microorganisms. Davisson[51] patented the preparation of 70% of hydrocortisone (XVI) from Reichstein's substance S (IV) by means of *Stachilidium theobromae*. Thoma and his collaborators[52] obtained prednisolone (XVII) from 17α,21-dihydroxypregna-1,4-diene-3,20-dione using *Coniothyrium helleborine*[52], and Sardinas and Shull[53] carried out 11β-hydroxylation with *Spondiocladium australe*, *S. xylogenum*, as well as *Epicoccum*. The 11β-hydroxylation is often accompanied by hydroxylation in position 14α,[47] and the reduction of the 20-oxo-group[54]. Schmidt-Thome[55] obtained hydrocortisone (XV) and epihydrocortisone (XVIII) in equal amounts by incubating compound S with *Absidia glauca*.

Schubert and his collaborators[56] carried out 12β-hydroxylation of progesterone (II) using *Calonectria decora*:

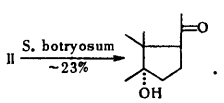


In their investigation of the effect of microorganisms on cardiac glycosides and aglycones Gibler and Tamm[57,58] established that *Fusarium lini* contains at least four enzymic systems, namely hydroxylase, capable of hydroxylating the 12β- and 15α-positions, esterase, capable of saponifying acetyl groups, hydrogenase, and β-glycosidase:

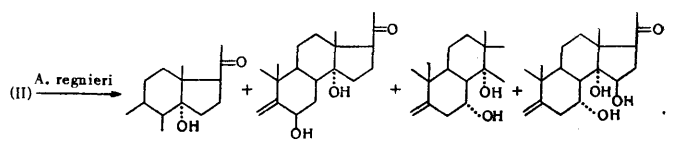




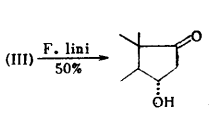
14α-Hydroxylation can be induced by microorganisms such as *Stemphilium botryosum*, *Curvularia lunata*, and *C.blakesleeana*[59]:



The preparation of 14α-hydroxyprogesterone[60] by means of *Bacillus cereus* is one of the comparatively few examples of hydroxylations carried out by bacteria. On incubating progesterone (II) with *Absidia regnieri*, Shirasaka[61] obtained a mixture of reaction products:

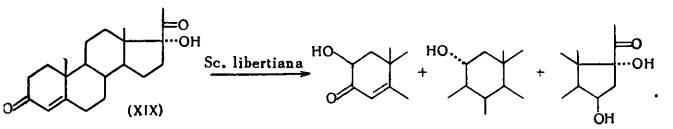


15α-Hydroxylation can also be effected by various microorganisms, most important being *Fusarium*[62,63] and *Penicillium*[64]:



There are comparatively few references to side reactions during the 15α-hydroxylation. On incubating substance S (IV) with a *Spicaria* species, Bernstein and his collaborators[65] obtained the corresponding 15β-hydroxy--derivative. Incubation of substance S (IV) with *Bacillus megatherium* gave 50% of 15β,17α,21-trihydroxypregn-4--ene-3,20-dione[66]. Incubation of progesterone gave a smaller yield of 15β-hydroxyprogesterone. An attempt to introduce the 15β-hydroxy-group into prednisone and prednisolone using this method was unsuccessful, hydrogenation of the double bond in the 1-position taking place instead[66].

A group of Japanese chemists[67] isolated 15β-hydroxy--derivatives from a complex mixture of products obtained on incubation of 17α-hydroxyprogesterone (XIX) with Sclerotinia libertiana:

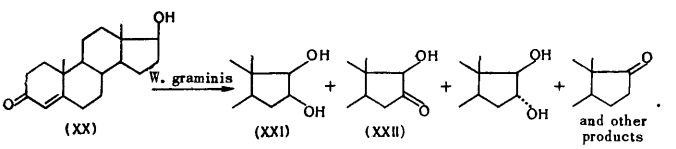


The important 16α-hydroxylation was effected using various species of *Actinomycete*. Perlman and his collaborators[68] obtained 30–40% of 16α-hydroxyprogesterone by incubating progesterone with the *Streptomycete* species MD2428. Incubation of 9α-fluorohydrocortisone with *Streptomyces roseochromogenus* gave 50% of 9α-fluoro--16α-hydroxyhydrocortisone[69].

11β,16α-Dihydroxy-9α-fluoroandrost-4-ene-3,17-dione was produced by *St.roseochromogenus*[70]. 16α-Hydroxylations induced by moulds *Pestalotia funerea*[71] and *Didymella vodakii*[25] have also been reported.

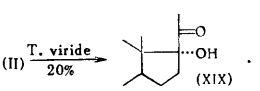
Despite the intensive search for microbial cultures capable of inducing steroid reactions, the microbiological introduction of the 16β-hydroxy-group was not discovered till 1960.[72]

An elaborate chromatographic technique applied to products obtained by incubation of testosterone (XX) with a *Wojnowicia graminis* (CBS) culture revealed ten products, including 16β-hydroxytestosterone (XXI) and 16-oxotestosterone (XXII):

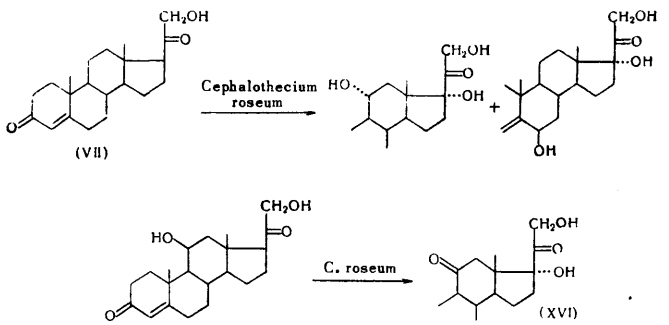


It had been reported earlier[73,74] that *W.graminis* can introduce a hydroxyl group in the 21-position of pregnene steroids.

The important 17α-hydroxylation has so far only been achieved using three microorganisms. *Trichothecium roseum*,[75], *Trichoderma viride*[76], and *Gliocladium*[77].

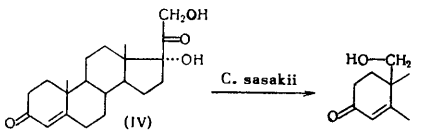


In other cases 17α-hydroxylation proceeds with concomitant 11α- and 6β-hydroxylations[33,76], and the oxidation of the hydroxyl group in position 11.[76]



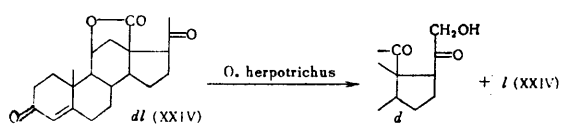
The Ciba group patented the preparation of 18-hydroxy--steroids by the action of fungi on 13-methylsteroids[78].

Hydroxylation in position 19 has been reported by Japanese workers[79]. They prepared 17α,19,21-trihydroxypregn--4-ene-3,20-dione (XXIII) by incubating compound (IV) with *Cotricium sasakii*:



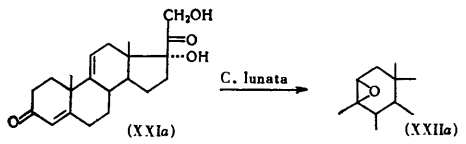
The same group carried out the 19-hydroxylation of hydrocortisone and 11-epihydrocortisone.

Hydroxylation in position 21, first effected by Wettstein's group[75], often proceeds exclusively. It can be induced by microorganisms such as *Aspergillus niger*[80], and the *Sphaeroidaceae*, *Hendersonia*[77], and *Wojnowicia*[81]. Vischer, Schmidlin, and Wettstein[82] used microbiological hydroxylation to separate the racemate of *dl*-11β-hydroxypregn-4-ene--3,20-dione-18-carboxylic acid (18→11)lactone (XXIV). Incubation of racemate (XXIV) with an *Ophiobolus herpotrichus* resulted in the 21-hydroxylation of the steroid with the natural configuration, while the *l*-form remained unchanged:

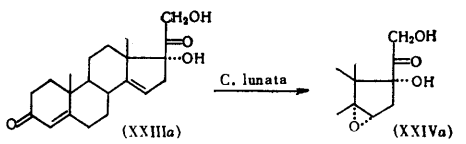


2. Formation and Opening of an Epoxide Ring

Closely related to microbiological hydroxylation is the microbiological formation of epoxide rings. The method was elaborated by Bloom and Shull[83] who, on incubation of 17α,21-dihydroxypregna-4,9(11)-diene-3,20-dione (XXI*a*) with *Curvularia lunata*, known to induce 11β-hydroxylation, or with *C. blakesleeana*, obtained 17α,21-dihydroxy-9β,11β--epoxypregn-4-ene-3,20-dione (XXII*a*):



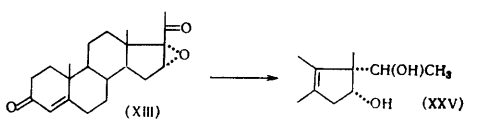
The same species was used for transforming 17α,21--dihydroxypregna-4,14(15)-diene-3,20-dione (XXIII*a*) into 17α,21-dihydroxy-14α,15α-epoxypregn-4-ene-3,20-dione (XXIV*a*):



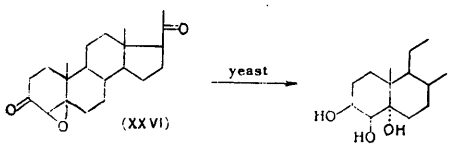
No epoxide was formed when the same substrate was incubated either with microorganisms which normally induce 11α-hydroxylation or those which are incapable of hydroxylating position 14. Perlman *et al.*[84] failed to obtain an epoxide by incubating pregna-4,16-diene-3,20-dione with an *Actinomycete* (which normally introduces a hydroxyl at 16α). As noted earlier, incubation of androst-5-en-3β--ol-17-one with *Rhizopus*[24] and of Δ^{16}-dehydroprogesterone with *Rh. nigricans*[35] also failed to produce epoxides. Perlman considers that microbiological epoxide formation can take place in steroids containing isolated double bonds, by means of microorganisms which are capable of introducing axial hydroxyl groups in positions corresponding to those taken up by the epoxide.

Quite recently Czech workers[85] found that the incubation of 3β-hydroxy-B-norandrost-5-en-17-one with *Rh. nigricans* yields 3β-hydroxy-5ξ,6ξ-epoxy-B-norandrostan-17--one and 3β,11α-dihydroxy-5ξ,6ξ-epoxy-B-norandrostan--17-one, together with 11α- and 6β-hydroxy-derivatives.

Epoxide rings can also be opened by microbiological reactions. Using yeast, Camerino and Modelli[86,87] opened the epoxide ring in 16α,17α-epoxyprogesterone (XIII). At the same time, rearrangement into 16α,20α-dihydroxy--17β-methyl-18-norpregna-4,13-dien-3-one (XXV) occurred:



In 1959 Camerino[86] succeeded in opening the epoxide ring in 4,5-epoxyprogesterone (XXVI), in 65% yield. Reduction of the 3-oxo-group took place simultaneously:

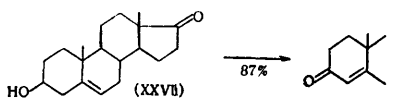


3. Introduction of an Oxo-Group

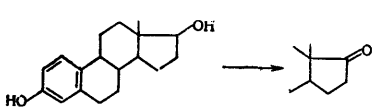
Enzymic transformations of steroids sometimes include the direct introduction of an oxo-group. For instance, hydroxylation of Reichstein's substance S with *C.blakesleeana*[49] also yields 20% of cortisone. If hydrocortisone is used as substrate, there is no formation of cortisone[89]. As already mentioned[24], an oxoderivative was also isolated after incubation of 3β-hydroxyandrost-4-en-17-one with *Rhizopus*. All this can be taken as evidence that in certain cases the formation of an oxo-group does not proceed *via* oxidation of a hydroxyl group, but by direct oxidation of a methylene group. Direct introduction is, however, not the only way of the microbiological formation of an oxo-group. Eroshin[90] showed that incubation of hydrocortisone (XV) with a *Cunninghamella elegans* culture yields cortisone (XVI), while under the same conditions Reichstein's substance S (IV) gives a mixture of hydrocortisone, epihydrocortisone, and cortisone. On incubating prednisolone (XVII) and epihydrocortisone with *C.elegans*, Eroshin found no such transformation products.

4. Oxidation of a Hydroxyl Group

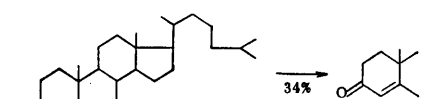
In 1937 Mamoli and Vercellone[1] published a paper on the oxidation (in Milan) of the 3β-hydroxy-group in dehydroepiandrosterone (XXVII) with yeast. When, however, Mamoli attempted to repeat this experiment in Berlin, using the local yeast, no oxidation could be detected. He established that the dehydrogenation of the hydroxyl group is carried out by aerobic bacteria, which were contaminating the Milan yeast[3].



Hanč and his collaborators[91] carried out a selective dehydrogenation of the 17β-epimer of oestradiol by means of *Actinomycete* species:

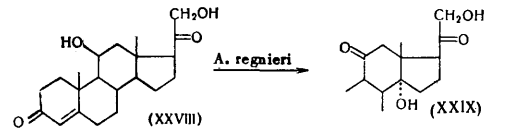


Turfitt[92,93] described the microbiological dehydrogenation of various steroids, including the oxidation of cholesterol (XXXV) in 34% yield,



and of testosterone, to yield 47% androstenedione, by means of *Proactinomyces erythropolis*.

Microbiological oxidation of the 3β-hydroxy-group is concomitant with the shift of the double bond from ring B into ring A. Incubation of corticosterone (XXVIII) with *Absidia regnieri*[94] gave 14α,21-dihydroxypregn-4-ene-3,11,20-trione (XXIX):

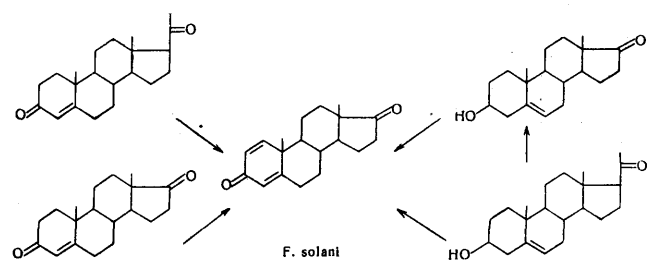


No transformation products were detected on incubation of epicorticosterone and hydrocortisone.

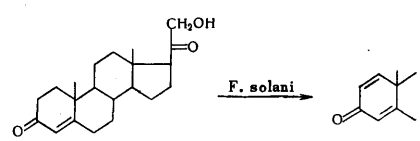
Oxidation of hydroxyl groups in positions 7 and 12 has also been described[95].

5. Dehydrogenation of the Steroid Skeleton

The discovery by Vischer and Wettstein[96] of microbiological dehydrogenation by the *Fusarium* fungi was followed by a number of papers and patents dealing with the microbiological dehydrogenation of steroids in the 1,2-position. On incubation of the pregnane steroids, a simultaneous oxidative degradation of the side-chain occurred:



Vischer *et al.*[97] carried out the dehydrogenation of pregn-4-enes with *F.solani* and *Calonectria decora*, without the concomitant degradation of the side-chain:

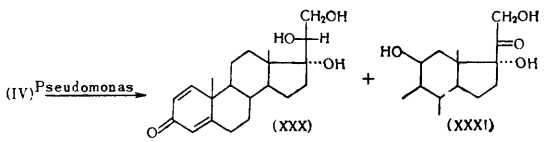


According to a Japanese patent[98], incubation of progesterone (II) with *F.solani* yields 30–50% of Δ^1-dehydroprogesterone and 30–40% of androsta-1,4-diene-3,17-dione. Degradation of the side-chain does not take place on incubation with *F.solani* if the substrates contain a dihydroxyacetone radical in position 17.[99]

Skryabin and his group[100,101] incubated cortisone (XVI) and hydrocortisone (XV) with a species of *Mycobacterium* and obtained 75–80% of prednisone and prednisolone, respectively.

Of special interest was the preparation of prednisolone from Reichstein's substance S (IV) by a group of Japanese workers. They first described the incubation of (IV) with a species *Pseudomonas* bacteria, which yielded a mixture

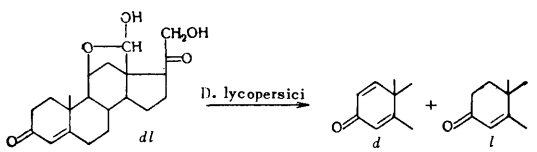
of 17α,20β,21-trihydroxypregna-1,4-dien-3-one (XXX) and 11β,17α,21-trihydroxypregn-4-ene-3,20-dione (XXXI), the latter in very small yield only[54].



They also obtained 30% of prednisolone (XVII) from Reichstein's substance S using a *Pseudomonas* mutant obtained by ultra-violet irradiation[102]. This example shows that the formation of enzymic systems in microorganisms has a certain flexibility, and that the methods of preparing mutant strains has a great future and is worthy of a systematic study.

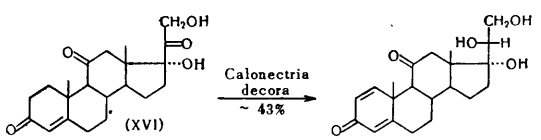
It has already been indicated that unfortunately in many cases microorganisms form not one, but several enzymic systems, giving rise to different reaction products, or attacking simultaneously several points in the steroid molecule. In the last example, however, the combination of Δ^1-dehydrogenase and 11β-hydroxylase was most advantageous, allowing a one-stage conversion of substance S to prednisolone.

According to the paper of Vischer *et al.* mentioned above[82], incubation of the racemate of aldosterone with *Didymella lycopersici* results in the dehydrogenation of the compound of natural configration only:

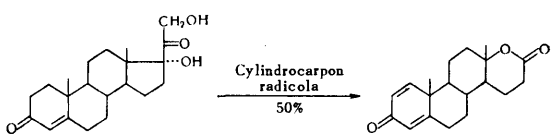


Charney and his group[103] prepared 95% of prednisone by incubating cortisone with *Corynebacterium simplex*.

The 1,2-dehydrogenation is often accompanied by the reduction of a 20-oxo-group to a 20β-hydroxy-group[104]:

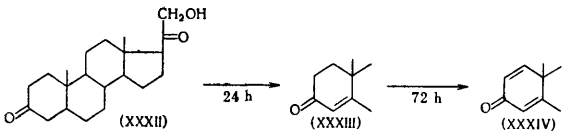


It is interesting that oxidative degradation of the D ring, yielding a lactone, often proceeds simultaneously with dehydrogenation[105]:



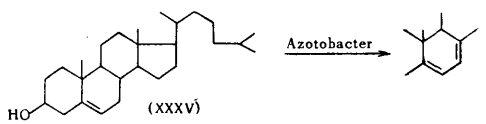
Incubation of 2α,17β-dihydroxyandrost-4-en-3-one[106] with *Bacillus sphericus* (ATCC 7055) gave 2α-hydroxyandrosta-1,4-diene-3,17-dione. To make certain that the last compound is not an artefact, the same substrate was incubated with a denatured culture of *B.sphericus*; it was fully recovered after incubation.

There are cases of microbial steroid dehydrogenation occurring at other positions in the molecule. On incubating 21-hydroxypregnane-3,20-dione (XXXII) with *Protaminobacter alboflavum*, Shull[107] obtained 21-hydroxypregn-4-ene-3,20-dione (XXXIII), and on longer incubation, 21-hydroxypregna-1,4-diene-3,20-dione (XXXIV):



On incubating 3β-hydroxyandrost-5-en-17-one with *F.solani*, Vischer and Wettstein[96] obtained androsta-1,4-diene-3,17-dione.

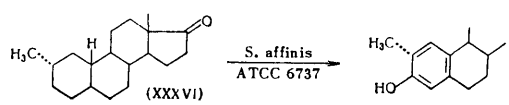
The introduction of a double bond in position 7 of cholesterol (XXXV) by incubation with a species of *Azotobacter*, carried out by Horvath and Kramli[108], was the first case of microbiological introduction of a double bond into a steroid molecule:



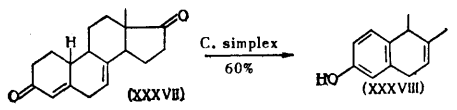
Peterson and his collaborators[109] showed that incubation of pregnane-3,11,20-trione and allopregnane-3,11,20-trione with *Septomyxa affinis* (ATCC 6737) gives, respectively, 5–10% and 40–45% of derivatives dehydrogenated in the 1,2-position. This is yet another clear example of the different behaviour of *cis*- and *trans*-isomers of condensed ring systems in microbiological reactions. The same work dealt with incubation of 17β-hydroxy-19-norandrost-4-en-3-one with *S.affinis*, which yielded 55% of oestrone and 12% of oestradiol. The absence in this case of an angular methyl group at position 10 resulted in the aromatisation of ring A.

On incubating Δ^4-3-oxo-19-norsteroids with *Corynebacterium simplex*, Kushinskii[110] obtained an aromatic A ring. A small yield of a compound containing a hydroxyl group in position 1 or 2 was also found among the reaction products. This may well indicate that dehydrogenation proceeds *via* hydroxylation and subsequent dehydration.

Peterson and his collaborators[111] found that aromatisation of 2α-methyl-19-norandrostan-17-one (XXXVI) with *Septomyxa affinis*, was accompanied by hydroxylation:

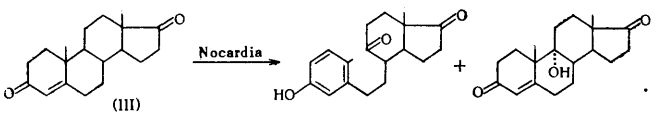


Djerassi and collaborators[112] incubated 19-nor androstan-4,7-diene-3,17-dione (XXXVII) with *C.simplex*, and obtained 60% of equilin (XXXVIII):



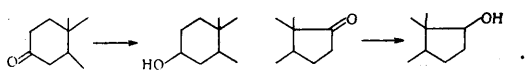
On incubating 19-norhydrocortisone with *Corynebacterium simplex* (ATCC 6946), Herzog and Nobile[113] obtained the corresponding compound with an aromatic A ring.

A condition for the microbiological aromatisation of ring A in steroids seems to be the absence of an angular methyl group at position 10. Nonetheless, aromatisation occurs simultaneously with the cleavage of the bond between carbons 9 and 10 when androstenedione (III) is incubated with *Nocardia*, apparently *via* a 9α-hydroxylation stage[114]:



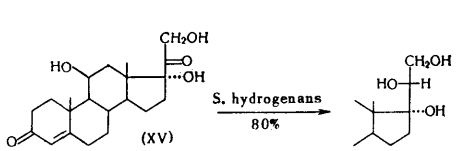
6. Reduction

Microbiological reduction of steroids is also of widespread occurrence, and in certain cases it has a great practical significance. As early as the thirties Mamoli and Vercellone[1,2,115,116] carried out the following transformations of the C_{19} steroids with yeast:



In their study of the microbiological transformations of androstenedione (III) with *Trichomonas gallinae* (*Protozoa*) Sebek and Michaels[117] established that incubation under aerobic conditions induces the oxidation of the hydroxyl group, while under anaerobic conditions it results in the reduction of the oxo-group at C_{17}. Incubation of 3β-hydroxyandrost-5-en-17-one acetate with *Penicillium notatum* gave 79% of testosterone[118].

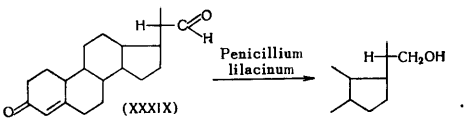
Many microorganisms are capable of the stereospecific reduction of the 20-oxo-group in various steroid substrates. Schmidt-Thome[55] reduced selectively the 20-oxo-group of hydrocortisone (XV) in 80% yield with a *Streptomyces* species from the soil (*S.hydrogenans*):



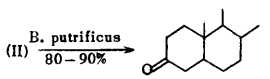
Later[119] Schmidt-Thome established the specificity of the action of *S.hydrogenans* upon the dihydroxyacetone group, since the incubation of progesterone (II) and deoxycorticosterone (VII) resulted in no change. This specificity of action on the dihydroxyacetone group in the 17-position has not been found in any other microbial species. Peterson[21] reduced the 20-oxo-group in deoxycorticosterone by incubation with a *Streptomyces* species.

The capacity to reduce the 20-oxo-group to form the 20β-hydroxy-group is characteristic of many species of *Actinomycete*[120]. Many other microorganisms, for instance *Curvularia lunata*[181], *Corynebacterium simplex*[122], *Pseudomonas*[123], and *Mycobacterium*[124,125], are also capable of reducing the 20-oxo-group.

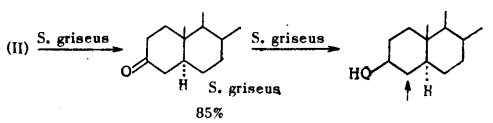
Peterson[126] reduced the aldehyde group in the 22-position of bisnorchol-4-ene-3,22-dione (XXXIX):



Microorganisms can also carry out the hydrogenation of double bonds. Hydrogenation of the Δ⁴-double bond in various steroids has been effected in high yields with *Bacillus putrificus*[127]:

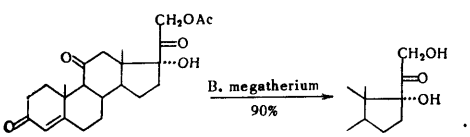


Weisz and his collaborators[34] noticed that incubation of deoxycorticosterone with *Ophiobolus herpotrichus* may induce the hydrogenation of the double bond. Using *Streptomyces griseus*, Vischer and Wettstein recently[128] carried out a stepwise reduction of a Δ⁴-3-oxo-steroid, first into an unsaturated ketone, and then into an alcohol.



7. Hydrolysis

The microbiological saponification of acetyl groups usually proceeds readily. It can be effected, for instance, by means of *Flavobacterium dehydrogenans*[129], or, as in Suvorov's laboratory, using *Bacillus megatherium*, which is specific in the deacetylation of 21-acetates[130]:



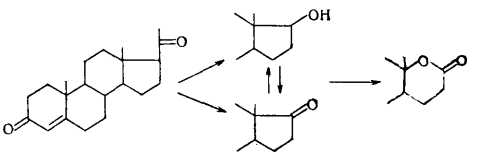
In many cases deacetylation proceeds alongside the main reaction characteristic of the given microorganism. Zetsche[131] showed that during incubation of the 21-acetate

derived from Reichstein's substance S with *Curvularia lunata* the rate of deacetylation exceeds the rate of hydroxylation of substance S, and that only the saponified diol is capable of undergoing hydroxylation. This is consistent with the results of Eroshin and Krasil'nikov[80] who incubated hydrocortisone 21-acetate with *Cunninghamella elegans*.

Certain microorganisms produce enzymes capable of hydrolysing steroid saponins to sapogenins and sugar[132].

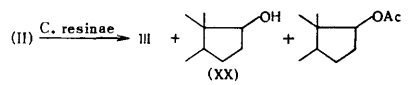
8. Cleavage of Carbon–Carbon Bonds

It has already been mentioned[105] that certain microbiological reactions, especially dehydrogenation, may be accompanied by the modification of the steroid D ring to a lactone. Microbiological formation of lactones can also proceed independently. Čapek and his collaborators[133] used microorganisms such as *Aspergillus orizae*, *A. chevalieri*, *Penicillium citrium*, etc. to carry out progesterone transformations according to the following scheme:



Microbiological degradation of the side chain in pregnane steroids, resulting in a 17-oxo- or 17β-hydroxy-group, is quite common. By incubating progesterone (II) with *Cylindrocephalum aureum* QM 610, Shull and Routien[134] obtained a mixture of androstenedione (III) and testosterone (XX). On incubating progesterone with *Neocosmospora vasinfecta*, they obtained 69% of testosterone[135]. Several other microorganisms are capable of inducing such degradation of the side chain[136].

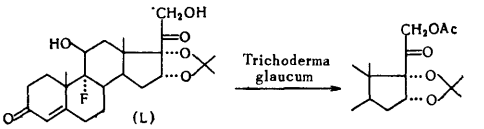
A paper appeared quite recently on the microbiological formation of steroid 17β-acetates. Incubation of progesterone with *Cladosporium resinae*[137] gave androstenedione, testosterone, and testosterone acetate:



Under the same conditions testosterone does not form testosterone acetate. Using [21-^{14}C]progesterone, it was shown that the formation of testosterone acetate is in fact an intermediate step in the degradation of the side chain.

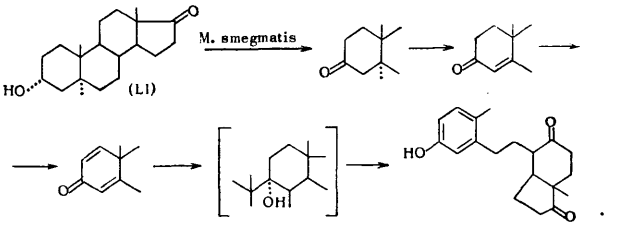
This path of the microbiological formation of acetates is obviously not the only one possible. Incubation of androstenedione (III) with *Saccharomyces fragilis* (ATCC 100222)[138] resulted in a mixture of testosterone and testosterone acetate. In this case it is difficult to guess the source of carbon used in the formation of the acetoxy-group.

The 21-acetates were isolated in high yields after incubation of 16α,17α-isopropylidenedioxysteroids with *Trichoderma glaucum* (Lederle No. Z-636)[139]. The yield of the corresponding 21-acetate obtained from 11β,21-dihydroxy-16α,17α-isopropylidenedioxy-9α-fluoropregn-4-ene-3,20-dione (L) was 70%:



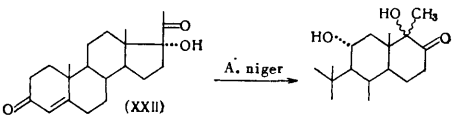
Incubation of steroids not containing the 16α,17α-isopropylidenedioxy-group with the same culture gave no acetylation products.

Among papers describing the cleavage of a carbon–carbon bond in the steroid skeleton that of Schubert and his collaborators[140] is worthy of note. On the basis of their kinetic data, they suggested the following scheme for the transformations of 3β-hydroxyallopregnan-17-one (LI) induced by *Mycobacterium smegmatis*:

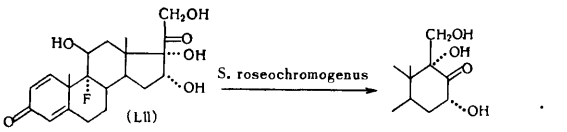


This mechanism for the opening of the B ring of the steroid skeleton has been confirmed by the work of Dodson and Muir[114,141,142].

The isolation[31] of a D-homosteroid after the incubation of 17α-hydroxyprogesterone (XXII) with *Aspergillus niger* is rather curious:



No less so is the formation of a D-homosteroid on incubation of triamcinolone (LII) with *Streptomyces roseochromogenus*:



Goodman and Smith[144,145] recently proved that D-homo-isomerisation in this case is caused by an excess of iron ions in the incubation medium, and not by the biological processes involved.

III. SOME ASPECTS OF THE MECHANISMS INVOLVED IN MICROBIOLOGICAL REACTIONS OF STEROIDS

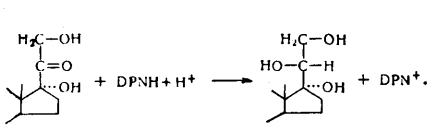
There is no doubt whatsoever that the microbiological transformations of steroids are caused by the enzymic systems produced by the microorganisms. Such systems contain several enzymes, each being responsible for one

definite step in the reaction. In certain cases the enzymes involved have been obtained in a reasonably pure state. The Talalay team is carrying on a systematic study of enzymes from the soil bacterium *Pseudomonas testosteroni*, which is capable of oxidising testosterone (XXVI) to androstenedione (III)[146]. They isolated 3β-, and 17β-dehydrogenases[147], and Δ^1- and Δ^4-5α-dehydrogenases[148] of high purity. In 1960 a paper appeared reporting the crystallisation of Δ^5-3-oxo- and Δ^4-3-oxo-isomerases[149].

The reason why microorganisms cause transformations in the steroids they come in contact with appears incomprehensible at first sight. In the overwhelming majority of cases microorganisms do not require steroids as food and they are perfectly capable of carrying out their metabolic functions in the absence of steroids. It is true that certain microorganisms contain and metabolise sterols[150], but their formation has no connection with the enzymes involved in steroid transformations. Vischer and Wettstein[151] showed that the ergosterol isolated from 11α-hydroxylating fungi of the *Rhizopus* species does not contain any 11-hydroxy--derivatives. Work done in recent years has thrown some light on this subject. Capek[152,153] established that the introduction of steroids, *e.g.* progesterone, into a culture of *Rh. nigricans* growing in a nutrient medium suspends the growth and respiration of the microorganism during the transformation of the progesterone into 11α-hydroxyprogesterone, while the introduction of 11α-hydroxyprogesterone has no such effect. Lester[154] showed that the growth of *Neocosmospora crassa* is inhibited by the addition of deoxycorticosterone into the culture medium. Maxwell and his collaborators[155] found that the addition of steroids (androstenedione, deoxycorticosterone, progesterone, and androstanedione), in a concentration of 0.13 mg ml^{-1}, inhibits the growth of *Saccharomyces fragilis*. Androstenedione is thereby transformed into testosterone acetate. It could be therefore that certain steroids act as poisons for a given microbial species, which subsequently adapt themselves by producing enzymes capable of catalysing the transformation of the steroids into a non-toxic form. There are also indications that the microorganism absorbs the steroid and discharges its transformation products into the culture medium[146,151].

The work of Talalay[147], Peterson[156], and some others has shown the adaptive character of the formation of enzymes capable of transforming steroids.

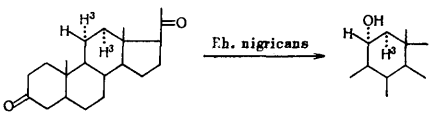
A great deal of interesting information which would help in explaining the enzymic mechanism of the biological steroid transformations could be expected from studies of the "fine" structure of enzymic reactions, the role of cofactors, and so on. Unfortunately, consideration of such work, *e.g.* Refs. 157 and 158, is outside the scope of this review. For detailed information about this subject, the reader is referred to the interesting review by Vischer and Wettstein[99]; only a few most recent communications will be considered here. Hübener and Lehmann[159] established that the reduction of 20-oxo-steroids by the action of an enzyme isolated from *Streptomyces hydrogenans* requires the presence of diphosphopyridine nucleotide and proceeds as follows:



A stoichiometeric amount of DPN is thereby oxidised.

It is remarkable that 2,4-dinitrophenol, which acts as an inhibitor of the most diverse processes in a living organism (processes associated with energy transfer), has no effect, even in large concentrations, on the hydroxylation of progesterone induced by *Curvularia lunata*[160].

In their study of the 7α-, 11α-, and 11β-hydroxylations of labelled steroids Peterson and his collaborators[161,162] showed that the Walden inversion did not take place in the process, and that the hydroxyl group assumed the position of the hydrogen atom, thus leaving the configuration unchanged:

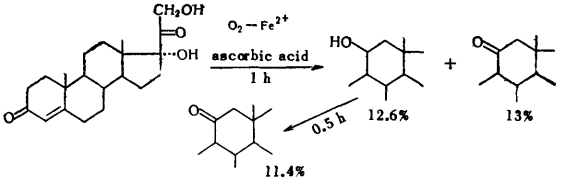


Schmidt-Thome and his collaborators[163] found that the addition of small amounts of a *Rh. nigricans* culture to the culture medium during the dehydrogenation of corticosteroids with *Bacillus subtilis* increases the yield of Δ^1-dehydro--derivatives, although *Rh. nigricans* itself is incapable of inducing dehydrogenation. It was also found that the addition of small amounts of certain steroids favours dehydrogenation. Murray[164] found that the addition of 0.1 mg of progesterone per 20 mg of cortisone undergoing dehydrogenation with *Septomuxa affinis* had a favourable effect on the reaction. The additives may possibly play a role of cofactors catalysing the hydrogen transfer in the substrate–enzyme system.

Zetsche[165] made a thorough investigation of steroid hydroxylations with 15 strains of *Curvularia*, and showed by experiments with filtered mycelial mass that the native liquid of *Curvularia* does not contain steroid hydroxylases. From a study of the effect of the addition of NaCN, NaN_3, 2,4-dinitrophenol, and NaF, he concluded that hydroxylation with *Curvularia* requires enzymes containing heavy metals, capable of catalysing the transfer of molecular oxygen to the steroid molecule. Hydroxylation requires Fe^{2+} ions, while Cu^{2+} ions are hardly needed at all.

From the difference in the effect on hydroxylation of various vitamins such as nicotinamide, pantothenyl alcohol, and vitamins B_1, B_2, and B_6, Zetsche concludes that hydroxylation is catalysed by flavin enzymes. According to him, the strongly lipophilic steroids block the active cell centres of the microorganism, and as hydroxylation lowers the lipophilic nature of the steroid, it consequently serves as a protective function of the microorganism. Hydroxylases from *Curvularia* are not produced by adaptation to steroids, and Zetsche accounts for their presence by the fact that under natural conditions the microorganism has to protect itself from similar, although non-steroid, lipophilic material.

A brief mention may be made of the interesting oxidation in systems modelling the multienzyme systems of microorganisms. A system consisting of ascorbic acid, iron sulphate, and molecular oxygen in pH 7.2 phosphate buffer, at 37°, acts upon Reichstein's substance S by inducing stereospecific hydroxylation, similar to the biological one, followed by the oxidation of the hydroxyl to an oxo-group[166]:



In concluding this section, it must be emphasised that, although microorganisms are capable of effecting a wide variety of transformations of various substrates, in certain cases they also display high specificity. Incubation of Reichstein's substance S with *Bacillus megatherium* yields 50% of the 15β-hydroxy-derivative, although such derivatives could not be obtained from prednisone and prednisolone[66]. *Absidia regnieri* cultures oxidise the 11β-hydroxy--group and introduce a 14α-hydroxy-group into corticosterone, but are without effect on epicorticosterone and hydrocortisone[95]. *Synceyphalostrum racemosum* induces hydroxylation of progesterone at the 7α-, 14α-, and 15β--positions, but has no effect on hydrocortisone and 6β-, 11α-dihydroxyprogesterone even on prolonged incubation[20]. These are only a few from a long list of such examples.

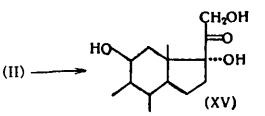
IV. APPLICATION OF MICROBIOLOGICAL REACTIONS

It is evident from this brief survey of the microbiological steroid transformations that there are prospects of many such reactions being used in the steroid hormone industry. Many are already being used as intermediate stages in the production of hormones. In the Soviet Union 11α-hydroxyprogesterone is obtained on a semiindustrial scale by incubation of progesterone with *Rh. nigricans*[167]. Microbiological 11β-hydroxilation is of great industrial importance, since introduction of an oxygen-containing functional group in the 11-position by chemical means is extremely complicated. Hydroxylation of steroids in positions 16α and 21, and dehydrogenation in the 1,2-position, makes it possible to obtain highly active hormone preparations. "Chemical" dehydrogenation by means of SeO_2 yields hormones contaminated with selenium, which rules out their clinical application. Microbial dehydrogenation competes with the chemical reaction not only in this respect, but also as regards yield.

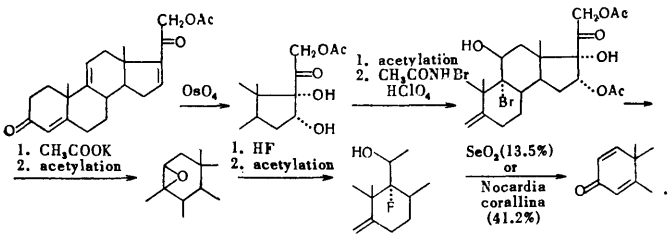
Industrial application of microbiological reactions is partly limited by the need to use large amounts of solvents to separate steroids from the fermentation broth, but this could be overcome by the development of a technological process for their recovery.

Of great interest to industry are reactions with mixed microbial cultures, which are able to induce hydroxylations at different positions of the molecule in one stage.

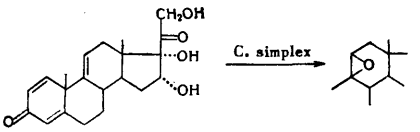
On incubating progesterone with three microbial species simultaneously, *i.e. Wojnowicia graminis*, *Trichoderma viridae*, and *Curvularia lunata*, McAleer[168] obtained hydrocortisone:



The significance of microbiological reactions is not limited to their industrial application. In the last few years they have often been used by chemists in synthetic projects in cases when they increased the yield of a particular stage, or helped to reduce the number of stages. In their synthesis of 16α-hydroxy-9α-fluoro-steroids Bernstein and his collaborators[169] chose microbiological dehydrogenation in preference to dehydrogenation by SeO_2, thus increasing the yield of that stage from 13.5 to 41.2%:



On incubating $\Delta^{9(11)}$-steroids with *Corynebacterium simplex*, they obtained the 9β,11β-epoxide:



This is only one of many examples of this kind.

Microbiological reactions are very important in establishing the structure of new natural and synthetic steroids. For instance, Fried[170] demonstrated the structure of 16α--hydroxyprogesterone by its conversion to 16α-hydroxytestosterone, after the microbiological degradation of the side chain. To prove the structure of 14α-hydroxyprogesterone, it was converted by a microbial reaction to 14α-hydroxyandrost-4-en-3,17-dione. Neher and Wettstein[171] employed microbial reactions for establishing the structure of compounds isolated from adrenal steroids, *e.g.* 6β-hydroxycorticosterone, 19-hydroxycorticosterone, etc. Talalay and Hurlock used purified steroid dehydrogenases for analytical assay of steroids in urea[172].

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NUCLEAR MAGNETIC RESONANCE IN HIGH POLYMERS

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I. INTRODUCTION

The method of nuclear magnetic resonance (NMR) was applied to polymers shortly after its discovery[1,2]. Since reliable and comparatively simple NMR spectrometers have become available in many countries, the number of experiments in this field is increasing rapidly.

The NMR method is especially valuable in its application to the investigation of stereospecific polymers and in the study of microstructure and molecular motion in polymers[3-6].

The purpose of the present review is to discuss the main trends in the investigation of high polymers by means of NMR. We assume that the reader is familiar with the principles of the method which is described in books[7-13] and in review articles published here[14-20] and abroad[21-24]. Reviews discussing the application of the NMR method to polymers have also been published[25-36].

In discussing NMR phenomena in polymers we must keep in mind certain special features of structure and properties of polymeric substances. There are two structural units in polymers, namely chain molecules and repeat (monomeric) units; "superstructures" can also be formed[37,38].

In the crystalline polymers there are non-ordered non-crystalline regions, non-crystallised packets, so that it is possible to have a "gaslike" structure with the chain centres forming crystalline domains with random orientation[39]. In glasslike polymers individual structural units may retain freedom of reorientation down to very low temperatures. A polymer in a viscoelastic state may be considered glasslike as far as whole chain molecules are concerned but liquid-like if only individual units are considered. Obviously the spectrum of a solid polymer will then be like that of a crystal or a liquid, depending on experimental conditions.

A very important property of polymers, which has to be taken into account when discussing the NMR data, is the complex nature of their relaxation processes. Dielectric and dynamic-mechanical measurements show that polymers do not have a single correlation frequency of molecular motion but rather a distribution of frequencies which in certain cases may be very broad. Therefore, the simple theory of nuclear magnetic relaxation, whose applicability to small molecule substances has been confirmed in many cases, may be applied to polymers only with reservations; sometimes this simple theory is not even in qualitative agreement with experiment.

The results obtained for the longitudinal, T_1, and the transverse, T_2, relaxation times in polydimethylsiloxane[40]

can be used as an example of a very pronounced divergence between theory and experiment. At the minimum of T_1 it was found that $T_1/T_2 \simeq 1300$, while the theory predicts $T_1/T_2 \simeq 2$. It is not surprising then that the interpretation of NMR data in high polymers is difficult. Often from the same experimental results different conclusions may be deduced (*e.g.* in the investigation of vulcanisation of rubber[30,41]).

These difficulties will probably be resolved with further developments of theory (see for example Ref. 42), and also because of the rapid progress in experimental techniques such as the use of high-resolution spectrometers for polymer solutions and melts, investigations of a large number of polymer homologues over a wide range of temperatures, application of spinning of a solid sample[43], isotopic substitution, study of oriented polymers, strained polymers, etc. Naturally, the NMR method should not be used alone but in conjunction with other physical and chemical methods.

II. THE STUDY OF THE STRUCTURE OF POLYMERS BY NMR

The NMR method has the advantage that it can give information about the location of protons, which cannot be obtained by the X-ray method commonly used in structural studies. At the same time we must remember that the amount of information contained in an NMR spectrum of a solid is rather small. It is not possible to determine even slightly complicated crystal structures merely on the basis of NMR data (*e.g.* second moment of the NMR line and its dependence on the crystal orientation in the magnetic field). Nevertheless the NMR spectrum can provide decisive evidence when, for example, we have to decide between two or more possible structures. In certain cases when the substance contains small groups of nuclei, *e.g.* protons in the water of crystallisation in gypsum[44] or in Rochelle salt[45], it is possible to determine the directions and magnitudes of interatomic vectors. The work of Aleksandrov[46-48] can serve as a good example of a successful analysis of crystal structure with the aid of NMR.

1. Crystalline Polymers

Even from the very early NMR experiments on polymers it was apparent that crystallisation of polymers strongly influences the magnitude and the shape of the signal. Holroyd *et al.*[49] showed that on rapid cooling of natural rubber to -35°C the signal remains large, since crystallisation does not take place, but when the sample is held at -25°C, close to the optimum crystallisation temperature, the line broadens and the signal becomes weaker.

The effect of crystallinity on line width was demonstrated for polytetrafluoroethylene[50]. Attention was drawn to the connection between the NMR spectrum and crystallinity by the work of Wilson and Pake[51,52], which showed that in a certain temperature interval the ^1H line in polyethylene and the ^{19}F line in polytetrafluoroethylene has a two-phase structure (Fig. 1). For temperatures above 0°C the line has two components, narrow and broad, as indicated by the dotted line in Fig. 1. Wilson and Pake showed that the narrow line corresponds to the amorphous part and the broad line to the crystalline part of the sample. In the absence of saturation effects the area under the line is proportional to the number of nuclei. Therefore, we can say that the ratio of the areas under the lines corresponding to

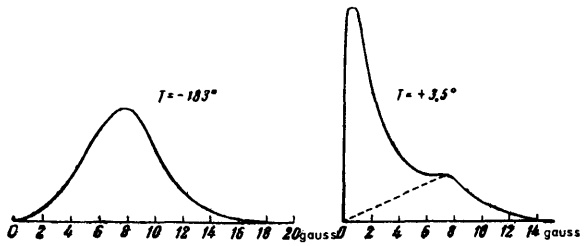


Fig. 1. Derivative of NMR absorption curve for polyethylene[51] (only right-hand half of the curve is shown).

the broad and the narrow line components is equal to the ratio of the numbers of nuclei in the crystalline and the amorphous regions of the sample. The area under the first derivative of the line, shown in Fig. 1, corresponds to the first moment of the line. Hence, it is possible to determine the "degree of crystallinity". Application of this principle to polyethylene at room temperature proved to be highly successful. For a number of polyethylenes[53] with a degree of crystallinity ϵ between 59–93%, the disagreement between ϵ as determined by X-ray and NMR methods was less than 1.8%; the NMR method had the advantage that the results were insensitive to orientation and had a better reproducibility. Smith[54] used the NMR method for a number of polyethylenes and ethylene copolymers with propene and but-1-ene. In the plot of crystallinity *vs.* specific volume the NMR points and the X-ray points fall on the same straight line; the infra-red measurements also give very similar values of ϵ. The composite line method for determining the degree of crystallinity was also used by Collins[55] in his studies of crystalline recovery of quenched polyethylene, by Fujiwara[56] for polyethylene and poly(vinyl chloride), by Fuschillo[57] for a number of polyethylenes, and by Nishioka[58] for polypropylene.

Attempts to apply this method to determine the crystallinity of other polymers and to use it over a wide range of temperatures did not give satisfactory results. Fuschillo and Sauer[59] note that for polyethylene and nylon over a wide range of temperatures the percentage of crystallinity as determined by the NMR method does not agree with the X-ray results. This is further confirmed by measurements made on irradiated polymers, *i.e.* though crystallinity is reduced to zero by irradiation the line remains broad due to the formation of cross-links. Subsequent experiments by Sauer *et al.*[60] on polybutene and polypropylene, and by Slichter and Mandell[61] on irradiated polyethylene, with the method of Wilson and Pake also gave values of crystallinity which were in disagreement with those obtained from X-ray and density measurements.

Slichter and McCall[62] and Fuschillo *et al.*[63] explained this discrepancy. In each of the three methods employed to measure crystallinity, the X-ray specific volume, and the NMR method, different physical quantities are being measured. The X-ray analysis obviously enables us to determine the degree of ordering in the sample, the specific volume depends on the closeness of packing; whereas the NMR signal does not depend on configuration of the chains and groups but on the nature of their motion. If a solid contains certain groups in motion, then the NMR line narrows as a result of averaging of local magnetic fields;

the narrowing occurs when the correlation time is smaller than 10^{-4} sec. If the sample contains regions (crystalline) with $\tau_{cc} \gg 10^{-4}$ sec and regions (amorphous) with $\tau_{ca} \ll \ll 10^{-4}$ sec, then it is possible to consider the sample as a two-phase system. The resulting line is compound and from the ratio of its components it is possible to derive the degree of crystallinity. Schematically we can represent other possible cases as shown in Fig. 2.

Curves *a*, *b*, *c*, and *d* represent the change in the shape of the absorption line as the temperature is increased: (*a*) $\tau_{ca} > 10^{-4}$ sec and $\tau_{cc} > 10^{-4}$ sec (low temperature), both phases give a broad line; (*b*) $\tau_{ca} \simeq 10^{-4}$ sec and $\tau_{cc} > 10^{-4}$ sec, certain segments or groups in the amorphous phase begin to move, and the curve shows an inflection; (*c*) $\tau_{cc} \gg 10^{-4}$ sec $\gg \tau_{ca}$, the amorphous phase has a narrow line, while the crystalline phase has a broad line; (*d*) $\tau_{cc} < 10^{-4}$ sec and $\tau_{ca} \ll 10^{-4}$ sec (high temperature), there is appreciable motion in both cases, even below the melting point, resulting in a single narrow line.

Obviously, the determination of crystallinity by the NMR method is possible only in case *c*. The condition that $\tau_{cc} \gg 10^{-4}$ sec $\gg \tau_{ca}$ can be satisfied only at a certain temperature; in some polymers, such as natural rubber[41], this condition is not satisfied at any temperature, because the line does not have any structure. Slichter and McCall[62] found that for linear polyethylene the NMR method gives a constant value of ϵ, in agreement with other methods, between 240° and 300°K, but for branched polyethylene the apparent value of ϵ decreases rapidly with temperature. Fuschillo *et al.*[63] compared the percentage of crystallinity of polyethylene (with $CH_3/CH_2 = 0.2$, and $M_n = 25\,000$) determined by NMR and density measurements. The two methods give the same value of ϵ only over a limited range of temperatures.

The difficulties associated with the determination of crystallinity by NMR arise also from the nature of crystalline polymers, which consist in fact of a number of crystalline regions. Hyndman and Origlio[64] recorded NMR spectra of parallel bundles of polyethylene fibres, oriented at various angles to the field (Fig. 3). In addition to the narrow and broad components, there is a third component giving rise to the middle peak in Fig. 3*a*. After annealing the third peak disappears. The authors conclude that the third component corresponds to amorphous regions which are oriented in drawing of the fibres. Miller[65], using a number of methods, including NMR, showed that when

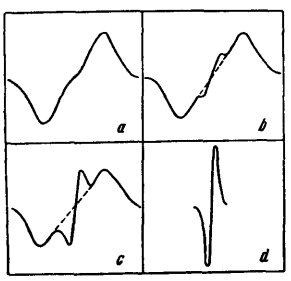


Fig.2. Dependence of NMR line shape on correlation times in a two-phase system[62].

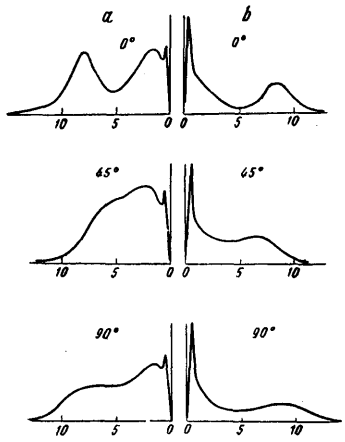


Fig.3. NMR spectrum of a bundle of polyethylene fibres oriented at various angles w.r.t. the field: *a*) cold-drawn; *b*) annealed[64].

molten polypropylene is poured into cold water one obtains a substance which is intermediate between crystalline and amorphous polymers. This he calls a "non-crystalline polypropylene" and concludes that it has a helical chain structure, but with little transverse order. Slichter[66] also observed this intermediate stage in the case of cold-drawn polyethylene fibres. The analysis of X-ray data and of the dependence of the second moment of the NMR line on temperature indicate that in these samples there are regions where chains are packed in a pseudohexagonal lattice, but configurational disorder remains due to the random orientations of zig-zag chains around the axes. Such structures may be considered as crystalline, but with major lattice imperfections. NMR can also reveal lattice defects in irradiated polyethylene[61] and in heat-treated polyethylene[67]. Comparative studies of polypropylene and polybutene by NMR and dilatometric methods over a wide range of temperatures[68] show that in polybutene the crystals are less perfect than in polypropylene. Therefore in a number of cases it is incorrect to describe the degree of ordering with a single parameter such as the "percentage of crystallinity". According to Kitaigorodski[5], this concept does not have any precise physical meaning. Apparently, the ratio of areas under the broad component and under the whole line, N_c/N, should be called an "index of high-frequency rigidity" of a polymer rather than the "percentage of crystallinity"[59,69]. If this index is high, the polymer is rigid and glasslike. This will be true whether the large value of N_c/N is due to high crystallinity, cross-linking, low temperature, hydrogen bonding, or dipolar effects. The value of N_c/N indicates to what degree the thermal motion of chains overcomes inter- and intra-molecular constraints.

In this way measurements of the relative intensity of the two components of a compound line can provide us with valuable information about the structure of the polymer. This method was used extensively in studies of the mechanism of the effects of radiation[70,71] and on polymers and of their degradation[72].

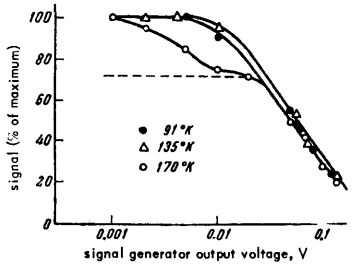


Fig.4. ^{19}F absorption curves at several temperatures in polytetrafluoroethylene[77].

If the line has a structure similar to that shown in Fig. 2*c*, then the "amorphous" and the "crystalline" components can be fairly accurately resolved simply by inspection. If, however, the derivative curve does not have distinct narrow and broad components, then special methods must be used. Urman[72], working under the direction of M.B.Heiman, G.I.Likhtenshtein , and Iu.S.Konstantinov, used the method of linear anamorphs to resolve the NMR line of polypropylene[73].

Other authors[74,75] in determining the two components, assume that the broad component does not vary with temperature and that it is given by the resonance line obtained at very low temperatures (below -150°C) when all motions are hindered. In polyethylene[76] this line shape resembles the line calculated for a proton pair.

The "two-phase" nature of a partially crystalline polymer is revealed not only by the line but also by the presence of two spin–lattice relaxation times, T_1, which can be determined either by the spin echo or the saturation method. For example, in polytetrafluoroethylene at 170°K,[76,77] the relationship between signal amplitude and r.f. field strength (Fig.4) has a step. Initially only 28% of all ^{19}F in the sample is saturated, and the remaining 72% becomes saturated later. For the narrow line (amorphous part) with $T_2 = 5 \times 10^{-5}$ sec, saturation occurs at a lower strength of the r.f. field than for the broad line with $T_2 = 0.9 \times 10^{-5}$ sec. The area under the narrow component is also close to 30% of the total area, *i.e.* the degree of crystallinity is 70%. As the temperature is lowered the relaxation times in the two phases become equal and at 135°K the usual saturation curve is obtained.

2. Stereoregularity

The study of the effect of stereochemical structure, *i.e.* stereoregularity, on properties of polymers presents one of the most pressing problems, as pointed out by Vol'kenshtein[78]. The NMR method can be used in this study. Here we shall consider only experiments on stereospecific solid polymers; some of the very interesting investigations of the stereochemical structure of macromolecules in solution will be discussed in Section V.

Bazhanov *et al.*[78] studied the stereoregularity of poly(methyl methacrylates). NMR spectra were recorded, between room temperature and 200°C, for five poly(methyl methacrylate) samples, two of which were atactic, in the form of technical Plexiglas obtained by radical polymerisation, and the remaining three samples (isotactic) were prepared by catalytic polymerisation.

In isotactic samples the line narrowing occurs much more abruptly and at lower temperatures than in atactic polymers (Fig.5). The higher mobility of chains in isotactic samples is in agreement with their lower glass points. Bazhanov *et al.* note that this rather unexpected result (increase in mobility with higher stereoregularity) implies a complicated relationship between dynamic and structural properties of this polymer.

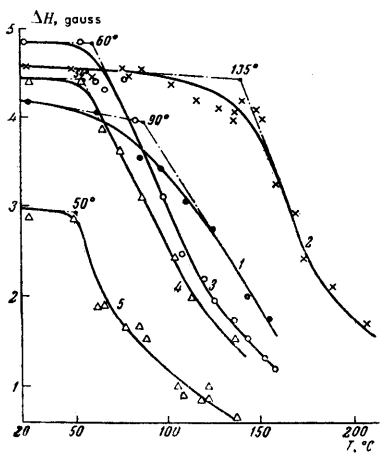


Fig.5. Temperature dependence of line width for poly(methyl methacrylate): 1) and 2) atactic; 3), 4), and 5) isotactic[78].

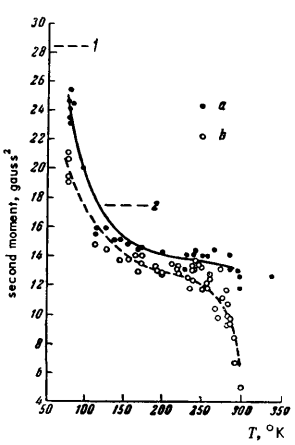


Fig.6. Temperature dependence of the second moment for polypropylene: *a*) isotactic; *b*) atactic. The theoretical values of ΔH_2^2 for rigid (1) and rotating (2) CH_3 groups are also shown[79].

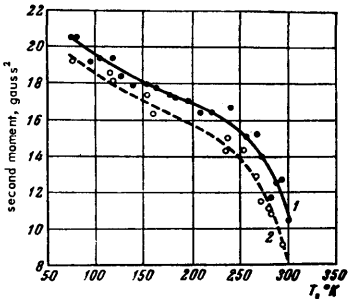


Fig.7. Temperature dependence of the second moment for polybutene: 1) isotactic; 2) atactic[34].

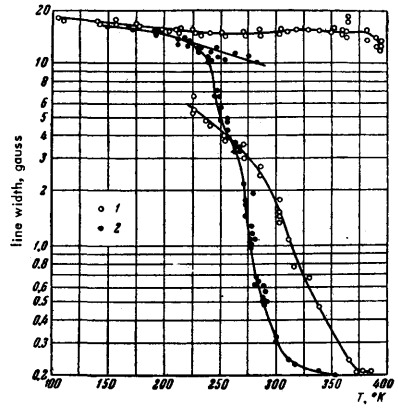


Fig.8. Temperature dependence of line width for polyethylene: 1) linear; 2) branched[86].

The effect of stereospecificity on NMR is more readily explained in other polymers. In their detailed study of polypropylene Slichter and Mandell[79,80] showed that the narrowing of the narrow component on heating occurs at a lower temperature in atactic polypropylene than in the isotactic variety, because crystallites impede motion in the amorphous region. The broad component remains constant; consequently there is little motion in the crystalline region. At low temperature the transition in the second moment in these polymers occurs within the same temperature range (Fig.6). Obviously, the rotation of CH_3 groups is independent of configurational ordering.

Sauer *et al.*[81] found that the decrease in ΔH_2^2, corresponding to the β-transition (glass transition in the amorphous region), for isotactic polypropylene takes place about 30° higher than in the atactic polymer. Nuclear magnetic resonance in isotactic polypropylene and polybutene was also reported by Sauer *et al.*[68]

Slichter[34] found that the second moment is smaller for atactic than for isotactic polybutene (Fig.7). In polystyrene at low temperatures the second moment does not depend on stereoregularity. With increasing temperature ΔH_2^2 (atactic) decreases faster than ΔH_2^2 (isotactic), since motion in the amorphous region, on account of its lower density of packing, is more intense than in the crystalline region. Tyuzyo[82] examined a theory of NMR in stereospecific polymers and obtained theoretical expressions and experimental data for relaxation times in polyethylene and polypropylene.

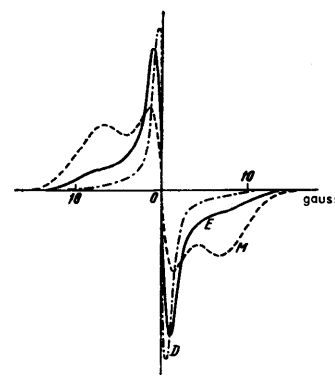


Fig.9. NMR line shape for three polyethylene samples at 20°C: *M*) linear; *E*) and *D*) branched[88].

3. Chain Structure

Chain structure [combination of the configurational order of repeat units (the way they are linked up) and of the degree of branching], which affects the density of packing and the mobility of molecular groups in polymers, should be reflected in NMR spectra of solid polymers. For asymmetric repeat units, the second moment of the "head-to--head" chain should be different from that of the "head-to--tail" chain. Thus, the chain structure can be determined by a comparison of experimental and theoretical values of ΔH_2^2.

High-resolution NMR spectra of polymers in solution also may be used to determine uniquely the configurational order of repeat units[83,84]. We shall consider this question in more detail later.

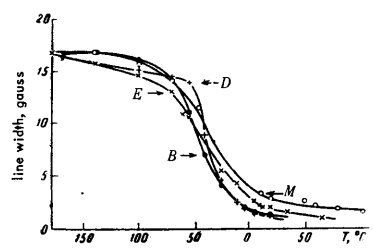


Fig.10. Temperature dependence of line width for four polyethylene samples: *M*) linear; *B*), *D*), and *E*) branched[88].

A number of experiments on polyethylene[57,66,85,86] indicate that in the branched polyethylene the mobility of spins is higher and the line narrower than in the linear polymer (Fig.8).

Peterlin *et al.*[87,88] undertook a special study of the degree of branching and crystallinity of polyethylene using dilatometric and NMR methods. The large difference in line shapes at room temperature is shown in Fig.9; similar differences are observed also at -170°C. The residual intensity of the narrow component at -170°C is proportional to the CH_3/CH_2 ratio in the polymer. The correlation frequency ν_C can be deduced from the narrowing of the line with temperature (Fig.10). In linear polyethylene the slope of $\log \nu_C$ *vs.* $(1/T)$ corresponds to an activation energy of 2.8 kcal mole^{-1}. For the branched polyethylene, there are two straight lines, intersecting at -63°C, corresponding to activation energies of 2.0 and 5.8 kcal mole^{-1}.

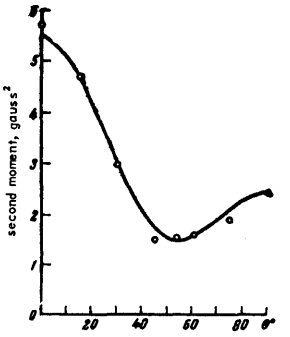


Fig.11. ΔH_2^2 as a function of θ, the angle between polytetrafluoroethylene fibres and the direction of the magnetic field[90].

4. Orientation

The NMR signal is strongly affected by any change in the orientation of polymer molecules, such as occurs in drawing of fibres. Ward[89] observed that in poly(ethylene terephthalate) and in a number of other polyesters the second moment increases with an increase in the degree of orientation; apparently, in stretched oriented polymer films molecular motion is considerably reduced. An analogous effect, *i.e.* increase in the line width on cold drawing, is observed in linear polyethylene[66], while in branched high-pressure polyethylene, there is no significant difference between NMR signals of unoriented and stretched samples.

Further opportunities for studying the structure of polymer fibres and films are furnished by the dependence of the NMR signal on the angle between the axis of orientation and the direction of the magnetic field. In this connection we have to distinguish between two cases, one of a rigid oriented lattice and the other of rotation of an interatomic vector around an axis. If the sample consists of weakly interacting pairs of atoms, and the interatomic vector is perpendicular to the molecular axis, then the dependence of the second moment on the angle θ between the molecular axis and the magnetic field is given by

$$\Delta H_2^2 = \tfrac{5}{4}(\Delta H_2^2)_{\text{isotr.rigid}}\left(\tfrac{27}{8}\sin^4\theta - 3\sin^2\theta + 1\right), \qquad (1)$$

where $(\Delta H_2^2)_{\text{isotr.rigid}}$ is the second moment of the rigid lattice in the absence of molecular orientation.

McCall and Slichter[86] measured the second moment for polyethylene fibres at room temperature. For the linear polyethylene, the experimentally determined dependence of ΔH_2^2 on θ is close to that given by theory if a certain degree of mobility of the chains, namely harmonic oscillations with an angular amplitude of 15° are allowed. For the branched polyethylene, the discrepancy between the experimentally and theoretically determined dependence of ΔH_2^2 on θ is much larger than in the linear polymer.

When molecules of the sample are oriented and interatomic vectors, perpendicular to the molecular axis, rotate about the axis with a frequency $\gg 10^4$ c/s, the variation of the second moment with θ is given by

$$\Delta H_2^2 = \tfrac{5}{4}(\Delta H_2^2)_{\text{isotr.rigid}}\,\tfrac{1}{4}(3\cos^2\theta - 1)^2. \qquad (2)$$

Fig.11 shows the change in ΔH_2^2 for polytetrafluoroethylene at room temperature[90]. The continuous curve is derived from Eqn.(2), with the origin and the scale on the ordinate axis chosen such that the experimental and the theoretical values at $\theta = 0°$ and 90° coincide. The remaining experimental points also fall close to the theoretical curve. In contrast with theory, the second moment at $\theta = 54°$ is not equal to zero, which implies incomplete orientation of molecules in the sample. Sometimes the NMR line of oriented polymers may have a compound structure as in the case of cold-drawn polyethylene fibres discussed earlier (see Fig.3).

5. NMR in Strained Polymers

NMR measurements in strained polymers have been done so far only in natural rubber. Experiments with vulcanised natural rubber subjected to moderate elongation (70%) did not reveal any appreciable change in the NMR spectrum[41]. However, Cohen-Hardia *et al.*[91] showed that the temperature variation of T_2 depends on elongation (Fig. 12). At low temperatures (between -20° and -30°C) T_2 is longer for stretched samples, and at high temperatures (between 10° and 20°C) stretching decreases T_2. For elongations between 70 and 300% and temperatures between -10° and 10°C, the slope $\Delta T_2/\Delta T$ decreases linearly with elongation. The authors

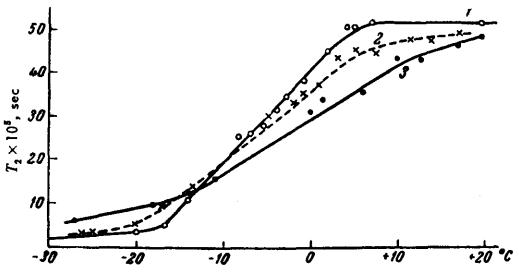


Fig.12. Temperature dependence of the transverse relaxation time T_2 for natural rubber at various degrees of elongation[91]: 1) 10%; 2) 170%; 3) 300%.

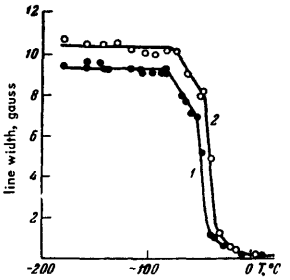


Fig. 13. Temperature dependence of line width for natural rubber: 1) unstretched; 2) with 500% elongation[92].

do not give any theoretical explanation of the observed effect. Lösche[27] assumes that this effect is associated with a decrease in the molecular spacing in stretched rubber; Oshima and Kusumoto[92] observed nuclear magnetic resonance in natural rubber subjected to a large elongation (500%) over a wide range of temperatures (Fig. 13). Between room temperature and -15 °C elongation does not affect the line width δH. As the temperature is lowered further, δH increases between -38° and -52 °C for unstretched samples and between -30° and -45 °C for stretched samples; it appears that the orientation of molecules hinders segmental motions. At low temperatures the second moment of the line is 20.3 gauss^2 and 18.5 gauss^2 in stretched and unstretched samples respectively. Slichter[30] and Powles[28] think that the increase of the second moment with elongation arises from closer packing of molecules resulting in a reduction of interproton distances. Vol'kenshtein[6] notes that this explanation can hardly be correct, since there is practically no change in density of rubber with elongation.

Probably more detailed information could be obtained by examining NMR in strained samples with different orientations between the axis of elongation and the magnetic field.

The effect of stretching on nuclear magnetic resonance in rubber is discussed by Tyuzyo[93].

6. The Effect of Fillers

Introduction of fillers into high polymers, for example, carbon black into rubber, is a commonly used method for achieving certain desirable properties of materials. In view of this even in the very early (1947) NMR experiments on polymers[94], such as natural rubber and its vulcanisates, the effect of loading with carbon black of natural and synthetic rubber was also investigated. Loading was found to produce a slight broadening of the line. Broadening of the line in synthetic rubber GR-S (70 : 30 butadiene–styrene copolymer) on loading with carbon black was also observed by Holroyd *et al.*[49,95]. At room temperature $\delta H \leq 0.19$ gauss for unvulcanised GR-S rubber (inhomogeneity of the magnetic field was 0.19 gauss). For vulcanised polymer δH = = 0.27 gauss; introduction of 30 and 50% of carbon black increased the line width to 0.57 and 0.67 gauss respectively. Mrowca and Guth[96] also reported a slight broadening of the line due to carbon black loading of natural rubber and of a number of synthetic rubbers. Holroyd *et al.*[97] made a detailed study of the effect of loading on nuclear magnetic resonance. In experiments on natural rubber, GR-S, and Hycar OS-10 (50 : 50 butadiene–styrene copolymer) it was found that there is no appreciable broadening on introduction of carbon up to 50%, but the signal decreases slightly. In butyl rubber, loaded with different types of carbon black, the broadening is only a little greater than the experimental error. These authors conclude that very weak physical bonding forces exist between rubber molecules and carbon. Slichter[30] points out that this conclusion is not sufficiently substantiated and suggests that the observed decrease in the signal strength arises from the reduction of the number of protons per unit volume of the sample. Lösche[27] suggests that NMR at very low temperatures, corresponding to the onset of CH_3 group rotation, would give more precise data on the effect of fillers.

III. THE STUDY OF MOLECULAR MOTION IN POLYMERS BY NMR

The properties of solid polymers in the glassy and especially in the viscoelastic state are intimately connected with motions of individual groups and chain segments. The NMR method is particularly well suited to the study of molecular motions; the method was used in one of the first demonstrations of rotation about the bonds in polymer chains[98].

NMR can be used to study molecular motions because they average out local magnetic fields and consequently narrow the line. By recording the NMR spectrum of the sample over a wide temperature range, we can observe "melting" of various molecular motions. Powles[98] notes that NMR measurements can determine in principle the nature of reorienting groups as well as the character and rapidity of their motion.

1. Variation of Line Width with Temperature

As the temperature is increased (or decreased) the line narrows (or broadens) in steps for a number of polymers; each change of δH corresponds to a certain change in the molecular motion. For example, Thurn[36,99] measured the line width of polyisobutene (molecular weight 1.75×10^6) and poly(methyl methacrylate). In polyisobutene (Fig. 14) there are three line-width transitions: at about -100 °C, between -30° and 10 °C, and between 30° and 40 °C. Correlating NMR data and results obtained by other methods, Thurn concludes that the first transition is connected with rotation of CH_3 groups about the axis of symmetry C_3, and the second with the onset of motion of the main chain. The third transition between 30° and 40 °C, observed only for samples of high molecular weight, is apparently associated with motions of large segments of the chain.

In poly(methyl methacrylate) there are four transitions, indicated in Fig. 15 by vertical broken lines. The same transitions were also observed by the dynamic-mechanical method. The transition at 75 °C is due to 0.2% of moisture present in the sample and the remaining transitions are associated with the onset of motion of CH_3 groups, monomeric units, and large segments of the chain.

Line-width transitions are in most cases interpreted in terms of rotational motions of individual groups or segments of the polymer chain. However, if δH continues to

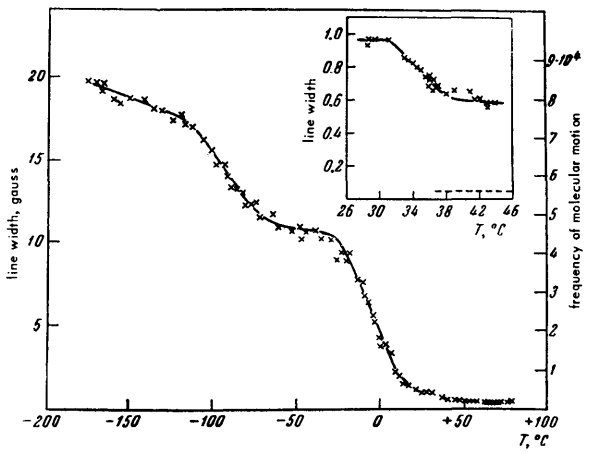


Fig.14. Temperature dependence of line width for polyisobutene[99].

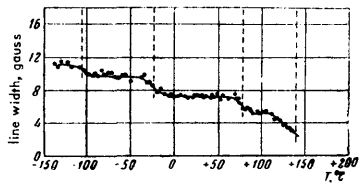


Fig.15. Temperature dependence of line width for poly(methyl methacrylate) containing 0.2% of water[99].

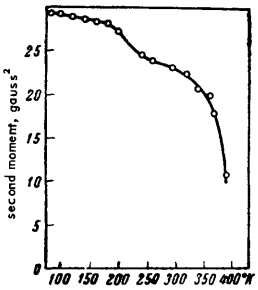


Fig.16. Temperature dependence of the second moment for high-density polyethylene[101].

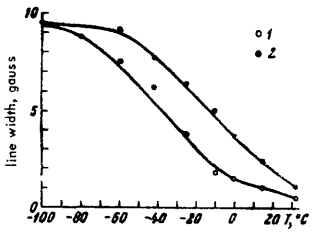


Fig.17. Temperature dependence of line width for polyisobutene: 1) at atmospheric pressure; 2) at 1060 atm.[104]

decrease to very small values (*e.g.* to 0.019 gauss in polydimethylsiloxane at 200°K and above[100]), then translational motion in crystallites must be possible. This unexpected conclusion was confirmed by other methods.

We should remember, however, that for certain polymers, changes in molecular motion, reflected by changes in a number of properties, do not affect the NMR line. For example, in high-density polyethylene[101] appreciable reduction in $\delta H_{max.slope}$ line width occurs only in the region of 200°K. The second moment of the line (Fig.16) exhibits two transitions: at 200°–250°K, due to the onset of cooperative motions of a small number of segments of the chain in the amorphous region of the polymer, and at ~350°K, due to disordering and melting of crystalline regions. In this case the second transition does not affect the line width $\delta H_{max.slope}$ because the maximum of the derivative curve is determined mainly by the magnitude of the narrow component of the compound NMR line, whereas melting of crystalline regions is associated with changes in the broad component.

If the line is compound, the temperature dependence of the line width may depend on the method of measurement. Thus, in polytrifluoroethylene[102] the half-height line width $\delta H_{\frac{1}{2}}$ and the maximum slope line width $\delta H_{max.slope}$ have different temperature dependence resulting in different activation energies and transition temperatures.

At temperatures considerably above the glass transition temperature of the polymer, the line width, as in liquids, is proportional to viscosity and inversely proportional to absolute temperature. A plot of $\log(\delta HT)$ *vs.* $(1/T)$ gives a straight line with a slope which is determined by the activation energy E of the liquid. Collins[103] found that for linear polyethylene at 134°C, E = 8.2 kcal mole^{-1}. For high-pressure polyethylene, the plot of $\log(\delta HT)$ *vs.* $(1/T)$ is curved; this is believed to be due to branching and changes in composition of the amorphous phase upon cooling. The apparent activation energy at high temperatures is 11.8 kcal mole^{-1}, which agrees reasonably well with the value of 12.8 kcal mole^{-1} derived from viscosity measurements above the melting point of the polymer.

Measurements of the temperature dependence of the line width in polymers subjected to different pressures can provide some information about their molecular motions. Nolle and Billings[104] showed (Fig.17) that an increase in pressure from 1 to 1000 atm broadens the line, which implies a reduction in molecular motion. The present author accounts for this effect by the reduction of the free volume in the polymer†.

† Igonin *et al.*[105] gave a direct demonstration of a reduction in molecular motion in polymers with an increase in pressure.

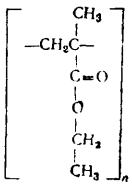
2. Variation of the Second Moment of the Line with Temperature

In polymers the second moment (ΔH_2^2) is the most important characteristic of the NMR line because ΔH_2^2 can be calculated for the rigid lattice as well as for the case of motion of individual molecular groups, so that experiment and theory may be readily compared.

It is convenient to consider the second moment of a polymer to be composed of two parts: the intramolecular contribution, arising from the dipole–dipole interaction of nuclei within a molecule, and the intermolecular contribution, associated with the interaction of nuclei located in different molecules. Since in the Van Vleck expression for ΔH_2^2 the internuclear distance enters to the power of -6, the magnitude of the second moment is determined mainly by the interaction between neighbouring atoms. In view of this, the intermolecular contribution is considerably smaller than the intramolecular one.

An estimate of the intramolecular contribution to the second moment of a polymer chain may be obtained by summing ΔH_2^2 for individual groups. Values of ΔH_2^2 calculated from the Van Vleck expression with the appropriate values of moments and interatomic distances are summarised in Table 1.

For example, a monomeric unit of poly(ethyl methacrylate) has 10 hydrogen atoms, 4 of which are in methylene groups and 6 in methyl groups.



$$\Delta H_2^2 = \tfrac{4}{10}\Delta H_{2(CH_2)}^2 + \tfrac{6}{10}\Delta H_{2(CH_3)}^2 =$$
$$= \tfrac{4}{10} \times 11.2 + \tfrac{6}{10} \times 22.5 =$$
$$= 4.5 + 13.5 = 18.0 \text{ gauss}^2.$$

The experimentally determined value of ΔH_2^2 for poly(ethyl methacrylate) is 21.5–22.0 gauss² (see Table 3). The difference is due to the intermolecular contribution. In certain cases, *e.g.* for polyethylene, this type of calculation cannot be used even as a rough estimate.

The quantity ΔH_2^2 can be calculated more accurately if the configuration of polymer chains is known. This calculation is most readily performed for a flat chain. Usually, however, the chains in crystalline polymers are coiled (as indicated by X-ray data), so that it is necessary to know the coordinates of each atom before any calculation of ΔH_2^2 may be attempted. Theoretical values of the second moment of spiral structures were derived for polyisobutene[106], polypropylene[59,79], and polytetrafluoroethylene[107]. In the amorphous region the polymer chains have many possible spatial arrangements depending on the angle between neighbouring segments (pairs of monomers). The chain conformation may be characterised by a local regularity parameter ξ — the fraction of bonds having the *gauche*-conformation. Miyake[108,109] calculated second moments for a number of amorphous vinyl polymers for the case where the fractions of *gauche*- and *trans*-bonds are ξ and $(1-\xi)$ respectively. In this calculation the following values of interatomic distances were used: C–H 1.09 Å; C–C 1.54 Å; C–F 1.33 Å; C–C 1.74 Å; and the following values of magnetic moments: $\mu_H = 2.793\ \mu_0$; $\mu_F = 2.627\ \mu_0$; $\mu_{Cl} = 0.7893\ \mu_0$, where $\mu_0 = 5.05 \times 10^{-24}$ erg gauss^{-1}. The second moment is given by

$$\Delta H_2^2 = a + b\xi + c\xi^2 + (d + e\xi + f\xi^2) \text{ gauss}^2, \qquad (3)$$

where the values of coefficients a, b, c, d, e, f are given in Table 2. For extended polyamide chains $[NH(CH_2)_mNHCO.(CH_2)_nCO]_p$, the intramolecular contribution to the second moment may be calculated from the following equation[110]:

$$\Delta H_2^2 = [18.5 - 22.7/(m + n + 1)] \text{ gauss}^2. \qquad (4)$$

For $m, n \geq 5$, the error in ΔH_2^2 derived from Eqn. (4) is less than 1%; if the paraffin segments separating amide groups contain less than five C atoms, then Eqn. (4) does not apply.

The intermolecular contribution to the second moment for a rigid lattice may be calculated directly from the Van Vleck equation only if the relative distribution of chains is known. For example, Bateman *et. al.*[111] using X-rays determined the parameters of an orthorhombic lattice in polyethylene terephthalate and other glycol terephthalate polymers and calculated both contributions to the second moment. Slichter[110] made a similar calculation for even-even polyamides (*m* and *n* even), based on X-ray data, and

TABLE 1. NMR second moment of molecular groups.

Group	$-CH_2$	$-CH_3$	$-CF_2$	$-CF_3$
ΔH_2^2, gauss	11.2	22.5	2.1	4.2

TABLE 2. Second moment of amorphous vinyl polymers[108,109].

Polymer	Stereoregularity	Resonance	Coefficients in the equation $\Delta H_2^2 = a + b\xi + c\xi^2 + (d + e\xi + f\xi^2)$, gauss²					
			a	*b*	*c*	*d*	*e*	*f*
Polyethylene $-CH_2-CH_2-$		^1H	18.82	—2.08	0.72	—	—	—
Polytetrafluoroethylene $-CF_2-CF_2-$		^{19}F	7.86	—1.46	0.63	—	—	—
Poly(vinyl chloride) $-CH_2-CHCl-$	isotactic	^1H	13.47	—2.89	1.34	0.06	0.01	—0.02
	syndiotactic	^1H	12.81	—0.90	—0.16	0.08	—0.05	0.03
Polytrifluorochloroethylene $-CF_2-CFCl-$	isotactic	^{19}F	6.08	—2.88	1.29	0.04	0.03	—0.03
	syndiotactic	^{19}F	5.40	—0.84	—0.23	0.07	—0.05	0.03
Poly(vinyl fluoride) $-CH_2-CHF-$	isotactic	^1H	13.47	—2.89	1.34	1.24	0.32	—0.26
	syndiotactic	^1H	12.81	—0.90	—0.16	1.51	—0.50	0.36
	isotactic	^{19}F	4.18	1.08	—0.88	2.50	—4.39	2.60
	syndiotactic	^{19}F	5.10	—1.68	1.19	0.47	1.70	—1.97
Polytrifluoroethylene $-CF_2-CHF-$	isotactic	^1H	3.70	0.96	—0.79	2.83	—4.97	2.94
	syndiotactic	^1H	4.52	—1.50	1.06	0.53	1.93	—2.25
	isotactic	^{19}F	6.08	—2.88	1.29	1.40	0.35	—0.29
	syndiotactic	^{19}F	5.40	—0.84	—0.23	1.71	—0.57	0.40
Poly(vinylidene fluoride) $-CH_2-CF_2-$		^1H	14.93	—3.41	0.98	1.11	0.32	—
		^{19}F	5.99	—2.69	0.56	1.25	0.37	—

TABLE 3. Second moment of the NMR line in polymers.

Polymer	Calculated ΔH_2^2, gauss^2: structure	intra-molecular contribution	inter-molecular contribution	total second moment	Measured ΔH_2^2, gauss^2: temperature, °K	ΔH_2^2	References
1	2	3	4	5	6	7	8
Natural rubber (vulcanised)	rigid structure rotn. of CH_3 group			18.5 11.8	77 225	18.4 13.0	41
Natural rubber (vulcanised) Ditto (elongated 500%)					77—190 77—190	18.3 20.3	92
Natural rubber					90	18	118
Natural rubber					82	18,4	119
Polyisobutene (Vistanex)					91	37	119
Polyisobutene	**rigid flat structure** **spiral structure**	20	4	24 33—40	77	41	106
Polychloroprene-(neoprene W)					82	22.0	119
Polystyrene (degree of polymerisation 4200)	rigid structure	7.7			room	11.9	120
Polystyrene	**rigid structure**	6.8			room	12.5	121
Poly(vinyl alcohol) ($M = 3.4 \times 10^4$)	rigid structure CH protons: syndiotactic structure isotactic structure OH protons	 9.6 8.2 2.0	7—8	19—20	293	20.4	122
Poly(vinyl acetate) (degree of polymerisation 2000)	rigid structure	7.85			room	11.0	120
Poly(vinyl chloride)	**rigid structure**	11.5			room	14.5	121
Poly(vinyl chloride)	**rigid flat structure**	12.7			room	14.4	120
Poly(vinyl chloride)	**rigid flat structure** **isotactic** **syndiotactic**	 12.7 12.1			243	14.6	123
Poly(methyl methacrylate) atactic	**rigid structure** **rotn. of CH_3 group** **rotn. of monomeric unit**	18.8 9.8 2.5	4 3 2	22.8 12.8 4.5	77	11.5	113
Poly(methyl methacrylate)	rigid structure rotn. of one CH_3 group rotn. of both CH_3 groups	19.7 13.5 7	5 3.5 2	24.7 16.9 9	77 198 403	24.1 15.7 8.0	112
Poly(methyl methacrylate)	**rotn. of CH_3 group**	7.8			room	8.5	121
Poly(methyl methacrylate)	**rotn. of two CH_3 groups**	6.9			room	9.0	120
Poly(methyl methacrylate)	**rigid structure**			26	77	21	124
Poly(methyl methacrylate) (isotactic, $M = 3 \times 10^5$)					323 393	7.8 1.9	78
Poly(methyl methacrylate) (atactic)	rigid structure rotn. of one CH_3 group rotn. of both CH_3 groups rotn. of monomeric unit	22.9 16.1 9.4 2.4	5 4 3 2	27.9 20.1 12.4 4.4	77	18.6	113
Poly(ethyl methacrylate)	**rigid structure**	18.0	4.0	22.0	93	22	28
Poly(ethyl methacrylate) (atactic)	rigid structure rotn. of ethyl group rotn. of ethyl and methyl groups rotn. of monomeric unit	21.5 13.6 8.2 2.0	5 4 3 2	26.5 17.6 11.2 4.0	77	21.5	113

TABLE 3.(cont'd.)

Polymer	Calculated ΔH_2^2, gauss^2: structure	intra-molecular contribution	inter-molecular contribution	total second moment	Measured ΔH_2^2, gauss^2: temperature, °K	ΔH_2^2	References
1	2	3	4	5	6	7	8
Poly(butyl methacrylate)	rigid structure			2.3	77	23	124
Poly(isobutyl methacrylate)	rigid structure			24	77	20	124
Poly(cyclohexyl methacrylate)	rigid structure			25	80	23.5	124
Poly(methyl α-chloroacrylate)	**rigid structure**	18	2	20	80	17	112
Poly(methyl α-chloroacrylate)	rigid structure rotn. of CH_3 group			24 10.5	77	11	124
Nylon 66	rigid extended chain rotn. of H about chain axis	16.8 5.5	9.7 3	26.5 8.5	77 298	26 18	110
Nylon 57	rigid chain rotn. of H	16.8 5.5	3	8.5	77 298	26 16	110
Nylon 79	rigid chain rotn. of H	17.2 5.6	3	8.6	77 298	26 13	110
Nylon 88	rigid chain rotn. of H	17.2 5.6	9.7 3	26.9 8.6	77 298	27 14	110
Nylon 610	rigid chain rotn. of H	17.2 5.6	9.7 3	26.9 8.6	77 298	28 15	110
Nylon 1010	rigid chain rotn. of H	17.4 5.7	9.7 3	27.1 8.7	77 298	28 15	110
Nylon 1018	rigid chain rotn. of H	17.7 5.7	9.7 3	27.4 8.7	77 298	28 15	110
Poly(ethylene terephthalate) (amorphous sample)	**rigid structure**	8.1	2.0	10.1	90	15.1	125
Poly(ethylene terephthalate)	rigid flat structure, orthorhombic lattice	8.2	1.9	10.1	90	13.0	111
Poly(ethylene deuterophthalate)	rigid structure			15.3	90	18.2	125
Poly(tetramethylene terephthalate)					90	19.3	111
Poly(pentamethylene terephthalate)					90	22.3	111
Poly(hexamethylene terephthalate)	rigid flat structure, orthorhombic lattice	14.4	1.8	16.2	90	23.1	111
Poly(hexamethylene terephthalate)					90	21.5	111
Poly(decamethylene terephthalate)	rigid flat structure, orthorhombic lattice	16.5	1.4	17.9	90	22.5	111
Polyethylene	**rigid structure**	19	8	27	87	28	126
Polyethylene	**rigid structure**	17.8	7.7	25.5	84	26.3	123
Polyethylene (high-pressure branched, $M_n = 25\,000$)	rigid structure	18.7	8.3	27	77	27.2	69
Polyethylene, (high-pressure, 70% cryst.)	rigid structure synchronous rotn. of CH_2 groups random rotn. of CH_2 groups	18.7	5.3	24.0 8.5 2.7	150	28	86
Polyethylene (cationic catalysis, 90% cryst.)	**rigid structure** **synchronous rotn. of CH_2 groups** **random rotn. of CH_2 groups**	18.7	7.6	26.3 8.5 2.7	100	34	86
Polypropylene (isotactic)	rigid spiral structure	23.5	5	28.5	77	23—25	79

TABLE 3. (cont'd.)

Polymer	Calculated ΔH_2^2, gauss²				Measured ΔH_2^2, gauss²		References
	structure	intramolecular contribution	intermolecular contribution	total second moment	temperature, °K	ΔH_2^2	
1	2	3	4	5	6	7	8
Polypropylene	rigid spiral structure	26.6					58
Polybut-1-ene					77	20	60
Poly(vinyl fluoride) NMR-^{1}H	rigid structure	14.3	3.3	17.6	77	18.8	90
	chain rotn.	4.8	1.1	5.9	310	10	
NMR-^{19}F	rigid structure	5.8	3.8	9.6	77	11.0	
	chain rotn.	1.9	0.9	2.8	340	3	
Poly(vinylidene fluoride) NMR-^{1}H	rigid structure	15.7	2.6	18.3	77	18.9	90
NMR-^{19}F		7.1	3.1	10.2	77	10.5	
Polytrifluoroethylene	rigid structure						
NMR-^{1}H		5.9	4.2	10.1	77	12.2	90
NMR-^{19}F		6.8	4.1	10.9	77	9.8	
Polytrifluoroethylene NMR-^{19}F	rigid flat structure				101	7.7	123, 126
	isotactic	7.4	0.6	8.0			
	syndiotactic	6.4	0.5	6.9			
Polytetrafluoroethylene	**rigid spiral structure**	8.4	2.5	10.9	77	11.5	107
Polytetrafluoroethylene NMR-^{19}F	rigid flat structure	9.2	2.4	11.6	100	11.7	123
Polytetrafluoroethylene NMR-^{19}F	rigid structure	7.5	2.5	10.0	77	10.9	90
	chain rotn.	2.2	0.6	2.8	400	2	
Polytetrafluoroethylene, 90% cryst.	rigid structure			11.4	200	13	50
Silicone rubber					77	10.0	127
Silicone fluid (Fluid 200 Dow Corp.)	rotn. of CH_3 group	5.4	2–3		77	7.8	128
Silicone resin (Gum 400 Dow Corp.)	rotn. of CH_3 group	5.4	2–3		77	8.4	128
Silicone rubber (Silastic 80 Dow Corp.)	rotn. of CH_3 group	5.4	2–3		77	8.4	128
Polydimethylsiloxane $M = 7.5 \times 10^4$	rotn. of CH_3 group	5.4	1.6	7.0	80	7.0	100

found that the intermolecular contribution is 9.7 gauss². In amorphous polymers the average interchain distance can be determined from the amorphous halo in the *X*-ray pattern; the method was used by Slichter[90], for example, for fluorine derivatives of polyethylene.

The theory of NMR in solids (see Refs. 7 and 9) enables us to calculate ΔH_2^2 for several types of molecular motion in polymers. For polyamides, in the case of rotation of protons around the chain, the intermolecular contribution to the second moment is 3 gauss², and the intramolecular contribution is

$$\Delta H_2^2 = [5.9 - 4.7/(m + n + 1)]\ \text{gauss}^2. \quad (5)$$

For torsional harmonic oscillations with a 15° amplitude,

$$\Delta H_2^2 = [17.0 - 21.2/(m + n + 1)]\ \text{gauss}^2, \quad (6)$$

and with a 30° amplitude,

$$\Delta H_2^2 = [12.3 - 15.4/(m + n + 1)]\ \text{gauss}^2. \quad (7)$$

Fig. 18 shows the intramolecular contribution to the second moment of polyamides for rigid chains, oscillations,

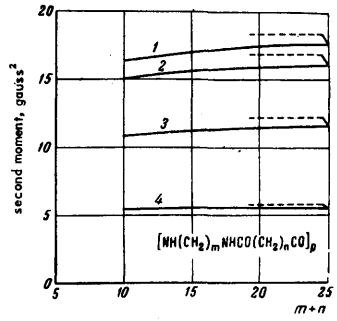


Fig. 18. Dependence of intramolecular contribution to the second moment on the number of methylene groups for several polyamides: 1) rigid structure; 2) 15° amplitude oscillation; 3) 30° amplitude oscillation; 4) free rotation[110]; the broken line corresponds to $(m + n \to \infty)$.

and free rotations as a function of the number of CH_2 groups in the monomeric unit. Fig. 19 shows the experimental and the calculated values of ΔH_2^2 for Nylon 610(polyhexamethylenesebacamide). It appears that chain motions start at ~360°K, *i.e.* some 100° below the melting point.

Further examples of changes in ΔH_2^2 with temperature are illustrated in Figs. 7 (polybutene) and 16 (polyethylene).

Fig. 6 shows the temperature dependence of ΔH_2^2 in isotactic and atactic polypropylene together with the theoretical values for rigid and rotating methyl groups.

In the case of a compound resonance line it is possible to determine the second moments of the narrow and the broad component and compare these results with theoretical values. The results of such an analysis are shown in Fig. 20 for linear and branched polyethylenes[86].

If the monomeric unit contains several molecular groups, then again ΔH_2^2 can be calculated for a rigid molecule and for rotation of any number or all the groups. Thus, Powles[112]

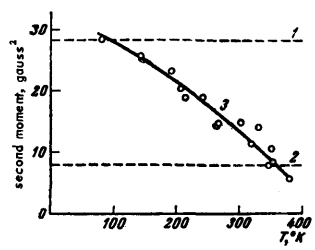


Fig. 19. Temperature dependence of the second moment for Nylon 610: 1) theoretical, rigid lattice; 2) theoretical, rotating chains; 3) experimental[110].

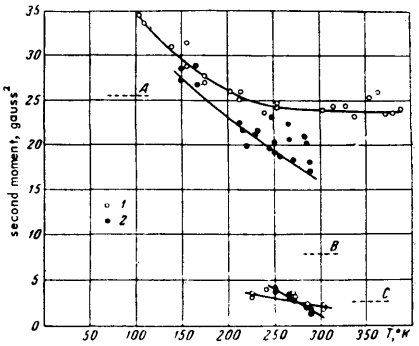


Fig.20. Temperature dependence of the second moment for polyethylene: 1) linear; 2) branched. *A*, *B*, *C* are the calculated values of the second moment: *A*) rigid lattice; *B*) synchronous rotation of neighbouring CH_2 groups; *C*) random rotation[86].

showed that for poly(methyl methacrylate) between 200°K and 340°K the experimental value of ΔH_2^2 agrees with the value calculated for rotation of main-chain CH_3 groups; at much higher temperatures the methyl groups attached to the oxygen atom also begin to rotate. Sinnot[113] performed analogous calculations for poly(ethyl methacrylate).

The temperature dependence of the second moment in polymers has been treated theoretically by Miyake *et al.*[114-117]

Table 3 lists some theoretical and experimental values of the second moment for a number of polymers.

Correlation of data obtained by different authors is made difficult by the fact that the samples used had different molecular weights and structure. There is some divergence in the calculated values of ΔH_2^2 since various models with different interatomic distances and angles were used. Also we have to remember that the accuracy of calculations and experimental determinations of ΔH_2^2 is not very high. Nevertheless, analysis of Table 3 leads to certain conclusions about molecular motion in polymers. In many cases (*e.g.* polyacrylates and polyesters) the experimental value of ΔH_2^2 is considerably smaller than the calculated one even at liquid nitrogen temperatures; apparently there is still some motion of molecular groups in polymers at these low temperatures.

Experimental data on transitions obtained from measurements of line width and second moment as a function of temperature for a number of polymers are listed in Table 4. In several polymers it was possible to identify the type of motion associated with each transition by comparing NMR data with results obtained by other methods. In particular, the glass transition is often accompanied by a change in δH or ΔH_2^2.

Kosfeld and Jenckel[134] working with pure and plasticised polymers obtained good agreement for the glass transition temperature as determined from narrowing of the NMR line and by other methods. The temperature at which the line width (in units of frequency) was equal to the correlation frequency was taken as the glass transition temperature.

TABLE 4. Polymer transitions, revealed by changes in NMR line width and in the second moment with temperature.

Polymer	Transition temperature, °K	Molecular motion associated with the transition	References
1	2	3	4
Natural rubber, vulcanised	155 225	rotn. of CH_3 group segmental rotn., glass transition	41
Natural rubber	195	rotn. of CH_3 group	129
Natural rubber, vulcanised Ditto, (elongated 500%)	221—235 228—243	rotn. of CH_3 group, glass transition ditto	92
Natural rubber	198 230	reorientation of CH_3 groups reorientation of segments	118
Divinyl – acrylonitrile copolymer (65 : 35)	140		129
Polyisobutene	140 240	reorientation of some CH_3 groups chain motion, glass transition	106
Butyl rubber	125—150		129
Polyurethane (Vulcalane)	253	glass transition	96
Polystyrene (degree of polymerisation 4200)	353 393	glass transition	120
Poly(methyl methacrylate)	270—290	monomeric reorientation, glass transition	113
Poly(methyl methacrylate)	313	glass transition at 276 °K	120
Poly(methyl methacrylate)	163 343	reorientation of CH_3 groups, glass transition	112
Poly(methyl methacrylate)	348 403	glass transition at 343 °K	120
Poly(methyl methacrylate) (atactic, $M \cong 10^6$)	363	glass transition	78
Poly(methyl methacrylate) (atactic)	130 360—370	rotn. of CH_3 groups segmental rotn., glass transition	113
Poly(methyl methacrylate) (isotactic, $M = 1.2 \times 10^6$) Ditto, ($M = 3 \times 10^5$) Ditto, ($M = 1.3 \times 10^6$)	333 327 323	glass transition glass transition glass transition	78
Poly(ethyl methacrylate) (atactic)	110 290 350	rotn. of CH_3 group rotn. of ester group glass transition	113
Poly(vinyl alcohol)	293—323 343—373	dilatometric measurements show transitions at 288° and 343 °K	130
Poly(vinyl acetate) (degree of polymerisation 2000)	323	glass transition at 303 °K	120
Poly(vinyl chloride) (degree of polymerisation 1300)	358	glass transition at 348 °K	120
Poly(ethylene terephthalate)	370	rotn. of phenyl groups	131
Polyethylene	245	segmental motion, glass transition at 243° K	132
Polyethylene	173	segmental motion	123
Polyethylene (high-pressure)	173 243 290	segmental motion segmental motion in amorphous regions motion in crystalline regions	75
Polyethylene (low-pressure)	173 273 348	segmental rotn. segmental motion in amorphous regions motion in crystallites	75
Polypropylene (atactic)	233	glass transition	58
Polypropylene (isotactic, 60% cryst.)	300	chain motion in amorphous regions	81
Polypropylene (isotactic)	263	glass transition	58
Polytetrafluoroethylene, NMR-^{19}F	210 270—310	2/3 of CF_2 groups rotating all CF_2 groups rotating	107
Polytetrafluoroethylene, NMR-^{19}F	173	segmental motion	123

TABLE 4.(cont'd.)

Polymer	Transition temperature, °K	Molecular motion associated with the transition	References
1	2	3	4
Polytetrafluoroethylene, NMR-^{19}F	285	rotn. in cryst. regions	133
Polytrifluorochloroethylene, NMR-^{19}F	243	segmental motion	123
Silicone rubber	164	crystallisation	127
Silicone rubber	150—180	rotn. about Si—O bond	128
Silicone resin	90	spiral motion of $(CH_3)_2$ Si groups	128
	150—180	rotn. about Si—O bond	
Silicone fluid	90	spiral motion of (CH_3) Si groups	128
	140—170	rotn. about Si—O bond	
Polydimethylsiloxane ($M = 7.5 \times 10^4$)	180	rotn. about Si—O bond and translational motion in crystallites	100

Nohara[135] notes that the agreement between transition temperatures determined by NMR and mechanical methods is closer in symmetric polymers (polyethylene, polytetrafluoroethylene) than in asymmetric polymers (buna-N, polystyrene).

The nature of a transition accompanied by a change in line width or in the second moment is more readily interpreted if the sample is oriented. Hyndman and Origlio[133] showed that rotation in crystalline regions of Teflon fibres at 285°K affects the NMR line width only when they are not parallel to the magnetic field.

3. Relaxation Times, Correlation Frequency, and Activation Energy of Molecular Motions in Polymers

Measurements of relaxation times T_1 and T_2 over a wide range of temperatures also provide information about polymer structure and internal motions.

Since high polymers may be considered as liquids (at least in the viscoelastic state), as far as motion of individual groups is concerned, the theory of relaxation for liquids may be employed in the interpretation of results. For example, spin-echo measurements of the spin–lattice relaxation time in natural rubber[118] show a typical liquid-like dependence of log T_1 on $1/T$, with a minimum (Fig.21). However, the shape of this curve is slightly different from the one predicted by theory. The disagreement cannot be accounted for by a distribution of correlation frequencies; an explanation in terms of cooperative molecular motions has been suggested[118]. In poly(methyl methacrylate) T_1, determined by the spin-echo method, exhibits complex behaviour with two minima[136].

The spin–spin relaxation in polymers also cannot always be described by a single relaxation time T_2. For instance, Powles *et al.*, using the spin-echo method, measured T_1 and T_2 in polyisobutene[137] and in dimethylsiloxane polymers[40]. T_2 is determined by using 90° and 180° pulses separated by time τ; the echo amplitude h at time 2τ is proportional to $\exp(-\tau/T_2)$ if the effect of self-diffusion is small. A plot of $\ln(h/h_{max})$ *vs.* 2τ should give a straight

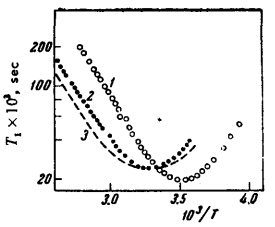


Fig.21. Temperature dependence of the longitudinal relaxation time T_1 in: 1) natural rubber; 2) vulcanised natural rubber; 3) a theoretical curve for vulcanised natural rubber[118].

line. In polyisobutene above 170°C the plot of $\ln(h/h_{max})$ *vs.* 2τ (Fig.22) shows two transverse relaxation times T_{21} = = 2.8 msec and T_{22} = 10.6 msec. Two values of T_2 were also found, above -42°C, in a number of dimethylsiloxane polymers whose chains contained more than 1000 atoms. It appears that the second relaxation mechanism involves an interaction between chains. Two T_2 values were also observed in polyethylene[138]. Measurements of T_1, line width, or the second moment as a function of temperature enables us to calculate the correlation frequency ν_c and the activation energy E of molecular motions. Such calculations were made for a number of polymers: branched and linear polyethylene[86,101], rubber[41], polyisobutene[106], and fluorine derivatives of polyethylene[90].

The activation energies deduced from the temperature dependence of ν_c, derived from ^{1}H and ^{19}F resonance in polytrifluoroethylene, were found to be 2.6 and 3.2 kcal × × mole^{-1} respectively[90]. For polyethylene[86] the plot of log ν_c *vs.* $1/T$ consists of two straight lines (Fig.23). The activation energies of molecular motions responsible for

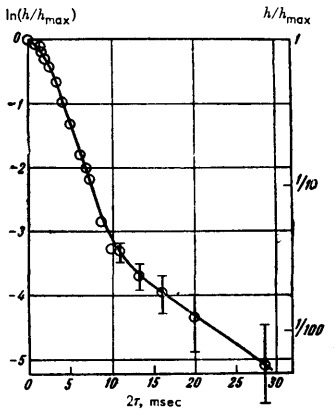


Fig.22. Determination of T_2 by the spin-echo method for polyisobutene at 194°C.[137]

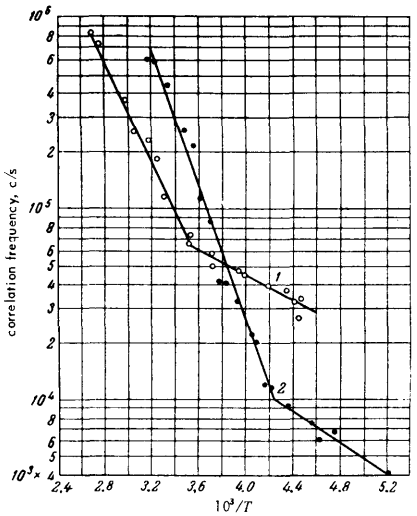


Fig.23. Correlation frequency as a function of temperature in polyethylene: 1) linear; 2) branched[86].

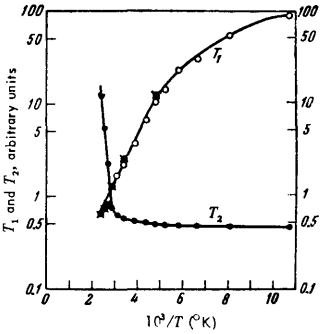


Fig.24. Temperature dependence of relaxation times for two polyethylene deuteroterephthalate samples[141].

the low-temperature and the high-temperature line-narrowing are respectively 1.5 and 6.1 kcal mole^{-1} in linear polyethylene, and 2.0 and 8.8 kcal mole^{-1} in branched polyethylene. However, a comparison of activation energies derived from NMR and other methods indicates that caution should be exercised in the calculation of E from the correlation frequency. Powles[28,139] gives a number of examples where low values of E were obtained on account of a distribution of correlation frequencies in polymers. Nolle and Billings[104] also found a large discrepancy in the value of E determined by NMR and that derived from viscosity measurements on a polyisobutene melt; they point out that the line width is affected by motion of individual methyl groups, while viscous flow involves cooperative motion of a large number of segments.

In addition to relaxation times, the coefficient of self-diffusion D can also be measured by the spin-echo method[17]. The lower limit of the method ($D \geq 10^{-7}$cm^2 sec^{-1}) allows measurements of D only in polymer melts. McCall *et al.*[140] measured D in polyethylene melts between 130° and 200°C and calculated the self-diffusion activation energy E. For chains longer than C_{20}–C_{30}, E becomes independent of chain length. The dependence of D on molecular weight is given by D = const $n^{-5/3}$, where n is the number of C atoms in the molecule.

4. Use of Isotopic Substitution in the Study of Motions in Polymers by NMR

The interpretation of NMR results in polymers, as in other branches of spectroscopy, is made easier by the use of isotopic substitution. Deuteration, *i.e.* replacement of ^{1}H by D, is most commonly used. The gyromagnetic ratios of ^{1}H [$\gamma/2\pi$ = 4257 (c/s) gauss^{-1}] and ^{2}H [$\gamma/2\pi$ = 654 (c/s) gauss^{-1}] are very different, so that deuterium resonance does not interfere with the hydrogen resonance.

Ward *et al.*[89,125,141] found that substitution of three H atoms in the benzene ring of polyethylene terephthalate by D gives rise to a compound line, because the remaining single proton in the ring interacts weakly with other protons and therefore has a narrow line, while methylene protons have a broad line. The line remains compound even down to -180°C. The mobility of CH_2 groups in polyethylene terephthalate can be measured if all the ring protons are replaced by deuterons. The temperature dependence of relaxation times in polyethylene deuteroterephthalate (Fig.24) indicates that between 200° and 400°K there is a hindered rotation of CH_2 groups about the C–C bond, with an activation energy of ~ 2 kcal mole^{-1}. Glick *et al.*[142] showed that the substitution of D for H in amide groups in amorphous regions of polyhexamethyleneadipamide has little effect on the temperature dependence of the second moment. Yoshida *et al.*[143] examined nuclear magnetic resonance in films of normal and deuterated polyvinyl alcohol. The method of isotopic substitution is also used for high-resolution NMR measurements of polymers in solution. Bovey *et al.*[144] employed the substitution of D for H in assigning peaks in the spectrum of polystyrene in solution.

5. Comparison of NMR Data with Results Obtained by Other Methods

A comparison of NMR data with dynamic-mechanical results was made even in Alpert's original nuclear resonance experiments on rubber[94]. A discussion of the relation between mechanical, dielectric, and nuclear resonance absorption in polyisobutene, poly(methyl methacrylate) and poly(methyl α-chloroacrylate) was given by Powles[98]. Sauer and Woodward[29] compared NMR and dynamic mechanical measurements for a number of polymers, both amorphous [polyisobutene, poly(methyl methacrylate)] and highly crystalline [poly(vinyl chloride), polyethylene, irradiated polyethylene, polypropylene, polybutene, polystyrene, polyamides, polytetrafluoroethylene]. In many cases a transition causing narrowing of the NMR line also appears in mechanical measurements as a sharp maximum in the logarithmic decrement of damping Δ and a decrease in the dynamic shear modulus G. A transition of this type is

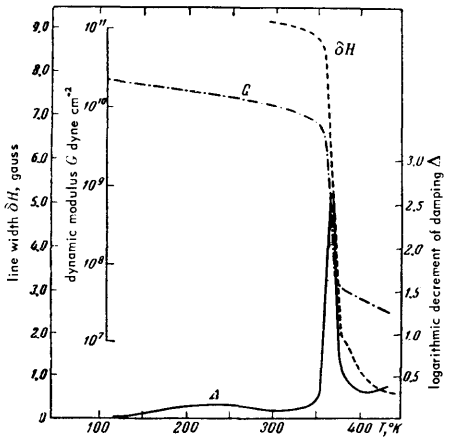


Fig.25. NMR line width, dynamic modulus, and logarithmic decrement of damping as a function of temperature for poly(vinyl chloride)[29].

observed for example in poly(vinyl chloride) at 350°–360°K, which corresponds to the glass transition temperature (Fig.25). The second slight maximum in Δ at ~240°K apparently corresponds to weak vibrations of methylene groups which have no appreciable effect on the NMR line width. Sauer and Woodward[29] conclude that the melting of crystallites is more readily apparent in dynamic-mechanical properties of the polymer, since local rotation and reorientation in the solid state generally narrow the NMR line prior to melting of crystallites so that any further narrowing is imperceptible.

The dynamical-mechanical method is superior also in detecting secondary amorphous transitions involving main chain segmental motion, such as the low-temperature transitions in polyamides. The glass transition (primary amorphous transition) is readily detectable by both methods, though with some discrepancy in the transition temperatures, possibly on account of different frequency ranges employed. The NMR method is much more sensitive to the rotation of side chains, *e.g.* CH_3 groups in polyisobutene, poly(methyl methacrylate), and polypropylene, than the mechanical method. Thus, the two methods are complementary.

Molecular motion in polymers containing polar groups can be investigated also with the aid of dielectric measurements. Thurn[36] gave an extensive review of mechanical, dielectric, and nuclear resonance measurements for many polymers.

IV. THE STUDY OF CHEMICAL PROCESSES IN POLYMERS

Chemical reactions between high polymers play an important role in engineering and biology and consequently their investigation belongs to one of the most important, though so far little explored, fields of polymer chemistry and technology. The known chemical reactions of macromolecules fall into four main groups: (1) intramolecular reactions, (2) polymer analogue transformations, (3) reactions involving a decrease in the degree of polymerisation, *e.g.* degradation due to the influence of various physical, chemical and mechanical factors, including high-energy radiation, and (4) reactions involving an increase in the degree of polymerisation, in particular, cross-linking, resulting in formation of three-dimensional structures (see for example, review articles by Berlin[145,146] and the Proceedings of the International Symposium on Macromolecular Chemistry, Moscow[147]).

The NMR method may be helpful in solving many problems connected with reactivity of macromolecules, and the structure and properties of end-products, but so far very few papers have been published in this field. We shall deal here only with cross-linking and degradation of polymers, with the effect of radiation on polymers, and with experiments on polymerisation related to this problem.

1. Polymerisation

The possibility of using NMR in the study of polymerisation was pointed out by Lösche[148]. Polymerisation measurements for ethyl acrylate, acrylonitrile, and methyl methacrylate were made by Shibata[149]. The increase in the second moment on polymerisation of ethyl acrylate under the influence of ^{60}Co γ-rays is shown in Fig.26. Theoretical interpretation of these results requires calculation of the effect of viscosity on relaxation times.

2. Cross-Linking of Polymer Chains

The effect of vulcanisation on NMR in rubber was described by several investigators. As long ago as 1950, Holroyd *et al.*[95] discovered that vulcanisation of GR-S (butadiene–styrene rubber 70:30), Hycar OS-10(butadiene–styrene rubber 50:50), and butyl rubber broadens the NMR line at room temperature. Measurements of the temperature dependence of the line width for Hycar, made by Holroyd *et al.*[49,96,150] (Fig.27) also show an appreciable difference in the nature of molecular motions of vulcanised and unvulcanised rubber, especially between -15° and -5°C. These authors conclude that vulcanisation impedes the formation of regions of unhindered rotation. Honnold *et al.*[97] studied the effect of vulcanisation of natural rubber on its NMR line width and showed that with 8% of sulphur the increase in δH for natural rubber is smaller than for butadiene–styrene copolymer; they argue that the cross-linking

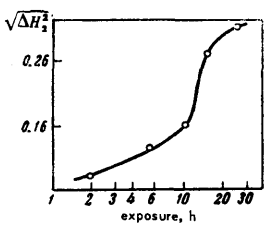


Fig.26. Variation of the second moment on polymerisation of ethyl acrylate under the influence of γ-rays.[149]

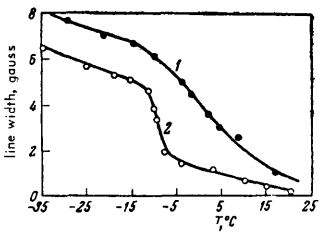
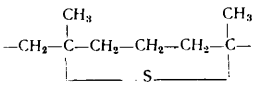


Fig.27. Temperature dependence of line width for Hycar OS-10 (butadiene–styrene 50 : 50 copolymer): 1) vulcanised; 2) unvulcanised[49].

taking place during vulcanisation is more "physical" in natural rubber and more chemical in synthetic rubber. Gutowsky *et al.*[41,118] showed that vulcanisation has a large effect on the NMR spectrum. It was found that in the region between 140° and 170°K an increase in the curing time of natural rubber appreciably shifts the narrowing of the line (due to CH_3 motion) to higher temperatures. The line-narrowing in the region of 225°K (due to segmental motion) is not affected by curing (vulcanisation) time. The activation energy, corresponding to the low-temperature narrowing, is 2.7 kcal mole^{-1} for a sample cured for 30 min, and it increases to 4.5 kcal mole^{-1} for a curing time of 90 min. The line width depends not only on the quantity of combined sulphur in the vulcanisate but also on the amount of raw sulphur in the initial mixtures. Also, the temperature of minimum T_1 (spin–lattice relaxation time) increases with the quantity of combined sulphur. The authors suggest that the formation of ring structures



and not cross-linking is the primary process in vulcanisation of rubber.

Slichter[30] notes that this hypothesis is not adequately substantiated and that more complete observations are required. Oshima and Kusumoto[151], who studied the NMR spectrum of rubber with 2–30% *S* over a wide range of temperatures, propose to apply NMR to the control of the degree of vulcanisation.

The effect of cross-lining on NMR of polymers was also investigated in connection with hardening (curing, heat-aging) of epoxy-resins[27,45,148,152]. The hardening process was found to have two stages. Jain[153] observed changes of the NMR line during hardening of epoxy-resin-modified esteramide. In a partially hardened resin the line is compound on account of protons in hardened and non-hardened regions. The percentage of the non-hardened material may be deduced from the ratio of the two components of the line.

3. The Effect of Radiation on Polymers

The effect of radiation on high polymers was studied by means of NMR mostly in polyethylene and to some extent in polytetrafluoroethylene and other polymers.

Fuschillo and Sauer[69,70,154] investigated the effect of irradiation of polyethylene with atomic pile neutrons and ^{60}Co γ-rays. The dynamic-mechanical method was used in addition to NMR. Irradiation with 8×10^{18} neutron cm^{-2} changes the absorption line at room temperature. The NMR line for polyethylene is compound and irradiation affects mainly the narrow component, associated with amorphous regions of the polymer. In strongly irradiated samples the line is similar to the one obtained in unirradiated samples at much lower temperatures.

Irradiation has little effect on the line shape at 77°K. The number of cross-links in the polymer was deduced from the value of the dynamic modulus. Changes in the properties of polyethylene induced by irradiation are summarised in Table 5.

The effect of irradiation on polyethylene can be explained in terms of two superimposed processes: (1) destruction of crystallites and (2) cross-linking. With a dosage of 0.3×10^{18} neutron cm^{-2} the first process predominates and the second moment decreases somewhat. With dosages of 1.2×10^{18} neutron cm^{-2} and above the second process is dominant and ΔH_2^2 increases. The index of high-frequency rigidity N_c/N has a similar radiation dosage dependence.

Slichter and Mandell[61] obtained analogous results on irradiation of polyethylene in an atomic pile and with electrons. The line narrows for all temperatures above 100°K even for small (5×10^8 rep) electron dosages (Fig. 28). In polyethylene exposed to high neutron dosages the line width at 250°K is larger than in unirradiated samples. In order to explain irradiation effects, these authors evaluated the

TABLE 5. Effect of irradiation on properties of polyethylene.

Dosage, 10^{18} neutron cm^{-2}	0	0.3	0.6	1.2	2.8	5.5	8.0
Number of cross-links per 100 C atoms	0	4	10	20	30		
% crystallinity (from X-ray data)	55	50	25		10	0	0
ΔH_2^2 at 77 °K, gauss^2	27.2	23.2	25.0	27.4		27.5	28.0
ΔH_2^2 at 295 °K, gauss^2	14.5	11.3	13.4	13.3	14.3	15.2	17.0
"% crystallinity" N_c/N (from NMR)	59	54		55	64	67	76

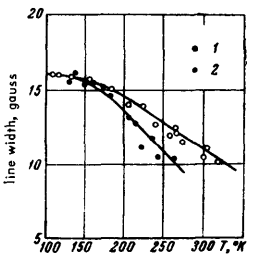


Fig.28. Effect of irradiation with an electron beam on the NMR line of polyethylene[61]: 1) unirradiated sample; 2) irradiated with 5×10^8 rep.

correlation frequency ν_c. The plot of $\log \nu_c$ *vs.* $(1/T)$, for polyethylene irradiated with 1.8×10^{18} neutron cm^{-2}, consists of two linear sections. At low temperatures a process (apparently small amplitude libration) with an activation energy E = 1.4 kcal $mole^{-1}$ is observed. At much higher temperatures, where large amplitude rotation, vibration, or even translational motion, are possible, the activation energy is 7.4 kcal $mole^{-1}$. For very large radiation does (1.49×10^{19} neutron cm^{-2}), $\log \nu_c = f(1/T)$ is represented by a single straight line (E = 1.8 kcal $mole^{-1}$); this implies that molecular chain movements are strongly hindered by the large number of cross-links. Glick *et al.* [101], who made a detailed study of neutron irradiation effects on high- and low-density polyethylene, confirmed these findings. The second moment falls on irradiation with small dosages (0.25×10^{18} neutron cm^{-2}) owing to the destruction of crystallites, but it rises when the dosage is increased beyond a critical value because of the effect of the large number of cross-links (Fig. 29). The critical dosage is higher for high-density polyethylene than for the low-density polymer.

Fujiwara *et al.* [71] observed changes in the NMR spectrum on irradiation of polyethylene with an intense beam of cyclotron-accelerated deuterons.

Irradiation of polytetrafluoroethylene film with accelerated deuterons in a vacuum results in broadening of the NMR line [155]. It is argued that molecular motion in polymers is hindered by the formation of double bonds cyclic units, and cross-links. Burget and Saha [156] also observed that the line width in Teflon increased by a factor of $1\frac{1}{2}$ after a 5 h exposure to 10^{12} neutron cm^{-2} sec^{-1} (total dosage 1.8×10^{16} neutron cm^{-2}).

Irradiation of poly(vinyl alcohol) films with less than critical dose range of γ-rays decreases the second moment and the "NMR degree of crystallinity"; [122] with doses larger than the critical the proportion of the broad component in the NMR line and ΔH_2^2 increases. The critical dose range is about 10^6 rad; its value depends on experimental conditions and intensity of radiation (dose rate).

Lösche also noted a large effect of dose rate [27,157,158]. Prolonged irradiation, for up to 5 months, of polyamides with a weak source (30 mc radium), resulting in absorption of 10^{16} γ-photons, produces a sharp decrease of the second moment from 14–16 $gauss^2$ to 0.07 $gauss^2$, at room temperature. It appears that with small radiation intensities very few cross-links are formed, since the probability of two photons striking simultaneously two neighbouring sites in the sample is quite small. This large change in the NMR line width following a prolonged exposure to low-intensity radiation is of interest in connection with dosimetry.

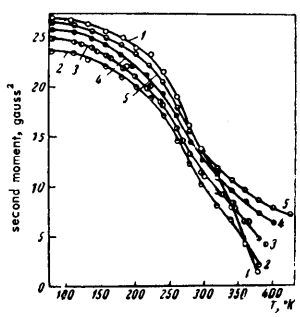


Fig. 29. Temperature dependence of the second moment for low-density polyethylene irradiated in a nuclear reactor. Neutron dosage (10^{18} neutron cm^{-2}): 1) 0; 2) 0.25; 3) 0.6; 4) 1.3; 5) 2.8. [101]

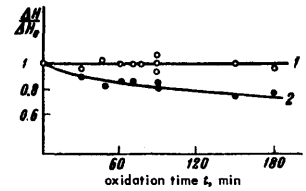


Fig. 30. Variation of NMR line width in polypropylene with oxidation: 1) broad component; 2) narrow component [72].

4. Degradation of Polymers

Aging of polymers by heat, light, atmospheric oxygen, and other factors, as well as irradiation, results in chain rupture, cross-linking, and reactions between functional groups, leading to changes in structure and in internal motions of polymers.

Urman [72] recorded a number of NMR spectra of polypropylene, oxidised at elevated temperatures. The lines were resolved into two components by the method of linear anamorphs. It was found that on oxidation the broad component remains unchanged and that the narrow component becomes narrower (Fig. 30). This implies [72] that oxidation takes place much faster in the amorphous phase than in the crystalline phase.

V. NMR IN "POLYMER–SMALL MOLECULE" SYSTEMS

1. Homogeneous (Single-Phase) Systems

(*a*) Changes in the NMR polymer spectrum on swelling. Nuclear magnetic resonance in swollen polymers enables us to follow any changes in the mobility of a chain as neighbouring macromolecules are replaced by small molecules of the solvent. So far very few experiments have been reported in this field, though it appears that, by using polymers and solvents with different nuclei (*e.g.* fluorine-containing solvents for organic polymers), one can obtain valuable results by examining NMR spectra over a wide range of temperatures and component ratios.

Holroyd *et al.* [49] showed that swelling of Hycar with benzene narrows the line and lowers the transition temperature (Fig. 31). They argue that the narrowing is caused by increased intermolecular distances due to swelling. As noted by Slichter [30], this explanation is incorrect, since the intermolecular contribution to the line is considerably smaller than the intramolecular one, and therefore a slight

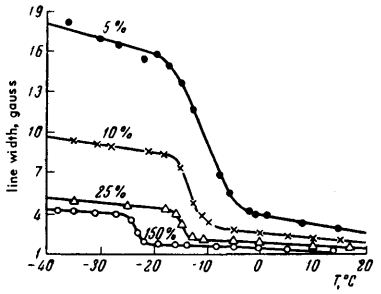


Fig.31. Temperature dependence of line width for Hycar OS-10 at various degrees of swelling with benzene[49].

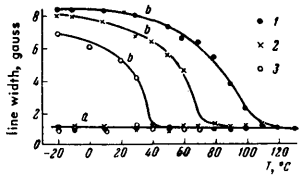


Fig.32. NMR line width for polystyrene as a function of the degree of swelling with methylene dichloride: *a*) narrow component; *b*) broad component[160]; 1) 55% CH_2Cl_2; 2) 11% CH_2Cl_2; 3) 15.7% CH_2Cl_2.

change in the interchain separation cannot cause any appreciable narrowing of the line. The effect of the solvent arises from enhancement of segmental motion in the polymer chain.

Cohen-Hardia and Gabillar[91] showed that, on swelling of natural rubber with CCl_4, T_2 increases (with 25% swelling T_2 rises from 6×10^{-4} to 8×10^{-4} sec). Narrowing of the line on swelling was also noted by Odajima and Nagai[159], who studied swelling of polystyrene in carbon disulphide and of other polymers in solvents not containing hydrogen. Kosfeld[134,160] examined in detail nuclear magnetic resonance in plasticised polystyrene. Plasticisers containing hydrogen (methylene dichloride and cyclohexane) and without hydrogen (CCl_4) were used. For the polystyrene–CH_2Cl_2 system, the line is compound, with a narrow and a broad component; as the temperature is increased, the line width of the narrow component remains unchanged but that of the broad component decreases (Fig. 32). Obviously, even when the system is in a glassy state the plasticiser retains most of its mobility. On lowering the temperature below the glass transition temperature, the intensity of the narrow component decreases, more of the molecules in the plasticiser become fixed. The diffusion coefficient D was also measured in these systems[134,160]; it was found that below the glass transition temperature D falls by several powers of ten. Probably, the molecular motion in the plasticiser is mainly rotational and not translational. In the polystyrene–CCl_4 system the narrow line is absent and swelling produces only narrowing of the whole line.

Powles[108,161] studied NMR in polyisobutene–benzene and polyisobutene–CCl_4 systems. He found that there is a critical solvent concentration at which the chains of the polymer become "free". This concentration corresponds to a ratio of one molecule of benzene, or CCl_4, to six monomeric units of polyisobutene. For molecular ratios of benzene to polymer larger than 1:6, the drop in the second moment occurs at temperatures 30° lower than in pure polymer. The activation energy of molecular motions can be calculated from the temperature dependence of the second moment; it appears that the activation energy is almost the same in both pure and swollen polymers, while the entropy of activation increases sharply with swelling, from 6.1 to 22.3 units. This large increase in the chain mobility of the polyisobutene–CCl_4 system, in the critical concentration region, is also indicated by a sharp increase in the transverse relaxation time T_2 and a decrease of the correlation time τ_C in this region (Fig. 33).

Deuterated solvents, among others not containing protons, may be used in NMR experiments on swelling. For example, Yoshida *et al.*[143] observed proton resonance in poly(vinyl alcohol) films swollen with heavy water.

(*b*) NMR in polymer solutions. NMR measurements in polymer solutions may be divided into two groups, one involving molecular motions in solutions and the other concerned with chain structure and polymer composition. The first group is based on measurements of relaxation processes in solution and is directly connected with problems discussed in the preceding section on polymer swelling.

Nolle[162,163], using the spin-echo method, measured relaxation times in solutions of polyisobutene and polystyrene in CCl_4. Odajima[164], combining Nolle's results and his own measurements on polyisobutene and polystyrene dissolved in CCl_4 and CS_2, developed a theory of relaxation

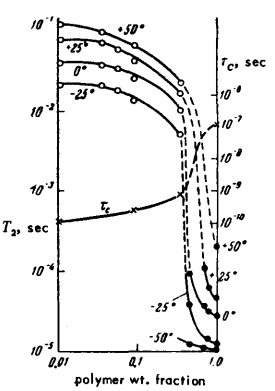


Fig.33. The transverse relaxation time T_2 and the correlation time τ_C as a function of the weight fraction of the polymer in the polyisobutene–CCl_4 solution[161].

for polymers in solution. He derives a formula for the critical concentration of solution at which the relaxation times change abruptly, *i.e.*

$$W_C = 7.1\, M_S^{3/2}/\alpha A l^3 M^{1/2}, \qquad (8)$$

where W_C is the critical concentration g cm^{-3}, M_S the molecular weight of the monomeric unit, α the "excluded volume", A Avogadro's number, l the segment length, and M the molecular weight; the formula is valid for $M > 10^5$. It was shown that for polyisobutene in solution the kinetic unit consists of a segment composed of 10 monomeric units. The activation energy of segmental motion approaches that of the solvent for small concentrations, but for high concentrations it is appreciably larger.

High-resolution NMR spectra of polymer solutions enable us to measure the relaxation of individual molecular groups, because we can determine the relaxation times T_1 and T_2 for each peak in the spectrum. T_1 may be obtained for example by direct measurement of signal amplitude recovery and T_2 from the line width. Bovey *et al.* [144] obtained NMR spectra for several polystyrene solutions with various number-average degrees of polymerisation.

The spectra of solutions of polystyrene, with number-average degree of polymerisation P_n = 500, and its small-molecule hydrocarbon analogue cumene $CH_3-\underset{\displaystyle C_6H_5}{\underset{|}{CH}}-CH_3$, are shown in Fig. 34. The chemical shift in parts per million (p.p.m.) is plotted as the abscissa. Tetramethylsilane was used as a standard with τ = 10. The polystyrene spectrum has four peaks: (1) *ortho*-protons in the aromatic ring, (2) *meta*- and *para*-protons in the ring; (3) protons in CH_2 and CH_3 chain groups, (4) reference standard peak from tetramethylsilane. These authors also compared the spectrum of high-molecular-weight polystyrene with those of polystyrene with P_n = 5–20 (Fig. 35). The line widths in the polystyrene spectrum are considerably larger than in the cumene spectrum and they do not depend on molecular weight or concentration of solution (for concentrations less than 50–60%). This shows that segmental motion and not motion of the whole molecule takes place. It should be noted that the viscosity of these solutions varied between that of the pure solvent to several thousand cP (slow-flowing liquid). In normal small-molecule liquids the value of $1/T_2$, and consequently the line width, is proportional to viscosity. Obviously, for polymers in solution the line

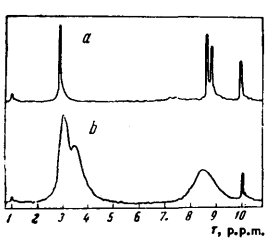


Fig.34. High-resolution spectra of CCl_4 solutions of (*a*) cumene (10% solution) and (*b*) polystyrene with $P_n \simeq$ $\simeq$ 500 (15% solution) [144].

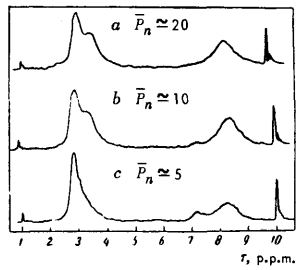


Fig.35. NMR spectra of CCl_4 solutions of polystyrene of low molecular weight [144].

width is determined by the local viscosity in the immediate vicinity of chain segments. The local viscosity is independent of molecular weight and the concentration affects it only when neighbouring segments begin to hinder motions. The magnitude of T_1 for the polystyrene benzene ring is 0.4 sec while T_1 in pure benzene at 25°C is 18.9 sec. It follows then that benzene rings in polystyrene chains rotate some 40–50 times slower than benzene molecules.

The spin-echo method may also be used in studies of relaxation phenomena of polymers in solution. McCall and Bovey [165] used this method for polystyrene dissolved in tetrachloroethylene and carbon disulphide and determined T_1 for aliphatic protons and for *ortho*-, *meta*-, and *para*-protons of the phenyl group.

The second group of high-resolution NMR measurements of polymers in solution is concerned with the determination of macromolecule structure and polymer composition.

Gutowsky [118] gives a spectrum of natural rubber dissolved in CS_2. The spectrum has four peaks corresponding to protons located in CH_3, CH, and two non-equivalent CH_2 groups.

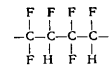
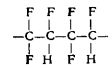
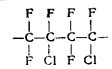
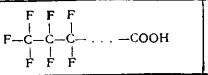
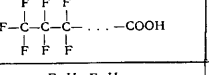
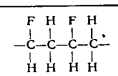
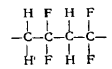
Spectra of several biological substances have also been recorded, *e.g.* deoxyribonucleic acid [166], and solutions of ribonuclease [167] and proteins [168] in heavy water. Jardetzky [169] gives an interpretation of the NMR spectrum of ribonuclease, assigning peaks to protons in aromatic groups and amino-acid α-CH and CH_2 groups. The development of NMR spectrometers with a field homogeneity of 1 in 10^8 has provided many new possibilities in the study of chemical structure of polymers. Several papers were published pointing out the great possibilities of the method. In two of these [83,84] fluorine-containing polymers are considered. Naylor and Lasoski [84] determined the chemical shift $\Delta\nu$, in frequency units, relative to trifluoroacetic acid, for a number of polymers in solution (Table 6).

Analysis of Table 6 leads to general rules for the effect of substitution on ^{19}F resonance.

(a) Substitution of F or Cl for H bound to the same carbon atom as F shifts the F resonance to higher frequencies. This agrees with the data obtained for small-molecule substances, *i.e.* raising the electronegativity of the substituent shifts the resonance to higher frequencies.

(b) Substitution of F for H bound to a carbon atom adjacent to the one with F shifts the resonance to lower frequencies. Apparently this shift is determined by the direct interaction between the F atom and the substituent at the

TABLE 6. Chemical shift of fluorine resonance [84].

Polymer	Structure (the atom in question is denoted by heavy type)	$\Delta\nu$ relative to CF_3COOH, c/s
Polytrifluoroethylene		—3950
Polytrifluoroethylene		—1150
Polytrifluorochloroethylene		—1500
Perfluorodecanoic acid		—1250
Perfluorodecanoic acid		— 100
Poly(vinyl fluoride)		—3100
Poly(vinylidene fluoride)		— 400

neighbouring C atom. The spectrum of poly(vinylidene fluoride) dissolved in dimethylformamide (Fig. 36) has two peaks, $\Delta\nu$ = 400 c/s (larger) and $\Delta\nu$ = 1100 c/s; the peaks correspond to two possible structures: "head-to-tail" and "head-to-head" configurations. The relative intensities of the two peaks show that poly(vinylidene fluoride), obtained by polymerisation with a diazo-type initiator, contains 8–10% of "head-to-head" structure.

Similarly, Fergusson [83], using semiempirical structure–chemical shift rules, analysed NMR spectra for a number of vinylidene fluoride–hexafluoropropylene copolymers (Fig. 37). Using the chemical shift and line intensity of the nine lines of ^{19}F resonance, he showed that the copolymers have a "random" linear structure, without a regular sequence of hexafluoropropylene residues — block polymer segments and branches. The structure of the copolymer may be represented by

$$\left[\left(\begin{array}{c}CF_3\\|\\CH_2CF_2CF_2CF\end{array}\right)_{0.93}-\left(\begin{array}{c}CF_3\\|\\-CH_2CF_2CF-CF_2\end{array}\right)_{0.07}-\right]_{1-n}-$$

$$-[(-CH_2CF_2CH_2CF_2)_{0.95}-(CH_2CF_2CF_2CH_2)_{0.05}]_{n/2},$$

where $n = (x-50)_x$ and x is the mole % of vinylidene fluoride in the copolymer. The composition of the polymer may be determined to within 1% from the intensity of CF_2 and CF_3 lines.

The work of Kubota and Takamura [170] may serve as a further example of the use of high-resolution NMR in determining polymer composition; they developed a quantitative analysis for copolymers based on the relative intensity of lines associated with individual groups. The method was successfully applied to the determination of

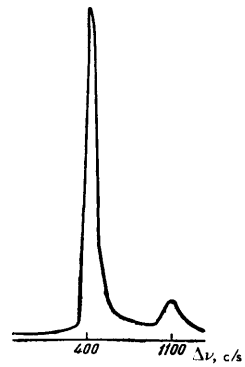


Fig.36. NMR spectrum of poly-(vinylidene fluoride) dissolved in dimethylformamide [84].

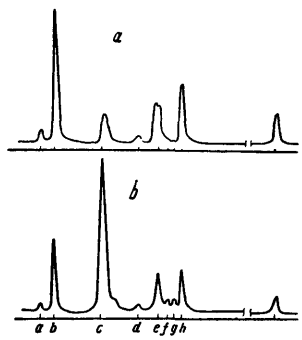


Fig.37. Fluorine NMR spectra of 50% acetone solutions of vinylidene fluoride–hexafluoropropylene copolymers;
a) 61 mole % vinylidene fluoride;
b) 85 mole % vinylidene fluoride [83].

phenyl and methyl groups in methylphenylsiloxane polymers dissolved in dioxane; the solvent serves also as an internal standard of signal intensity.

Stereoregularity of polymers can be determined from their high-resolution NMR spectra. Bovey and Tiers [171] studied spectra of chloroform solutions of a number of poly(methyl methacrylate) samples polymerised under the influence of γ-rays and with different initiators. Fig. 38 shows the spectra of poly(methyl methacrylate) prepared with (*a*) benzoyl peroxide in toluene at 100°C, resulting in a mainly syndiotactic configuration, and (*b*) prepared with butyllithium in toluene at -62°C, having predominantly isotactic structure. The peak at the extreme left in these spectra corresponds to chloroform protons and the one on the right is due to the reference substance (tetramethylsilane). The methoxy-group peak is at 6.40 τ. The α-methyl group gives a triplet at 8.78, 8.95, and 9.09 τ; the relative intensities of this triplet are proportional respectively to the amount of isotactic (*ddd*, *lll*), heterotactic

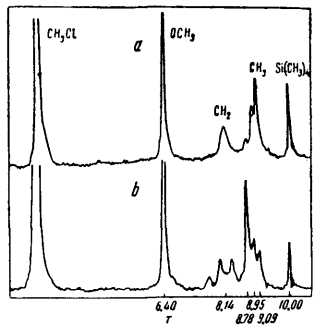


Fig.38. NMR spectra of chloroform solutions of poly(methyl methacrylate); *a*) syndiotactic; *b*) isotactic [171].

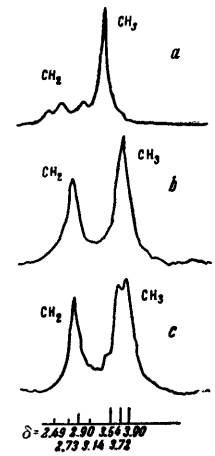


Fig.39. Sections of NMR spectra of chloroform solutions of poly-(methyl methacrylate): *a*) isotactic; *b*) syndiotactic; *c*) atactic [172].

(*ldd*, *dll*, *ddl*, *lld*), and syndiotactic (*ldl*, *dld*) sequences in the polymer chain. CH_2 protons give a signal at 8.14 τ. In the syndiotactic polymer (*a*) both protons are equivalent and give a single line. In the isotactic poly(methyl methacrylate) (*b*) the CH_2 protons experience different screening fields and consequently are non-equivalent. Each proton, due to spin–spin interaction, gives a doublet resulting in four peaks (one of the peaks is obscured). Thus it is possible to determine the polymer structure from the analysis of the NMR spectrum of poly(methyl methacrylate).

Johnson and Tessmar [172] come to similar conclusions by comparing NMR spectra of three samples of poly(methyl methacrylate). Sections of NMR spectra of poly(methyl methacrylate) dissolved in chloroform with CH_2 and α-CH_3 lines are shown in Fig.39 (the chemical shift δ is expressed in p.p.m. relative to H_2O). In the atactic polymer the methyl protons have a triplet with δ = 3.54, 3.72, 3.90. In the isotactic polymer there is only one line with δ = 3.54, and in the syndiotactic polymer δ = 3.90. It appears that the structure of ordinary atactic poly(methyl methacrylate) is similar to that of the syndiotactic polymer.

Nishioka *et al.* [173] obtained high-resolution spectra for 3% chloroform solutions of several stereoregular poly-(methyl methacrylate) of samples prepared with various Grignard reagents. It was found, in agreement with the results discussed above, that in the spectrum of the isotactic polymer, having a helical conformation, the CH_2 signal shows a hyperfine splitting arising from different screening effects for the two protons by the carboxyl group. In the syndiotactic poly(methyl methacrylate) the shielding of the two protons is identical, so that a single broad line is obtained.

Kern and Pustinger [174] found that the NMR spectrum of isotactic polystyrene dissolved in deuterochloroform and in thionyl chloride contains two lines due to protons in CH and CH_2 chain groups in addition to those for *ortho*-, *meta*-, and *para*-protons. The spectra of technical atactic polystyrene and of polystyrene prepared with an n-alkyllithium or alkylsodium catalyst contain only one line due to chain protons.

Analysis of high-resolution NMR spectra enables us to distinguish between *trans*- and *cis*-isomers. Chien and Walker [175] showed that the spectra of solutions of *trans*- and *cis*-isomers of dimethyl 1,4-cyclohexanedicarboxylate are different and that the spectra of samples prepared with ethylene glycol polyesters are identical. Comparison of line intensities in the polyester and dimethyl ester spectra shows that on polyesterification parts of the resulting polymer have *trans*- and *cis*-configuration in the ratio of 3 : 2, independently of whether the initial ester has *cis*- or *trans*--configuration.

2. Heterogeneous (Two-Phase) Systems

The shape of the NMR signal obtained from a two-phase sample, containing a polymer (solid) and a small-molecule substance (liquid or gas), depends on the nature of interaction between the molecules of the two phases.

The degree of mobility of molecules of the low-molecular-weight substance plays a decisive role. We can distinguish three possible cases: (1) the gas or liquid is loosely bound to the solid phase and retains most of its mobility, (2) the structure of the small-molecule substance is somewhat changed under the influence of the solid phase and the mobility is partially reduced, and (3) the gas or liquid molecules are strongly bound to the solid. All the three cases are encountered in real systems and the NMR technique enables us to obtain data on the composition and interaction of the two phases.

If the sample consists of a solid and a loosely bound liquid, the NMR line has two components. A strong narrow liquid line is superimposed on a weak broad line of the solid material; the intensity of the narrow line depends on the amount of the small-molecule substance. A line shape of this type has been observed in nylon containing 5% of water [176]. This characteristic line structure of a two-phase system, solid–water, enables us to determine the moisture content of hygroscopic materials. Shaw and Elsken [177] show that the height of the derivative of the water absorption line

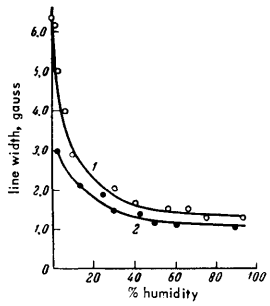


Fig.40. NMR line width for water adsorbed on (1) cellulose and (2) charcoal as a function of relative humidity of the air [197].

in various materials, *viz.* wood, apple pulp, etc., is proportional to the water content. The NMR method of determining moisture content is used for many plant materials [178], and is particularly useful for granulated materials [179]. It has many advantages [180]: the determination takes only a few minutes, the sample is not damaged, and the method is quite general. Equipment required for the determination of moisture content by NMR has been described [241] — commercial NMR spectrometers have become available [181].

NMR spectra of many large molecule–water systems reveal that there is an interaction between water molecules and polymer macromolecules, so that the structure of water changes, resulting in an appreciable broadening of the water signal. This phenomenon was investigated in detail for a starch–water system [182,183]. It was shown that broadening of the water line in starch gels is accounted for by formation of a four-coordinate water lattice. Icelike orientations of water molecules were also revealed by NMR spectra of biological substances; suspension of tobacco mosaic virus [184], eye humour [185], etc.; the water proton signal is also broadened in the presence of deoxyribonucleic acid [186].

An appreciable broadening of the line is observed when molecules of the low-molecular-weight substance are strongly bound to the polymer, *e.g.* adsorbed on its surface. The theory of nuclear magnetic resonance of a system in adsorption equilibrium [187,188] shows that the relaxation time depends on the rate of exchange between free and adsorbed phases. The NMR method was used in measurements of adsorption of vapours and gases on activated charcoal [189], water and methane on titanium dioxide [190,191], water on silica gel [187,192] and clays [193], organic materials on various sorbents [194–196], and other systems, but a discussion of these results falls outside the scope of the present review. The dependence of line shape [197] and correlation time τ_c [198,199] on ambient humidity was studied in a cellulose–water system. Fig. 40 shows the dependence of absorbed water line width on the ambient humidity of air [197]. It appears that even for high humidities (40%) (considerable adsorption) the line remains broad. Correlation of the dependence of δH on humdity with adsorption isotherms [197] indicates that multimolecular layers are formed on cellulose. Comparison of correlation frequencies obtained from NMR and from dielectric measurements shows that the water adsorbed on cellulose has low mobility [199]. Sasaki *et al.* [200], using the spin-echo method, determined the mean lifetime of adsorbed water molecules in the water–cellulose system.

The theory of relaxation in water adsorbed by polymers was developed by Miyake [201].

VI. BIBLIOGRAPHY OF NMR EXPERIMENTS ON POLYMERS‡

Natural rubber [41,49,91–97,118,129,131,150,151,202–205].
Butadiene copolymers [49,94–97,129,135,150,202,204,205].
Isobutene polymers and copolymers [49,95–99,104,106,115,119,129,137,161–164,167,216].
Polyisoprene, polychloroprene [119].
Polyurethane [119].
Polystyrene [49,120,121,132,135,144,159,160,163–165,168,174,206–210].
Polyacrylates [49,78,98,99,112,113,120,121,124,134,136,149,171–173,210–215,217–222].
Poly(vinyl chloride) [56,108,109,120,121,123,131,132,159,223,224].
Poly(vinyl alcohol) [122,130,134,143,225–228].
Poly(vinyl acetate) [120,136,212,213].
Polyamides [59,110,131,142,157,158,176,229–237].
Polyesters [89,111,125,131,141,175,226,238,239,242–247].
Polyethylene [41,52,54–57,59–64,66,67,69–71,74,75,77,85–88,94,97,101,103,108,109,123,132,135,138,140,201,228,248–254].
Polypropylene [58,64,65,68,72,79,80,81,97,103,255–258].
Polybutene [34,68,258].
Polypentene [68,258].
Epoxy-resins [45,148,152,153].
Proteins [144,166–169,233,234,240,259–261].
Fluorine-containing polymers [50,52,76,77,83,84,90,102,107,108,109,123,126,131,133,135,155,156,223,228,262–270].
Organosilicon [40,100,127,128,170,203,271–274].

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CATALYTIC POLYMERISATION OF 1,2-EPOXIDES

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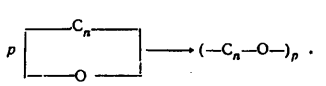
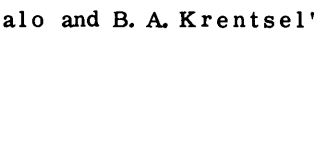
1. INTRODUCTION

Following the discovery that the simplest aldehyde would yield a stable polymer, polyformaldehyde, which possesses valuable complex technological properties, greater interest was shown in the various problems of polymerising aldehydes and ketones using the C = O bond and polymerising 1,2-epoxyalkanes by opening the three-membered heterocyclic ring[1-15]. Thanks to their valuable properties the polyethers so formed, which possess hetero-chains, have found application in many fields of present-day technology.

The polymerisation of oxygen-containing monomers to form polyethers can be represented in general as follows:



Various types of polymer are formed depending on the value of n: polyaldehydes (polyformaldehyde, polyacetaldehyde, etc.) when $n = 1$, polyoxyalkenes when $n = 2$,



, Penton, when $n = 3$, and polytetrahydrofuran when $n = 4$.

In this article we shall consider only one of the possible ways of obtaining polyethers — the catalytic polymerisation of 1,2-epoxyalkanes and their derivatives.

2. STRUCTURAL FEATURES OF MONOMERS CONTAINING THE EPOXIDE GROUP

Organic oxides can be considered to be internal ethers of 1,2-glycols, but they possess a higher reactivity than ordinary ethers, as noted by Würtz[1] and Brühl[2]. The explanation of the increased reactivity as due to the presence of strain in the three-membered ring, in accordance with Baeyer's theory[3], was widely accepted. Zimakov[4] made a detailed study of the structural features of epoxyethane in relation to its chemical and physical properties. Epoxyethane was found to be similar in its reactions to ethylene; this similarity must arise from the structures of the two molecules being analogous[5]. In 1947 there was some discussion in "Nature" on the structure of epoxyethane and cyclopropane[6], which led to Walsh's paper[7]. He concluded, from experimental results, that epoxyethane contains electron bonds which, in their lability, are more like the π bonds in alkenes than normal C–C and C–O bonds. It was shown by independent methods that in the epoxyethane and cyclopropane molecules the hybridisation of the valence electrons of the carbon atoms is not sp^3 as in alkanes, but sp^2 as in alkenes. At the present time it is widely acknowledged that the bonds in alkenes and 1,2-epoxides are of a related type[8]. The particular reactivity of 1,2-epoxides is attributed to a change in the valence state as a consequence of the considerable distortion of the

valence angles in the molecule. This results in the formation of easily polarisable bonds of a new type which are therefore very reactive. Different substituents in the three-membered ring either weaken or strengthen the polarisation and hence affect the reactivity of the oxide substantially. It follows, from the similarity between the structures of ethylene and epoxyethane, that, under certain conditions, epoxides can undergo polymerisation, like the alkenes, to form macromolecular compounds.

3. CATALYSTS FOR THE POLYMERISATION OF EPOXIDES

There has been considerable research on the polymerisation of 1,2-epoxides, and in particular of epoxyethane [9,10] and 1,2-epoxypropane [11-25].

The catalytic polymerisation of epoxyethane was first carried out by Staudinger and Schweitzer [5,6,26,27]. The catalysts used were alkali metals (Na, K), their hydroxides, and ammines. The catalytic action of a number of Lewis acids ($AlCl_3$, $FeBr_3$, $SnCl_4$), metal oxides (Al_2O_3, SiO_2), and organometallic catalysts was investigated [9,12,17,28-31]. The polyoxyalkenes so obtained are liquid or waxy with molecular weights of the order of several ten thousand. With alkaline-earth metal hydroxides, in particular $Be(OH)_2$ and $Mg(OH)_2$, as catalysts the molecular weight of the polymer was increased to a hundred thousand [31].

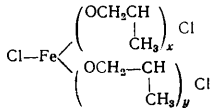
The active catalysts for the polymerisation of organic oxides are shown in Table 1. Catalysts I, II, and III are metal alkoxides with or without added metal halides [12,14,15,32,33]. Catalysts IV and V [13,34] are organometallic compounds which react with epoxides to form the corresponding metal alkoxide:

$$MR' + CH_2(O)CH{-}R \rightarrow M{-}O{-}CH_2{-}CH(R')(R)$$

The activity of the catalyst in the polymerisation process is therefore determined to a considerable extent by the reactivity of the corresponding alkoxide.

The following structures are proposed for the active catalysts VI [16,35,36]: $RMO(MO)_pMR$, $ROM(OM)_pOMR$, $ROM(OM)_pOMOR$. Catalyst VII is not very active and gives low-molecular-weight polymers [17]. However, in the presence of organometallic cocatalysts (AlR_3, ZnR_2) it will produce high-molecular-weight polymers from epoxyethane and 1,2-epoxypropane [13]. Catalyst IX, the so-called "complex" catalyst of Pruitt and Baggett [18], is obtained from anhydrous ferric chloride or bromide and 1,2-epoxypropane. Price and coworkers [11], and later Colclough and Gee [12], observed that the polymerisation of 1,2-epoxypropane on anhydrous ferric chloride takes place in two stages. The first, which is fast, proceeds at room temperature but the polymerisation goes no further at this temperature. On raising the temperature to 80° (optimum), polymerisation occurs with 100% conversion of the monomer.

Colclough and Gee [12] examined the product from the first stage. They found that five moles of 1,2-epoxypropane are combined with each mole of anhydrous ferric chloride, and showed that the Cl^- content in the catalyst obtained slightly exceeds one equivalent on the basis of the original $FeCl_3$-1,2-epoxypropane complex. This indicated that only two chlorine atoms in the ferric chloride molecule are replaced by 1,2-epoxypropane. The structure proposed for the reaction product is



where $x + y = 5$.

It was shown in our paper [20] on the production and investigation of this catalytic system that the catalysts prepared according to Pruitt and Baggett [18] and Price [11] on the one hand, and according to Bořkovec and Jackson [19] on the other, have different elemental composition, infra-red spectra, and catalytic activity in the polymerisation of 1,2-epoxypropane and 3-chloro-1,2-epoxypropane. The difference in their composition is shown in Table 2.

TABLE 1. Catalysts for the polymerisation of organic oxides*.

No.	Name	Formula	References
I.	Metal alkoxides	Al $(OR)_3$; Zn $(OR)_2$; Fe $(OR)_3$	12, 14, 3, 2
II.	Alkoxide complexes	$MgAl(OR)_5$; $CaAl(OR)_5$	15
III.	Metal alkoxides + metal halides	Al $(OR)_3 + ZnCl_2 + FeCl_3$ Ti $(OR)_4 + ZnCl_2$	32, 33
IV.	Metal alkyls	AlR_3, ZnR_2, MgR_2	13, 34
V.	Metal alkyls + metal halides	$AlR_3 + FeCl_2$; $AlR_3 + NaF$	15, 34
VI.	Metal alkyls + water	AlR_3, MgR_2, $ZnR_2 + H_2O$	16, 35, 36
VII.	Alumina	Al_2O_3 (activated)	13, 17
VIII.	Aluminosilicate + metal alkyls	$Al_2O_3 : SiO_2$ (13 : 87 by weight) $+ZnR_2$, AlR_3	13
IX.	Pruitt-Baggett catalyst	$FeCl_3$-1,2-epoxypropane complex	11, 18, 19, 37
X.	Partly hydrolysed $FeCl_3$-1,2-epoxypropane	$FeCl_3$-1,2-epoxypropane + water	12, 38
XI.	Alkaline-earth metal carbonates	$SrCO_3$; $CaCO_3$; $BaCO_3$	23
XII.	Alkali metal hydroxides	KOH, NaOH (powdered)	11, 39
XIII.	Lewis acids	$FeCl_3$; $AlCl_3$; $SnCl_4$; BF_3	12, 40
XIV.	Boron trifluoride-ether complex	$BF_3 \cdot Et_2O$	41

* The catalysts listed are active in the polymerisation of various epoxides. The polymers obtained have different molecular weights and, therefore, different properties.

TABLE 2. Composition of $FeCl_3$-1,2-epoxypropane catalysts.

Catalyst		C, %	H, %	Cl, %	Fe, %
$FeCl_3$-1,2-epoxypropane	ether	41.31 41.35	7.35 7.40	18.90 18.88	11.95 11.36
$FeCl_3$-1,2-epoxypropane	CCl_4	30.45 30.25	5.58 5.44	21.26 21.28	16.22 16.12
$FeCl_3$ – ether		11.02 12.05	4.11 4.17	38.51 38.49	24.17 24.40

In our opinion this difference is explained by the occurrence of coordinate bonding of ether to anhydrous $FeCl_3$ or to the $FeCl_3$-1,2-epoxypropane catalyst when the catalyst is prepared in ether, an oxonium type compound being formed. This produces additional steric hindrance in polymerisation. To confirm this hypothesis, anhydrous ferric chloride was dissolved in dry ether under the conditions for synthesis of the "complex". After removing the ether and evacuating to a very low pressure, the residue had the composition indicated above (see Table 2).

1,2-Epoxypropane was polymerised on this catalyst to a degree of conversion not exceeding 40–50%, giving a low-molecular-weight polymer (intrinsic viscosity in benzene 0.08–0.1). We showed that four moles of 1,2-epoxypropane are combined with one mole of anhydrous ferric chloride and this is confirmed by results on the preparation and examination of the catalyst obtained[20]. This catalyst is of great interest because polymerisation of a number of epoxides (1,2-epoxypropane, epoxybutane, 3,4-epoxybut-1-ene, 3-chloro-1,2-epoxypropane) takes place on it stereospecifically, like the polymerisation of alk-1-enes on Ziegler–Natta catalysts[21,22]. The catalyst dissolves in the monomer and can be modified by various additives so that polyoxyalkenes with regular structure and different molecular weights are obtained[12].

Catalysts XI (see Table 1), the alkaline-earth metal carbonates, are extremely active in the polymerisation of epoxyethane[23]. Powdered alkali metal hydroxides are also active in polymerisation. Price and coworkers[11,24] showed that potassium hydroxide is an active catalyst for the polymerisation of 1,2-epoxypropane at room temperature.

TABLE 3. Polymerisation of epoxyethane on the catalysts Al_2O_3, SiO_2, and Al_2O_3–SiO_2, with metal alkyls (0.25 mole monomer, 5 g of first component, 0.0125 mole metal alkyl, room temperature, 20 h, nitrogen atmosphere).

Catalyst	Solvent	Percentage conversion	$[\eta]$
Al_2O_3[a]	benzene	56	1.0
$Al_2O_3 + B(n\text{-}C_4H_9)_3$	benzene	40	0.6
$Al_2O_3 + Zn(C_2H_5)_2$	benzene	87	4.1
$Al_2O_3 + Cd(C_2H_5)_2$	benzene	34	9.4
$Al_2O_3 + C_2H_5MgBr$	ether + benzene	29	3.4
$Al_2O_3 + C_4H_9Li$	benzene	2.7	3.5
SiO_2	hexane	0	—
$SiO_2 + Zn(C_2H_5)_2$	hexane	0	—
$Al_2O_3 : SiO_2$[b]	benzene	0	—
$Al_2O_3 + B(n\text{-}C_4H_9)_3$	benzene	13	
$Al_2O_3 + Zn(C_2H_5)_2$	benzene	26	2.9
$Al_2O_3 + Cd(C_2H_5)_2$	benzene	3	
$Al_2O_3 + C_2H_5MgBr$	ether + benzene	44	1.7
$Al_2O_3 + C_4H_9Li$	benzene	traces	—
Pure metal alkyls are inactive		0	—

[a] Industrial catalyst (8–14 mesh).
[b] Catalyst for cracking petroleum, $Al_2O_3 : SiO_2$ (13:87).

TABLE 4. Polymerisation of 1,2-epoxypropane on the catalysts Al_2O_3, SiO_2, and Al_2O_3–SiO_2, with metal alkyls (0.25 mole monomer, 5 g of first component, 0.0125 mole metal alkyl, room temperature, 65 h, nitrogen atmosphere).

Catalyst	Solvent	Percentage conversion	$[\eta]$
Al_2O_3[a]	hexane	24	0.6
$Al_2O_3 + B(n\text{-}C_4H_9)_3$	benzene	10	slightly viscous
$Al_2O_3 + Al(C_2H_5)_3$	hexane	21	1.3
$Al_2O_3 + Zn(C_2H_5)_2$	hexane	27	2.3
$Al_2O_3 + Cd(C_2H_5)_2$	benzene	38	4.2
$Al_2O_3 + C_2H_5MgBr$	ether + benzene	9	0.5
$Al_2O_3 + C_4H_9Li$	hexane + benzene	8	0.9
SiO_2	hexane	0	—
$SiO_2 + Al(C_2H_5)_3$	hexane	20	1.9
SiO_2 + remaining metal alkyls	benzene, hexane	0	—
$Al_2O_3 + SiO_2$[b]	hexane	3	liquid
$Al_2O_3 + B(n\text{-}C_4H_9)_3$	benzene	32	liquid
$Al_2O_3 + Al(C_2H_5)_3$	hexane	23	0.4
$Al_2O_3 + Zn(C_2H_5)_2$	hexane	60	3.1
$Al_2O_3 + Cd(C_2H_5)_2$	benzene	1	0.6
$Al_2O_3 + C_2H_5MgBr$	ether + benzene	20	viscous semi-solid
$Al_2O_3 + C_4H_9Li$	hexane + benzene	1	liquid
Pure metal alkyls, other than $Al(C_2H_5)_3$, are inactive			

[a] Industrial Al_2O_3 (8–14 mesh).
[b] Catalyst for cracking petroleum, $Al_2O_3 : SiO_2$ (13:87).

Furukawa and coworkers[13] propose a binary system consisting of industrial granulated aluminium oxide or a catalyst for petroleum cracking, $Al_2O_3 : SiO_2$ (13 : 87 by weight) and an organometallic compound.

The catalytic activity of a large number of metal alkyls has been examined, the polymerisation of epoxyethane and 1,2-epoxypropane being widely studied (Tables 3 and 4).

It is interesting, and it has been noted a number of times, that polymerisation of 1,2-epoxyalkanes on pure organometallic systems does not produce regular polymers of high molecular weight[16,35]. Water and alcohols play a definite part. The work of Furukawa *et al.*[35] illustrates this cocatalytic effect.

The optimum molar ratio of water to diethylzinc is 1 : 1. This catalyst gives a crystalline polymer of racemic 1,2-epoxypropane (15.9% crystalline). When water is added to diethylzinc in hexane, a semisolid precipitate is formed and the solution turns yellow. After the hexane and excess diethylzinc had been removed by evacuating, a yellow, viscous oil, named fraction A, which was extremely active in polymerisation, was obtained from the residue. Its composition is 15.4% C, 3.27% H, 14.2% O, 67.1% Zn, gramme-atomic ratios C : H : O : Zn = 4.0 : 10.1 : 2.8 : 3.2. The following reactions have been proposed:

$$C_2H_5ZnC_2H_5 + H_2O \rightarrow C_2H_5ZnOH + C_2H_6,$$
$$C_2H_5ZnOH + C_2H_5ZnC_2H_5 \rightarrow C_2H_5ZnOZnC_2H_5 + C_2H_6,$$
$$C_2H_5ZnOZnC_2H_5 + H_2O \rightarrow C_2H_5ZnOZnOH + C_2H_6,$$
$$C_2H_5ZnOZnOH + C_2H_5ZnC_2H_5 \rightarrow C_2H_5ZnOZnOZnC_2H_5 + C_2H_6, \text{ etc.}$$

TABLE 5. Conditions: 3.5 ml 1,2-epoxypropane, 3.5 ml hexane, 3 mole % diethylzinc, room temperature, 24 h, nitrogen atmosphere.

$H_2O/Zn(C_2H_5)_2$, mole/mole	Conversion, %	$[\eta]$
0	0	—
0.25	traces	—
0.50	10.7	2.3
1.00	78.3	5.4
2.00	0	—
3.00	0	—

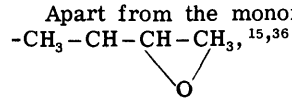
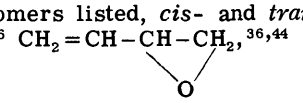
TABLE 6.

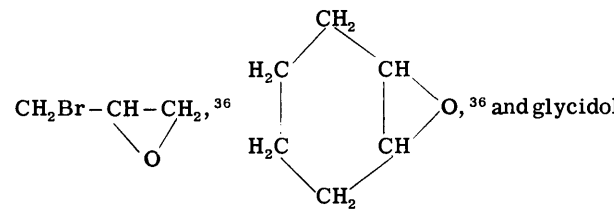
Monomer	Catalyst	Polymerisation conditions: T, °C	Polymerisation conditions: time	Conversion, %	Yield of solid polymer, %	Physical properties: m.p., °C	Physical properties: $[\eta]$	References
	Al_2O_3+Zn $(C_2H_5)_2$	room	20 h	87			4.1	42
	$FeCl_3$-1,2-epoxypropane	80	55 h	80	10	71—77		11
	Al $(CH_3)_3$ in n-hexane	(78) room	6 days	57.2	91.4	155		41
	$BF_3 \cdot Et_2O$	(—68) room	24 h	98	viscous liquid			41
	$BF_3 \cdot Et_2O$	room	72 h	51.3	does not melt even above 300°			41
	$FeCl_3$-1,2-epoxypropane	80	41 h	78.5	60.7	115		43
	KOH, NaOH	80				180—190		39
	$AlCl_3$	80	3 days	52	viscous liquid		0.018	12

We thus obtain a mixture of compounds of general formula $C_2H_5ZnO(ZnO)_pZnC_2H_5$, where $p = 0$ or any positive integer. These catalysts are insoluble in the reaction medium.

Okazaki[25] has examined the properties of a large group of inorganic oxides used in conjunction with diethylzinc. The binary catalysts were prepared by treating previously activated oxides with various amounts of diethylzinc. Bi_2O_3, MgO, CaO, BaO, Cr_2O_3, MoO_3, WO_3, TiO_2, SnO, MnO_2, V_2O_5, Sb_2O_3, ZnO, and also CaF_2 and NaF, were examined, the monomer being 1,2-epoxypropane. The yield of polymer and its intrinsic viscosity depended on the amount of diethylzinc added. The catalytic activity of the system is higher, the more ionic the binding in the metal oxide or fluoride.

Results on the synthesis of polyepoxy compounds using the catalytic systems described above are given in Table 6. Experiments have been selected which produce solid polymers of high molecular weight in good yield, or, if a solid polymer has not been obtained in a particular case, high-molecular-weight liquids.

Apart from the monomers listed, *cis*- and *trans*-  , [15,36]  , [36,44]

 , [36] and glycidol

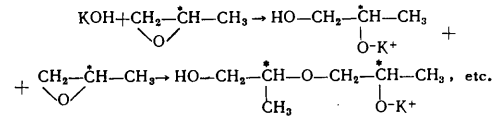
ethers (methyl, ethyl, isopropyl, isobutyl, allyl) can undergo polymerisation. However, there are only isolated data, in patents[15,44] and letters to editors[36], on the polymerisation of these monomers.

4. MECHANISM OF POLYMERISATION

Mechanisms of the polymerisation of organic oxides are only hypothetical as there has been almost no specialised research on this point[45]. The polymerisation is said to be a chain process involving slow production of active centres and fast chain propagation with a comparatively small increase in molecular weight from the start of the reaction to the end[23].

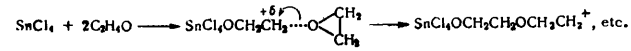
The polymerisation of epoxyethane on a $Be(OH)_2$ catalyst is different from this, the molecular weight of the polymer rising continuously during the process[30,31]. As the total amount of polymer formed grows, there is an almost parallel increase in molecular weight (Table 7).

There are various hypotheses as to the nature of the polymerisation. Price[11] showed that two polymers can be formed from 1,2-epoxypropane using a powdered potassium hydroxide catalyst — a crystalline polymer with m.p. 55.5° — 56.5° from the *l*-form of the monomer, and a liquid amorphous product of the same molecular weight (of the order of tens of thousands) from the racemic mixture. Retention of configuration of the asymmetric carbon atom is attributed to the ring's breaking at the primary carbon atom to give a secondary alkoxide of potassium:



A racemic mixture of polymer molecules is obtained from a racemic monomer. The polymerisation is anionic.

Worsfold and Eastham[40] proposed a cationic mechanism for the polymerisation of epoxyethane with Lewis acids as catalysts:



As noted above, polymerisation on anhydrous ferric chloride takes place in two stages. Gee[12] found, by studying the product from the first stage, that it proceeds by a cationic path:

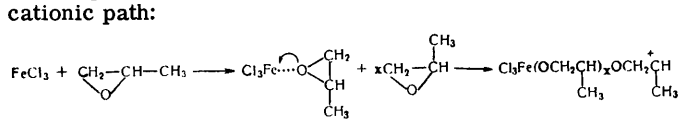
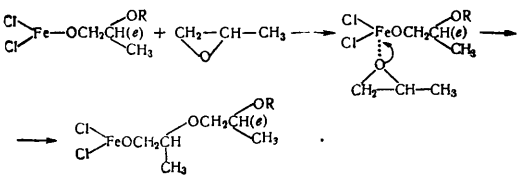


TABLE 7. Polymerisation of epoxyethane on $Be(OH)_2$ at 75°.

Polymerisation time, h	Polymer yield, %	η_{sp}/C	Mol. wt.
4	5.7	0.17	6200
9	50.3	0.48	28600
20	78	0.73	72500
29	90	0.85	115000

The second polymer chain grows at the iron atom similarly. The first stage is terminated by transfer of chloride ions with formation of a compound to which the structure $ClFe(OR)_2Cl_2$ is ascribed.

Further polymerisation occurs by a coordination mechanism. Price's scheme [11] for the complex formation and growth is given below for one OR group (it is similar for the second).



In this instance, besides the crystalline polyoxypropene, an amorphous material is always formed which has the same molecular weight regardless of whether it is obtained from the *l*- or *d*-monomer, or even from the racemic mixture. We may therefore suppose that a change in configuration of the asymmetric carbon atom is possible in the polymerisation process. Corey [45] agrees with the "coordination polymerisation" mechanism proposed by Price [11] but considers that polymerisation on ferric chloride takes place with retention of configuration because the polymer obtained from *l*-epoxypropane has the same specific rotation as that obtained using a potassium hydroxide catalyst. However, he does not take into consideration that, in the polymerisation of *l*-epoxypropane, an amorphous, optically inactive polymer is obtained as well as the crystalline, optically active one. He considers that, in the polymerisation of the *dl*-epoxide, the growing chain reacts selectively with that enantiomer which is involved in the catalyst formation stage, because such addition is the most favourable sterically. The polymeric racemate is shown to be a mixture of *l*- and *d*-macromolecules by the melting points of the crystalline fractions from *l*- and *dl*-monomers being the same and by the lack of optical activity in the crystalline polymer obtained from the racemate monomer.

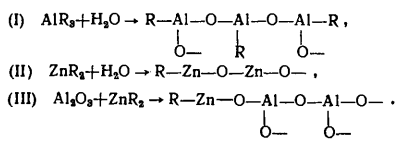
In Price's opinion the steric regularity is due to the heterogeneity of the catalytic system used. Formation of the coordination complex occurs as a result of chemisorption of the monomer on microcrystals of catalyst dispersed in the reaction medium [11]. However, this hypothesis of Price is open to argument because we have shown that the monomer–catalyst system ($FeCl_3$-1,2-epoxypropane + + 3-chloro-1,2-epoxypropane) is completely homogeneous [20]. The latter was confirmed by filtering a solution of the catalyst in the monomer through a bacteria filter with a pore size of 0.7–1 μ. The filtrate was just as active as the original solution.

In our view the cause of the steric regularity is the optically active nature of the monomers and the extremely complex structure of the catalysts, of the alkoxide type, which result in steric hindrance in the addition of a monomer molecule. The orientation of the monomer molecule takes place at the stage in which the coordination complex of the monomer and catalyst is formed. Coordination is achieved because there is a lone pair of electrons on the oxygen of the three-membered ring and an unfilled *d*-electron shell in the iron atom.

In the presence of water the third chlorine is removed from the $Cl-Fe(OR)_2$ catalyst on heating to the polymerisation temperature (80°).[12] It is still not known whether this hydrolysed catalyst is a compound of the type $OHFeOR_2$, $Fe(OR)_3$, or $(OR)_2Fe-O-Fe(OR)_2$. The action of water raises the yield of crystalline polymer and therefore such a catalyst must result in great steric hindrance to the addition of the monomer.

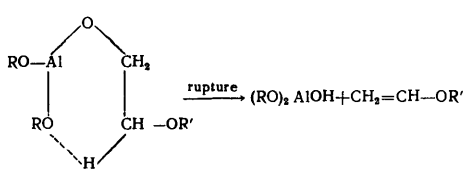
It has been noted that, in polymerisation of epoxy-compounds on organometallic and alkoxide systems, the cause of steric regularity is the heterogeneity of the system. Ebert and Price [46] report that catalytic solutions of triethylaluminium give a Tyndall cone and therefore contain colloidal particles, which are probably formed by reaction of the alkylaluminium with water or oxygen. The surface of these colloids creates a general steric hindrance and provides the necessary short-range order in the system being polymerised.

The structure of the alkylaluminium + water catalytic system is to some extent similar to the diethylzinc + water and Al_2O_3 + $ZnEt_2$ systems, suggested by Furukawa [35]:



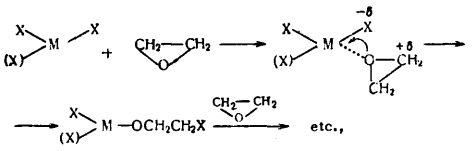
Although the surface of these structures provides activity, it also causes the chief steric hindrance which results in the monomer being absorbed regularly.

Proposals as to the mechanism of polymerisation on aluminium propoxide and isopropoxide in conjunction with anhydrous zinc chloride are not quite clear. In their earlier work, Price and coworkers [32] noticed that, in the polymerisation of 1,2-epoxypropane with aluminium isopropoxide, the reaction stopped after an initial period in which it proceeded rapidly. This "autoinhibition" was prevented by adding anhydrous zinc chloride. Starting from the "coordinate propagation" scheme, it was proposed that chain initiation and growth take place on the Al(iso-$-OC_3H_7)_3$. Rupture of the chain produces an unsaturated polymeric molecule and inactive $(OR)_2AlOH$:



The action of the zinc chloride is to change the inactive $Al(OR)_2OH$ into the active $Al(OR)_2Cl$.

In later work [10] it was found that the two catalysts (aluminium alkoxide and zinc chloride) react with the epoxyethane or epoxypropane independently of each other and a "coordinate propagation" scheme can be proposed for each:



where M = Zn or Al, and X = Cl or $OCH(CH_3)_2$.

As only a monomeric molecule is coordinated with the metal atom, the cationic character of the carbon atom bound to the oxygen is highly developed. The anionic character of the chlorine atom or isopropoxide group also increases, promoting migration of the monomer. Furthermore, zinc chloride by itself is a catalyst for polymerisation of epoxyethane and 1,2-epoxypropane.

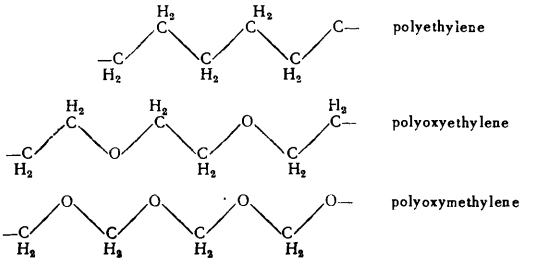
5. PROPERTIES AND STRUCTURE OF POLYMERISED OXIDES

The properties of known polyethers have been little studied. There are several references to melting points, intrinsic viscosities, solubilities, and, less often, X-ray diffraction patterns and infra-red spectra, but only a few to determinations of molecular weights by various methods [10,13,24,33]. Terminal hydroxyl groups have been determined by esterification with phthalic anhydride [10], and the possible unsaturation by bromination of the polymer dissolved in chloroform [10]. Polyoxypropylene prepared on powdered potassium hydroxide at room temperature contained both hydroxyl groups and double bonds [24]. The ratio of the hydroxyl number to the bromine number was 1 : 0.67.

There are contradictory data for the properties of the epoxyethane polymer obtained on the aluminium isopropoxide + zinc chloride system. Miller and Price [33] found one double bond per polymeric molecule, but Ebert and Price [10] did not detect any double bonds in polyoxyethylene prepared under similar conditions. Our determination of hydroxyl groups and the degree of unsaturation in polyoxychloropropylene prepared on Pruitt and Baggett's catalyst ($FeCl_3$--1,2-epoxypropane), using the methods described [10,47], did not give reproducible results. The reasons for this are unknown.

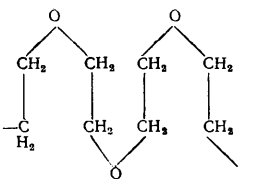
The molecular weights of liquid polymers were determined cryoscopically in benzene, by Rast's method in cyclopentadecanol (K_f = 21.3) or *p*-nitrotoluene (K_f = 7.8), [10] or by calculation from the intrinsic viscosity. For polyoxypropylene in benzene, $[\eta] = 1.4 \times 10^{-4} M^{0.8}$ [46]. For polyoxyethylene in aqueous solution at 20°, the formula $\eta_{sp}/C = 9.8 \times 10^{-4} M^{0.59}$ was used [33].

No papers specially devoted to the structure of the main chain in polymerised oxides have been published. According to Staudinger [26], if crystalline polyoxyalkenes are assumed to have a chain structure similar to the paraffins and polyoxymethylene, these materials should have similar melting points and solubilities, polyoxyethylene occupying a position intermediate between polyethylene and polyoxymethylene.



However, the properties of polyoxyethylene do not agree with this hypothesis. Thus polyethylene with a degree of polymerisation equal to 90 has m.p. 110° and is soluble in chloroform with difficulty. The dimethyl ether of polyoxymethylene with $\bar{p}$ = 44 has m.p. 160° and is also soluble in $CHCl_3$ with difficulty. Polyoxyethylene with $\bar{p}$ = 30 has m.p. 40°–55° and dissolves easily in $CHCl_3$.

The viscosity of its solutions shows, moreover, that for the same degree of polymerisation the chain of polyoxyethylene is considerably shorter than expected (and in fact equal in length to the chain of polyoxymethylene). This, and also the extremely high solubility of polyoxyethylene in water, can be explained by a twisted or puckered form of chain [26].



In mono- and di-substituted polyoxyethylenes, all the forms of chain proposed for substituted polyalkenes (isotactic, syndiotactic, atactic) are probably obtained. The course of oxygen ring opening on polymerisation is determined by the nature of the substituents and the reaction conditions [48]. There is a greater probability of breaking the bond between the primary carbon atom and the oxygen than of the bond between the secondary carbon and the oxygen. This leads to retention of configuration in the polymer link after migration of the monomeric, optically active molecule. An isotactic polymer chain structure has been proposed for polyoxypropylene [47]. Its supermolecular structure is spherulitic [13].

The properties of the known polymerised epoxides show an extreme variety, and therefore some of these polymers have already found application in many branches of industry. Polyoxyethylene of various molecular weights is widely used in the pharmaceutical industry as a hydrophilic base, owing to its high solubility in water and its complete physiological inactivity [50,51]. It is also used as a plasticiser for polyurethane resins [41].

Solid polymers of 1,2-epoxides (of 1,2-epoxypropane, 3-chloro-1,2-epoxypropane, epoxybutane, etc.) can be used to produce castings, films, fibres, and in various compositions for coatings. They possess high strength, owing to their regular structure, good dielectric properties, and keep their elasticity even at temperatures as low as -70°. [23]

It is clear that the polymerisation of 1,2-epoxides and investigation of the structure and properties of the polymers obtained are of great theoretical and practical interest. The synthesis of sterically regular polyether compounds from optically active monomers and racemic mixtures forms part of the extremely interesting and complex problem of directed stereosynthesis.

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APPLICATION OF POLAROGRAPHY TO ORGANIC CHEMISTRY

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I. INTRODUCTION

The present review is dedicated to the centenary of Butlerov's theory of the structure of organic compounds and to the fortieth anniversary of the invention by J. Heyrovský of the polarographic method of analysis, which is being successfully employed at the present time for the investigation of the structure, properties, and reactions of organic compounds.

By 1959 the number of publications on the theory and practical applications of polarography exceeded 10 000, with a steady increase in the annual output[1]. The award in 1959 of a Nobel prize to Heyrovský testifies to world recognition of the scientific and practical value of polarography.

The polarographic method consists essentially in an examination of the relation between current and potential in the electrolysis of a dilute solution of the test material in the presence of an inert electrolyte. The electrolysis is carried out in a special cell at a polarised microelectrode (usually a dropping mercury electrode), the potential of which is measured relative to that of a macroelectrode, most often a saturated calomel half-cell.

The relation between current and potential is expressed graphically in the form of polarisation curves or polarograms. These make it possible to estimate the quantity of the test material from the magnitude of the limiting current i_d and to determine its nature from the half-wave potential.

The main parameters in polarography are the half-wave potential $\pi_{\frac{1}{2}}$ and the wave height i_d. The former is defined as the potential corresponding to the point on the polarogram whose ordinate is $\frac{1}{2}i_d$. Quantitative polarographic analysis is based on measurement of the limiting current (wave height), which in most cases is governed by diffusion of the substance towards the electrode, and is represented by the Ilkovič equation[2]

$$i_d = 60.7\, n D^{1/2} m^{2/3} t^{1/6} C,$$

where n is the number of electrons involved in the electrode reaction, D the diffusion coefficient of the test substance (in $cm^2\ sec^{-1}$), m the quantity of mercury flowing through the capillary (in $g\ sec^{-1}$), t the drop time (in sec), and C the concentration of the polarographically active substance (in moles $litre^{-1}$).

In deriving this equation, Ilkovič introduced the concept of the half-wave potential and elucidated its physical significance. Lingane and Loveridge[3], Stackelberg and Strehlow[4], and Koutecký[5] subsequently modified the Ilkovič equation to allow for the fact that diffusion takes place, not linearly, but towards a curved surface.

The theory of polarography has now been developed in considerable detail, and accounts of it can be found in several textbooks, monographs, and handbooks[6-15]. The main literature on polarography is listed in the monograph mentioned in Ref. 13.

Among the early polarographic investigations, quite a large number were concerned with the reduction of organic compounds. Nevertheless, during the first decades it was the polarography of inorganic compounds which was mainly developed, since the reactions of organic compounds at a mercury electrode proved to be too complex to be interpreted unambiguously at that time. With the development of the theory of polarography, the investigation of organic compounds, which had been spasmodic in character, began to play an important part in the experimental verification of theory.

The publication of several monographs on polarography in the early 1940's contributed to the further development and growth in popularity of the method. Until recently, however, it has evolved solely as a highly sensitive electrochemical method of analysis. By means of polarography, it became possible to analyse complicated systems, both inorganic and organic, without preliminary separation, isolation, or purification of the components.

The value of the method, however, is not exhausted merely by its analytical application. While remaining a very convenient method of analysis, polarography has also become an important means for solving various problems of theoretical chemistry, mainly organic; applied in combination with one or more physicochemical methods, and sometimes alone, it can give extremely valuable results.

Research workers have recently taken an increasing interest in the polarography of organic compounds, since it has proved possible to solve several quite complicated problems of the structure and reactions of organic compounds.

The surveys of the polarography of organic compounds published regularly by Wawzonek[16-21] normally cover all the work in which polarography has been used, and the still not very numerous theoretical investigations of organic compounds and their chemical reactions are lost among the hundreds of papers of an analytical character.

The present review represents an attempt to summarise the principal achievements of the application of the polarographic method to organic chemistry.

At the present time polarography is employed in organic chemistry in several ways: (1) in studying the structure of organic compounds; (2) in studying the nature and positions of substituents and their effect on reactivity; (3) in detecting hydrogen bonds and chelate rings; (4) in studying tautomeric changes; (5) in studying geometrical isomerism; (6) in solving problems of chemical kinetics; (7) in studying molecular rearrangements and reactions; (8) for identifying natural products[22]; and (9) in studying the physical properties of compounds (for example, diffusion coefficients, surface activity[23]).

A large amount of experimental results has been amassed since the invention of polarography, and this cannot be reported and discussed in detail in a single paper. The present review covers mainly work carried out during recent years, which, in the opinion of the reviewers, is of the greatest significance for organic chemistry.

II. INVESTIGATION OF STRUCTURE AND THE EFFECT OF SUBSTITUENTS ON THE REACTIVITY OF ORGANIC COMPOUNDS

The reactivity of a compound is determined by its structure. In polarography the electrochemical reaction taking place at the electrode has a numerical characteristic, the half-wave potential. Since an electrochemical reaction does not differ in principle from a chemical reaction, the half-wave potential to a certain extent characterises not only the "electrochemical" but also the "chemical" reactivity of a compound.

The half-wave potential of an organic compound is determined both by the nature and also by the position of the polarographically active group in the molecule, since, when more than one substituent is present, the value of $\pi_{\frac{1}{2}}$ is affected by their relative positions in the molecule. Thus the value of $\pi_{\frac{1}{2}}$ is directly related to the nature and the position of a substituent: *i.e.* both molecular structure and the effect of substituents on reactivity can be assessed from polarographic data.

During the early development of the polarographic method, Shikata and Tachi formulated their experimental "electronegativity rule of reduction potentials", according

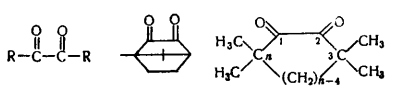
to which reduction of organic compounds is facilitated by the presence of electronegative groups in the molecule[24]. This rule enabled the influence of different substituents on the polarographic behaviour of organic compounds to be characterised qualitatively. Numerous investigations on this problem have confirmed the correctness of the Shikata–Tachi rule.

Thus it has been established that the introduction of electronegative groups into the α-position with respect to a carbon atom combined with a halogen atom facilitates the electrochemical reduction of the $-C-Hal$ bond, which is shown as a shift in $\pi_{\frac{1}{2}}$ to lower cathodic potentials. On passing from CH_3Br to CBr_4, the value of $\pi_{\frac{1}{2}}$ corresponding to reduction of the first carbon–bromine bond is displaced respectively from -1.60 V to -1.44, -0.60, and then to -0.26 V.[25] When oxygen-containing groups are introduced into the α-position with respect to the bromine in alkyl bromides, the shift in $\pi_{\frac{1}{2}}$ towards more positive potentials increases in the sequence CHOH < CHO < COOH.[26]

As Mairanovskii *et al.*[27] have shown, introduction of nitro-groups into the α-position also considerably facilitates reduction of a carbon–halogen bond, their effect increasing with increase in their number. In the series of bromides from bromonitromethane to bromotrinitromethane the half-wave potential shifts from +0.06 to +0.36, *i.e.* changes by 0.30 V. A similar effect is observed with the corresponding chlorides, the difference between the first and last members being still greater (0.76 V). Knowledge of the polarographic behaviour of various halogen derivatives enabled Postovskii and Beiles to establish the structure of the compounds obtained by the chlorination of naphthacene-5,11-quinone with sulphuryl chloride[28].

Polarographic investigation of several cyclic disulphides has shown that their ease of reduction is appreciably affected by the size of the ring[29]. It has been suggested on the basis of a polarographic study that α-lipoic acid is a six-membered cyclic disulphide[30].

Laitinen *et al.*[31] made a detailed study of the behaviour of the following 1,2-diketones:



and established in particular that the ease of reduction of cyclic diketones depends on the size of the ring and the extent of alkyl substitution at the α-carbon atom.

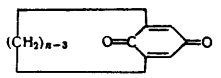
Krupička[32] investigated the effect of substituents in the 2-position on the ease of reduction of 4-hydroxy-3-methylcyclopent-2-en-1-one.

Several papers give values of $\pi_{\frac{1}{2}}$ obtained under comparable conditions for substituted nitrobenzenes[33,34], benzaldehydes[33,35,36], and iodobenzenes[33,37]. The results conform to the Shikata–Tachi rule, and explain the orienting effect of substituents in the benzene ring.

Coulson and Crowell[35] have established that an *ortho*-substituent has a weaker effect in benzaldehydes than in the corresponding acetophenones.

Valyashko and Rozum[38] showed, in a detailed investigation of the effect of substituents on the reduction of acetophenones, that, when one or two hydroxy- or methoxy-groups are introduced into the acetophenone molecule, reduction is most facilitated by a *para*-substituent.

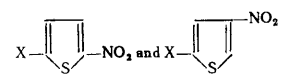
Prelog *et al.*[39] used a polarographic method to determine the effect of the size of the polymethylene ring in the 2,6-position on the reduction of a series of benzoquinones having the structure



where n was varied from 9 to 19. The values of $\pi_{\frac{1}{2}}$ obtained were close to those for 2,6-diethyl- and 2,6-dimethyl-benzoquinones. From this Prelog concluded that the polymethylene ring in these compounds is unstrained.

A polarographic study by Vladimirtsev and Postovskii[40] of some hydroxyazo-compounds showed that introduction of a hydroxy- or a methoxy-group *para* to the azo-group shifts the half-wave potential to more negative values owing to an increase in electron density on the azo-group. Introduction of a sulpho-group into the *para*-position, however, facilitates reduction, also in conformity with the electron-acceptor properties of this substituent.

The influence of substituents on the half-wave potentials of the following substituted nitrothiophens was studied by Tirouflet[41]:



where X = CH_3, I, $CH(OCOCH_3)_2$, CH=NOH, COOH, $COCH_3$, CN, $C(CH_3)$=NOH, CHO, $COOC_2H_5$. He also explained the mechanism of the nitration of substituted thiophens on the basis of the polarographic data.

The arrangement of the conjugated bonds involved in the reduction can be assessed from polarographic data, since reduction is known to take place more readily the longer the conjugated system and the larger the number of π-electrons participating in the conjugation.

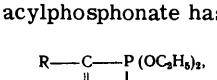
Fields and Blout[42] investigated the polarographic behaviour of a series of unsaturated aldehydes of general formula $CH_3[CH=CH]_xCHO$, where x = 1–5, and established that the half-wave potentials become more positive as double bonds accumulate in the molecule.

$CH_3CH=CHCHO$	1.20 V (relative to sat. calomel electrode)	
$CH_3(CH=CH)_2CHO$	0.98 V	ditto
$CH_3(CH=CH)_3CHO$	0.83 V	»
$CH_3(CH=CH)_4CHO$	0.72 V	»
$CH_3(CH=CH)_5CHO$	0.64 V	»

An analogous shift in half-wave potentials with accumulation of double bonds occurs also with ketones, indicating an increase in reactivity of the reducible multiple bond.

The existence of a double bond in the side-chain of 4-(4′-hydroxyphenoxy)-3,5-diiodocinnamic and 4-(4′-hydroxy-3′,5′-diiodophenoxy)-3,5-diiodocinnamic acids was demonstrated polarographically by Wawzonek *et al.*[43]

Ackerman *et al.*[44] showed on the basis of polarographic data that a diethyl acylphosphonate has the structure



and not one containing tervalent phosphorus, for in the latter case there would be no conjugation of the oxo-group with the $P\rightarrow O$ bond, and such a molecule could not be reduced at least up to -2 V; these workers confirmed this structure spectroscopically.

Polarography has been used also to determine the structure of the bactericidal preparation Allicin[45], the results indicating that it contains the compound

$$CH_2{=}CH{-}CH{=}CH{-}S{-}S{-}CH{=}CH{-}CH{=}CH_2.$$
$$\quad\quad\quad

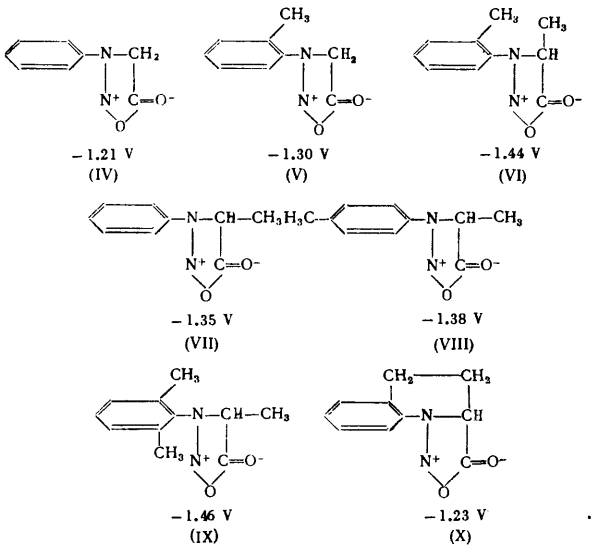
expected that hydrazones will be reduced at a dropping mercury electrode at more positive potentials than will enehydrazines, as was confirmed experimentally. The difference between the values of $\pi_{\frac{1}{2}}$ for these forms can serve as a quantitative measure of the bond interaction energy in these systems.

The reactivity and the properties of organic compounds are influenced by all the types of interaction between structural units in the molecule[50]. In most cases these interactions develop simultaneously, and it is by no means always possible to separate them. Since, however, polar effects and those due to conjugation often predominate over steric influences, they were assumed to be responsible for the polarographic behaviour of the compounds.

It has been shown recently that steric effects also can play a decisive part in the polarographic behaviour of some classes of organic compounds. The effect of spatial interaction on the polarographic behaviour of a molecule may hinder its reduction. Table 2 illustrates the influence of branching in the alkyl radical of an alkyl bromide on the reduction of a C – Br bond[51].

The more negative half-wave potentials observed with the *o*-alkylated compared with the *p*-alkylated nitrobenzenes, acetophenones, benzophenones, and azobenzenes[52,53] are also due to the steric effect of the *ortho*-substituent on the reduction of the polarographically active group (the so-called *ortho*-effect[50]).

Zuman[53] examined in detail various cases of a steric effect in the reduction of organic compounds at a dropping mercury electrode. Thus, for example, he detected the steric inhibition of coplanarity in alkylphenylsydnones[53,54] for which he found the following half-wave potentials:



Introduction of a methyl group into the *para*-position in the benzene ring causes a shift in $\pi_{\frac{1}{2}}$ of -0.025 V. The polar effect of an *ortho*-group should be of the same order. The negative shift in $\pi_{\frac{1}{2}}$ is considerably greater with the *o*-methylated than with the *para*-substituted 3-phenylsydnone and 4-methyl-3-phenylsydnone. Zuman explains this by the breakdown in coplanarity of the rings caused by an *ortho*-substituent. The relative positions of the rings should not be affected by a second *o*-methylation. The shift in the half-wave potential observed with di-*o*-methylated compared with the mono-*o*-methylated compounds is only that due to the polar effect of the methyl group.

TABLE 2.

Compound	$-\pi^*_{\frac{1}{2}}$, V
Ethyl bromide	2.13
Propyl bromide	2.20
Isobutyl bromide	2.32
Neopentyl bromide	2.37

* Relative to saturated calomel electrode. Supporting electrolyte — tetrabutylammonium iodide in dimethylformamide.

On ring closure between substituents (compound X), the benzene ring again becomes coplanar with the sydnone ring. Therefore the half-wave potential of X is more positive than that of 4-methyl-3-*o*-tolylsydnone.

With the polarographic behaviour of aldehydes of the holarrhiminic series as an example, Zuman showed that the spatial configuration of the molecule may affect the hydration of the functional group[53,55,56]. It was known that aldehydes are more difficult to reduce at a dropping mercury electrode than the corresponding aldimines. Aldehydes of the holarrhiminic series do not obey this rule: they are reduced at considerably more positive half-wave potentials than the steroid aldehydes, for example, which are similar in structure, and their aldimines are reduced at more negative potentials than the free aldehydes. Zuman explains such anomalous polarographic behaviour of these compounds by assuming that the aldehyde group is not hydrated owing to steric hindrance, whereas the carbonyl group of the steroid aldehydes is hydrated, which makes it more difficult to reduce than the carbonyl group in the holarrhiminic aldehydes. Therefore the possible hydration of the carbonyl compounds must be taken into account in assessing the intensity of reduction of such compounds and of their azomethine derivatives. In a review[53] Zuman quotes other examples of the application of polarography to the solution of stereochemical problems, which we shall discuss in greater detail below.

One of the most urgent problems of modern organic chemistry is to establish a quantitative relation between the structure of an organic compound and its reactivity. In the general case this problem still remains very complex, but partial regularities, represented by empirical and semiempirical equations, are readily available, and make it possible to express numerically the influence of structural units on the reactivity of a compound. This applies primarily to the well-known Hammett rule[57,58], which covers the rate constants and the equilibrium constants of nucleophilic substitution reactions of aromatic derivatives having substituents in the *meta*- and *para*-positions, and also the Taft rule[50], derived from the rate of hydrolysis of esters of aliphatic carboxylic acids. We shall discuss in greater detail the use of these semiempirical rules in organic polarography.

Most electrochemical reactions involving organic substances take place irreversibly; the value of $\pi_{\frac{1}{2}}$ is proportional to the logarithm of the rate constant of the irreversible process[59-61]:

$$\pi_{1/2} = \frac{RT}{\alpha n F} \ln 0.87 k_f \cdot \sqrt{\frac{t_1}{D}},$$

where α is the transport number, t_1 the drop time of the mercury electrode, D the diffusion coefficient, and k_f° the specific rate constant of the electrode process, the magnitude of which is determined by the free energy change for the compound.

In order to establish a quantitative relation between the value of $\pi_{\frac{1}{2}}$ and the effect of substituents on reactivity, it is necessary to investigate the electrochemical behaviour under identical conditions of a series of compounds containing the same polarographically active group and different substituents, and the mechanism of the electrochemical reaction undergone by the functional group must be identical within this series.

If $\pi_{\frac{1}{2}}^0$ and $\pi_{\frac{1}{2}}^*$ represent half-wave potentials of unsubstituted and substituted compounds respectively, the following relation is obtained for irreversible processes:

$$\pi_{1/2}^* - \pi_{1/2}^0 = \Delta\pi_{1/2} \simeq \Delta \ln k_f^\circ = \ln \frac{k_{f^\circ}^*}{k_{f^\circ}^0}.$$ [61]

This expression corresponds to Hammett's equation[57], which for an electrochemical reaction becomes

$$\Delta\pi_{1/2} = \rho'\sigma, \qquad (A)$$

where ρ' is a constant for a certain type of electrochemical reaction, and measures the susceptibility of the reactive centre (polarographically active group) to the influence of substituents; and σ is a constant measuring the effect of a given substituent in the benzene ring on the reducibility of the compound, its value depending on the position and the nature of the substituent.

Using the principles of theoretical organic chemistry, Taft[50] divided the changes produced by substituents into polar, steric, and conjugation effects. As mentioned above, these effects are in most cases additive, *i.e.* the value of $\Delta\pi_{\frac{1}{2}}$ is governed by the sum of these three factors. When the polar effect predominates, Taft's equation becomes for an electrochemical process

$$\Delta\pi_{1/2} = \rho'\sigma^*; \qquad (B)$$

where σ^* is the polar constant of the substituent in an aliphatic compound. This σ^* is analogous to the Hammett constant, but is written with an asterisk to denote the difference in its nature and origin[61]. Values of σ and σ^* have been tabulated[50,57,58].

We considered above the effect of different substituents on the ease of reduction of different benzene derivatives. The conclusions reached on the basis of the experimental data were qualitative in character. Recently the validity of Eqn. (A) has been demonstrated for a large number of electrochemical reactions of benzene derivatives containing substituents in the *meta*- and *para*-positions[61-68], and the possibility of a quantitative assessment of the effect of substituents was shown. Each series of reactions studied is characterised by a definite value of ρ'.

Fig. 1 shows the dependence of $\pi_{\frac{1}{2}}$ on σ values given in Zuman's review[61]. Some substituents [NH_2, $(CH_3)_2N$, OH] can conjugate, when in the *para*-position, with the double bond of the reducible group. This explains frequent deviations in the values of $\Delta\pi_{\frac{1}{2}}$ found for these substituents from those required by a linear relation between $\pi_{\frac{1}{2}}$ and σ.

Some authors[62] ascribe the discrepancies in the values of $\pi_{\frac{1}{2}}$ with *p*-amino-compounds to the influence of the supporting electrolyte (participation of the amino-group in salt formation), which increases the σ value.

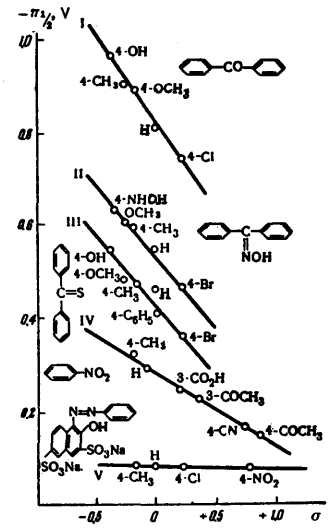


Fig. 1. Variation of half-wave potential with the σ value of substituent:
I) benzophenones (pH 0); II) oximes of benzophenones (pH 0); III) diphenyl sulphones (pH 0); IV) nitrobenzenes (pH 2.0); V) phenylazonaphthalenes (pH 2.6).

Where the values of $\pi_{\frac{1}{2}}$ for *para*-substituents deviate from a linear variation with the σ values, ρ' can be determined from the plot of $\pi_{\frac{1}{2}}$ against σ for the corresponding *meta*-substituents. This can then be used to calculate more exact σ values for the *para*-substituents from the half-wave potentials of the compounds. In this way polarographic results can be used to calculate σ values from the known value of ρ' and these can be used for the quantitative characterisation of homogeneous organic reactions.

If the half-wave potential shifts to more positive potentials with increase in the positive σ value of the substituent (*i.e.* with increase in its electrophilic character), the sign of ρ' will be positive, in conformity with the kinetics of homogeneous reactions. This is the case with the vast majority of electrochemical reactions undergone by organic compounds at a dropping mercury electrode. The mechanism of the potential-determining stage was found to be the same for these reactions — nucleophilic addition of an electron.

When the benzene ring contains more than one substituent in the *meta*- and *para*-positions or the compound contains two substituted benzene rings combined with the polarographically active group, the effects due to the substituents have been shown to be additive[61,63-67]:

$$\Delta\pi_{1/2} = \rho\Sigma\sigma.$$

With *ortho*-substituted benzene derivatives, in which, as mentioned above, steric interaction occurs, Zuman[61] suggests using the Hammett equation in the following form:

$$\Delta\pi_{1/2} = \rho'\sigma_0 - \delta E_0. \qquad (C)$$

where E_0 is a steric coefficient, values of which are given in Tables[50], and δ is a steric constant of the electrochemical reaction, which is found in a similar manner to ρ'.

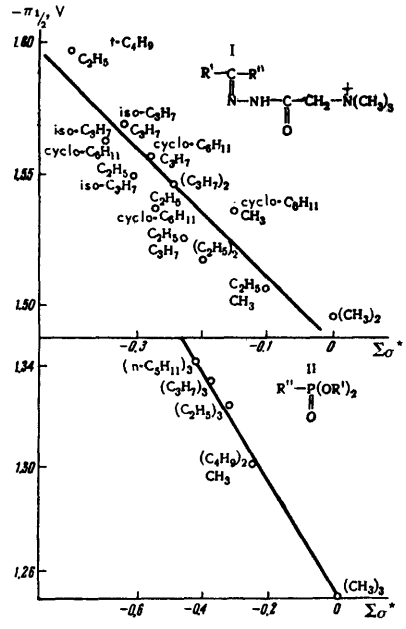


Fig. 2. Dependence of half-wave potentials on the $\Sigma\sigma$ values of substituents:
I) β-ene hydrazones; II) phosphonic esters.

Thus by means of Eqn. (C) it is possible to give a numerical value to the steric effect of an *ortho*-substituent on the reduction of a particular group in an aromatic compound. Elving *et al.*[69] were the first to point out the possibility of using the Taft equation (B) in the polarography of aliphatic compounds. Subsequently Zuman[61] confirmed the validity of Eqn. (B) for sixty series of electrochemical reactions undergone by various aliphatic derivatives. When more than one substituent is present in a compound, Eqn. (D) can be used with some approximation:

$$\Delta\pi_{1/2} = \rho'\Sigma\sigma^*. \qquad (D)$$

Here, too, the relation between $\pi_{\frac{1}{2}}$ and $\Sigma\sigma^*$ is satisfactorily represented by a straight line (see Fig. 2). With many electrochemical reactions of aliphatic compounds, it was found that ρ' could have a negative value, and steric effects as well as those due to conjugation are encountered far more often than in the aromatic series. The relation between $\pi_{\frac{1}{2}}$ and $\Sigma\sigma^*$ can, by analogy with the benzene series, be used to form the basis of a quantitative measure of these effects.

Kabachnik and his collaborators[70] have been carrying out a great deal of work on the quantitative assessment of the reactivity of several organophosphorus compounds using the Hammett equation. Although the polarographic study of such compounds has been far from adequate, and it is as yet difficult to say anything about the mechanism of their electrode reactions, we have used published data[71] to plot $\pi_{\frac{1}{2}}$ against $\Sigma\sigma^*$ for phosphonic esters (see Fig. 2), for which the values of $\pi_{\frac{1}{2}}$ lie satisfactorily on a straight line.

The value of ρ' may depend on the pH of the solution, the solvent, etc. It is better to compare half-wave potentials of substituted compounds under conditions such that $\pi_{\frac{1}{2}}$ is independent of pH, or else in a pH range where $d\pi_{\frac{1}{2}}/d\text{pH}$ has approximately the same value for compounds of the given series.

More detailed accounts of the problem of assessing quantitatively the effect of substituents on the reactivity of organic compounds, as well as various cases of the use of Eqns. (A)–(D) for predicting half-wave potentials and establishing the mechanism of an electrode process, can be found in papers by Zuman[61] and Nürnberg[65].

III. DETECTION OF HYDROGEN BONDS AND CHELATE RINGS

A hydrogen bond represents a special type of intermolecular or intramolecular interaction between a hydrogen atom which tends to ionise and an atom which has a lone pair of electrons and is located close to the hydrogen atom in space.

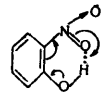
Although the hydrogen bond has attracted the attention of many investigators during the past two decades, its nature has still not been finally elucidated. Whether a hydrogen atom forming such a bond remains in a fixed position or whether it oscillates between two equilibrium positions remains an unsolved problem.

The presence of hydrogen bonds in compounds produces changes in several of their physical properties, such as solubility, boiling and melting points, optical properties, etc. A hydrogen bond also has a certain effect on the chemical behaviour of compounds. Hydrogen bonds are studied mainly by infra-red spectroscopy (the occurrence of shifts in the characteristic frequencies of functional groups).[72] If, however, hydrogen bonding involves a polarographically active group, it can be successfully detected by a polarographic method, which is considerably simpler and more convenient than infra-red spectroscopy.

The present section will be confined to a consideration of intramolecular hydrogen bonds. Intermolecular bonds, which result in the association or hydration of molecules, and determine the state of a substance in solution, will be discussed in the section on the kinetics of chemical reactions.

The earlier work, referred to in Terent'ev and Yanovskaya's monograph[14], was concerned with hydrogen bond formation in various aliphatic and aromatic hydroxy-nitro-compounds and flavanols. A hydrogen bond, for example, facilitates the reduction of *o*-nitrophenol, whereas the esterification of this compound, by destroying the hydrogen bond, increases the value of $-\pi_{\frac{1}{2}}$. The half-wave potential of *o*-nitrophenol is also displaced towards negative values at pH ~11, which indicates that the hydrogen bond has disappeared owing to formation of the phenoxide, in which hydrogen bonding is impossible.

The formation of a hydrogen bond usually facilitates the electrochemical reduction of an active group; for example, several *ortho*-substituted benzaldehydes and nitrobenzenes are reduced at a more positive potential than the *para*-isomers (by about 0.05–0.07 V). This is probably due to a strengthening of conjugation by intramolecular hydrogen bonds, which complete a ring of conjugated multiple bonds in these compounds.

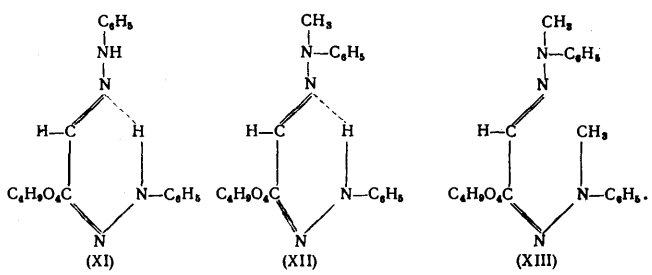


Cases are known, however, in which hydrogen bonding hinders reduction. The hydrogen bond weakens the conjugation, lowering the activity of the reducible group, as in the flavanols, for example.

Rabinowitz and Wagner[73] showed by a polarographic method that a hydrogen bond is formed between the nitro- and the imino-groups in 4-nitrobenzoimidazole. This method has also enabled the presence of a chelate ring to be demonstrated in *o*-nitroaniline[74], *o*-nitroacetanilide, and *N*-*o*-nitrophenyl-*N'*-phenylacetamidine[75], and also the presence of a hydrogen bond in 2-cyclohexyl-4,6-dinitrophenol and 4-cyclohexyl-2,6-dinitrophenol[76].

Wiles[77] also detected the presence of hydrogen bonds in several hydroxyanthraquinones, and Miller and Wagner found them in nitrobenzotriazole[78]. Holleck *et al.*[79] have published a quite detailed survey of work on the effect of a hydrogen bond on the half-wave potentials of various nitrobenzenes, -benzaldehydes, and -naphthols, so that there is no need to give here a list of all the cases of the polarographic detection of hydrogen bonds.

Study of the behaviour of glucosazones at a dropping mercury electrode has shown that compounds (XI) and (XII) have a chelate structure, since they are reduced at the same potential, whereas osazone (XIII), in which a hydrogen bond cannot be formed, is reduced at a potential which is 200 mV more positive[80].



(XI) (XII) (XIII)

Haas and Lynch[81] investigated the hydrazones of aldopentoses, and found that the observed currents were kinetic in character, since they were independent of the height of the mercury reservoir. The kinetic nature of the reduction process was indicated also by the high temperature coefficient (6.86% deg^{-1}). They concluded that these hydrazones have a cyclic structure. The rate of the kinetic process

hydrazone (cyclic form) → hydrazone (acyclic form)

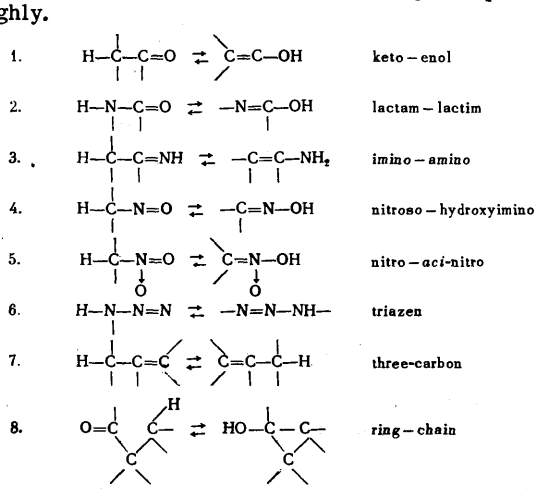
governs the height of the polarographic wave.

In a polarographic study of the complexes formed by 2,3-dimercaptopropanol with heavy metals, Zuman and Zumanova[82] found that Au^{III}, Hg^{II}, $C_6H_5Hg^{I}$, and Cu^{II} form mainly chelate compounds. They determined the composition of the complexes from the anodic wave.

Polarography has been used also to study the stability of some internal complexes (chelate compounds)[14]. The half-wave potential of the metal ion in the complex is shifted towards negative values on formation of a chelate compound. The magnitude of this shift is a measure of the stability of the resulting complex. Several amino-acids, which are polarographically inactive but give chelate compounds in solution, can be determined polarographically by utilising the internal complexes they form[12], most often with copper ions.

IV. STUDY OF TAUTOMERIC CHANGES

The phenomenon of tautomerism, or dynamic isomerism, first correctly explained by A. M. Butlerov, constitutes one of the main branches of theoretical organic chemistry. The most important tasks in studying the tautomerism of organic compounds are to define the tautomeric forms, study their interconversion, and determine the position of tautomeric equilibrium as a function of the medium and the structure of the compounds. The following are the principal tautomeric systems which have now been investigated quite thoroughly.



1. keto – enol
2. lactam – lactim
3. imino – amino
4. nitroso – hydroxyimino
5. nitro – *aci*-nitro
6. triazen
7. three-carbon
8. ring – chain

The phenomenon of dynamic isomerism occurs also in more complicated systems.

The problem of determining the position of equilibrium and the influence of the medium and of various substituents in displacing this equilibrium is often difficult to solve or even altogether insoluble by chemical methods. Various physical methods (spectroscopy, determination of magnetic susceptibility, refractive index, etc.) are therefore most often used in the study of tautomerism. However, these methods frequently prove to be ineffective, and therefore here too the application of polarography seems to be very promising.

The difference in structure between tautomeric forms results in a difference in energy, and hence in polarographic behaviour. It is possible by means of polarography to study the kinetics of tautomeric conversion, determine the equilibrium constant, investigate the effect of solvent and of structural changes on the position of equilibrium, etc. The brief electrolysis at a mercury electrode which is involved has no effect on the tautomeric system. However, many difficulties are still encountered in realising these possibilities. By obtaining polarograms in different solvents and at different pH values, it is easy to establish the presence of tautomerism and to ascertain the conditions for the existence and interconversion of the tautomers. But in the interpretation of a polarogram the presence of tautomeric forms may be assumed erroneously if it is not borne in mind that the presence of more than one wave may be due also to a stepwise reduction, the dissociation or hydration of the compound, a change in the mechanism of reduction with change in the pH of the solution, etc.

In order to avoid errors in deducing the structure of tautomers, it is necessary to apply where possible other physicochemical methods as well, and it is also essential to study the mechanism of the reduction of the compounds at the electrode, the effect of the pH of the medium, the

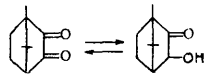
concentration of depolariser, and other factors on their polarographic behaviour. A chemical proof of tautomerism is also undoubtedly important.

A paper by Muller and Baumberger[83] provides an example of an incorrect conclusion that keto–enol tautomerism is present in pyruvic acid. Brdička[84] showed, on the model of the polarographic behaviour of phenylglyoxylic acid, in which enolisation is impossible, that the reason for the appearance of two waves with change in pH in Muller and Baumberger's experiments was not enolisation, but the existence of undissociated and dissociated forms of these acids in solution.

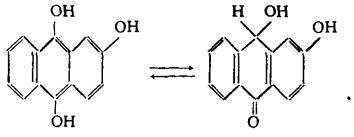
The polarographic method was used by Shikata and Tachi for studying keto–enol tautomerism as early as 1931,[85] and it has been subsequently employed many times for the same purpose. A large proportion of the earlier work, much of which is now only of historical interest, has already been discussed more than once (see for example Refs. 14 and 86).

Strange as it may seem, the classic example of keto–enol tautomerism, the acetoacetic ester, has not yet been subjected to polarographic investigation. It is mainly more complicated systems which have been studied. Thus a polarographic study of *l*-α-hydroxybenzyl methyl ketone and of 1-hydroxyethyl phenyl ketone in aqueous–alcoholic solutions showed that these compounds are in tautomeric equilibrium, and exhibit on the polarograms two waves in the pH range 4.5–7. The tautomeric equilibrium constants were found to be 0.6 and 1.8 in alkaline and hydrochloric acid solutions respectively[87].

Modiano[88] applied polarography to the study of the keto–enol tautomerism of camphorquinone. At pH ~12 its reduction uses up one electron, which Modiano explained by enolisation of the quinone:

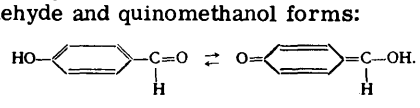


Gill and Stonehill[89] investigated the tautomerism of 2-hydroxy- and 2,6-dihydroxyanthraquinols. They found that within a certain pH range each compound gives an oxidation wave, the height of which diminishes with time. A new cathodic wave develops simultaneously, this being caused by reversible tautomeric conversion of the compounds to the corresponding oxanthranols:



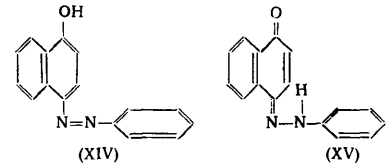
The position of tautomeric equilibrium varies with pH, maximum conversion to the oxanthranol occurring at pH 8.85–9.52.

The two waves of *p*-hydroxybenzaldehyde at pH 5.4–7.2 were ascribed by Kemula *et al.*[90] to tautomeric equilibrium between aldehyde and quinomethanol forms:



A study of methods for purifying and crystallising streptomycin revealed that it exists in two tautomeric forms, as was subsequently confirmed by a polarographic investigation of its solutions. Henser *et al.*[91] observed that fresh solutions of crystalline and amorphous streptomycin each give one wave, and then a second wave develops. A solution of the double salt of calcium chloride and streptomycin trihydrochloride gave two waves at once. These tautomeric changes were ascribed to changes in the aldehyde group of the streptomycin molecule, since they do not occur with salts of dihydrostreptomycin.

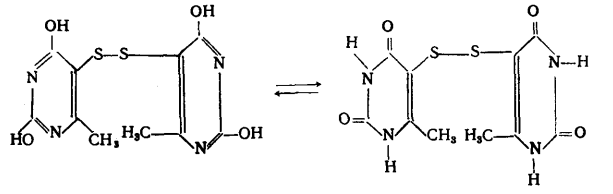
Phenylazo-1-naphthol showed no tautomerism under the polarographic conditions (aqueous–alcoholic acetate buffer solution)[40]:



(XIV) (XV)

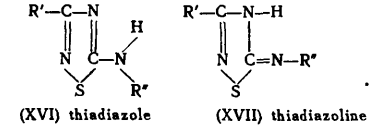
No wave was observed at the potential at which the fixed form of (XV) (the hydrogen atom on the N atom replaced by methyl) is reduced, which indicates the overwhelming predominance of structure (XIV) in the system.

A "lactam–lactim" type of tautomeric change was observed in a polarographic study of bis-2,4-dihydroxy-6--methylpyrimidin-5-yl disulphide, which in alkalis undergoes tautomeric conversion to a polarographically inactive lactim form, the polarogram showing a decrease in wave height with time:



It also proved possible to confirm the presence of a disulphide group in this compound[92].

Interpretation of polarograms obtained in the investigation of tautomerism usually requires that polarograms should also be obtained for solutions of model substances of rigorously fixed structure. This approach was employed, for example, by Sturm and Hans[93] in studying the imino–amino tautomerism of thiadiazoles:

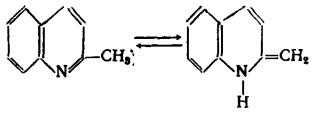


(XVI) thiadiazole (XVII) thiadiazoline

Compounds having a fixed thiadiazole ring, which is aromatic in character, are reduced at negative potentials (around 2.1–2.2 V). Thiadiazoline derivatives are reduced at half-wave potentials of about -1.6 V (relative to the saturated calomel electrode). The thiadiazoles (XVI) studied by Sturm and Hans gave no wave with $\pi_{\frac{1}{2}} \simeq -1.6$ V. These workers concluded that the compounds have the enamine type of structure, but this cannot serve as a rigorous proof that the imino-form is completely absent, since the concentration of the latter might be below that which can be detected polarographically (10^{-5} M). These workers also demonstrated the absence of tautomerism in 2-aminobenzothiazole, in agreement with the spectroscopic data.

Stromberg[94] investigated the mechanism of the electrochemical reduction of quinoline, isoquinoline, and quinaldine in buffered solutions, and observed two waves on the

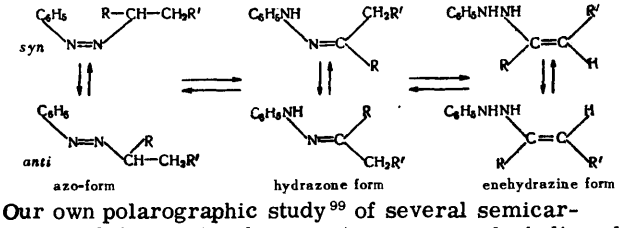
polarogram of quinaldine in the pH range 6.2–9.9, which were ascribed to its two tautomeric forms:



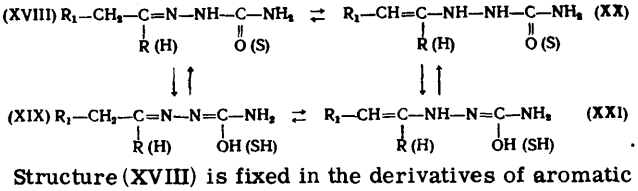
Korshunov and Shchennikova[95] consider, however, that both hydrogen ions and water molecules can take part in the reduction of the compounds, which then takes place at different potentials. In their opinion reduction involving hydrogen ions should take place in acid solutions, reduction involving water molecules in alkaline solutions, and both mechanisms should be possible in neutral solutions. But if this explanation is accepted as correct, it is still not clear, as Stromberg remarks, why two waves are absent from the polarograms of quinoline and isoquinoline at pH ~7.4.

Kitaev and Arbuzov[96-98] investigated the changes undergone by several arylhydrazones in methanol. By recording polarograms during the storage of alcoholic solutions of the phenylhydrazones of aldehydes and ketones, they obtained a set of curves for each compound. In order to interpret these curves, polarograms were also obtained for methanolic solutions of azobenzene and phenylazomethane as models of the azo-form, acetone *N*-ethyl-*N*-phenylhydrazone as a compound incapable of forming an azo-modification but able to form an enehydrazine, and benzaldehyde phenylhydrazone as a compound for which an enehydrazine form is impossible. Inspection of the polarograms established that phenylhydrazones of aliphatic and alicyclic ketones have the enehydrazine structure in freshly prepared solution. When solutions of these compounds are stored in the dark, the latter are converted *via* the hydrazone forms to mixed azo-compounds, and rearrangement of labile *syn*-isomers into stable *anti*-isomers also occurs. These workers found that potentials between -1.4 and -1.55 V correspond to waves due to enehydrazines; stereoisomers of mixed azo-compounds are reduced at potentials between -0.6 and -0.9 V, and those of hydrazones between -1.05 and -1.30 V.

In freshly prepared solutions the phenylhydrazones of aldehydes and of alkyl–aryl ketones have the hydrazone structure, and they are also gradually converted to the azo-compounds. On the basis of the polarographic data the following scheme was suggested for the tautomeric and stereoisomeric changes undergone by arylhydrazones:



Our own polarographic study[99] of several semicarbazones and thiosemicarbazones in aqueous–alcoholic solution showed that these compounds can in general exist in the following four forms:

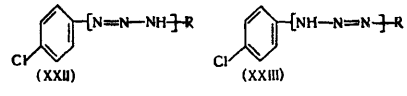


Structure (XVIII) is fixed in the derivatives of aromatic aldehydes. The semicarbazones and thiosemicarbazones of aliphatic aldehydes and ketones and of alicyclic ketones have structure (XX). These compounds probably have the same structure in the crystalline state as well, since it appears unlikely that, at the instant of dissolution, the multiple bond of the azomethine group would be almost entirely converted to a carbonyl group at a rate which cannot be measured. In alkaline solution form (XX) passes into the tautomer having structure (XXI). Structure (XIX) is fixed in benzaldehyde *S*-methylthiosemicarbazone. We have observed the equilibrium between forms (XVIII) and (XX) in the thiosemicarbazone of acetophenone. Solutions of cyclohexanone *S*-methylthiosemicarbazone yielded two waves corresponding to the two possible tautomers (XIX) and (XXI), which are in equilibrium. In the course of time, changes occur in alcoholic solution of the thiosemicarbazones of acetone and cyclohexanone, the enethiosemicarbazide form passing into a tautomer having a carbonyl structure. This information is the result of a preliminary study of these compounds.

The above technique for investigating tautomeric reactions, by recording the changes taking place in solution with time, appears to us to be most convenient for slow reactions. However, several conditions must be observed: the solvent should not vaporise on storage, the substance must not be subjected to the action of light, which might cause secondary processes, and it should not undergo oxidation, since the resulting products would give their own polarographic waves, which could be wrongly ascribed to tautomers[100]. Therefore before any conclusions are drawn it is first necessary to ascertain carefully the reasons for changes in the polarographic behaviour of solutions.

The only polarographic investigation of nitroso-hydroxyimino tautomerism which will be mentioned is the work of Tyutyulkov[101], who observed two waves with the *syn*-isomers of the oximes of aromatic aldehydes, which he ascribed to tautomers.

In a study of the structure and properties of some aromatic diazoamino-derivatives of guanidine it was found that compounds containing a triazen –N=N–NH– group can exist as two tautomeric forms:



[where R = CN or C(=NH)–C(CH$_3$)$_2$], which on polarographic reduction yield waves having different half-wave potentials. The compound having structure (XXII), like azobenzene, is reduced at -0.4 V (relative to the saturated calomel electrode), whereas the compound with structure (XXIII) is reduced at -0.21 V.[102] Polarographic data for the diazoamino-tautomeric equilibrium have enabled the differences in the behaviour of these compounds towards mineral acids to be explained.

The above work shows conclusively that polarography can be used to establish the presence of tautomerism and to determine the conditions for the existence and the interconversion of the tautomers. Furthermore, by enabling the concentrations of tautomers in solution to be followed separately, the polarographic method may provide great help in calculating the tautomeric equilibrium constants, *i.e.* in the quantitative characterisation of equilibrium isomerism. However, very few papers have been published on the quantitative study of the tautomerism of organic compounds.

Quite recently papers have appeared on the nitro–*aci*-nitro tautomerism of nitrocyclohexane [103] and of phenylnitromethane [104,105]. The nitro-form of the first compound gives a distinct wave over a wide pH range; the *aci*-form is stated [103] not to be reduced at a dropping mercury electrode. The investigation showed that at pH > 9.5 the nitro-form of nitrocyclohexane is completely converted to the *aci*-form (N → A), whereas at pH 4.5–7 the *aci*-form can be completely converted to the nitro-form (A → N). At pH 7.0–9.5 an equilibrium is established, which can be reached from both sides. The kinetics of the tautomeric conversion of nitrocyclohexane are represented by the equations

$$K_0\, a_{OH^-} = K_N = \frac{2.3}{t}\log\frac{C_0}{C_N}\ (N \rightarrow A),$$

$$\frac{K_0'\, a_{H^+}}{1+\frac{a_{H^+}}{K_1}+\frac{a_{H^+}^2}{K_1 K_2}} = K_A = \frac{2.3}{t}\frac{C_\infty}{C_0}\log\frac{C_\infty}{C_\infty - C_N}\ (A \rightarrow N),$$

where C_N is the concentration of the nitro-form at time t, K_N the experimental rate constant for the reaction N → A at constant pH, K_A the corresponding rate constant for the reaction A → N, K_0, K_0', K_1, and K_2 are constant at a given ionic strength, and a_{H^+} and a_{OH^-} represent the activities of the proton and of the hydroxide ion.

The following mechanism has been suggested for these reactions, based on the idea of an acid–base catalysis of the nitro–*aci*-nitro tautomeric conversion:

$$[C_6H_{10}=NO_2H]\,H^+ \overset{H^+}{\underset{K_2}{\rightleftarrows}} C_6H_{10}=NO_2H \overset{H^+}{\underset{K_1}{\rightleftarrows}} C_6H_{10}=NO_2^- \overset{\text{slow stage}}{\underset{\text{slow stage}}{\overset{H^+,K_0'}{\underset{OH^-,K_0}{\rightleftarrows}}}} C_6H_{11}NO_2\ ,$$

where K_0 and K_0' are the corresponding rate constants, $K_1 = [C_6H_{10}=NO_2^-][H^+]/[C_6H_{10}=NO_2H]$, and K_2 is the corresponding constant for the protonated complex $[C_6H_{10}=NO_2H]H^+$. The results obtained enabled the equilibrium constant of the process N → A to be calculated, as well as the activation energies of the processes N → A (18.4 kcal × × mole^{-1}) and A → N (16.0 kcal mole^{-1}).

Mairanovskii *et al.* [104,105] made a detailed polarographic investigation of the mechanism of the tautomeric changes undergone by phenylnitromethane. In conformity with the general principles of protolytic equilibria, they adopted a scheme of tautomeric conversions involving a single anion, similar to that given above for nitrocyclohexane. However, comparison with published data showed the inadequacy of such a scheme.

Using an original technique of investigation, these workers first established the polarographic activity of the *aci*-form of phenylnitromethane. When a solution of a salt of phenylnitromethane is acidified, the *aci*-form is formed practically instantaneously, and then changes gradually into the nitro-form at a rate depending on the acidity of the medium. Since the wave for the nitro-form is lower than that for the *aci*-form of phenylnitromethane, the isomerisation is accompanied by a gradual decrease in the limiting current of the polarographic wave due to the *aci*-form, which enabled the kinetics of its isomerisation to be studied. It was found that at pH < 2 the rate of isomerisation is independent of the hydrogen ion concentration, and represents the rate of interaction of the *aci*-form with water according to the equation

$$C_6H_5CH{=}NOOH + H_2O \rightarrow C_6H_5CH{=}NOO^- + H_3O^+.$$

With increase in pH the rate of isomerisation begins to rise, the pH at the start of the rise depending on the concentration of bases in the buffering system. With decrease in the concentration of the latter the inflection on the curve relating the rate of isomerisation and pH shifts to higher pH values. It was concluded from these results that the rate of isomerisation is governed by the rate of dissociation of the *aci*-form:

$$C_6H_5CH{=}NOOH + B \rightarrow C_6H_5CH{=}NOO^- + BH^+.$$

Mairanovskii *et al.* also studied the kinetics of the dissociation of phenylnitromethane when it reacts with various bases (B) and the kinetics of its recombination.

Brønsted's equation was applied to the reactions of *aci*-phenylnitromethane and phenylnitromethane with various bases and acids.

Kinetic analysis of the tautomeric changes undergone by this compound showed the existence of two types of anions, the *aci*- and the nitro-forms. As a result, the tautomerism of phenylnitromethane in aqueous solution, for the particular case in which water alone acts as base and H_3O^+ as acid, was represented by the following scheme:

$$\begin{array}{ccc} C_6H_5CH_2NO_2 + H_2O & \overset{K_{ND}}{\underset{K_{NR}}{\rightleftarrows}} & C_6H_5C{-}HNO_2 + H_3O^+ \\ K_1 \downarrow\uparrow K_2 & & \\ C_6H_5CH{=}NOOH + H_2O & \overset{K_{AD}}{\underset{K_{AR}}{\rightleftarrows}} & C_6H_5CH\,NOO^- + H_3O^+ \end{array},$$

where the subscripts attached to the rate constants K have the following significance: A and N the *aci*- and nitro-forms, and D and R dissociation and recombination, respectively.

This scheme is probably valid for other nitro-compounds as well. Thus the potentialities of the polarographic method are not confined to the qualitative identification of the reactions undergone by organic compounds, but also enable these reactions to be elucidated and evaluated quantitatively.

Until recently it was considered that tautomerism causes compounds to have dual reactivity. Nesmeyanov and Kabachnik [106] clearly showed the error of such a view. They concluded that dual reactivity is often due to the migration of a reactive centre along a conjugated chain. Polarography will probably be used in the near future to study the dual reactivity of organic compounds, of which, according to present-day ideas, tautomerism forms a particular case.

V. STUDY OF THE STEREOISOMERISM OF ORGANIC COMPOUNDS

The polarographic method for studying geometrical isomerism can be employed in all cases where the isomerism is due to different positions of substituents relative to an electrochemically active double bond, since the structure of organic compounds is known to have a definite effect on their polarographic behaviour. The different behaviour of isomers is caused by steric factors either hindering or facilitating the approach of the electrochemically active group to the electrode surface.

The investigations have shown that it is usually more difficult to reduce the *trans*-forms than the *cis*-forms, but cases are also known in which the opposite relation between the structure of isomers and their ease of reduction holds. In addition, the difference in adsorption and solvation properties between isomers also affects their electrochemical behaviour, and in some cases even the mechanism of cathodic reduction can change with structure. However,

the difference in the behaviour of stereoisomers at a dropping mercury electrode depends in most cases on the pH of the solution, and within a certain pH range the stereoisomers may give identical waves. This often complicates the polarographic study of stereoisomerism, and sometimes even makes it impossible.

Elving *et al.*[107] made a detailed study of the polarographic behaviour of maleic and fumaric acids, and found that, between certain pH values, the difference in half-wave potential is so great that the acids can be determined when present together.

Fig. 3 shows the relation between $\pi_{\frac{1}{2}}$ and solution pH for maleic and fumaric acids plotted from published data[107]. The difference in the relative reducibility of the C=C bond in these molecules is evidently determined by the difference between their dissociation constants. This is further confirmed by the fact that the ethyl esters of these acids, which contain no free carboxyl group, show essentially the same type of variation of $\pi_{\frac{1}{2}}$ with pH (Fig. 3), the difference in half-wave potential being almost independent of pH. The polarographic behaviour of *cis-cis-* and *trans-trans-*muconic acids proved to be identical, *i.e.* the polarographic method is unsuitable for their determination[108].

Ryvolova[109] investigated the conversion of *trans*-dibenzoylethylene to the *cis*-isomer on exposure of its solution to ultra-violet radiation. It was found that in acid medium the *cis*-isomer is reduced at a more negative range of potentials than the *trans*-isomer.

Mairanovskii and Bergel'son[110] made a polarographic study of the *cis-* and *trans*-isomers of some 1,2-dibromoethylenes having a hydroxyl group in the allyl position. They found the *trans*-isomers to be more readily reduced than the *cis*-isomers (see Table 3), which in their view is associated with the easier *trans*-elimination of two neighbouring bromine atoms.

Among the various derivatives of aldehydes and ketones which are used in analysis, considerable attention has been paid to the polarography of oximes[101,111-113] but no systematic study of their stereoisomerism has yet been made. Tyutyulkov[101,113] derived an empirical rule, according to which isomers which give two polarographic waves have the *syn*-configuration; if, however, only one wave is obtained on the polarogram of a solution of an isomer, this isomer has the *anti*-configuration. This rule was derived

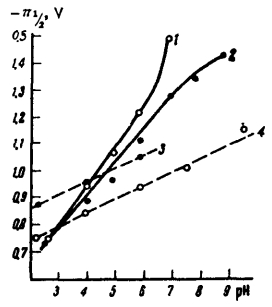
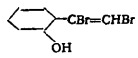
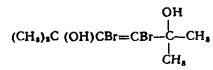


Fig. 3. Variation of half-wave potential with pH for maleic and fumaric acids and their diethyl esters:
1) fumaric acid; 2) maleic acid; 3) diethyl maleate; 4) diethyl fumarate.

TABLE 3.

Compound	$\pi_{\frac{1}{2}}$, V (relative to sat. calomel electrode)	
	trans-form	*cis*-form
	—1.15	—1.80
$(CH_3)_2C(OH)CBr{=}CHBr$	—1.42	merges with supporting electrolyte [LiBr + $(C_2H_5)_4NBr$ in 60% methanol]
	—0.72	—1.19

from the behaviour of the oximes of benzaldehyde and four of its derivatives in unbuffered solutions, but it can probably be applied to the stereoisomeric pair of other oximes.

In buffered solutions at pH ~4 the stereoisomeric oximes of benzaldehyde are indistinguishable polarographically, and it is only at higher pH values that distinct waves can be obtained for the *syn-* and *anti*-isomers[112]. With the oximes of cinnamaldehyde no separation of the waves was observed over the pH range 1.05–7.4.

Thus the half-wave potentials of stereoisomers depend on the pH of the solution, the form of the variation in $\pi_{\frac{1}{2}}$ with pH being different for each stereoisomer, so that the difference $\Delta\pi_{\frac{1}{2}}$, which is to some extent a measure of the energy of the stereoisomeric conversion, also depends on the acidity of the medium. This makes it difficult to use polarographic data to calculate this energy, since it is evidently not always possible to create standard conditions under which the values of $\pi_{\frac{1}{2}}$ for the stereoisomers would be governed solely by the free energy of the molecule.

A polarographic study of arylhydrazones by Kitaev and Arbuzov[96-98] showed that in general two geometrical isomers are possible for each tautomer. Thus the polarograms of benzaldehyde phenylhydrazone contained two pairs of waves, the first corresponding to the two stereoisomers of the azo-form ($\pi_{\frac{1}{2}}$ = -0.56 and -0.89 V), while the second pair (-1.08 and -1.20 V) were due to the *syn-* and *anti*-isomers of the hydrazones. Three pairs of waves could be traced on the polarograms of the phenylhydrazone of ethyl methyl ketone: in this case all three tautomers exhibited stereoisomerism.

Brockman and Pearson[62] investigated the polarographic reduction of stereoisomeric pairs of semicarbazones in a series of benzophenones. They found that in this case the difference in half-wave potential between the stereoisomers was quite insignificant (see Table 4).

Semicarbazones and thiosemicarbazones of aromatic aldehydes and aryl alkyl ketones can exist in two stereoisomeric forms, as our own polarographic study has shown[114]. On exposure of solutions of these compounds to ultra-violet radiation, a new wave appears on the polarograms, with a more positive half-wave potential. The height of this wave increases with increasing duration of irradiation. The appearance of a second wave on the polarogram is due to the formation of a labile species.

Much work has been done on the behaviour of *cis-* and *trans*-azobenzenes at a dropping mercury electrode, and this has been quite thoroughly discussed in monographs[12,14]. At pH ~8.5 both stereoisomers give waves at the same

TABLE 4.

Compound	$-\pi^*_{1/2}$, V
Benzophenone semicarbazone	1.104
4-Methoxybenzophenone α-semicarbazone	1.114
4-Methoxybenzophenone β-semicarbazone	1.117
4-Bromobenzophenone α-semicarbazone	1.048
4-Bromobenzophenone β-semicarbazone	1.050

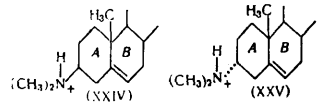
* At pH ~5.1, relative to 3.5M calomel electrode.

potential, and it is only in a faintly alkaline medium that they can be distinguished polarographically when they are present together. These results were subsequently confirmed by Castor and Saylor [115].

Freeman [116] found that *anti*-diazosulphonates are reduced polarographically at more negative potentials than the corresponding *syn*-isomers. Exposure of an aqueous solution of the stable isomer of a diazosulphonate to ultra-violet radiation or to sunlight, results in the appearance of a second wave on the polarogram, owing to formation of the labile species.

The polarographic behaviour of compounds is affected not only by geometrical isomerism but also by molecular conformation. The effect of the latter on the polarographic reduction of organic compounds was discovered with halogenated cyclohexanes [53,117].

Recently a study has been made of the effect of the geometrical configuration of organic molecules on their adsorption, which produces various capacitive phenomena [53,55]



A comparison was made of the behaviour of compounds (XXIV) and (XXV), which differ only in the location in space of the tertiary amino-group in position 3 of the steroid skeleton. The α-isomer (XXIV)† showed an increase in the capacitive current in a 0.1 M solution of LiOH in 50% ethanol. No such phenomenon was observed with the β-isomer. The isomers also differ in the suppression of polarographic maxima. Thus the α-isomer suppresses the oxygen maximum more strongly than does the β-isomer. The concentration of the latter required to halve the maximum is six times as great as that of the α-isomer. These results indicate that the α-isomer is more readily adsorbed on the dropping mercury electrode than is the β-isomer.

Differences in half-wave potentials cannot be expected with optical enantiomorphs, since such isomers do not differ in energy, and therefore polarography cannot be used to study this phenomenon. Diastereoisomers, in contrast, should differ in polarographic behaviour. Study of the cathodic reduction of the epimers of αα′-dibromotartaric acid [58,118,119] showed that the *erythro*-acid is reduced at a more positive potential than the *threo*-form, and by a different mechanism. The *threo*-dibromotartrate anion, however, is more readily reduced than the *erythro*-anion. With the dibromotartaric esters the difference in half-wave potential between the two epimers is insignificant.

† In I.U.P.A.C. nomenclature XXIV is the β-form.(Ed.of Translation).

The diastereoisomers of phenylcysteine have different catalytic effects on hydration evolution [120]. In ammoniacal Co^{2+} solution the *erythro*-form gives a higher catalytic wave than the *threo*-form of phenylcysteine. This difference is due to different values of the dissociation constants of the acids and also to a difference in the instability constants of the complexes formed by Co^{2+} with phenylcysteine.

VI. STUDY OF THE KINETICS OF CHEMICAL REACTIONS

The polarographic method has proved extremely convenient for observing the course of reactions, studying their kinetics and mechanism, and determining the structure of the final reaction products [121]. This field of application of the method has recently acquired very great importance both for organic and for physical chemistry. Opportunities for and ways of polarographic study of the course of a particular reaction depend on its velocity.

If the half-period of the reaction exceeds 0.5 min but is less than an hour, it is convenient to employ continuous recording of the change in concentration of one or more reactants. For this purpose a potential in the region of the limiting current of the corresponding reaction component is applied, the second reactant is introduced, and the magnitude of the limiting current, which is proportional to the concentration, is continuously recorded.

When the reaction is very slow (taking several hours or even longer), continuous recording is replaced by the usual method of obtaining polarographic waves from readings at definite time intervals, from which the concentrations of the reactants are found. Further, it is then no longer difficult to calculate the rate constants or the equilibrium constants of the processes by means of the well-known equations of reaction kinetics. From the temperature dependence of the resulting constant, the activation energy is obtained by means of the Arrhenius equation, and the entropy of activation by using the transition state theory. The following examples may be cited of the large amount of work on reaction kinetics based on such measurements.

Kastening *et al.* [122] studied the kinetics of the hydrolysis of benzylideneaniline and of the condensation of benzaldehyde with aniline. They found that hydrolysis of the anil was of first order, that its velocity depended on the acidity of the medium, and that it could be followed polarographically within the pH range 6–13.3, for hydrolysis is very rapid in a more acid medium. The effect of temperature on the hydrolysis was also investigated.

Fig. 4 shows plots of $\log K$ against solution pH, where K is the rate constant of the hydrolysis, whose value was calculated by means of the formula $K/2.3 = t^{-1} \log C_0/C_t$, C_0 being the initial concentration of anil in the solution and C_t the variable concentration determined polarographically. This investigation confirmed the hypothesis that hydrolysis takes place in two stages, the first involving addition of water at the azomethine double bond to form an amino-alcohol, which decomposes in the second stage.

The polarographic study showed that the condensation of benzaldehyde with excess aniline takes place by a mechanism similar to the hydrolysis but at a somewhat greater rate. Fig. 5 gives graphs for the dependence of the logarithm of the rate constant of condensation ($\log K$) on the pH of the solution. The values of K at different temperatures were used to calculate the thermodynamic properties of the reaction.

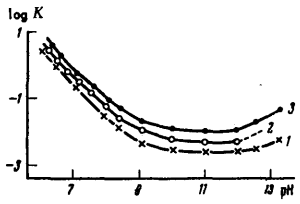


Fig.4. Variation with pH of the logarithm of the rate constant for the hydrolysis of benzylideneaniline:
1) 20.2°; 2) 30.4°; 3) 41.0°.

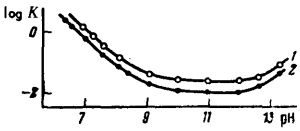


Fig.5. Variation of the logarithm of the rate constant with pH:
1) condensation of aniline with benzaldehyde;
2) hydrolysis of benzylideneaniline.

Crowe and Lynch [123,124] made a polarographic study of the kinetics of the condensation of formaldehyde with urea, acetamide, and benzamide. The reactions were followed by the change in height of the formaldehyde wave. These workers showed that the reaction of urea with formaldehyde to form monohydroxymethylurea is reversible. The activation energy of this reaction calculated from the polarographic data is 15.9 kcal mole^{-1} at pH 12.7, while that for the condensation of formaldehyde with acetamide is 13.85 kcal mole^{-1}, of the same order as in the condensation of formaldehyde with benzamide. The polarographic method showed that the increase in the rate of condensation with increase in pH is more rapid with benzamide than with urea or acetamide, owing to the influence of the phenyl radical on the reactivity of the carbamoyl group. Change in temperature has a considerably smaller effect than change in acidity of the medium on the rate of condensation. In view of the above facts, Crowe and Lynch suggested the following mechanism for the reaction of formaldehyde with amides:

$$H^+ + R{-}\overset{\overset{O}{\|}}{C}{-}NH^- + HCHO \rightleftarrows R{-}\overset{\overset{O}{\|}}{C}{-}NH{-}CH_2O^- + H^+ \rightleftarrows R{-}\overset{\overset{O}{\|}}{C}{-}NH{-}CH_2OH.$$

The rate of hydrolysis of nitrosamines in acid medium has been studied, the velocity constant being correlated both with the wavelength of maximum absorption and with the half-wave potential [125].

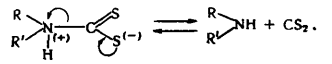
The results of a polarographic investigation of the course of hydrolysis of the sodium salt of *N*-*p*-chlorophenyldiazothiourea were used to study the stability of the preparation Muritan during storage and application [126].

The alkaline hydrolysis of some substituted isothioureas was measured by the growth of the anodic wave due to the thiol formed in this reaction [127].

Kofod [128] studied polarographically the kinetics of the isomerisation, in buffered solutions of pH 9.2–13.3, of the low melting hydroxyurea isomer. He found that, when the temperature is raised at pH ~12, the isomerisation is accompanied by partial decomposition of the hydroxyurea into hydroxylamine and a cyanate.

Zahradnik [129] studied the rate of reaction of some amino-acids with carbon disulphide in aqueous medium and in aqueous acetone in the presence of a buffer. From polarographic, spectroscopic, and chromatographic results, he suggested a reaction mechanism for the decomposition of dithiocarboxy-aminocarboxylic acids in acid medium.

Somewhat later Zahradnik and Zuman [130] investigated the kinetics of the decomposition of nine monoalkyl- and nine dialkyl-dithiocarbamic acids as a function of pH. They found that decomposition yields an amine and carbon disulphide, the rate-determining process being breakdown of the zwitterion, the concentration of which is governed by the dissociation equilibrium



Zuman *et al.* [131] investigated the rate of periodate oxidation of nine epimeric pairs of acyclic 1,2-diols of general formula RCH(OH)CH(OH)R'; they found the reaction to be of second order and catalysed by acids and alkalis. Zuman suggested that the rate-determining process in this reaction is proton transfer following interaction between the diol and the periodate. He also studied the effect of substituents (phenyl, alkyl) on the rate of oxidation of these diols. With hydrogen peroxide at pH > 6, dimercaptopropanol is readily oxidised, by a second-order reaction, to a disulphide [132–134]. Polarographic measurements showed that, when 2,3-dimercaptopropanol reacts with cystine, formation of a disulphide is accompanied by that of a monothiol by a second-order reaction [132–134].

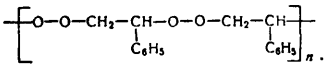
The same workers found that the anodic wave of dimercaptopropanol gradually disappears on reaction with benzoquinone, 1,4-addition taking place with two moles of the quinone. Both SH groups take part in the reaction, which occurs rapidly at pH 4–7.

A polarographic method has also been used to study the decomposition of adrenochrome during storage [135], and the photochemical decomposition of riboflavin, which was found to yield a mixture of glycolaldehyde, glyceraldehyde, and lumichrome [136].

Kreyči [137] investigated the variation with time, temperature, and solution pH of the concentration of the polarographically active intermediate formed in the decomposition of penicillin in acid medium. Comparison of the polarographic data with the ultra-violet absorption of penicillin solutions showed the intermediate to be very probably penicillic acid. He discussed in detail the reaction scheme suggested earlier, and calculated the rate constant at 25°.

Bricker and Vail [138] showed polarographically that the alkaline decomposition of streptomycin is of first order. Comparison of its velocity with that of the rearrangment of 2-hydroxy-2-methylpropionaldehyde into 3-hydroxybutan-2-one showed that both reactions were of first order, had the same activation energy, and exhibited the same dependence on pH. It was concluded from these observations that the rate-determining stage in the decomposition of streptomycin is rearrangement of the streptose residue to form a six-membered ring.

Barnes *et al.*[139] showed polarographically that, during the induction period in the emulsion polymerisation of styrene, oxygen plays an active part in the polymerisation, by forming with the styrene a polymeric peroxide:



The polarographic method has also been used to investigate the reaction mixture in the polymerisation of acrylonitrile and butyl methacrylate[140].

Sartori and Furlani[141] studied the kinetics of the following disproportionation reaction:

$$2C_6H_5IO \rightarrow C_6H_5IO_2+C_6H_5I,$$

all the components in which are electrochemically reducible.

Many interesting cases of the application of polarography to the study of the kinetics of organic reactions are discussed in Schwabe's booklet[142]. References to the original literature can also be found in the reviews by Wawzonek[16-21] and by Nürnberg[65].

Use of the polarographic method for studying kinetics is not confined to reactions in which polarographically active substances are obtained from inactive substances or in which the reactants show up polarographically at different potentials. Theoretically the method can also be employed in cases in which the reaction product is reduced at the same potentials as the starting materials but has a different diffusion coefficient[143], the reaction being followed in this case by the change in height of the wave.

The study of rapid reactions requires a sensitive method for recording the currents due to electrochemical reactions. When the half-periods of the reactions lie between 3 and 15 sec, continuous recording of i_d-t curves at individual drops of the mercury electrode at constant potential can be employed[144]. The effect of depletion of the solution in the vicinity of the electrode can be eliminated by means of a special bend in the capillary or by obtaining a calibration curve[145]. In this way the rates of change of the products formed in the electrochemical reduction of quinonoid dyes of the safranine type with hydrogen on palladium can be measured, and hence the hydrogenating activity and mode of action of different palladium catalysts can be determined[65].

With still more rapid reactions (having a half-period less than 3 sec) recourse is had to oscillographic polarography, with which the time required to obtain a polarogram can be reduced to fractions of a second. Examples are provided by the coupling of diazotised sulphanilic acid with sulphonated pyrazolone[146] and the reaction of pyruvic acid with ammonia[65].

During recent years the so-called "rapid" and "very rapid" reactions, the rate constants of which lie within the range 10^3-10^{11} sec^{-1}, have attracted particular interest. They include protolytic reactions, rapid hydrolyses, rearrangements, etc.

After Wiesner's early fundamental work[147] on the catalytic role of the leuco-form of some quinonoid dyes in the oxidation of hydrogen on palladium, polarographic kinetic currents came to be used, together with other modern methods (the relaxation method, measurements using nuclear magnetic resonance, etc.), to calculate the rate constants of rapid reactions.

For a complete theory of kinetic currents we are indebted primarily to the Prague school of polarography; a substantial contribution has been made also by our own Soviet and by foreign scientists. Much work has been done on the problem of kinetic currents in polarography. In the present paper we shall consider only a few cases of the application of kinetic currents in the polarography of organic compounds and their reactions. More detailed accounts of the main achievements of research on kinetic currents and references to the original literature can be found in the papers by Koutecký[148] and by Nürnberg[65].

Kinetic currents are not only governed by the diffusion of depolariser to the electrode but also depend on the relative rates of diffusion and of the chemical reaction preceding the electrochemical process. A condition for the occurrence of kinetic waves is that the depolariser should be present in the solution in at least two forms differing in their depolarising properties[149].

In order to distinguish a diffusion current from a kinetic current, the dependence of the height of the polarographic wave on the height of the mercury reservoir is determined. It follows from the Ilkovič equation that i_d varies linearly with the square root of the reduced height h of the mercury reservoir (*i.e.* the height of the reservoir less the back pressure determined by the geometry of the capillary).

For a kinetic process i_k should be independent of the pressure on the dripping mercury. However, some effect of h on i_k is often observed, and is determined by the relative rates of diffusion and of the chemical reaction. The temperature dependence of a kinetic current is usually much greater than that of a diffusion current, for which the temperature coefficient lies within the range $1-2\%$ deg^{-1}.

A simplified scheme for the formation of a depolariser B from an electrochemically inactive substance A can be written as follows:

$$A \underset{K_2}{\overset{K_1}{\rightleftarrows}} B \xrightarrow{e} R.$$

The dissociation of weak acids (I) or the recombination of protons with the anion of an acid (II) belongs to this type of reaction:

$$\text{(I)}\quad RCOOH \underset{K_2}{\overset{K_1}{\rightleftarrows}} H^+ + RCOO^-,\ H^+ + e \rightarrow {}^1/_2H_2,$$

$$\text{(II)}\quad H_3C{-}CO{-}COO^- + H^+ \underset{K_1}{\overset{K_2}{\rightleftarrows}} H_3C{-}CO{-}COOH,$$

$$H_3C{-}CO{-}COOH \xrightarrow{2e+2H^+} H_3C{-}CHOHCOOH.$$

In the case of acid dissociation an equilibrium (I), which governs the concentration of protons, is established in the solution. Owing to the occurrence of the electrochemical process, however, this equilibrium is continually disturbed near the electrode, being displaced towards dissociation of the acid by an amount depending on the rate of such dissociation. At the same time molecules of acid are brought by diffusion from the bulk of the solution to the electrode, these compensating for the amount of acid used up in the dissociation. No doubt some of the protons recombine with the anions. The nearer to the electrode that dissociation takes place, the greater is the probability that the protons formed by dissociation will diffuse to the electrode surface and be discharged there.

Thus the kinetic limiting current depends on the rate of dissociation of the acid (K_1), the rate of diffusion of molecules of acid from the bulk of the solution to the layer adjacent to the electrode (D_{HA}), and the rate of diffusion of protons from the bulk of the solution. This last factor can

be neglected when pH ≥ 5 owing to the low proton concentrations. In the case of acid dissociation the equation for the kinetic current is

$$i_k = i_d \frac{0.87\sqrt{\frac{D_{H^+}}{D_{HR}}}\sqrt{\frac{K_1 K_D t}{[A^-]}}}{1+0.87\sqrt{\frac{D_{H^+}}{D_{HD}}}\sqrt{\frac{K_1 K_D t}{[A^-]}}},$$

which shows that the kinetic current differs from the diffusion current by a kinetic factor. If this factor exceeds 0.95, the current has a pseudo-diffusion character when K_1 is large, *i.e.* the limiting current behaves as a diffusion current, although a chemical reaction precedes the electrochemical stage. Only acids having dissociation constants (K_D) below 5×10^{-6} give a marked kinetic limiting current.

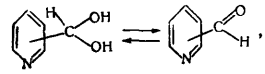
In the case of the recombination of the anion with a proton (II), when both the acid molecule and its anion contain reducible groups, the value of K_2 can be calculated directly from the kinetic limiting current, and hence K_1 can be determined, for $K_1/K_2 = K_D$. With pyruvic acid, for example, two waves are obtained, since the carbonyl group is reduced at a more positive potential in the acid molecule than in the anion. The limiting current of the first wave is governed by the rate of recombination, whereas the second wave should have a limiting current depending on the rate of diffusion of the anion. In an adequately buffered medium recombination may be pseudounimolecular, and the value of i_k can be found from the above formula for acid dissociation. Over seventy weak acids have been studied up to the present [150].

A definite relation exists between the rate constants of protolytic reactions and the dissociation constants of the acids and bases involved. Mairanovskii and Lishcheta [151] studied the variation of the limiting kinetic current, determined by the rate of reaction of the doubly charged maleate anion with proton donors, with the concentration of the acid components (in Brønsted's sense) of buffer systems at constant solution pH. They showed that, with all the buffer systems which they studied, the height of the kinetic polarographic wave increases with increase in the concentration of the proton donor, and that the rate constants for recombination of the maleate ion with proton donors satisfy the Brønsted equation.

In the study of polarographic currents limited by the rate of a chemical reaction preceding electron transfer the effect of adsorption of the substances on the dropping mercury electrode must be taken into account. Mairanovskii has recently shown [149,152] that when an electrochemically inactive form of the depolariser is adsorbed (which almost always occurs with organic depolarisers), the chemical reaction not only takes place in solution near the electrode surface but also involves the adsorbed material. The observed current then represents the sum of two quantities, the kinetic current limited by the occurrence of the chemical reaction in space (in the "reaction" layer), *i.e.* the "bulk" current, and a "surface" current, controlled by the occurrence of the same reaction but involving adsorbed reactant [152].

Mairanovskii found that even slight coverage of the electrode surface (of the order of 0.1%) increases the concentration of the substance in the reaction layer to such an extent that the observed current can be considerably increased, and the rate constant of the chemical reaction calculated from it exceeds the true value by several powers of ten.

Polarography can conveniently be used to study not only the above protolytic reactions but also the kinetics of other rapid reactions, such as the dehydration of formaldehyde hydrate [153] and also those of other aldehydes where only the dehydrated form acts as a depolariser. The formation of additional free aldehyde from its hydrate is catalysed by acids and bases [150]. Similar phenomena have been observed with a group of pyridine aldehydes [154,155]. It was found that these compounds exist in solution in equilibrium with the hydrated form:



and the rate of dehydration governs the magnitude of the limiting current.

In exactly the same way acids and bases catalyse the conversion of α- and β-pyranoses and of α- and β-furanoses to their polarographically active forms containing free carbonyl groups [156].

Los *et al.* [157] made a polarographic study of the kinetics of the mutarotation of α-glucose using Delahay's results on the reduction of aldoses.

Since we cannot consider further the various cases of the occurrence and use of kinetic currents in polarography, we shall just mention one further type of reaction undergone by organic compounds at a dropping mercury electrode:

$$A + e \rightarrow B,\ B + C \xrightarrow{K} A.$$

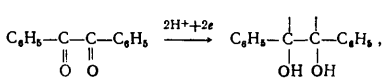
Here the gradually regenerated depolariser A acts as a catalyst for the polarographic reduction of the inactive substance [65,150]. The product of the reduction of haemin, for example, reacts with hydrogen peroxide to form a compound which is reduced at a more positive potential than is hydrogen peroxide. The ferric complexes of catechol, pyrogallol, ascorbic acid, peroxidase, and haemoglobin act similarly. These reactions, too, are utilised in studying the kinetics of chemical reactions [65].

VII. STUDY OF MOLECULAR REARRANGEMENTS AND REACTIONS

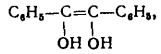
The polarographic method can be used to study molecular rearrangements and changes in polarographically active compounds. However, the number of papers on this application of polarography is small.

Ried and Wilk [158] used this method to follow the conversion of *o*-nitrobenzaldehyde to *o*-nitrobenzoic acid under the influence of light. The velocity of the Smiles rearrangement of 2-hydroxyphenyl 2-nitrophenyl sulphones into 2-*o*-nitrophenoxybenzenesulphonic acids has been studied in a similar way [159]. In the latter work the dependence of $\pi_{\frac{1}{2}}$ on solution pH was determined for each pair of sulphone and sulphonic acid. The pH range was then selected in which the reduction potentials of the nitro-groups of the sulphone and the sulphonic acid showed the greatest difference. The rate of the rearrangement as a function of temperature, nature of the compound, and position of substituents in the benzene ring was then studied within this pH range.

In a study of the reduction of benzoin and benzil it was found that the intermediate in the reduction



isomerising into an enediol [160]



is partly converted, at the electrode surface, to benzoin, which is detected polarographically [161].

Polarographic studies have also been made of the isomerisation of formazans [162] and of the mechanism of the Cannizzaro intramolecular rearrangement of mandelic acid to phenylglyoxal [163].

VIII. RELATION BETWEEN POLAROGRAPHIC DATA AND THOSE OF OTHER METHODS OF INVESTIGATION

The employment of different physical and physicochemical methods for investigating organic compounds has enriched and developed the Butlerov concept of chemical structure. The theory of chemical structure is based on an immense amount of experimental information. Recently many new facts have been established, most of which relate to the problem, posed long ago by A. M. Butlerov, of the mutual influence of atoms in a molecule. This problem is now one of the most important and general problems of chemistry. In this connection great interest attaches to the study of the structure of organic compounds, which determines the behaviour of the molecule in chemical reactions. The extensive use of dipole moments, optical spectroscopy, refractometry, radiospectroscopy, etc. has enabled investigators to reach a number of important conclusions on the molecular structure of several classes of organic compounds, and hence to obtain definite information on their reactivity.

Polarography occupies a leading position among the various methods which to a greater or lesser extent enable the problem of the mutual influence of structural units in organic molecules to be elucidated, the information obtained in this way about the structure of a substance in solution agreeing with the results of other methods of investigation.

It has been found that the general factors governing the ability of molecules to undergo an electrochemical reaction at a dropping mercury electrode are the presence in the molecule of certain polar bonds which possess electrophilic properties, the polarisability of atoms or bonds under the influence of the electric field of the electrode, and also the spatial arrangement of structural units in organic molecules.

Thus the value of $\pi_{\frac{1}{2}}$ depends on the polar and steric factors which govern the state of the molecule at the electrode surface, and bears a definite relation to the distribution of bonds in the molecule, the presence and state of certain groups of atoms, and their electrophilic character [164].

One method which makes it possible to characterise the distribution of electron density in molecules from chemical shifts is nuclear magnetic resonance. In essence, all types of polarographically active compounds can be investigated by this method [165,166]. Bennett and Elving [166] found that the $\pi_{\frac{1}{2}}$ values vary linearly with the values of the chemical shifts for aliphatic aldehydes and *meta*- and *para*-substituted benzaldehydes, iodobenzenes, and nitrobenzenes. With brominated aliphatic compounds and chloroacetic esters, and also with *ortho*-substituted benzene derivatives, however, this linear relation is not maintained. In these cases the value of $\pi_{\frac{1}{2}}$ is probably determined not only by the distribution of electron density in the molecule but also by adsorption on the electrode and by steric effects.

Several papers have been concerned with the relation between the value of $\pi_{\frac{1}{2}}$ and the energetic properties of the π electrons of reducible organic compounds. Such a relation has been found in hydrocarbons having conjugated bonds [167-170] and in several nitro-compounds [171].

Calculation of electron density based on molecular orbital theory was used by Fernandez-Alonso and Domingo [172] to compare values of $\pi_{\frac{1}{2}}$ with the reactivity and structure of polycyclic hydrocarbons. Values of $\pi_{\frac{1}{2}}$ for these hydrocarbons show good agreement with potentiometric data [169]. On the assumption that in the reduction of polycyclic hydrocarbons at a dropping mercury electrode protons add on at the same position as hydrogen atoms in reduction reactions, the localisation energy has been found [168] to be proportional to $\pi_{\frac{1}{2}}$. Table 5 lists values of $\pi_{\frac{1}{2}}$ and localisation energies (E).

The accumulated information in the literature has enabled Voitkevich [173] to link the ease of reduction of organic compounds with their polarity. He states that reduction at a dropping mercury electrode takes place by the transfer of electrons from the cathode surface to a positively charged part of the molecule with simultaneous or subsequent addition of protons at points of high electron density; the role of the polarity of the molecules then becomes quite obvious: electrons are most readily captured by molecules which have the greatest effective positive charge oriented towards the cathode, *i.e.* by molecules whose reducible groups posess the greatest dipole moment. Comparison of the depolarising ability displayed by different organic compounds on reduction at a mercury cathode shows that substances whose molecules possess large dipole moments are liable to be reduced. Table 6 compares the dipole moments and the reducibility of several compounds.

These data confirm the direct relation between ease of reduction and the polarity of molecules. With molecules containing more than one polar functional group, however, this simple relation between ease of reduction and dipole moment is somewhat complicated by the fact that the dipole moments of groups can partly offset one another, so that the net dipole moment is diminished.

TABLE 5.

Compound	Positions	$-\pi^*_{\frac{1}{2}}$, V	E, kcal mole^{-1}
Naphthalene	1:4	2.5	4.00
Anthracene	9:10	1.94	3.31
Phenanthrene	1:4	2.46	3.77
1,2-Benzanthracene	5:10	2.03	3.41
Biphenyl	1:4	2.70	4.38

* Relative to saturated calomel electrode.

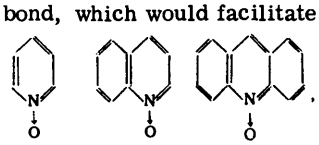
TABLE 6.

Compound	Dipole moment, 10^{18} e.s.u.	Ease of reduction
Unsymmetrical hydrocarbons containing one double bond Aliphatic carboxylic acids Aliphatic alcohols	0.3—0.5 0.8—1.6 1.6—1.7	not reduced
Aliphatic aldehydes and ketones	2.3—2.9	moderate reduction
Unsaturated aldehydes	3.5—3.6	readily reduced
Nitrobenzene Aromatic mono- and di-nitro--compounds containing a single substituent	4.2 3.1—4.8	very readily reduced

In the polarography of molecules containing more than one polar group the most important quantity is not the dipole moment of the whole molecule but only that of the reducible group, or in effect the magnitude of the effective positive charge which is oriented towards the cathode. Of course, a correction must be introduced each time for the mutual inductive effect of other functional groups.

A study of heterocyclic *N*-oxides by Pushkarëva and Varyukhina [174,175] showed that the dipole moment of the N→O bond decreases, and at the same time its ease of electrochemical reduction at a dropping mercury electrode increases, on passing from the *N*-oxide of the simplest six-membered *N*-heterocycle, pyridine, to those with fused ring systems, and also on passing from the *N*-oxides of monoheterocycles to the corresponding *N*-oxides of the pyrazine system. This fact is inconsistent with the generalisation established by Voitkevich. An attempt at an explanation was made by assuming that in this case reduction takes place as a heterogeneous process involving adsorbed molecules of the reducible organic substance. The greatest adsorption will apparently occur when the dipole moment of the N→O bond is least, since the geometry of the molecule is such that the negative end of the dipole will repel the molecule from the cathode surface, and hence will prevent adsorption of the compound on the surface. It seems to us that such an interpretation of the results is not altogether correct, and that the observed regularities can be explained on the basis of the general theory of conjugation [106].

The increase in ease of reduction on passing from *N*-oxides of pyridine to those of quinoline and acridine is obviously explained by a strengthening of conjugation between the N→O bond and the C=C double bonds of the fused benzene rings, not by increased adsorption. In this series of compounds such intensified conjugation should actually result in a decrease in electron density of the reducible N→O bond, which would facilitate the reduction



although the dipole moment decreases in this series. This again indicates that, in the investigation of complicated systems, the mutual inductive effect of all groups or heteroatoms in the molecule must be taken into account, and that the overall dipole moments of complicated molecules cannot give any indication of their polarographic behaviour.

Work aimed at establishing a relation between the electrochemical and the spectroscopic characteristics of compounds is of great interest. Indeed, the chemical action of an electric current resembles in many respects the action of light on a substance, the elementary act of change in the substance consisting in both cases in the transfer of electrons and in a change in the electronic state of the reactant molecules.

Gorbachev and Belevskii [176] attempted to link the absorption spectra of a series of nitro-derivatives of benzene with their reduction potentials on solid electrodes. They were able to establish a linear relation between the reduction potentials and the energy of the long-wave edge of the band of continuous absorption in the ultra-violet. It was found that the reduction potential falls as this energy increases. This was explained in terms of the donor–acceptor theory of A. N. Terenin.

It is obvious that, the larger the quantum which the molecule absorbs, the deeper is the electron which is expelled and the greater is the electron affinity of this molecule. In electrochemical reduction the electron affinity is measured by the reduction potential. Consequently, the higher the reduction potential of a molecule, the lower is the energy of the quantum which it absorbs. This relation is interesting, for, if it is observed with different classes of compounds, it will become possible to predict spectroscopic characteristics from electrochemical data, and to assess the electrochemical behaviour of compounds from their absorption spectra.

Holleck and Schindler [177] also established a definite relation between ease of reduction and position of the long-wave edge of the absorption bands of some substituted nitrobenzenes, expressing it by the empirical formula

$$E_{eV\,(energ)} = \alpha\pi_{1/2} + C,$$

where C depends on the energy state of the molecule, and α is a constant depending on the nature of the substance.

Komenda [178] studied the polarographic behaviour and ultra-violet spectra of 2-amino-4-hydroxy-6-methylpteridine, and found that the anion formed in alkaline medium is reduced at a more negative potential than is the neutral molecule. This worker also investigated the changes in the spectra of such compounds caused by dissociation and tautomerism.

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Polarography now occupies a leading position among physicochemical methods for the investigation of organic compounds. About 10% of organic compounds, which represents over 300 000, can be reduced or oxidised at microelectrodes, but only ~2000 compounds have yet been studied. There is no doubt that the polarographic method will play a leading part in further improvement of organic structural theory.

In the present survey an attempt has been made to report the main results of the polarographic study of organic compounds during the last decade, without considering the application of several new methods, such as oscillographic, derivative, and differential polarography, etc., which have developed only during the past few years.

Classical polarography is certainly no universal method of investigation, since it is unable to determine concentrations below 10^{-5} or above 10^{-2} M, and its resolving power is not very high. The production of oscillographic and other instruments of high sensitivity and resolving power has considerably broadened the possibilities of the method. By means of oscillographic polarography, it became possible to study complicated systems, the components of which are reduced at very similar potentials (see, for example, the papers by Volke [179-187]). Oscillographic polarography enables the kinetics of electrochemical reactions of organic compounds to be studied, and permits a more profound understanding of the relation between the behaviour of a substance at the electrode and its reactivity [188-192].

Only qualitative measurements have been made in by far the greatest proportion of the work in which polarography has been applied to organic chemistry. Quantitative calculations in organic chemistry based on polarographic data encounter a number of difficulties arising from the irreversibility of electrode reactions.

Knowledge of polarographic half-wave potentials provides great opportunities for energy calculations, since all the relations necessary for the transition from electrical characteristics to units of heat energy are known. Calculations are usually based on differences in $\pi_{\frac{1}{2}}$ for a standard and the unknown compound or between two forms of one compound. Since the charge on an equivalent of a substance is 94 600 C, while the electrical work associated with a charge of 1 C at a potential of 1 V is equivalent to 0.239 cal, it is easy to calculate that the work involved in the conversion of 1 mole of polarographically active substance at $\Delta\pi_{\frac{1}{2}} = 1$ V is $23.06n$ kcal, where n is the number of electrons taking part in the electrode reaction. This work corresponds to the difference in free energy between the molecules which are being compared.

Polarographic data can be used to calculate bond interaction energies (see, for example, Ref. 48), energies of interconversion of tautomers and geometrical isomers [97,98], etc. However, the irreversibility of a large proportion of electrode reactions undergone by organic compounds during polarography hinders such calculations, since the value of $\pi_{\frac{1}{2}}$ in such cases often varies in a complex fashion with the concentration of the substance, the pH of the medium, the composition of the electrolyte, and other factors. But even these obstacles can undoubtedly be overcome, and it is to be hoped that during the next few years the polarographic method will find still more extensive and fruitful application in organic chemistry as a quantitative instrumental method for investigating the structure and reactions of many classes of compounds.

Great progress has been made during recent years in the instrumental development of the method. The increase in sensitivity and resolving power of the apparatus has considerably extended the limits to the application of polarography. Much can be expected also from the application of oscillographic polarography to organic chemistry. The great development of polarography is due to its experimental simplicity and the properties of the dropping mercury electrode as an ideally polarisable electrode. Nowadays solid electrodes are being more and more widely used, and in some cases are indispensable. However, research workers are not inclined to forget the "mercury drop": "... it will still be many years before all its advantages have been investigated and exploited" (J. Heyrovský).

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HIGH-TEMPERATURE GAS-LIQUID CHROMATOGRAPHY

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Two trends have arisen in the gas chromatography of high-boiling substances. The first is based on the use of

moderate working temperatures, but with sensitive detectors having a low noise level. The second is based on the use of conditions leading to a decrease in retention volumes, *i.e.* increase in working temperatures, operation under vacuum, decrease in the percentage of stationary phase, etc. The future of gas chromatography will naturally depend on the progress and synthesis of the two trends.

The present review deals with problems relating to separations at high working temperatures. The reason for dealing with the high-temperature method separately is not only that the method is particularly promising for further extension of the boundaries of gas chromatography, but also that it requires the use of special materials and the application of special principles in the design of apparatus.

As early as 1952, James and Martin[1] suggested that gas–liquid chromatography might be used for the analysis of mixtures of substances with high boiling points. The use of gas–liquid chromatography at temperatures above 200° was first described in 1953 by Cropper and Heywood[2,3] for the analysis of the methyl esters of aliphatic acids with up to 22 carbon atoms. Subsequently a number of papers were published on the use of gas–liquid chromatography at temperatures up to 260° [4,5] and above[6–8].

The extension of the method of gas–liquid chromatography to the region of high temperatures involves a number of serious difficulties. The majority of solvents used as stationary phases are too volatile or unstable, or often both, at high temperatures. Increase in temperature, moreover, leads to a decrease in the separation factor. Gas–liquid chromatography at temperatures in the range 250°–350° involves special problems associated with the design of the apparatus, the choice of materials, seals, etc. When the separate parts of the apparatus are connected *via* glass-metal junctions, the difference in the expansion coefficients may lead to leaks in the apparatus; this does not usually occur at low temperatures. The most difficult problem, however, appears to be the choice of stationary liquid phase, with thermal stability and minimum volatility. At present there are no definite, generally accepted technical conditions which a liquid for use as stationary phase should satisfy when tested for volatility. It has been recommended[9] that when a given substance is used in a chromatographic column for 3 months its retention volume under comparable conditions should not change by more than 2%, but this criterion is not quite precise, since the retention volume may alter for other reasons, for which it is difficult to make allowance and which are not related to the volatility of the stationary phase.

Tuey[8] takes as limiting temperature the temperature at which the column loses 50% of the stationary phase in 1000 h of continuous operation at a carrier gas velocity of 15 ml min^{-1}. The tests were carried out in a column containing 2 g of stationary phase, so that this limit corresponds to a volatility of about 1×10^{-3} g per litre of gas.

Harvey and Chalkley[10] state that the upper temperature limit of operation of the stationary phase should be at least 100° below its boiling point. In any case, although this has not been proved experimentally, the vapour pressure of the liquid of the stationary phase should not exceed 1 mm Hg at the working temperature, otherwise the column soon ceases to function.

Despite the difficulties associated with the choice of stationary phase for high-temperature chromatography, a number of substances have been studied and have proved suitable for work in the temperature range 250°–350°. Keppler *et al.*[11] tested some substances which have found application as stationary phases at high temperatures (polyethylene, silicone high-vacuum greases and elastomers, Apiezon greases, etc.). These substances (deposited on Celite 545) gave the following figures for the loss (g h^{-1}) from the column at a gas flow rate of 15 ml min^{-1} in the range 210°–250° (the percentage of the stationary phase was different in each case):

Silicone elastomer DS No. 123	3
Apiezon grease M	5
Silastomer DS No. 156	8
Polyethylene (average mol. wt. 30 000)	8

Different opinions have been put forward regarding the mechanism of the loss (migration) of stationary phase from the chromatographic column. Franke[12] suggested a purely mechanical model of stationary phase removal and recommended that the working life of the column be prolonged by placing at its outlet a short section containing solid carrier without the stationary phase. In the author's opinion, the migrating liquid would saturate the surface of the solid carrier in this section and hence retard slightly its removal from the column.

Van de Craats[12] considers that the removal of stationary phase from the column takes place entirely as a result of its volatilisation and that there are no grounds for assuming that the stationary phase will be held back in the section of the column filled with dry solid carrier.

Some of the loss of stationary phase is apparently due to the dissolution, in the stationary phase, of components of the specimen when the latter is present in high concentrations in the gas phase, particularly in an overloaded column. This leads to a decrease in the viscosity of the stationary phase and hence to an increase in its mobility.

No matter which mechanism is suggested to explain the loss of stationary phase from a chromatographic column, it undoubtedly involves both purely mechanical removal of liquid and a volatilisation–condensation cycle. A slight vapour pressure of the stationary phase at a given temperature will cause it to be moved by the gaseous phase, as are the components of the specimen.

When gas–liquid chromatography is carried out at high temperatures, no attempt is made to work with a high percentage of stationary phase on the solid carrier; its concentration is usually reduced to 10% and less. Calculations show that only a small percentage (by weight) of liquid is sufficient to cover the surface of the solid carrier completely; any liquid in excess of this amount, deposited on the carrier but not held to it by adhesive forces, will soon be removed from the column at high temperatures.

Gerrard *et al.*[9] have studied the factors determining the maximum temperature at which a given substance can be used as stationary phase. They state that when polymeric substances (polypropylene glycol sebacate, silicone oils, etc.) are used as stationary phase, their thermal decomposition is more important than their volatility. The authors studied the thermal decomposition of two silicone oils recommended for use as stationary phase at high temperatures (240° and above): Embaphase silicone oil and E-301 elastomer, which proved to be stable up to 260° and 300° respectively. The time dependence of the loss in weight of a specimen of silicone oil at 260° is shown in Fig. 1.

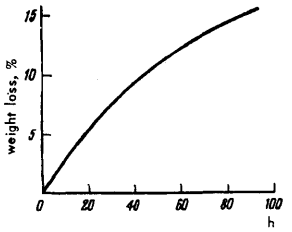

Fig.1. Weight loss of a specimen of silicone oil with time at 260°.

Analogous studies of stationary phases for high temperatures were made by Baxter and Keen[13], who determined the upper temperature limits at which the following substances can be used: Apiezon L (350°), high-vacuum silicone grease (250°), polyethylene (300°), asphaltenes (300°), and polyphenyl tars with molecular weights of 800 and 2100 (400° and 450° respectively).

When gas–liquid chromatography is used for preparative purposes in large-diameter columns, the choice of stationary phase is subject to more stringent requirements than when the process is carried out in analytical columns. Gerrard and coworkers put forward an equation for calculating the limiting permissible volatility of the stationary phase in a preparative column:

$$V = \frac{10Cw}{ft},$$

where V is the volatility (mg per litre of gas), C the maximum permissible percentage of stationary phase in the sample, w the weight of material condensed in the trap (mg), t the period of trapping (min), and f the flow rate of the gas stream (ml min^{-1}).

In the temperature range 250°–350° most workers generally use as stationary phase high-vacuum silicone greases of different grades. It has been found, however, that the separating power of columns with this stationary phase depends to a considerable extent on the quality of the grease. Cropper and Heywood[3] note that, in the analysis of esters of aliphatic acids, a much improved separation could be achieved by preliminary treatment of the silicone grease with ethyl acetate, subsequent addition of ethyl alcohol, and decantation of the solvent. This treatment removed the oily fractions from the grease.

Felton[6] states that columns containing silicone grease as stationary phase should be subjected to preliminary "treatment" ("conditioning"), in which the column is heated at 400° for 2–3 h while the carrier gas is passed through. If this preliminary treatment of the column is not carried out, the chromatogram usually shows, after the introduction of the specimen, a series of non-reproducible unstable peaks, whose formation is apparently due to the presence of volatile substances in the grease. The need for preliminary treatment of silicone grease was also pointed out by Cason and Miller[14].

In addition to silicone and Apiezon greases, asphaltenes have also been used as stationary phase at high temperatures for the separation of normal paraffins up to C_{38} at temperatures up to 320° [15] and for the analysis of phenylalkanes at 240°.[16] Asphaltenes have proved to be thermally stable and sufficiently non-volatile in the temperature range 300°–400°.

Recently there has been a tendency to use inorganic salts as stationary phase at high temperatures. Hanneman *et al.*[17] have successfully used a eutectic mixture of sodium, potassium, and lithium nitrates, deposited on brick, for the separation of normal paraffins up to C_{28} and polyphenyls at temperatures up to 400°. De Boer[18] has used a stationary phase consisting of 20% molten lithium chloride (m.p. 606°) deposited on sea sand, for the separation of an alloy of cadmium and zinc at 620°. Juvet and Wachi[19] have used a eutectic mixture of bismuth and lead chlorides for the separation of titanium and antimony halides at 520°.

In gas–liquid chromatography at high temperatures the thermal stability of the specimens being separated is not generally as important as expected. Kirkland[20] states that many organic compounds have a higher stability in the vapour than in the liquid state. Moreover, the inert carrier in gas chromatography reduces considerably the possibility of decomposition of the components of the specimen by oxidation, which is usually more marked than the actual thermal decomposition.

The difficulties associated with gas–liquid chromatography at high temperatures have led research workers to seek ways of reducing the temperature of the process. In many cases chromatography at high temperatures has been carried out at reduced pressures, on the erroneous assumption that, by analogy with vacuum distillation, the rate of displacement of a component with low volatility in a chromatographic column should increase at low pressures. Later, however, it was shown that this velocity depends only to a very slight extent on the absolute pressure in the column[21] being proportional to the pressure drop in the column and dependent to a marked extent on the distribution coefficient of the component between the gaseous and liquid phases. Although operation at reduced pressures does not increase the efficiency of the column or accelerate the analysis, it does have some advantages, of which the following may be noted. (1) There is an increase in the sensitivity of the katharometer due to the increase in the concentration of the specimen in the carrier gas at low pressures. Fig.2 shows the dependence of the sensitivity factor (expressed as the ratio of the peak height in cm to the weight of the corresponding component in the specimen in mg) on the pressure at the outlet from the column. The

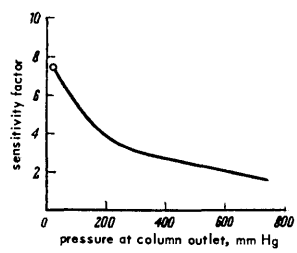

Fig.2. Dependence of the sensitivity factor of a katharometer on pressure.

katharometer was used on the peak for methyl palmitate (stationary phase — silicone grease[7]). (2) If the pressure at the column inlet is less than atmospheric, it is easier to achieve rapid volatilisation of the specimen, and this is very important for a good separation. (3) The katharometer apparently gives a more linear response at low pressures.

In columns in which the packing has a high hydraulic resistance, operation under inefficient conditions is unavoidable at reduced pressures, due to the marked increase in the velocity gradient of the gas. This explains the tendency of some workers, when carrying out gas–liquid chromatography at reduced pressures, to decrease the hydraulic resistance of the column packing by choosing an appropriate solid carrier.

In the analysis of mixtures of hexadecanol and octadecanol and of brominated technical methyl oleates Cropper and Heywood[3] were able, by replacing Celite by NaCl crystals (with 5% silicone grease), to reduce the pressure at the column inlet from 40 to 4 mm Hg, and that at the column outlet from 20 to 2 mm Hg, with a corresponding decrease in the temperature of the process from 265° to 190°–200° and consequent avoidance of thermal decomposition of the specimen.

In the determination of the esters of aliphatic acids up to C_{18} at reduced pressures Sörensen and Söltoft[22] used as solid carrier crystals of NaCl, and also small rings of stainless steel wire gauze (stationary phase silicone oil). The data on the pressure drop in the column (Table 1) show that the hydraulic resistance of the gauze rings is less than that of the NaCl crystals by a factor of 12–13.

In a short communication Hishta *et al.*[23] report that they were able to carry out the process at temperatures 200°–250° lower than the boiling point of the compound. At these temperatures many organic compounds have a vapour pressure which is still sufficient to enable gas–liquid chromatography to be carried out. The retention times of the compounds were decreased considerably by decreasing the quantity of stationary phase on the solid carrier to 0.05–0.2% instead of the 10–30% usually employed. The adsorption effect of the solid carrier, at this low concentration of stationary phase, was reduced to a minimum by using as carrier glass microbeads 200 μ in diameter instead of the carriers usually employed (brick, Celite). Because of the marked decrease in the quantity of stationary phase, it was necessary to decrease the size of the specimen to several tenths of a milligramme, to prevent saturation of the gas phase by the vapour of the specimen. The specimens were injected in the form of solutions in a volatile solvent. A flash evaporator was used (at 375°) for rapid volatilisation of the specimen. The authors obtained chromatograms for an extensive range of high-boiling substances using a 2 m column packed with glass microbeads + 0.05% silicone oil. Table 2 gives some of the compounds studied, their melting and boiling points, and the temperatures at which the process was carried out. As pointed out by the authors themselves, the efficiency of this column is lower than that of ordinary analytical columns. The authors give examples of chromatograms only for pure compounds and mention only one example of a separation, that of a mixture of isomeric eicosanes at 127° (b.p. of n-eicosane 205° at 15 mm Hg). Unfortunately the authors give no details of their work. Further data appear for an estimation of the value of this method for separating high-boiling compounds.

TABLE 1.

Solid carrier	NaCl	Rings	Rings
Length of column, m	2	2	2
Temperature, °C	200	200	180
Gas velocity, ml min^{-1}	8	8	8
Pressure at inlet, mm Hg	72	24.5	24
Pressure at outlet, mm Hg	20	20	20
Pressure drop, mm Hg	52	4.5	4

TABLE 2.

Compound	B.p., °C	Temperature of column, °C	Compound	B.p., °C	Temperature of column, °C
n-Octacosane	412	200		210 at 15 mm Hg	200
Anthracene	354	100	Octadecane		
Chrysene	448	190	1,3-Diphenylbenzene	363	200
Anthraquinone	380	175	Methyl oleate	216 at 20 mm Hg	148
p-Dibromobenzene	218	103			

In gas–liquid chromatography at high temperatures the great majority of workers have used thermal-conductivity detectors — katharometers — of varying design. Other detecting devices have been used in only a few cases: Martins' gas balance[5,24], hydrogen flame detectors[25,26], an emission detector[27], etc. Glass and metallic katharometers have been proposed. Glass conductimetric cells have been used by Sörensen and Söltoft[22] (up to 240°), Keppler *et al.*[11] (up to 300°), Dal Nogare and Safranski[8] (up to 300°) and others[28]. Metallic katharometers[11,29] with a taut platinum filament are of complicated construction and are generally used in the lower temperature range up to 250°. Felton and coworkers[6,30] constructed a katharometer in which the sensing elements were made from the glow plugs from a model aeroplane engine. The authors report that these katharometers are of simple construction and operate successfully in the range 400°–500° with a sensitivity of the same order of magnitude as that of ordinary katharometers with a taut platinum wire.

The question of retaining the high sensitivity of the katharometer at high temperatures is a special problem. It has been found that at high temperatures a large number of substances, for example alcohols, give negative peaks. A chromatogram for methanol[11] (Fig.3) shows that, with increase in the temperature of the sensing wire of the katharometer, the start and finish of the peaks become more negative, until the positive peak disappears completely. The usual explanation of peak inversion is that dehydrogenation of the compound takes place on the surface of the hot platinum wire. This dehydrogenation on the surface of a hot platinum wire has been observed for a large number of compounds, including ethanol (at 186°), butanol (at 220°), glycol (at 230°), cyclohexane (at 245°), ether (at 215°), etc.[11].

In gas–liquid chromatography, considerable difficulties may also be associated with the introduction of the specimens on the column[31] and their rapid volatilisation, the thermostatic control of the column and detector, etc. Since the components of a specimen with high boiling point are usually either solids or very viscous liquids, it is often necessary, when introducing them on the column, to

heat both the specimen itself and the syringe to a sufficiently high temperature to enable the specimen to pass readily through the needle of the syringe. Another method of introducing specimens, particularly solids, is by injecting their solution in a suitable solvent. This method is often inconvenient, since the emergent peak of the solvent may complicate the interpretation of the resulting chromatogram, although sometimes it is possible to select a solvent which can serve as an internal standard in quantitative analysis.

Dubsky and Janàk[32] have suggested using thin-walled capillaries of Wood's metal for the introduction of liquid and solid specimens at high column temperatures (up to 500°). The capillary containing the specimen was placed in the cold section of the column over a special tap. When the tap was turned, the capillary fell into the high-temperature zone, where the casing of the capillary melted and the specimen volatilised.

In the analysis of high-boiling specimens it is necessary to have at the column inlet a heated section, normally filled with glass wool, to ensure rapid volatilisation of the specimen. Sometimes volatilisation devices of special design are used for this purpose, for example the flash evaporator described by Taylor[33,34], operating at temperatures up to 425°.

Temperature control is less important in high-temperature chromatography than in low-temperature chromatography. Normally the temperature of the column is kept constant only to within ± 1°. Preference is given to separate thermostatic control of the column and detector, since this permits more flexible control of the process and makes it possible to keep the temperature of the detector 50°–70° higher than that of the column. The latter is necessary to prevent condensation of the components in the detector. Water or oil thermostats cannot be used for the thermostatic control of columns above 200°. In some cases it is possible to use vapour jackets containing the vapour of high-boiling liquids at known pressure, but the choice of thermally stable liquids suitable for this purpose is limited. Lewis and Patton[35] and Hawkes[24] used a vapour jacket containing dimethyl phthalate vapour (b.p. 283°) for thermostatic control of the column. Air thermostats, with and without circulation, have been most widely used for thermostatic control. Air thermostats with circulation, which make it possible to alter the temperature rapidly and to keep it constant with sufficient accuracy, have been described by Ashbury *et al.*[29], Dubsky[36], and others.

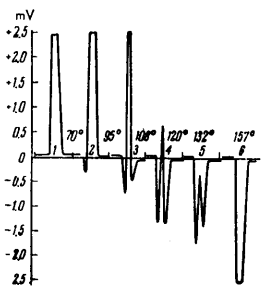

Fig.3. Influence of the temperature of the wire in the sensing element of a katharometer on peak inversion.

Table 3 gives some of the most characteristic results on the analysis of different substances by gas–liquid chromatography at high temperatures, together with the working conditions and the chief parameters relating to the columns.

High-temperature gas–liquid chromatography has been applied by various workers to the analysis and separation of organic compounds of different classes: the methyl esters of aliphatic acids from C_6 to C_{34}[5,7,11,29,37–44], aliphatic monobasic and dibasic acids[45], high-molecular-weight fluoro-esters of camphoric acid[6,34], amines[46], amino-acids[47], phenols and cresols[24,48,49], normal paraffins and polyphenyls[17], phenylnaphthylamines[34], phenyl-substituted benzenes[33] and thiodan[50], n-tetradecane, hexadecane, and octadecane[25], etc. The method has been applied successfully to the analysis of petroleum wax and lubricating oil fractions[7,15], coal tar and its products[51,52], plasticisers of the phthalic ester type[35], and compounds of complex composition – lipids, steroids, and sterols[53–56].

Adlard and Whitham[7] have used high-temperature chromatography for the analysis and separation of the methyl esters of aliphatic acids up to C_{35}, paraffinic hydrocarbons up to C_{40}, gas oil C_{10}–C_{19}, wax C_{19}–C_{36}, lubricating oil fractions, and some industrial insecticides and antioxidants at temperatures up to 300°. Some pure substances and wax and lubricating oil fractions with very similar boiling points were isolated for further study on a mass spectrometer. Considerable difficulties were encountered through condensation of the high-molecular-weight components in the gas leaving the column in the form of a mist. Satisfactory condensation was achieved by using low pressure (40–200 mm Hg at the column outlet and 360–645 mm Hg at the inlet) and traps consisting of a large number of concentric tubes.

The authors also analysed some liquids recommended for use as stationary phases at temperature up to 150°, namely benzylbiphenyl (at 200°), dinonyl phthalate (at 254°), and squalane (at 290°). In all cases the stationary phase used for the analyses was E-301 silicone oil (on Sterchamol). For hydrocarbon mixtures at temperatures up to 270°, Apiezon grease L gave better separation, but a disadvantage was the fact that on this stationary phase the light fractions or decomposition products were often separated with great difficulty from the chief components of the specimen and contaminated the fractions intended for subsequent spectral analysis. Fig. 4 gives as an example the chromatogram for a purified low-melting paraffin wax, obtained at 270°.

In the analysis of petroleum wax fractions (normal paraffins from C_{20} to C_{38}) at 320° Ogilvie *et al.*[15] used asphaltenes as stationary phase, with a special procedure for depositing them on the solid carrier (brick). A 0.7 m steel column was filled with brick (20–40 mesh fraction), wound into a spiral, and, together with the pre-column heater and katharometer, fused into an aluminium block fitted with an electric heater. The calculated quantity of asphaltene (10 wt.%) was dissolved in sufficient ethyl ether to fill the free volume of the column. The solution was passed into the column under pressure of nitrogen. The apparatus was then heated slightly with the simultaneous passage of helium through the column, and finally a small

TABLE 3.

Mixture being separated	Volume of specimen, ml	Column dimensions		Column packing		Carrier gas		Temperature of column, °C	References
		diameter, mm	length, mm	inert solid carrier	stationary phase	nature	velocity, ml min^{-1}		
1	2	3	4	5	6	7	8	9	10
Methyl esters of aliphatic acids ($C_{12}-C_{26}$)	0.006—0.014	4.0	1.13	Celite 545 20—30 mesh	Apiezon L, silicone oil, silicone grease, 17%	nitrogen	20—30	257	5
Methyl esters of aliphatic acids	0.01	6.0	3.6	Celite 545 80—100 mesh	Reoplex 400, 30%	helium	75	240	37
Methyl esters of aliphatic acids	0.005	6.0	2.4	Chromosorb 30—60 mesh	poly(vinyl acetate), 15%	helium	83	205	38
Methyl esters of aliphatic acids ($C_{18}-C_{24}$)	0.021	6.0	0.86	brick 52—85 mesh	E-301 silicone grease	nitrogen	23	295	7
Methyl esters of aliphatic acids (C_6-C_{22})	—	5.0	1.0	Sterchamol	Apiezon M, 25%	hydrogen	180	265	39
Fluoro-esters of camphoric acid	0.01	6.0	2.0	Celite 60—100 mesh	silicone grease, 25%	helium	25	325	6
Methyl esters of resin acids		4.0	3.7	Celite	Apiezon grease, polyesters, 28.4%	helium	100	270 225	57
Methyl esters of aliphatic acids ($C_{12}-C_{22}$)		5.0	0.9	Celite	silicone grease, 50%	nitrogen	8	230	2
Plasticisers of the ester type	0.01	5.0	0.6 1.2	Celite 545 50 mesh	Apiezon oil, 30%	helium	50	285	35
Primary aliphatic amines (C_6-C_{18})		4.0	1.37	NaCl crystals 40—60 mesh	silicone grease, 5%	helium	23	330	46
			1.525	Chromosorb W 50—60 mesh	silicone oil, 26%	helium	45	340	
n-Paraffins ($C_{16}-C_{26}$) Polyphenyls (biphenyl, *m*-terphenyl, etc.) Phenyl-*m*-terphenyl	0.001—0.0015	6.0	15.0	C-22 brick 42—60 mesh	eutectic mixture of $NaNO_3$, KNO_3, and $LiNO_3$, 28.6%	helium	35	250—400	17
n-Tetradecane, n-hexadecane, n-octadecane	0.00175		1.2	Celite	Apiezon grease, 20%	hydrogen	40	298	25
Phenyl-substituted benzenes	0.005		1.2		Apiezon grease L	helium	90	300	33
Phenol, 2-hydroxybiphenyl 3-hydroxybiphenyl, 4-hydroxybiphenyl, diphenylsulphone				Celite 545	Apiezon grease, 33%	nitrogen	18	290—295	24
Lipids	1	4.0	1.5	brick 42—60 mesh Sterchamol 80—100 mesh	silicone adhesive or grease, 5—25%	helium	60—90	245—300	53
Steroids	0.05	2.0	1.0	Celite 545	polyethylene glycol isophthalate	argon	50—100	220—280	53
Petroleum wax fractions: 1. n-paraffins ($C_{20}-C_{30}$) 2. n-paraffins ($C_{20}-C_{38}$)	0.1—0.05	9.5	7.0	C-22 brick 20—40 mesh	asphaltenes, 10%	helium	42—50	282—320	15
Heavy oil tar fractions		6.0—8.0	2.5	brick 60—80 mesh	silicone grease, 23%	helium	50	40° above b.p. of specimen	51
Cadmium—zinc alloy	0.18	13.0	0.5	sea sand	$ZnCl_2$, 20%	helium	150	620	18
1. Purified low-melting paraffin wax	0.025	6.0	0.86	Sterchamol 52—86 mesh	silicone grease	nitrogen	21	270	7
2. Raw low-melting paraffin wax, lubricating oils	0.025	6.0	0.86	Sterchamol 52—86 mesh	silicone grease	nitrogen	21	270	—
Phenylalkanes ($C_{12}-C_{26}$)		6.35	3.66	firebrick 42—60 mesh	asphaltenes, 28.6%	helium	35	240 270 320	16
Biphenyl and *o*-, *m*-, and *p*-terphenyls	—	—	2	Chromosorb 30—60 mesh	Polyphenyl resin (M-2100), 20%	helium	48—125	375—445	13
Mono-, di-, and tri-ethylene glycol	—	—	2		Apiezon L	helium		200	58
Brominated esters of stearic and oleic acids	—	—	2.44	Celite 545 60—80 mesh	Poly(diethylene glycol glutarate), 10%	argon	60	205	59
Determination of phenyl and chloromethylphenyl ethers in chloromethylation products	—	6	4.58	Chromosorb 30—60 mesh	bis[*α*-(*x*-tolyl)-*p*-Tolyl] ether	helium	130	250	60

quantity of pentane and ether was introduced into the column to remove volatile substances. In the analysis the wax specimens were injected into the column by means of a syringe, in the molten state or in solution in a volatile solvent. The components of the wax were identified by comparing the retention times with those for known normal paraffins and also by means of a mass spectrometer. The authors state that the apparatus can be used for the analysis of high-boiling substances with molecular weights above 500.

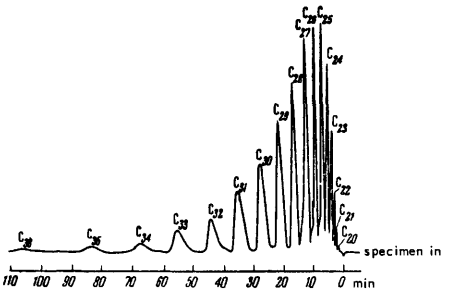

Fig.4. Chromatogram for purified low-melting paraffin wax. Volume of specimen 25 μl; column length 0.86 m; column diameter 6 mm; packing — Sterchamol (52-85 mesh) + E-301 silicone grease; nitrogen velocity 22 ml min^{-1}; pressure at outlet 63 mm Hg; pressure at inlet 383 mm Hg.

Taylor and Fawcett[33,34] analysed high-boiling substances (the methyl esters of aliphatic acids, phenyl-substituted benzenes, and α- and β-*N*-phenylnaphthylamines) on a Fisher–Gulf model 300 "partitioner" at 250°–400°. The stationary phases were silicone grease and Apiezon L. Rapid volatilisation of the specimen was achieved by means of the so-called flash evaporator, which can be used to volatilise specimens with boiling points up to 400°. The carrier gas was helium.

Felton[6] analysed fluoro-esters of camphoric acid (b.p. 320°–460°), isomers of *N*-phenylnaphthylamine (b.p. 400°) and tolyl isocyanates in the temperature range 250°–370°, and established that better separation is achieved in a column with silicone grease (20%), previously "conditioned" at 400° for 2–3 h with simultaneous passage of helium at 25 ml min^{-1}. In the katharometer the sensing elements were prepared from the glow plugs from a model aeroplane engine.

Cropper and Heywood[2,3] analysed a mixture of the methyl esters of aliphatic acids (C_{12}–C_{22}) in a 0.9 m column packed with equal quantities of Celite and silicone grease (internal standard — naphthalene) at 230° and reduced pressure (40 mm Hg at column inlet and 20 mm Hg at column outlet). Under these conditions the esters were separated efficiently, with the exception of the oleates and stearates. Subsequently, in the analysis of technical brominated methyl oleates and hexadecanol–octadecanol mixtures, difficulties were encountered due to the thermal decomposition of the specimens on the column. By replacing the Celite by NaCl crystals (with 5% silicone grease), the authors were able to reduce considerably the hydraulic resistance of the packing and thus to decrease the column temperature from 265° to 190°–200°. The separation achieved on this column was better than that on the column with Celite at a higher temperature. The authors used a katharometer with a coiled platinum wire in a small glass envelope, five times more sensitive than the katharometer with taut wire, used in earlier work.

In the analysis of the methyl esters of C_8–C_{18} aliphatic acids Sörensen and Söltoft[22] used solid carriers consisting of NaCl crystals and Dixon rings of wire gauze, with silicone oil as stationary phase. The different columns showed different efficiencies. The specimens were introduced in sealed ampoules. The sensing element of the katharometer consisted of two platinum spirals on a glass holder.

Dal Nogare and Safranski[8] have described an apparatus which gave trouble-free operation for one year at temperatures up to 350°. The authors analysed mixtures of compounds with boiling points in the range 150°–350° (polyethylene glycols, esters of phthalic and adipic acids, C_{10}–C_{18} hydrocarbons, etc.). The columns and katharometer were of glass and the stationary phases were silicone grease and polyethylene. Fig. 5 shows chromatograms for hydrocarbon mixtures.

Chromatogram *A*, obtained for 4 μl of a liquid mixture of C_{14}–C_{20} olefines and paraffins at 175°, shows that the separation was almost complete. By increasing the temperature and reducing the gas velocity, it was possible to separate the series of paraffins from C_{12} to C_{26} (Fig. 5, *B*), but indistinct peaks were obtained for the higher members of the series up to C_{36} (Fig. 5*C*). The authors obtained a chromatogram for DS-200 silicone oil at 350° (Fig. 6). The large number of peaks apparently corresponds to successive homologues.

Dupire[52] has separated fractions from coal tar and its products in glass columns up to 6 m long, packed with "Silocel" S-22 silicone grease. In the analysis of complex mixtures containing components boiling over a wide temperature range (50°–500°) it was necessary to carry out the separation at various increasing temperatures: 130°, 185° and 260°, and 360°. The components were identified from their retention times and infra-red spectra. Indene, naphthalene, and anthracene were used as internal standards.

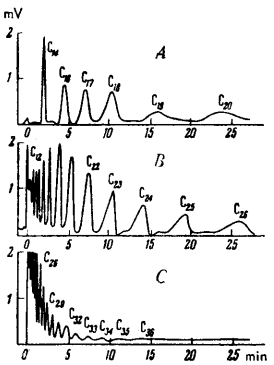

Fig.5. Chromatograms for hydrocarbon mixtures:
A) C_{14}–C_{20}; column temperature 175°; detector temperature 265°; helium, 124 ml min^{-1}.
B) C_{12}–C_{26}; column temperature 226°; detector temperature 302°; helium, 40 ml min^{-1}.
C) C_{12}–C_{36}; column temperature 285°; detector temperature 340°; helium 56 ml min^{-1}.

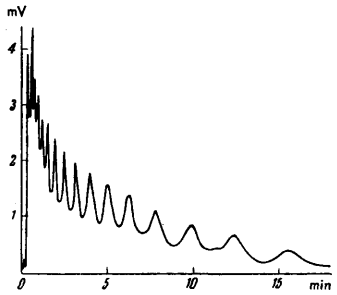

Fig.6. Chromatogram for DS-200 silicone oil.

Guillet *et al.*[61] developed a method for determining the monomeric composition of methacrylate polymers and copolymers. The specimen being studied was decomposed on a heated spiral at the inlet to the chromatographic column and the resulting monomers were analysed at 255° in a column with Apiezon L on Celite.

Franc and Wurst[62] developed a method for the analysis of the technical mixture formed in the manufacture of phenylchlorosilanes, containing benzene, chlorobenzene, phenyldichlorosilane, biphenyl, and diphenyldichlorosilane, using a column packed with Chromosorb + 20% silicone elastomer at 240°. At the column outlet the components were burnt to CO_2 and water. The carbon dioxide was absorbed and the water was reduced to hydrogen, which was detected at 20° by means of a katharometer. The areas under the hydrogen peaks are proportional to the number of H atoms in the molecules of the compounds.

Cacace *et al.*[63] analysed high-boiling organic compounds containing ^{14}C in a column with Apiezon L at 400°. The components leaving the column were burnt to CO_2 and the radioactivity of the gas was measured by means of an ionisation chamber. The authors obtained chromatograms for the ethyl ester of phenylacetic acid containing ^{14}C.

Gudzinowicz and Smith[64] studied the separation of high-boiling aromatic hydrocarbons, solid at room temperature, on a modified standard chromatograph with an ionisation detector and radium source. At 303° low retention times were obtained for *p*-quaterphenyl (b.p. 520°), coronene (b.p. 577°), and hexaphenylbenzene (b.p. 525°). Chromatograms were obtained for the high-boiling resin formed when terphenyls are irradiated (22 peaks).

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High-temperature gas–liquid chromatography is now a fully-developed method for analysing complex mixtures of high-boiling organic substances, and is applicable at temperatures up to over 500°. Efforts are being made to extend this upper temperature limit. Work is also being carried out on the study of new conditions which would make it possible to analyse high-boiling substances at much lower temperatures than is possible at present. The use of high-temperature chromatography on a preparative scale, although involving considerable difficulties, may compete with molecular distillation in the laboratory.

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NEW METHODS FOR THE SYNTHESIS OF NUCLEOTIDE COENZYMES

V.M.Berezovskii and R.V.Artemkina

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I. INTRODUCTION

Consideration of synthetic methods for obtaining nucleotide coenzymes is of considerable interest in view of their important role in metabolic processes and especially in view of the fact that most nucleotide coenzymes have been obtained artificially only during recent years by new methods of organic synthesis.

Nucleotide coenzymes combined with a specific protein form numerous enzyme systems, in which they catalyse various chemical reactions occurring in the living organism. Nucleotide coenzymes are the monomers of nucleotides (phosphoric esters of nucleosides) and are structurally similar or analogous to units in ribonucleic acids (RNA) or deoxyribonucleic acids (DNA), which are polymers of nucleotides.

The molecules of nucleotide coenzymes are based on those of nucleosides, *N*-glycosides of heterocyclic bases, linked *via* the ring nitrogen atom with the primary carbon of D-ribose, and in this respect all natural nucleotide coezymes have the β-configuration.

Complex nucleotide coenzymes can be regarded as made up of two simpler compounds joined by a pyrophosphate link: flavin-adenine dinucleotide (FAD) consists of adenosine-5′ phosphate and riboflavin-5′ phosphate, uridine diphosphate glucose (UDPG) of uridine-5′ phosphate and α-D-glucose-1-phosphate, nicotinamide-adenine dinucleotide (NAD)† of adenosine-5′ phosphate and nicotinamide mononucleotide, nicotinamide-adenine dinucleotide phosphate (NADP)† of adenosine-2′,5′ diphosphate and nicotinamide mononucleotide, and coenzyme A (CoA) of adenosine-3′,5′ diphosphate and the 4′ phosphate of D-pantetheine, etc.

Among the various methods for obtaining nucleotide coenzymes from nucleosides or simple nucleotides, the very complex specific methods for producing a pyrophosphate link, which we shall examine in the present paper, are of considerable interest.

In a simple nucleotide coenzyme molecule, which is a monoester of a polyphosphoric acid, the pyrophosphate link is produced either by direct phosphorylation of a nucleoside or by forming di- and tri-phosphates from the nucleoside monophosphate. In the molecule of a complex nucleotide coenzyme which is an unsymmetrical P^1P^2-diester of pyrophosphoric acid, the pyrophosphate link is produced mainly in two ways: (*a*) condensation of two different

† According to the nomenclature recommended by the Commission on Enzymes of the International Biochemical Congress and by the Commission on Biochemical Nomenclature of the International Union of Pure and Applied Chemistry–Chem.Abs., 55, 6558 (1961); Biokhimiya, 26, 563 (1961).

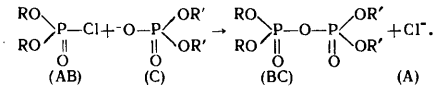
nucleoside monophosphates, for example adenosine-5′ phosphate and riboflavin-5′ phosphate, nicotinamide nucleoside monophosphate and adenosine-5′ phosphate, etc.; (*b*) condensation of a nucleoside diphosphate with an unphosphorylated nucleoside, such as adenosine-5′ diphosphate and riboflavin, or riboflavin-5′ diphosphate and adenosine, etc.

Up to the present time attention has been paid mainly to the study of methods for condensing two molecules of nucleoside monophosphates. The second method for producing a pyrophosphate link appears very infrequently in the literature.

The formation of a pyrophosphate link by the condensation of two nucleoside monophosphates can be accomplished by three main methods: (1) the phosphorochloridate method, consisting in the condensation of halogenated phosphates or halogenated nucleotides, containing protected hydroxyl groups, with salts of phosphates or of nucleotides, followed by removal of the protective groups; (2) the carbodiimide method, consisting in the direct condensation, under the influence of carbodiimides (dicyclohexylcarbodiimide, di-*p*-tolylcarbodiimide, etc.), of two nucleoside monophosphates; and (3) the phosphoramidate method, consisting in the condensation of a phosphoramidate derivative of a nucleoside containing unprotected hydroxyl groups with another mononucleotide, which is likewise unprotected.

II. SYNTHESIS OF NUCLEOTIDE COENZYMES BY THE PHOSPHOROCHLORIDATE METHOD

The phosphorochloridate method is based on exchange between pyrophosphates, or mixed anhydrides of phosphoric and other acids, and phosphate anions. Two different acids A and B form an anhydride AB, which comes into contact with the anion of acid C, and if A is stronger than B and C, exchange takes place with the formation of the free acid A and the anhydride BC:



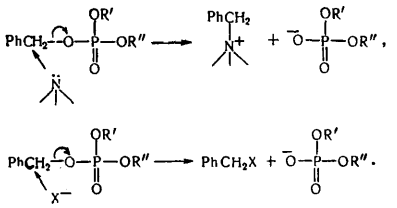
In this example B and C are phosphate anions, A is hydrogen chloride, AB is a phosphorochloridate, derived from the anhydride of phosphoric acid and hydrogen chloride, and BC is the pyrophosphate to be synthesised.

Completely or partly esterified phosphates are most often used in phosphorylation by the phosphorochloridate method. Completely esterified pyrophosphates are extremely labile, readily undergoing exchange with other anions, as a result of which they are more active phosphorylating agents than the partly esterified phosphates. However, owing to this ready reaction with other anions, very complex mixtures, which are difficult to separate, are formed. This may explain the low yields obtained in many syntheses.

The subsequent removal of the protective groups, which is necessary at the final stages of the synthesis, results in some breakdown in the pyrophosphate link, which also decreases the yield. Since partly esterified phosphates have far less tendency to undergo exchange reactions, their use enables the formation of side-products to be avoided, and thereby an increased yield of polyphosphates can be achieved.

The choice of protective groups and their removal constitute a separate problem. Benzyl groups are most commonly employed as protective groups, since debenzylation is possible under relatively mild conditions. Dibenzyl phosphorochloridate is usually employed as phosphorylating agent, even though it is less stable and has a weaker phosphorylating action than, for example, diphenyl phosphorochloridate.

The traditional method of debenzylation is catalytic reduction over Pt, Pd, or Ni catalysts in ethanolic or dioxane solution. Reduction with sodium in liquid ammonia is also used, but partial breakdown of the pyrophosphate link then takes place. A very successful method for the removal of benzyl groups from phosphate compounds has been solvolysis in phenol. Selective monodebenzylation can be successfully achieved by nucleophilic substitution in the presence of quaternary bases[1] or of anions (chlorides, thiocyanates, iodides):



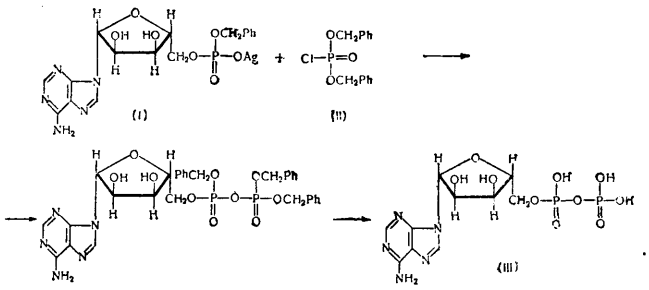
Removal of all the benzyl groups from completely esterified pyrophosphates cannot be achieved by means of lithium chloride, for example, but P^1P^2-dibenzyl pyrophosphate can be obtained from tetrabenzyl pyrophosphate. Such incomplete debenzylation can be conveniently employed because partly esterified pyrophosphates are more stable during isolation than are the completely esterified pyrophosphates. Undesirable debenzylation during formation of the pyrophosphate link can be suppressed by the use of 2,6-lutidine. The initial phosphates are normally employed in the form of their metal or amine salts, the latter being the more advantageous, since they are much more soluble. Anhydrous benzene, phenol, acetonitrile, or their mixtures are used as solvents.

1. Adenosine-5′ Di- and Tri-phosphates

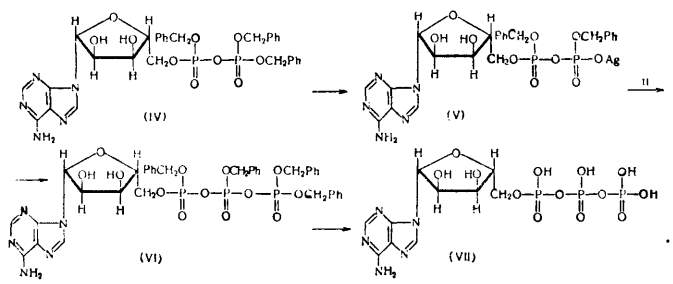
Nucleotide coenzymes such as FAD and UDPG were first obtained by the phosphorochloridate method of synthesis. This method had first been used to synthesise several simple coenzymes, such as adenosine-5′ diphosphate (ADP), adenosine-5′ triphosphate (ATP), uridine-5′ diphosphate (UDP), uridine-5′ triphosphate (UTP), and also a series of symmetrical pyrophosphates (P^1P^2-diadenosine-5′ and P^1P^2-diuridine-5′ pyrophosphates).

ADP (III) was obtained by the reaction of silver adenosine-5′ benzyl phosphate (I) with dibenzyl phosphorochloridate (II) in warm glacial acetic acid followed by catalytic hydrogenation of the resulting adenosine-5′ tribenzyl diphosphate in alcoholic solution[2]. ADP was isolated in low

yield as its acridinium salt. However, its yield can be increased to 55% by using a mixture of phenol and acetonitrile in the place of glacial acetic acid[3].



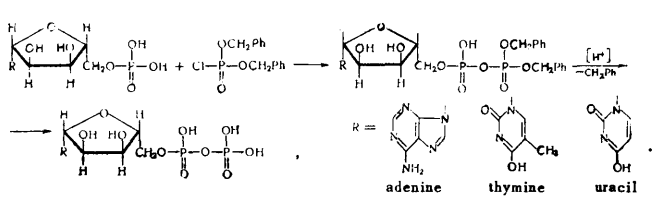
The starting material used for the synthesis of ATP (VII) was silver adenosine-5′ dibenzyl diphosphate (V), obtained by the monodebenzylation of adenosine-5′ tribenzyl diphosphate (IV)[4]. Compound (V) was condensed with dibenzyl phosphorochloridate (II) to yield the tetrabenzyl ester of ATP (VI):



If reduction of compound (VI) is carried out in glacial acetic acid, the product of the reaction contains 7–15% of ATP.[3] When the medium is a mixture of phenol and acetonitrile, the ATP content increases to 40%. The chief impurities were ADP and inorganic polyphosphates. The triacridinium salt of ATP which was isolated was identical with the same salt of natural adenosine-5′ triphosphate.

The principal difficulties in the synthesis of ADP and ATP by the phosphorochloridate method are encountered in the choice of conditions for the selective monodebenzylation of compound (IV). If 4-methylmorpholine is used for this purpose, the yield of ATP can be almost doubled[3] compared with the catalytic hydrogenation method. However, in this case too the substance is strongly contaminated with inorganic pyrophosphate.

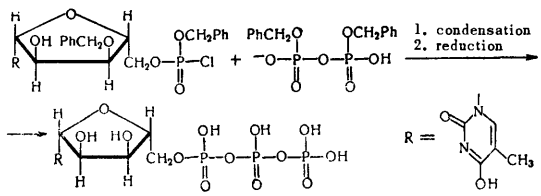
The yields of nucleoside-5′ diphosphates can be considerably increased by starting from unprotected nucleotides and acting on them directly with dibenzyl phosphorochloridate (II)[5-7]. Benzyl groups are removed from the resulting diphosphate compounds by catalytic hydrogenation. This method gave 80–90% yields of ADP and UDP in the form of their calcium salts[6].



2. Thymidine-5′ Di- and Tri-phosphates

Thymidine-5′ diphosphate (TDP) was prepared by the condensation of the tri-n-octylammonium salt of thymidine-5′ phosphate with dibenzyl phosphorochloridate in anhydrous dioxane at room temperature, the yield being 85% and the purity 92% (as the calcium salt)[6]. Thymidine-5′ phosphate (TMP) and inorganic phosphate were detected among the small amount of impurity. The benzyl groups were removed by reduction.

A 43% yield of thymidine-5′ triphosphate (TTP) was obtained by the interaction of 3′-*O*-benzylthymidine-5′ benzyl phosphorochloridate with the di(phenyltrimethylammonium)salt of P^1P^2-dibenzyl pyrophosphate in a benzene–acetonitrile mixture at room temperature, followed by debenzylation. It was shown by means of paper chromatography that the main product was TTP with small amounts of TMP and inorganic pyrophosphates and traces of TDP. After neutralisation of the solution with ammonia to pH 6, the reaction products were separated on Dowex-2 ion-exchange resin (in the chloride form). The TTP was finally purified *via* the barium salt.



3. Flavin-Adenine Dinucleotide

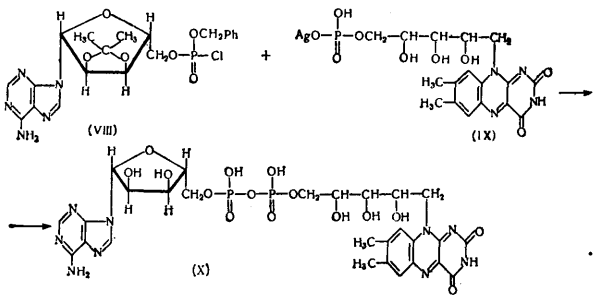
In the search for methods of synthesising natural unsymmetrical pyrophosphates (FAD, UDPG, NAD, CoA), symmetrical pyrophosphates were obtained, in particular such compounds as P^1P^2-diadenosine-5′ and P^1P^2-diuridine-5′ pyrophosphates[8]. The results of these investigations showed that synthesis of unsymmetrical nucleotide coenzymes occurring in Nature is possible. In subsequent work an effort was made to avoid reaction conditions which would result in symmetrical pyrophosphates.

The first complex coenzyme to be obtained synthetically was FAD. One of the components of the FAD molecule – adenosine-5′ monophosphate (muscle adenylic acid, AMP) – was prepared by the direct phosphorylation of adenosine with phosphoryl chloride in pyridine[9,10], and also by the treatment of 2′,3′-*O*-isopropylideneadenosine with phosphoryl chloride[11], by the interaction of 2′,3′-diacetyladenosine with diphenyl phosphorochloridate followed by removal of the protective groups[12], by the phosphorylation of 2′,3′-*O*-isopropylideneadenosine with phosphoric acid in the presence of trichloroacetonitrile[13], and by phosphorylation with a phosphorodichloridate[14].

The second component of the FAD molecule, riboflavin-5′ phosphate, usually termed "flavin mononucleotide" (FMN)‡, has been synthesised by several methods: by the phosphorylation of riboflavin with phosphoryl chloride after preliminary protection of the primary and secondary hydroxyl groups[15-17], by phosphorylation with phosphorochloridates without preliminary protection of the hydroxyls[18-20], and by phosphorylation with metaphorphoric acid[21,22] and with alkyl phosphorochloridates also without protection of the hydroxyl groups[23-26].

‡ Riboflavin-5′ phosphate is a hydrogenated nucleotide.

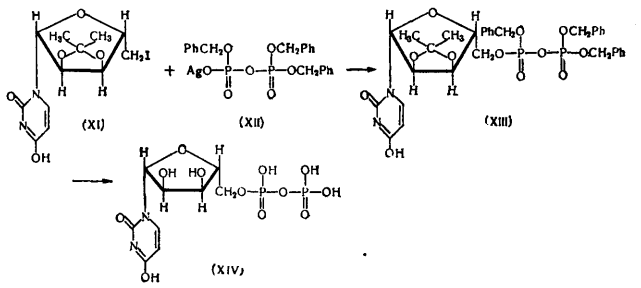
An attempt to use 4',5'-anhydroriboflavin as an intermediate in the synthesis of FAD proved unsuccessful[27]. The first successful synthesis of FAD (X), by condensation of the silver salt of riboflavin-5' phosphate (IX) with 2',3'-*O*-isopropylideneadenosine-5' benzyl phosphorochloridate (VIII) in the presence of triethylamine, was accomplished by Christie *et al.*[28,29] in 1954. Phenol was chosen as solvent, since FMN is readily soluble in it, and formation of a pyrophosphate link takes place quite readily in this medium. Use of this solvent offered the further advantage that, as noted above, phenols are able to monodebenzylate the benzyl pyrophosphates which are formed. The protective isopropylidene group was subsequently removed by treatment with acid. However, the yield of FAD was only 6%, partly owing to cleavage of the pyrophosphate link on elimination of the protective groups.



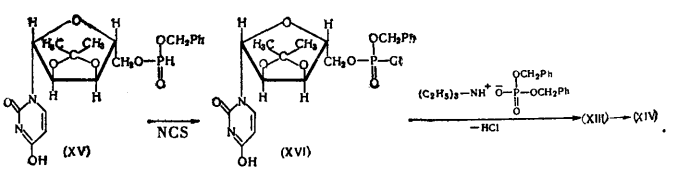
The isolation of coenzymes was always a complex and laborious task, both from natural sources and from synthetic products. With the development of chromatography, which in recent years has found wide application in organic chemistry, more effective isolation and separation of nucleotide coenzymes has become possible. Various methods were applied, for example, to the isolation and purification of FAD: partial separation of flavin nucleotides can be achieved on IRC-50 ion-exchange resin, whereas anion-exchange resins in general adsorb them very strongly. Better results were obtained by the use of adsorption chromatography on Florisil[30], partition chromatography in the phenol–butanol–water system[30], paper chromatography[31], column electrophoresis[32,33], and chromatography on powdered cellulose[34-36], the last method proving the most effective. Paper chromatography in various solvent systems has been used for the identification of flavin compounds[37,38].

4. Uridine Diphosphate Glucose

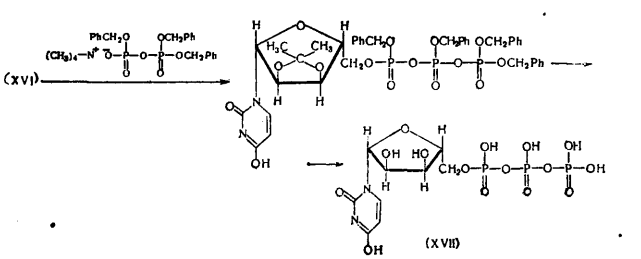
One of the products of the cleavage of UDPG is UDP which was synthesised by condensing 5'-deoxy-5'-iodo-2',3'-*O*-isopropylideneuridine (XI) with silver tribenzyl pyrophosphate (XII) in benzene solution[39]. The resulting good yield of 2',3'-*O*-isopropylideneuridine-5' tribenzyl diphosphate (XIII) was debenzylated with lithium chloride in 2-ethoxyethanol to uridine-5' dibenzyl diphosphate. The use of lithium chloride for the debenzylation proved to be very convenient, since it enabled the reaction to be carried out under mild conditions[40]. Although all the protective groups could not be removed in this way, this reaction was nevertheless of great importance, since the partly debenzylated compound was more stable in acid medium than the completely esterified compound. This facilitated the removal of the remaining benzyl groups by catalytic hydrogenation with subsequent elimination of the isopropylidene groups by mild acid hydrolysis:



UDP (XIV) can be synthesised also by the reaction of 2',3'-*O*-isopropylideneuridine-5' benzyl phosphorochloridate (XVI) with triethylammonium dibenzyl phosphate[41] and subsequent removal of benzyl and isopropylidene groups from the intermediate product in a manner similar to that described above. Compound (XVI) is obtained from 2',3'-*O*-isopropylideneuridine-5' monobenzyl phosphite (XV) by treatment with *N*-chlorosuccinimide (NCS). UDP (XIV) was isolated as the barium salt in 25% yield; the use of phenols for partial debenzylation considerably increases the yield[42].

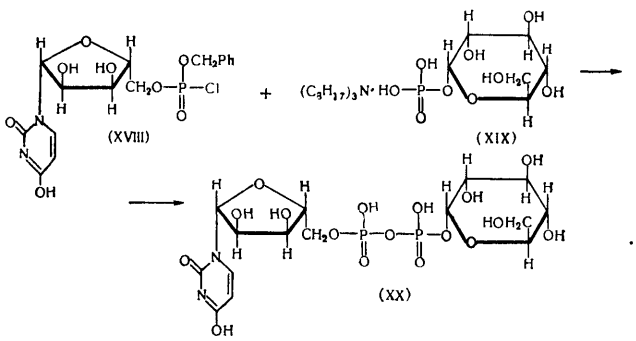


UTP (XVII), which probably takes part in the enzymic synthesis of uridine derivatives[43], was prepared by condensation of compound (XVI) with tetramethylammonium tribenzyl pyrophosphate[42]. Partial debenzylation of the intermediate product was effected by means of *m*-cresol in the presence of small amounts of hydrochloric acid, with subsequent removal of the remaining benzyl groups by catalytic hydrogenation and removal of the isopropylide group by the usual method:



After treatment with lithium hydroxide, the reaction mixture contained ~ 37% of UTP as the lithium salt. The

pure barium salt of UTP was isolated in 29% yield after chromatographic purification on carbon or on Dowex-2 ion-exchange resin.



(XVIII) (XIX) (XX)

UDPG (XX) was obtained by condensing 2',3'-dibenzyluridine-5' benzyl phosphorochloridate (XVIII) with tri-n-octylammonium α-D-glucose-1-phosphate (XIX) in the presence of tri-n-butylamine in benzene[44]. Uridine diphosphate galactose also was obtained by the same method.

The choice of the benzyl group instead of isopropylidene for protecting the hydroxyls is explained by the considerably greater lability in acid medium of UDPG than, for example, FAD, where isopropylidene protection is employed, since the isopropylidene group in the condensation product is removed in acid medium. After the pyrophosphate link had been formed, the benzyl groups were removed by catalytic hydrogenation.

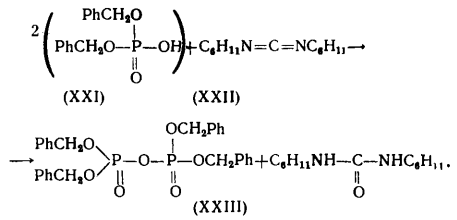
UDPG was isolated as its calcium salt (30% UDPG) with an overall yield of 15%. The chief impurities were UMP and α-D-glucose-1-phosphate. Further purification resulted in the calcium salt of UDPG of 92% purity (according to enzymic assay).

The above phosphorochloridate method for producing a pyrophosphate link possesses, in spite of its apparent specificity, several substantial defects: (1) the necessity for protecting the hydroxyl groups of the nucleoside makes it a multistage method; (2) removal of the protective groups after the condensation is always accompanied by partial cleavage of the pyrophosphate link, resulting in low yields of the nucleotide coenzymes; (3) the laborious synthesis of the initial phosphorochloridates gives rise to additional complications.

The low yields are also due to the fact that completely esterified pyrophosphates readily undergo exchange reactions, leading to complex mixtures[45,46], which are difficult to separate.

III. SYNTHESIS OF NUCLEOTIDE COENZYMES BY THE CARBODIIMIDE METHOD

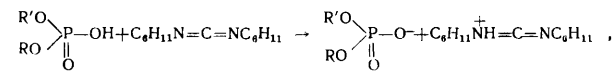
In the search for a more specific and simple method of synthesising nucleotide coenzymes, the condensation of two nucleotides in the presence of such condensing agents as dicyclohexylcarbodiimide, di-*p*-tolylcarbodiimide, etc. was investigated. This method was first tried with the synthesis of benzyl esters of pyrophosphoric acid[47]. In anhydrous pyridine dibenzyl phosphate (XXI) reacts instantaneously with dicyclohexylcarbodiimide (DCC) (XXII) to form tetrabenzyl pyrophosphate (XXIII) and *NN'*-dicyclohexylurea. It was found that even a considerable excess of water does not interfere with the formation of the anhydride, the yield of tetrabenzyl pyrophosphate being in all cases ~ 50%.



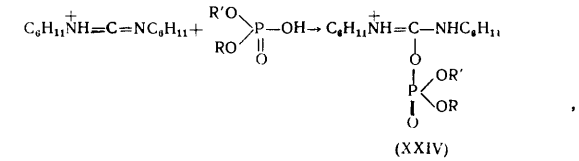
(XXI) (XXII) (XXIII)

This constitutes the great value of the carbodiimide method, since even a small amount of water greatly increases the solubility of nucleotides and orthophosphoric acid, which are insoluble in the anhydrous pyridine usually employed as reaction medium.

Formation of the pyrophosphate link probably consists in the initial addition of a proton to the dicyclohexylcarbodiimide[48,49]:

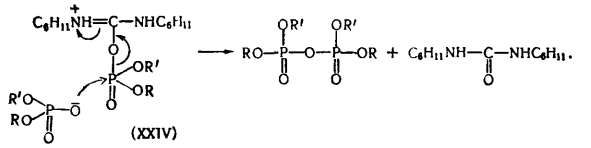


with subsequent addition to the protonated carbodiimide of a phosphoric acid or ester molecule to yield an adduct such as the intermediate compound (XXIV)[49-52]:



(XXIV)

which is then attacked by the phosphate anion to form a pyrophosphate and a substituted urea. The intermediate compound was not isolated from the reaction mixture



(XXIV)

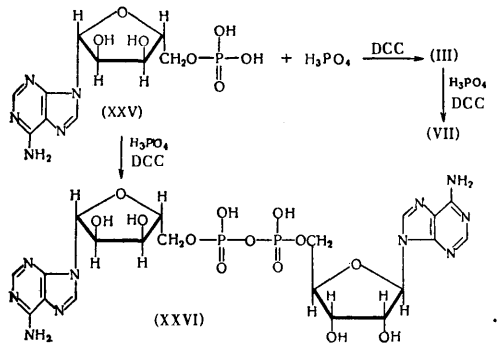
A pyrophosphate link can be formed only with the protonated form of carbodiimides, when, under the influence of the proton, an O–P instead of a C–O bond is ruptured in the intermediate adduct (XXIV) on attack by the phosphate anion, and a new O–P bond is established in the resulting pyrophosphate.

In the absence of bases, carbodiimides react quite readily with acids[49]. In the presence of bases, especially tri-n-butylamine, the reaction velocity is considerably diminished owing to the decrease in concentration of the protonated carbodiimide and the intermediate compound (XXIV). In pyridine the reactions take place at a great rate, obviously because the carbodiimide is sufficiently basic compared with the pyridine to complete with the latter.

The starting materials for condensations in the presence of carbodiimides are taken in the form of the free acids with unprotected hydroxyl groups, or as their pyridinium or trialkylammonium salts. Apart from pyridine containing moderate amounts of water, dimethylformamide is used as solvent. The presence of considerable amounts of water is undesirable, since it is then necessary to use a large excess of the carbodiimide.

1. Adenosine and Uridine Di- and Tri-phosphates

The one-stage synthesis of ADP (III) and ATP (VII) from AMP (XXV) and 85% orthophosphoric acid in the presence of an excess of dicyclohexylcarbodiimide (DCC) in aqueous pyridine was undertaken by Khorana[53]:



ADP and ATP were isolated from the reaction mixture by precipitation as the mercuric salts with Lohmann's reagent [100 g of $Hg(NO_3)_2.8H_2O$ in 25 ml of water + 25 ml of concentrated nitric acid] at a low pH, with further separation on Dowex-2 ion-exchange resin. The ADP and ATP were isolated as their barium salts with an overall yield of 33%. Subsequent purification was effected *via* their mercuric salts by the method of LePage[54]. They were identified by paper chromatography in different solvent systems. It was found by means of ion-exchange chromatography that the ADP obtained was contaminated with ATP (up to 2%), while the ATP was in turn contaminated with ADP (up to 5%).

Use of a slight excess of 85% orthophosphoric acid results in the formation of a considerable amount (up to 55%) of the symmetrical P^1P^2-diadenosine-5′ pyrophosphate (XXVI). Since the presence of symmetrical pyrophosphates in the reaction mixture is undesirable in the preparation of natural unsymmetrical nucleotide coenzymes, conditions were studied under which the formation of by-products would be reduced to a minimum. It was found that use of a fivefold molar excess of 85% orthophosphoric acid yields only ~ 10% of P^1P^2-diadenosine-5′ pyrophosphate; a tenfold excess of the acid almost completely suppresses the formation of this compound, but it is then difficult to obtain a homogeneous mixture of the reactants.

UDP and UTP were obtained in an analogous fashion from UMP and 85% orthophosphoric acid in the presence of dicyclohexylcarbodiimide in aqueous pyridine at room temperature[55], the reaction occurring at a great rate. Increase in the duration of the reaction is undesirable, since this can lead to the formation of a large amount of organic and inorganic polyphosphates. A considerable excess of orthophosphoric acid is also undesirable, since it involves the formation of higher inorganic polyphosphates. Isolation of uridine phosphates by selective precipitation at different pH values as the barium, magnesium, and mercuric salts was unsuccessful. Direct purification on ion-exchange resins did not give yields of UTP exceeding 50% . The most satisfactory method was to isolate a mixture of UDP and UTP from the reaction mixture by passing the latter through Dowex-50 ion-exchange; further separation of the nucleotides was effected on Dowex-2. UDP and UTP were isolated as their barium salts. In spite of the considerable losses, the yield of UDP was 20–25% (purity 98%), and that of UTP 20% (purity 96%).

Reaction of FMN with 85% orthophosphoric acid in the presence of dicyclohexylcarbodiimide yielded riboflavin-5′ diphosphate[56], while uridine-5′ phosphate gave the symmetrical P^1P^2-diuridine-5′ pyrophosphate[8].

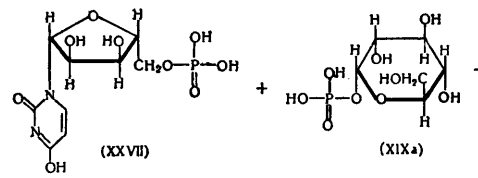
As mentioned above, the value of the carbodiimide method for producing a pyrophosphate link consists in the possibility of carrying out the reaction in aqueous pyridine. In many cases, however, a homogeneous solution of the nucleotide and the dicyclohexylcarbodiimide cannot be achieved, which probably explains the relatively low yields of coenzymes obtained. Attempts were therefore made to use the more polar, water-soluble carbodiimide[57] $(C_2H_5)_2\overset{+}{N}(CH_3)-[CH_2]_3-N=C=N-C_6H_{11}$, which was employed in the condensation of AMP to P^1P^2-diadenosine-5′ pyrophosphate[57]. The reaction velocity was found to be greater in homogeneous solutions, but the presence of an aqueous medium makes it necessary to use a very large excess of the carbodiimide.

Trialkylammonium salts tend to increase the solubility of phosphoric esters in anhydrous solvents, so that both carbodiimides and orthophosphoric acid can be used in this form for the preparation of nucleoside polyphosphates. Thus condensation of uridine-5′ phosphate in a mixture of pyridine, tri-n-butylamine, and dicyclohexylcarbodiimide gives a quantitative yield of P^1P^2-diuridine-5′ pyrophosphate[57]. The same carbodiimide and 85% orthophosphoric acid were used in the presence of two equivalents of tri-n-butylamine in anhydrous pyridine for the synthesis of nucleoside-5′ triphosphates, the yield of UTP being ~ 65%, and of ATP ~ 40%.[57]

This last variant of the carbodiimide method can be recommended in many cases for the preparation of nucleoside-5′ triphosphates.

2. Uridine Diphosphate Glucose

Direct condensation of the unprotected initial phosphates was of some interest for the preparation of UDPG, which is extremely unstable towards acids and alkalis, since this method eliminated the necessity for employing the acid or alkaline media used in the removal of protective groups. UDPG (XX) was obtained by the condensation of UMP (XXVII) with α-D-glucose-1-phosphate (XIXa) under the influence of dicyclohexylcarbodiimide[58]. The proportions of the reactants were as follows: 1 mole of the pyridinium salt of UMP + 1.9 moles of the pyridinium salt of α-D-glucose-1-phosphate + 1.7 moles of the carbodiimide in dimethylformamide. The reaction resulted in a complex mixture of substances containing only ~ 3.5% of UDPG.

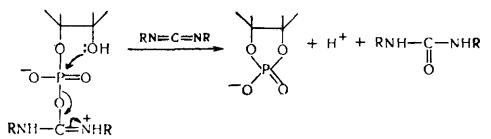


Anion-exchange chromatography proved to be unsuitable for separating the substances in the reaction mixture, since the UDPG apparently decomposed on the ion-exchange resin. Chromatography on activated charocal was more effective. One of the fractions contained ~ 42% of the ammonium salt of UDPG, which was identical with the

natural coenzyme. However, the overall yield of the substance was low. The reaction was accompanied by the formation of considerable quantities of a cyclic α-D-glucose-1,2-phosphate [58].

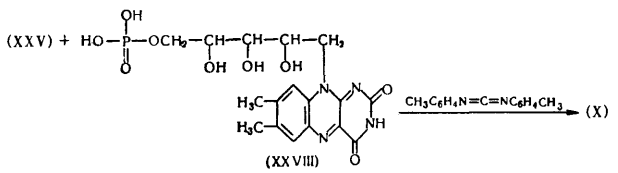
A similar result occurred in the reaction of uridine-2′ or uridine-3′ phosphate with dicyclohexylcarbodiimide in aqueous pyridine, when cyclic uridine-2′,3′ phosphate was obtained, while yeast adenylic acid (a mixture of adenosine-2′ and adenosine-3′ phosphates) under the same conditions yielded cyclic adenosine-2′,3′ phosphate [54]. However, no cyclic phosphate is formed even by the prolonged action of this carbodiimide on AMP, the symmetrical P^1P^2-diadenosine-5′ pyrophosphate being obtained in good yield instead [53].

The tendency of cyclic phosphates to be formed is probably associated with the *cis*-configuration of the hydroxyl and phosphate groups in such compounds as adenosine- and uridine-2′ and -3′ phosphates, which creates conditions favourable to intramolecular cyclisation [49]

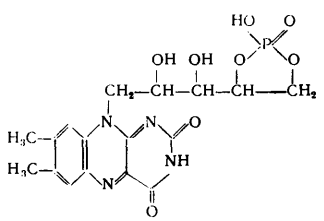


3. Flavin-Adenine Dinucleotide

FAD (X) was prepared from FMN (XXVIII) and AMP (XXV) in the presence of di-*p*-tolylcarbodiimide in aqueous pyridine [31]. Reaction was continued in the dark for 24 h, after which the resulting di-*p*-tolylurea was filtered off, and the coenzyme isolated from the reaction mixture by paper chromatography with subsequent purification *via* the uranyl salt [59]. The yield was ~ 4% and the purity 90%. The solvent systems employed were n-butanol – acetic acid – water (4 : 1 : 5), in which FAD has R_f = 0.12, for the isolation, and t-butanol – water (60 : 40), in which R_f = 0.40, for the purification.



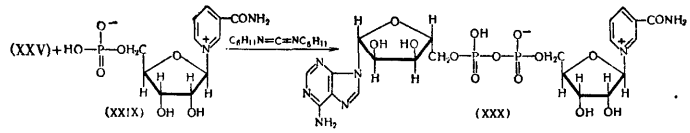
As was to be expected, the reaction product contained large quantities of the cyclic riboflavin-4′,5′ phosphate. This is consistent with the tendency of reactions with dicyclohexylcarbodiimide to form cyclic nucleotides [60,61], *e.g.* the sole product of the reaction between FMN and AMP (XXV) in the presence of this carbodiimide was the cyclic riboflavin-4′,5′ phosphate [17]:



The low yield of FAD synthesised by the carbodiimide method is associated with the fact that the reaction is directed mainly towards formation of a cyclic monophosphate owing to the *cis*-configuration of the hydroxyl groups relative to the phosphate group.

4. Nicotinamide-Adenine Dinucleotide

Little work has been done on the synthesis of this coenzyme. Nicotinamide mononucleotide (XXIX) is insoluble in anhydrous pyridine and in dimethylformamide, the solvents which are most widely used in syntheses of nucleotide coenzymes by the carbodiimide method, and therefore aqueous pyridine in the presence of excess dicyclohexylcarbodiimide was used to obtain NAD (XXX) from AMP (XXV) and nicotinamide mononucleotide (XXIX) [62], the reaction being carried out at 0°. After separation of the dicyclohexylurea which had been formed, more of the carbodiimide was added, and the reaction continued at the same temperature; this was repeated three times



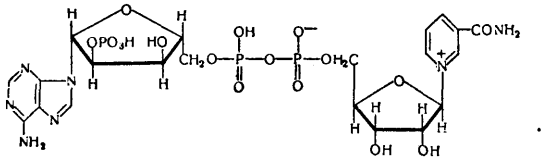
Paper chromatography enabled NAD, two symmetrical pyrophosphates (P^1P^2-dinicotinamide-nucleoside-5′ and P^1P^2-diadenosine-5′ pyrophosphates), and small amounts of the starting materials to be detected in the reaction mixture. About 50% of the nicotinamide nucleotide was converted into NAD, and only about 10% into the symmetrical P^1P^2-dinicotinamide-nucleoside-5′ pyrophosphate.

The substances in the reaction mixture were separated on Dowex-2 ion-exchange resin. The aqueous fractions contained nicotinamide nucleotide and symmetrical P^1P^2-dinicotinamide-nucleoside-5′ pyrophosphate, while the NAD was retained on the resin together with the AMP and P^1P^2-diadenosine-5′ pyrophosphate. These last three substances were eluted from the resin with 0.01 *N*, 0.1 *N*, and 1 *N* formic acid respectively. The NAD was isolated as an amorphous powder containing ~ 70% of the coenzyme.

The α- and β-anomers of nicotinamide nucleotide (approximately in the proportions 80 : 20) were used in the reaction, and therefore condensation resulted in a mixture of α- and β-anomeric forms of the coenzyme, which were difficult to separate on ion-exchange resins. An elegant method was therefore used in which the NAD was reduced with alcohol dehydrogenase to dihydro-NAD with subsequent alkali treatment to cleave the α-anomer. The NAD obtained in this way was identical with the natural product, as shown by paper chromatography and electrophoresis. The optical data ($[\alpha]_{0D}$ = 31.5 ± 0.5°) and the enzymic activity indicated that the sample was 90% pure.

In a similar way nicotinamide-adenine dinucleotide phosphate (NADP) was synthesised from adenosine-2′(3′),5′ diphosphate and nicotinamide mononucleotide in the presence of dicyclohexylcarbodiimide in aqueous pyridine. The NADP was isolated on a column containing Dowex-50, and paper electrophoresis showed it to contain small

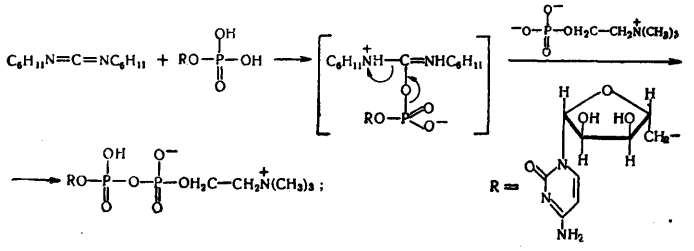
amounts of nicotinamide mononucleotide and adenosine-2′,5′ and -3′,5′ diphosphates as impurities



The considerably higher yields of NAD (XXX) and of cytidine diphosphate choline (see below) compared with FAD and UDPG can be explained by the fact that both nicotinamide mononucleotide and choline phosphate are zwitterions, and are therefore weaker nucleophilic agents than the anions of adenosine-5′ phosphate and cytidine-5′ phosphate. An adduct like the intermediate compound (XXIV) will therefore be formed mainly by attack on the protonated carbodiimide by the adenosine-5′ or cytidine-5′ phosphate, not by that of the nicotinamide mononucleotide or choline phosphate respectively. Subsequent attack on the electrophilic phosphorus of the phosphate–carbodiimide adduct of the (XXIV) type is possible both from the nicotinamide mononucleotide or choline phosphate anion and from the adenosine-5′ or cytidine-5′ phosphate anion. This leads to the formation of the required unsymmetrical pyrophosphate together with some of the symmetrical pyrophosphates P^1P^2-diadenosine-5′ and P^1P^2-dicytidine-5′ pyrophosphates, and traces of P^1P^2-dinicotinamide-nucleoside-5′ pyrophosphate, but no P^1P^2-dicholine pyrophosphate.

5. Cytidine Diphosphate Choline

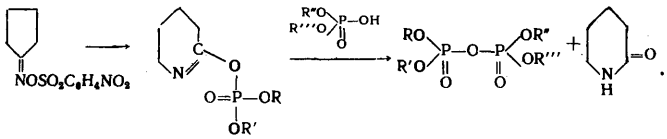
Cytidine diphosphate choline was obtained by the interaction of cytidine-5′ phosphate and choline phosphate in the presence of excess dicyclohexylcarbodiimide in aqueous pyridine at room temperature[63]. The condensation products were separated on Dowex-1 (in the formate form). The yield was 46%.



The carbodiimide method has also been used to synthesise adenosine diphosphate choline (yield 30–40%), uridine diphosphate choline (30–40%), and guanosine diphosphate choline (30–40%)[63], as well as cytidine diphosphate glycerol[64], cytidine diphosphate ribitol[65], and cytidine diphosphate ethanolamine in moderate yields.

Such reagents as derivatives of imidoyl phosphates[66–68], trihalogenoacetonitriles[13,49,51], isocyanates[69], and cyanamides[70] were also used in the formation of a pyrophosphate link, for they react with orthophosphoric acid or its esters by a mechanism similar to that characteristic of the carbodiimides, with the formation of analogous intermediate compounds.

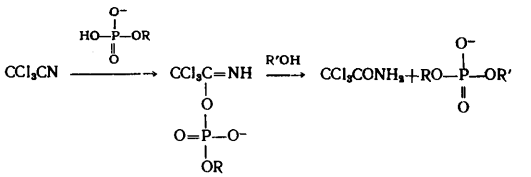
For example, derivatives of the imidoyl phosphate (XXXII),[66–68] which are structurally analogous to the intermediate compound (XXIV), are obtained by Beckmann rearrangement of the *p*-nitrobenzenesulphonate of cyclopentanone oxime (XXXI), and interact with diesters of orthophosphoric acid to form a tetraester of pyrophosphoric acid (XXXIII):



(XXXI) (XXXII) (XXXIII)

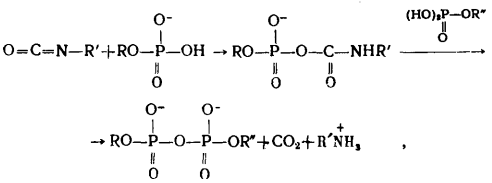
In this way UDP was obtained by the interaction of tetra-n-butylammonium 2′,3′-isopropylideneuridine-5′ benzyl phosphate and compound (XXXI), with subsequent treatment of the intermediate substance (XXXII) with dibenzyl phosphate, the yield being 40%. However, this method too is not strictly specific in syntheses of nucleotide coenzymes.

Imidoyl phosphate derivatives, formed from trichloroacetonitrile by the action of monoesters of orthophosphoric acid in the presence of pyridine[13], are able to give unsymmetrical diesters of orthophosphoric acid with alcohols, and pyrophosphates with monoesters of phosphoric acid:



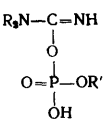
The preparation of monobenzyl phosphate and of di-*p*-chlorophenyl pyrophosphate by means of this reagent has been described.

Isocyanates[69] react with orthophosphoric acid and its monoesters to give carbamoyl phosphates[71,72], which react further with phosphoric monoesters to yield pyrophosphates:



where R = C_6H_5 and R′ = C_3H_7. P^1-Adenosine-5′ P^2-uridine-5′ pyrophosphate has been synthesised by this method using dimethylcyanamide[70].

Reactive adducts of the type

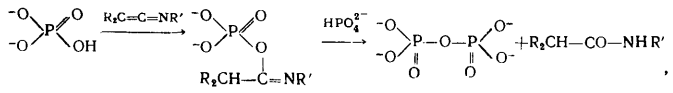


structurally similar to the intermediate (XXIV) which probably occurs in reactions with carbodiimides, are formed from dialkylcyanamides and orthophosphoric mono- and di-esters[70]. The tautomeric form of substituted cyanamides is of the carbodiimide type:

$$R_2N{-}C{\equiv}N \rightleftarrows RN{=}C{=}NR.$$

A 40% yield of cytidine-5′ diphosphate was obtained by this method from the monophosphate, by reaction with an aqueous solution of dimethylcyanamide.

Diphenylketen *p*-tolylimide and dimethylsulphonylketen methylimide are able to give symmetrical and unsymmetrical pyrophosphates with dibenzyl and diphenyl phosphates[73]:

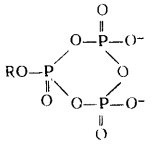


where R = C_6H_5 and R′ = $C_6H_4CH_3$, or R = CH_3SO_2 and R′ = = CH_3. Diphenylketen *p*-tolylimide with dibenzyl phosphate in benzene gives a 44% yield of tetrabenzyl pyrophosphate[73]. On treatment with an equimolar mixture of dibenzyl and diphenyl phosphates, dimethylsulphonylketen methylimide yields mainly the unsymmetrical P^1-dibenzyl P^2 diphenyl pyrophosphate[73].

The above reagents, which can be used to obtain pyrophosphates, have not yet found extensive application in the synthesis of nucleotide coenzymes.

Thus the advantages of the carbodiimide method of condensation over the phosphorochloridate method are firstly that it can be carried out in one stage without preliminary protection of the hydroxyl groups of the nucleoside, and secondly that the reaction can conveniently be carried out in a medium containing water. Nevertheless, it is not always possible to obtain homogeneous solutions of the reactants with the carbodiimide method. The formation of cyclic phosphates of the origina' nucleotides (for example in the synthesis of FAD and UDPG) also imposes considerable limitations on this method. Furthermore, in several cases symmetrical pyrophosphates are obtained as by-products with carbodiimides. All this results in yields of the synthetic nucleotide coenzymes which are not very high.

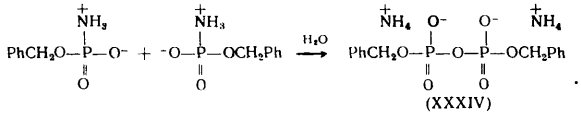
In many cases, however, the carbodiimide method can be recommended for the preparation of nucleoside-5′ triphosphates. The preferential formation of triphosphates perhaps results from hydrolysis of a cyclic metaphosphate, which is stable during the reaction but is converted into a linear phosphate in the process of isolation



IV. SYNTHESIS OF NUCLEOTIDE COENZYMES BY THE PHOSPHORAMIDATE METHOD

The efforts of research workers have been directed towards finding derivatives of phosphoric acid and its esters which would be readily available, sufficiently reactive, stable under the experimental conditions, and specific with respect to the synthesis of nucleotide coenzymes.

For example, the phosphorylation of alcohols with monobenzyl phosphoramidate yielded, not the intended phosphoric esters of the alcohol, but the diammonium salt of P^1P^2-dibenzyl pyrophosphate (XXXIV).[74] The same compound was obtained on prolonged storage (for about 5 years) of monobenzyl phosphoramidate:

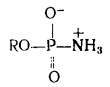


(XXXIV)

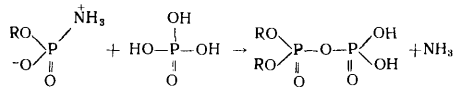
These observations suggested that monoesters of the amide of orthophosphoric acid are able to react with phosphate anions to form a pyrophosphate link. No phosphorylation of alcoholic hydroxyl groups in the molecule takes place, so that phosphoramidates can be used for the synthesis of unsymmetrical dinucleotides.

The insignificant reactivity of phosphoramidates towards alcoholic hydroxyl groups allows unprotected nucleotides to be used, which avoids the exchange reactions possible in the presence of completely esterified pyrophosphates, as was observed with the phosphorochloridate method.

Crystallographic analysis showed[75] that phosphoramidic monoesters are zwitterions, with the nitrogen atom carrying a positive charge:



Such a compound can react with nucleophilic phosphates to form pyrophosphates and polyphosphates:



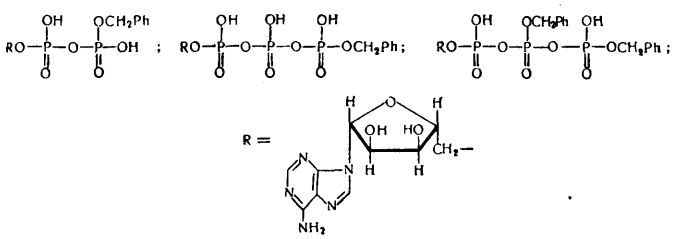
Phosphorylation takes place smoothly in the presence of pyridine or a trialkylamine. The starting materials are most often used in the form of their salts with metals (potassium, sodium) and organic bases (pyridine, trialkylamines). These salts are readily soluble in formamide, dimethylformamide, pyridine, *o*-chlorophenol, and a mixture of pyridine and *o*-chlorophenol, which are the solvents most frequently employed in this method.

1. Adenosine, Uridine, and Cytidine Di- and Tri-phosphates

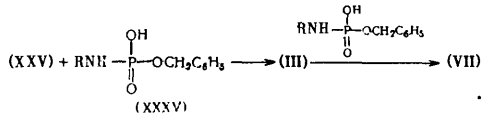
Reaction of the dipyridine salt of AMP (XXV) with benzyl phosphoramidate (XXXV) [74] in dimethylformamide containing 5% of water at 100° yielded the monobenzyl ester of adenosine-5′ diphosphate, from which a 48% yield of ADP (III), isolated as the lithium salt, was obtained after catalytic elimination of the benzyl group.

A side-reaction, resulting in the formation of a minute amount of P^1P^2-diadenosine-5′ pyrophosphate, occurs in an anhydrous medium. The presence of a small quantity of water completely suppresses this reaction, though the yield of ADP is then not very high, and a large proportion of the AMP remains unchanged.

Subsequent reaction of the ADP with compound (XXXV) or with *N*-benzyl- or *N*-cyclohexyl-phosphoramidate gave a 71% yield of ATP (VII) contaminated with a minute quantity of higher polyphosphates of adenosine. The presence of only small amounts of polyphosphates is explained by the lability of benzyl polyphosphates compared with the free polyphosphoric acids and monoesterified phosphates. Thus, for example, the monobenzyl esters of ADP and ATP proved to be quite stable during isolation, whereas the dibenzyl ester of ATP was broken down

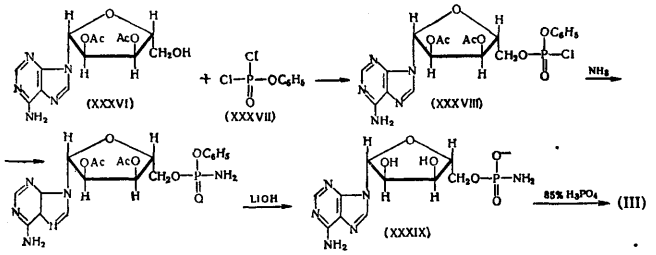


It is interesting that the phosphorylation of unprotected nucleotides with monoesterified phosphoramidates takes place in stages, ATP (VII) not being obtained directly from AMP (XXV). In order to ascertain whether it was possible to use the phosphoramidate method to synthesise natural nucleotide coenzymes, an investigation was made of the reaction between AMP and an excess of phosphoramidate in diethylformamide[76]. Ion-exchange chromatography showed the presence in the product of 34% AMP + 27% ADP + 21% ATP + 18% of higher nucleotide polyphosphates. Hence it follows that a pyrophosphate link can be produced by the phosphoramidate method, but, like the carbodiimide method, this method is not absolutely specific.



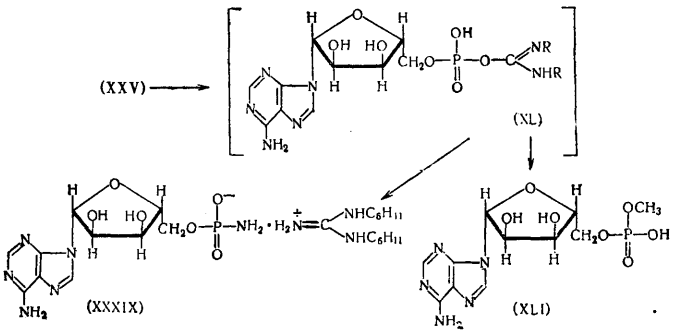
(XXXV)

Another variant of the phosphoramidate method was suggested, based on the use of a phosphoramidate derivative of a nucleotide instead of an amide of phosphoric acid. Thus 2',3'-di-*O*-acetyladenosine (XXXVI) and phenyl phosphorodichloridate (XXXVII) in the presence of quinoline were used to synthesise 2',3'-di-*O*-acetyladenosine-5' phenyl phosphorochloridate (XXXVIII), treatment of which with dry ammonia in dioxane followed by lithium hydroxide removed the acetyl and phenyl groups, giving a 25% yield of adenosine-5' phosphoramidate (XXXIX):[76]



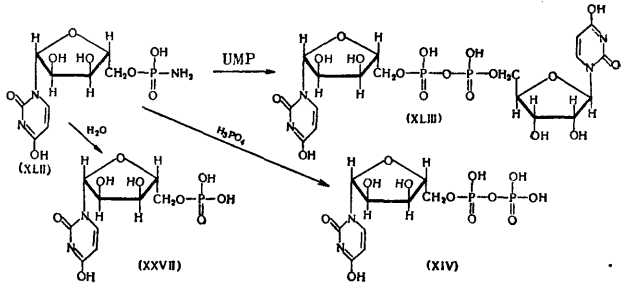
A 50% yield of ADP (III) was obtained from compound (XXXIX) by the action of a fivefold excess of 85% orthophosphoric acid in *o*-chlorophenol at 0°. No side-reactions were observed during this process, apart, perhaps, from some hydrolysis of the adenosine-5' phosphoramidate to AMP. However, such a multistage route for the synthesis of phosphoramidates is unsuitable for preparative purposes.

A simpler and more convenient method for preparing nucleoside-5' phosphoramidates from nucleotides and an excess of dicyclohexylcarbodiimide in the presence of ammonia was proposed by Khorana[77]. It was found that, in the preparation of adenosine-5' phosphoramidate from AMP (XXV) by the action of an excess of this carbodiimide, the treatment with ammonia was best carried out in t-butanol and formamide at 80° for 3 h.[78] By this method, adenosine-5' phosphoramidate (XXXIX) was isolated as the crystalline dicyclohexylguanidinium salt with a yield of 85–92%.



When the reaction was carried out in aqueous pyridine, the main product was unchanged AMP. It is difficult to believe that the AMP is obtained as a result of hydrolysis of the adenosine-5' phosphoramidate in aqueous pyridine, since phosphoramidates are known to be stable in basic and neutral media. This is most probably explained by the lability of the hypothetical intermediate compound (XL) in this medium. Methyl alcohol also proved to be unsuitable as a solvent, since the methyl ester of AMP (XLI) was then formed instead of the expected phosphoramidate.

A 75% yield of the crystalline dicyclohexylguanidinium salt of uridine-5' phosphoramidate (XLII) was obtained[79] in a similar manner, and from it UDP (XIV) was synthesised in 50% yield by the action of 85% orthophosphoric acid. The presence of UMP (XXVII) in the reaction product can be explained by the possible hydrolysis of uridine-5' phosphoramidate in acid medium, and the presence of traces of the symmetrical P^1P^2-diuridine-5' pyrophosphate (XLIII) by reaction of UMP with uridine-5' phosphoramidate. An effective method for separating the components of the reaction mixture was to absorb them on Dowex-1 (in the chloride form) and then to elute them with lithium chloride solution.



The phosphoramidate method for producing a pyrophosphate link was extended to the synthesis of cytidine-5' diphosphate (CDP) and guanosine-5' diphosphate (GDP).[30] Cytidine-5' phosphoramidate was obtained in the usual way, but difficulties were encountered in obtaining the phosphoramidate derivative of guanosine-5' phosphate, especially in isolating it, since the substance decomposed at room temperature into guanosine-5' monophosphate (GMP) and ammonia.

GDP was obtained from the ammonium salt of guanosine-5' phosphoramidate and 85% orthophosphoric acid in *o*-chlorophenol at 0°. Apart from the GDP (58%), the reaction product was found to contain GMP (34%) and P^1P^2-diguanosine-5' pyrophosphate (~ 1%).[80]

Similar results were obtained by the reaction of dicyclohexylguanidinium cytidine-5' phosphoramidate with 85% orthophosphoric acid in *o*-chlorophenol[80], the products

being 50% CDP + 31% cytidine-5′ phosphate + 3% P^1P^2-dicytidine-5′ pyrophosphate.

If phosphorylation is carried out with anhydrous orthophosphoric acid in dioxane solution, the yield of the diphosphate can be raised to 83%.[80]

Condensation of 1,3-dicyclohexylguanidinium adenosine-5′ phosphoramidate (XXXIX) with di(triethylammonium) pyrophosphate in a mixture of "tricresol" and acetonitrile yields a mixture of products containing 78% ATP + 10% ADP + 12% AMP (in molar proportions). After purification on the resin Amberlite CG-400 (in the chloride form), the ATP was isolated as its barium salt with an overall yield of 43%.[81] The 5′-triphosphates of uridine, cytidine, and deoxyadenosine were obtained in a similar manner[81].

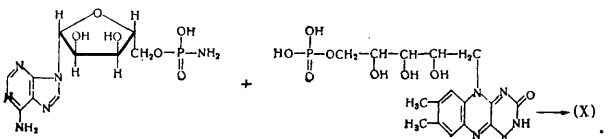
Reaction of the dicyclohexylguanidinium salts of adenosine-5′ and uridine-5′ phosphoramidates with phenyl phosphate in anhydrous pyridine gave P^1-adenosine-5′ P^2-phenyl pyrophosphate and P^1-uridine-5′ P^2-phenyl pyrophosphate in yields of 70% and 87% respectively[77].

The application of derivatives of nucleoside phosphoramidates (morpholidates, imidazolidates) to the synthesis of di- and tri-phosphates is described below.

The method described above for the synthesis of ADP (III)[75] from adenosine-5′ phosphoramidate and an excess of orthophosphoric acid was utilised by Moffatt and Khorana to prepare complex nucleotide coenzymes such as UDPG and FAD.

2. Flavin-Adenine Dinucleotide

An important problem in the synthesis of FAD (X) by the phosphoramidate method was to find a solvent system which would dissolve riboflavin-5′ phosphate (XXVIII) and adenosine-5′ phosphoramidate (XXXIX) equally well. Anhydrous pyridine is unsuitable for this purpose, but a mixture of it with *o*-chlorophenol proved satisfactory. Condensation was carried out in the presence of a 2.5 molar excess of the pyridine salt of FMN in a mixture of these solvents at room temperature for 4 days[82].

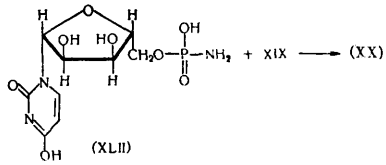


(XXXIX) (XXVIII)

A diethylaminoethylcellulose column (in the chloride form)[82] was successfully used to separate the reaction products, the FAD being isolated as the lithium salt (90%) with a yield of 40%.

3. Uridine Diphosphate Glucose

The starting materials for the synthesis of UDPG (XX)[82] were the dicyclohexylguanidinium salt of uridine-5′ phosphoramidate (XLII) and the tri-n-octylammonium salt of α-D-glucose-1-phosphate (XIX). Since these salts are readily soluble in anhydrous pyridine, the reaction can be carried out in a homogeneous medium, a fourfold excess of the sugar phosphate being used:



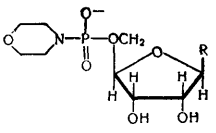
(XLII)

Apart from UDPG the reaction mixture contained UMP and small amounts of the symmetrical P^1P^2-diuridine-5′ pyrophosphate. A very effective method for isolating the coenzyme was based on the use of Dowex-2 anion-exchange resin in the chloride form. The yield of UDPG (as the amorphous lithium salt) was 59%, and the material was quite pure.

Uridine-5′ phosphoramidate is stable in aqueous pyridine, which could therefore be employed in the reaction. It was found, however, that increasing quantities of water lead to a diminution in the yield of UDPG, with a simultaneous increase in the uridine-5′ phosphate content and the formation of small quantities of P^1P^2-diuridine-5′ pyrophosphate. Phosphate anions may catalyse hydrolysis of the phosphoramidate, and the appearance of the symmetrical P^1P^2-diuridine-5′ pyrophosphate can be explained by interaction between the uridine-5′ phosphate and the uridine-5′ phosphoramidate. For the preparation of unsymmetrical pyrophosphates, therefore, it is better to employ an anhydrous medium in order to avoid the formation of undesirable by-products.

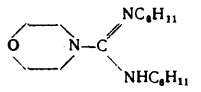
The phosphoramidate method, while possessing certain advantages over the methods previously described, is not sufficiently general or satisfactory for the synthesis of nucleotide coenzymes. Further research was therefore directed towards reactive substituted nucleoside phosphoramidates derived from various aromatic amines and nitrogen heterocycles. Nucleoside phosphoropiperidates, phosphoranisidates, and phosphoromorpholidates were therefore prepared and investigated[83]. With strong bases, for example piperidine, the extent of reaction was only 20%, whereas with weak bases (*p*-anisidine and morpholine) the yield is almost quantitative. The nucleoside phosphoropiperidates were found to be more reactive than the anisidates, the morpholidates occupying an intermediate position. Subsequent syntheses of nucleotides and nucleotide coezymes were based on the use of nucleoside phosphoromorpholidates because they were quite reactive and readily obtainable.

Nucleoside phosphoromorpholidates are obtained as their crystalline morpholino-*NN*′-dicyclohexylamidinium salts by slowly running a solution of dicyclohexylcarbodiimide in t-butanol into a boiling solution of the nucleoside-5′ phosphate and morpholine in aqueous t-butanol:



where R = adenine, uracil, cytosine, guanine.

The formation of nucleoside phosphoromorpholidates is accompanied by the side-reaction of morpholine with the carbodiimide to form guanidines of the type



The stronger the base, the more rapidly the guanidine is formed.

The possibility of using substituted nucleoside phosphoramidates in the formation of a pyrophosphate link was investigated with the synthesis of P^1-adenosine-5′ P^2-phenyl pyrophosphate as a model. In the case of the phosphoranisidate this was obtained in 90% yield, although a long time was required. The phosphoropiperidate was the most reactive, but its application was restricted by the difficulty of preparing it[83].

The phosphoramidate method using nucleoside phosphoromorpholidate derivatives was extended further to the preparation of complex nucleotide coenzymes.

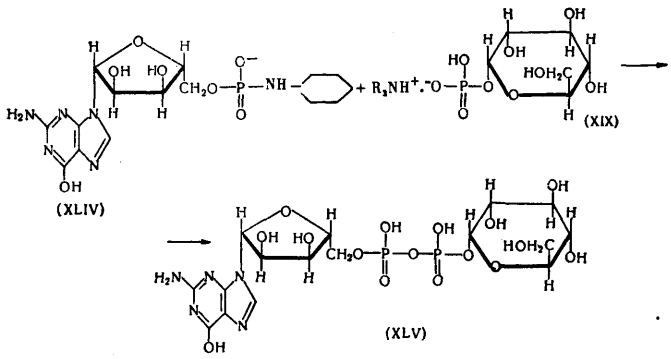
UDPG (XX) was obtained by condensing morpholino-*NN*′--dicyclohexylamidinium uridine-5′ phosphoromorpholidate with three equivalents of tri-n-octylammonium α-D-glucose-1-phosphate (XIX) in anhydrous pyridine at room temperature for 3 days[84,85]. The reaction product was chromatographed on Dowex-1 (in the chloride form), and the UDPG was isolated as its lithium salt in 70% yield. UDPG is obtained in better yield and by a far shorter route by the phosphoramidate than by other methods.

Uridine diphosphate galactose, cytidine diphosphate glycerol, and guanosine diphosphate mannose were prepared in a similar manner, the overall yields being 63–70%.[84] The same method was utilised to obtain nucleoside diphosphates. Nucleoside-5′ phosphoromorpholidates were condensed with trialkylammonium orthophosphates in anhydrous pyridine at room temperature for 2–3 days. Cytidine-5′ diphosphate and uridine-5′ diphosphate were obtained with yields of 78% and 67% respectively[83].

An overall yield of 43% of ATP could be obtained[83] by the reaction of adenosine-5′ phosphoromorpholidate with the inorganic di(tri-n-butylammonium) pyrophosphate in anhydrous pyridine for 5 h. It is interesting that a considerable quantity of ATP is formed right at the start of the reaction, but then its concentration falls rapidly, most probably owing to the effect of the excess of inorganic pyrophosphate present in the reaction mixture.

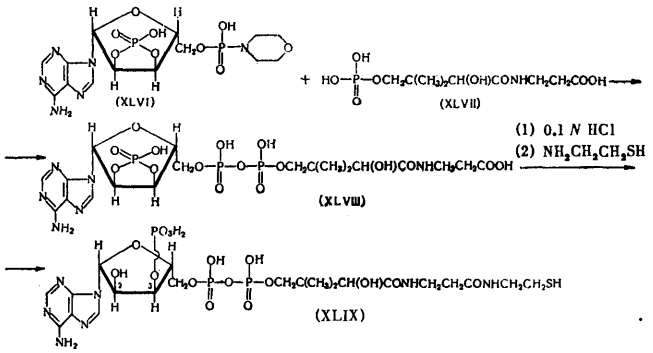
4. Guanosine Diphosphate Glucose

The phosphoramidate method has been used in the synthesis of guanosine diphosphate glucose (XLV) (isolated from *Eremothecium ashbyii*). The starting material was guanosine-5′ *N*-cyclohexylphosphoramidate (XLIV). The phosphoramidate itself and the phosphoromorpholidate did not react owing to their poor solubility in pyridine[86]. Compound (XLIV) was condensed with tri-n-octylammonium α-D-glucose-1-phosphate (XIX) in anhydrous pyridine. The synthetic product was purified by ion-exchange chromatography on Dowex-1 in the chloride form and isolated as the lithium salt.



5. Coenzyme A

Moffatt and Khorana[87,88] based their synthesis of CoA (XLIX) on the principle of the phosphoramidate method, using a phosphoromorpholidate derivative for the purpose. A 98% yield of adenosine-2′(3′)phosphate-5′ phosphoromorpholidate (XLVI) was first obtained from adenosine--2′(3′),5′ diphosphate and morpholine in the presence of dicyclohexylcarbodiimide. Compound (XLVI) was then condensed with the 4′-phosphate of DL-pantothenic acid (XLVII) in anhydrous pyridine at room temperature. The condensation product (XLVIII), after isolation and purification by ion-exchange chromatography, was treated with 0.1 *N* hydrochloric acid to open the cyclic phosphate link, after which it was brought into reaction with 2-aminoethanethiol:

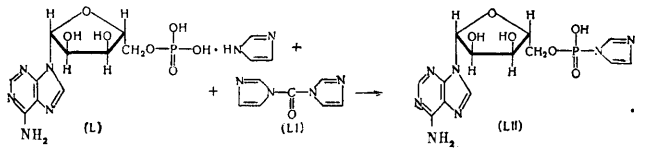


A mixture of CoA and iso-CoA (the 2′-phosphate isomer) was isolated, with an overall yield of 50%, by chromatography on an adsorption column; it possessed only 33% of the biological activity of natural coenzyme A, since the isomeric form is practically inactive.

Compound (XLVI) was also condensed with the 4′-phosphate of D-pantetheine, which also yielded the isomeric forms CoA and iso-CoA[87]. The enzymic activity of the synthetic coenzyme A was greater (86%) than that of the isocoenzyme (4%).

The possibilities of using nucleoside phosphoramidates derived from various aromatic amines and nitrogen heterocycles to produce a pyrophosphate link were further investigated by preparing adenosine-5′ phosphorimidazolidate (AMP-I) (LII) and studying its reactions with nucleophilic reagents[89–92]. The imidazolium salt of AMP-I is readily

obtained by the action of 1,1′-carbonyldiimidazole (LI) on imidazolium adenosine monophosphate (L) in anhydrous dimethylformamide, and also, in almost quantitative yield, by the reaction of 1 mole of AMP with 2–4 moles of 1,1′-carbonyldiimidazole:



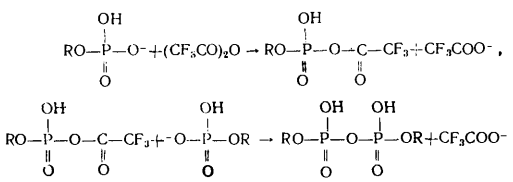
P^1P^2-Diadenosine-5′ pyrophosphate was prepared from the imidazolium salt of AMP-I and AMP, and a 57% yield of the crystalline form was isolated by chromatography on Dowex-1 (in the formate form). Condensation of AMP-I with uridine-5′ phosphate produces P^1-adenosine-5′ P^2-uridine-5′ pyrophosphate.

Reaction of the imidazolium salt of AMP-I with an excess of 85% H_3PO_4 at -10° to -20° gives a 25% yield of ADP. Treatment of the salt with aqueous ammonia in dimethylformamide–t-butanol results in cleavage of compound (LII) and the formation of adenosine-5′ phosphoramidate[89].

The phosphoramidate method of producing a pyrophosphate link is more satisfactory and simpler than other methods. Firstly, the condensation of two nucleotide molecules is carried out without preliminary protection of the hydroxyl groups, which greatly shortens and simplifies the synthesis; the carbodiimide method also requires no preliminary protection of the hydroxyl groups, but condensation often produces a complex mixture of substances, which makes it difficult to isolate the synthetic coenzyme. Secondly, the value of the method consists in the possibility of using an aqueous medium, which is very important in those cases in which the presence of even a small amount of water increases the solubility of the reactants. Furthermore, higher yields of nucleotide coenzymes can be obtained by this method.

Apart from the above three most important methods of forming the pyrophosphate link in nucleotide coenzymes, other methods, employing various condensing agents, have been used[93].

Trifluoroacetic anhydride has been used as condensing agent for the synthesis of FAD from FMN (as the sodium salt) and AMP[94]. Preliminary work on these lines was carried out by Shuster and his collaborators[95]. The phosphate anion attacks the trifluoroacetic anhydride to form an intermediate anhydride, which reacts with a second phosphate anion to form the P^1P^2-dinucleoside-5′ pyrophosphate:



Although considerable amounts of FAD can be obtained by this method, the yield is not very high (~ 10%). The FAD was isolated and purified by chromatography on powered cellulose[35].

A low yield of nicotinamide-adenine dinucleotide was obtained by a similar method from adenosine-5′ phosphate and nicotinamide mononucleotide[95].

It is interesting that condensation in the presence of acetic anhydride[96] leads to the exclusive formation of symmetrical compounds. A yield of ~ 55% of P^1P^2-dithymidine-5′ pyrophosphate has been obtained by this method from 3′-*O*-acetylthymidine-5′ phosphate by treatment with 0.275 millimole of acetic anhydride; it was shown that a twentyfold molar excess of acetic anhydride results in complete cleavage of the pyrophosphate link.

Use of a mixture of phosphoryl chloride and phosphorus pentoxide for the condensation of the appropriate two unprotected mononucleotides makes it possible to prepare FAD[97]. The reaction was carried out in phenol, in which the reactants are readily soluble[98,99]. Apart from FMN and AMP, riboflavin-5′ diphosphate and adenosine, riboflavin and ADP, and also other starting materials have been used in this synthesis.

When phosphoryl chloride was used as condensing agent, 2′,3′-*O*-isopropylideneadenosine gave 2′,3′-*O*-isopropylideneadenosine-5′ triphosphate, the yield being 45% and the purity 60–65%.[100]

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THE CHEMICAL EFFECTS OF NUCLEAR REACTIONS. THE ISOTOPIC EFFECT IN SECONDARY REACTIONS OF RECOIL ATOMS, ACCOMPANYING (n,γ) REACTIONS

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INTRODUCTION

In view of their marked theoretical and practical importance, the chemical changes accompanying nuclear reactions have recently been extensively studied[1-5]. The study of the chemical effects of nuclear reactions is theoretically important in relation to the kinetics of chemical reactions involving atoms with excess kinetic energy or excitation energy. The practical importance of such studies lies in the possibility of preparing "labelled" compounds by direct irradiation in a reactor, cyclotron, etc. The synthesis of new compounds by irradiating substances with neutrons from a uranium reactor has been developed extensively. Here the simplest process is the (n,γ) reaction, which gives isotopes of the original element. As recent studies have shown, the radioactive isotopes of a given element, produced as the result of a nuclear reaction, in a number of cases do not always show identical behaviour. The difference is shown as a difference in the magnitude of the retention for each isotope, *i.e.* the proportion of labelled products formed in secondary chemical processes taking place after the nuclear reaction.

For example, when certain alkyl bromides, such as CCl_3Br, were irradiated with neutrons, it was found that the retention for the ^{82}Br isotope was 48%, while that for the ^{80m}Br isotope produced at the same time was 38%. This difference is small and therefore cannot play an important part in problems of the practical preparation of labelled compounds, but the existence of such differences, which have been called "isotopic effects", has further stimulated the development of the theory of the secondary reactions of recoil atoms.

1. SECONDARY REACTIONS OF RECOIL ATOMS IN ORGANIC COMPOUNDS. THE "APPARENT ISOTOPIC EFFECT" AND ITS ORIGIN

The difference in the behaviour of isotopes formed as a result of the same nuclear process (the isotopic effect) may be due to a difference in the kinetic energy of recoil resulting from the emission of γ-quanta after neutron capture, or to a difference in the energy state of the electron clouds of the recoil atoms. Many studies have been made on the influence of the initial kinetic energy of recoil on the yield of the products of the secondary chemical reactions. From Libby's work[6,7] it follows that the initial kinetic energy of recoil atoms activated by nuclear reactions may influence the yield of organic derivatives if the nuclear reactions are carried out in a solid organic medium. The radioactive isotopes of a given element, even if they are activated by one type of nuclear reaction, may give different yields of organic compounds. This conclusion is based on the assumption that elastic and inelastic collisions take place between the recoil atoms and the atoms and molecules of the medium. Let us consider the deceleration of a "hot" atom in more detail. The recoil atom, which as a result of the nuclear reaction has acquired a high kinetic energy, is "cooled" by collision with the atoms of the surrounding medium; some of the atoms, as a result of elastic collision, enter the organic compounds and replace those atoms in the surrounding molecules whose masses do not differ significantly from that of the recoil atom. When the kinetic energy of the recoil atom decreases to a value comparable to the energy of the bonds formed by the atoms in the molecules, inelastic collisions between the recoil atom and the molecules become possible. Dissociation of the molecules then takes place with the formation of compounds containing radioactive recoil atoms. On going from the liquid to the solid phase, the quantity of products formed by elastic collisions remains unchanged, since the collision process takes place as a single elementary act and the bonds between the atoms do not change with change in the state of aggregation. The yield of compounds, whose formation is regarded as the result of inelastic collisions between the recoil atoms and the molecules, increases sharply on going to the solid phase, since the recoil atom has to move in a medium where the intermolecular bonds have become much stronger. According to Libby's calculations[6], a recoil atom with an initial energy of 0.3 MeV forms a "liquid drop" in the solid phase as the result of the fusion of a small local volume. The reaction involving elastic collisions takes place at the start and in the central part of the path of the recoil atom, *i.e.* in the centre of the "liquid drop", while reactions involving inelastic collision take place at the end of the path, at the boundary with the solid phase, where the physical properties of the medium change considerably. It is possible that at the end of the path the recoil atom, as a result of the loss of a considerable proportion of its energy, is unable to break the bond between the molecules to an extent sufficient to form a "liquid drop", as suggested by Libby. It is possible that at the end of the path of the recoil atom the substance again exists as a crystalline solid phase with some degree of amorphous character. For substances whose molecules consist chiefly of atoms whose masses differ considerably from those of the recoil atoms (for example ^{82}Br), such as CH_3Br, C_2H_5Br, C_3H_7Br, etc., we should expect a considerable increase in the yield of organic products or retention on going to the solid phase, as a result of the considerable proportion of super-thermal processes of inelastic collision. According to Libby's views, the yield of organic products in the solid phase *increases with decrease in the initial energy* of recoil, since in this case the medium surrounding the recoil atom will show less resemblance to the liquid phase, in which the retention is generally smaller. In other words, with decrease in the initial energy there is an increase in the local concentration of molecular fragments, leading to an increase in the yield of organic compounds as a result of fragment recombination. For other substances, such as CBr_4, in which the deceleration of the "hot" ^{82}Br atom takes place chiefly at bromine atoms, the retention will not change significantly on going to the solid phase, since in this case the major contribution to the retention is made by reactions induced by elastic collisions. In the case of CBr_4 we should not expect a difference in the behaviour of the bromine isotopes ^{80m}Br and ^{82}Br, although the recoil energy of ^{80m}Br is greater than that of ^{82}Br.

According to Libby's theory, a difference in retention for isotopes of a given element may result on irradiation in the solid phase because of a difference in recoil energy. This difference should be revealed as a difference in the yield of products formed in reactions induced by inelastic

collisions in the super-thermal energy range. In the irradiation of n-propyl bromide[7] in the crystalline state by thermal neutrons, the values of the retention or yield of organic compounds for the three bromine isotopes obtained by the reactions $^{81}Br\ (n,\gamma)\ ^{82}Br$ and $^{79}Br\ (n,\gamma)\ ^{80m}Br$ were 86.7% and 78.2% respectively, whereas in the irradiation of solid CBr_4 the values of the retention for ^{82}Br and ^{80m}Br were 86.8% and 86.9% respectively, *i.e.* it therefore appears that an isotopic effect exists for compounds in which super--thermal processes play a significant part in the stabilisation of the recoil atom. Other data, however, indicate the absence of an isotopic effect. Schuler and McCauley[8] carried out experiments involving the irradiation of n-propyl bromide with fast neutrons, in order to examine the influence of the initial kinetic energy of recoil on the yield of organic products after an (n,γ) reaction. The maximum fraction of the kinetic energy which a neutron can transfer on collision with a nucleus can be calculated from the formula[5]

$$E_m = \frac{4M}{(M+1)^2} E,$$

where E is the energy of the neutron and M the mass of the recoil atom.

The authors obtained bromine recoil atoms with an initial kinetic energy of ~100 000 eV, which is about 10^3 times greater than the recoil energy of bromine atoms on irradiation with thermal neutrons; no isotopic effect was observed. Data on the retention of ^{82}Br and ^{80m}Br isotopes activated by neutrons with different energies, given by different authors, are shown in Table 1.

The behaviour of the ^{78}Br isotope (6.4 min), obtained by the reaction $^{79}Br\ (n,2n)\ ^{78}Br$, was found to be different, its retention being higher in both liquid and solid phases, with mean values of 93% and 43% respectively. These data do not agree with Libby's suggestions regarding the relationship between the initial recoil energy and the retention. It is evident that the "liquid drop" in a solid body is of little importance in determining the fate of the recoil atom.

The "chance fragmentation" model proposed by Willard[3] may partly explain the increase in retention for a high recoil energy, as has been found for ^{78}Br recoil atoms. The fragmentation of molecules is obviously greater for a high recoil energy, so that an isotopic effect may be produced during subsequent diffusion–recombination reactions.

During the deceleration of, for example, a ^{78}Br recoil atom at propyl bromide molecules radical fragments are formed in much larger quantities than during the deceleration of ^{80}Br, ^{80m}Br, or ^{82}Br recoil atoms. But the recoil energy for the ^{78}Br isotope is 10^3 times greater than the kinetic energy of recoil of the latter! Labelled organic molecules are formed by subsequent radical reactions between the fragments and the recoil atoms. There will naturally be more molecules labelled with the ^{78}Br isotope than with, for example, the ^{82}Br isotope. If this is the case, the isotopic effect should disappear when small quantities of elementary bromine are added as radical acceptor before irradiation. Schuler and McCauley found that the isotopic effect, *i.e.* the difference in the retention for ^{78}Br and ^{82}Br, was equal to 7.0% in the absence of bromine, 5.5% in the presence of 5 mole % bromine, and 1.5% in the presence of 25 mole % bromine, *i.e.* the effect does in fact disappear. Richardson and Voigt[9] carried out experiments on the preparation of ^{80m}Br, ^{77}Br, and ^{76}Br isotopes by means of the photonuclear reactions $^{81}Br\ (\gamma,n)\ ^{80m}Br$, $^{79}Br\ (\gamma,2n)\ ^{77}Br$, and $^{79}Br\ (\gamma,3n)\ ^{76}Br$ in n-propyl bromide and isopropyl bromide in the liquid and solid states. Their values of the retention for ^{80m}Br, ^{77}Br, and ^{76}Br in the absence of bromine were found to be 87%, 62%, and 67% respectively. It would appear, as the authors state, that an isotopic effect exists for ^{80m}Br on the one hand and ^{77}Br and ^{76}Br on the other. When 5 mole % of elementary bromine was added, however, the retention for the bromine isotopes obtained by the (n,γ) and (γ,n) reactions became almost identical (24.0% and 27.6% respectively). Thus an isotopic effect may appear at high recoil energies due to the large number of radicals formed by the moving atoms, and disappears on the addition of bromine, which effectively combines with the radicals. The data in Table 2 show that in fact the yield of organic products obtained during the irradiation of propyl bromine with neutrons and γ-quanta depends on the type of activation. The difference in the type of activation is reflected in the yields of the dibromo--derivatives produced as a result of fragmentation of the mother compound (methylene bromide). The addition of 5 mole % of elementary bromine before irradiation decreases considerably the yield of the mother compound in the case of both (n,γ) and (γ,n) reactions, and also decreases to a considerable extent the yield of 1,2-dibromopropane. In solid propyl bromide no difference in retention was observed for the ^{80m}Br and ^{82}Br isotopes at -196°, but there was an overall increase in the retention, chiefly in the form of the mother compound, and also as 1,3-dibromopropane and ethyl bromide.

These results do not agree with Libby's theory, which predicts the appearance of isotopic differences only in the solid phase. The yields of the products can be explained qualitatively on the basis of Willard's theory, which assumes the random formation of radicals in the track of the hot atom. With increase in the recoil energy there is an increase in the proportion of C–C bonds broken, and a result of this may be an increase in the yield of organic products, which are formed in subsequent diffusion–recombination reactions. Thus in the liquid phase a difference in the retentions for the ^{82}Br and ^{80m}Br isotopes (see Table 2) is produced. In the solid phase, where diffusion is much less marked, there should be no such differences, since the part played by diffusion–recombination reactions is much smaller. At first sight this shows good agreement with experiment. According to Richardson and Voigt's data, the difference in the retention for isotopes obtained by the same nuclear reactions can also be explained from Willard's viewpoint, *i.e.* it is attributed to the difference in the recoil energy, leading to the production of different quantities of radicals in the track of the hot atom.

There are, however, certain facts which cannot be explained by Willard's theory. The retention does indeed

TABLE 1. Retention for different bromine isotopes in propyl bromide (%).

Reaction	Type of neutron	Phase		References
		liquid	solid	
$^{79}Br(n,2n)^{78}Br$	fast	42.6	92.5	8
$^{79}Br(n,\gamma)^{80}Br$	thermal	37.8	79.1	8
		34.0	—	6
$^{79}Br(n,\gamma)^{80m}Br$	thermal	34.0	78.2	6,7
$^{81}Br(n,\gamma)^{82}Br$	fast	33.4	76.2	8
		36.5	79.4	8
$^{81}Br(n,\gamma)^{82}Br$	thermal	—	86.7	7
(with 5% Br_2)	thermal	24.0	—	9
$^{81}Br(\gamma,n)^{80m}Br$		54.0	88.7	9
$^{79}Br(\gamma,2n)^{77}Br$		62.0		9
$^{81}Br(\gamma,n)^{80m}Br$		67.0		9
(with 4.7% Br_2)		27.6		9

TABLE 2. Yields of products (%) containing the radioactive isotopes ^{80m}Br and ^{82}Br obtained by (γ, n) and (n, γ) reactions respectively in propyl bromide.

Reaction	Phase	Total retention	Yields of products								
			CH_3Br	C_2H_5Br	isopropyl bromide	n-propyl bromide	CH_2Br_2	1,2-dibromoethane	1,2-dibromopropane	1,3-dibromopropane	polymeric substances
$^{81}Br(\gamma, n)^{80m}Br$	liquid	54	1.4	1.2	1.9	19.7	4.0	5.8	13.0	4.7	2.2
	solid	88.7	2.0	2.9	3.8	32.3	2.3	5.0	15.6	10.0	15.0
$^{81}Br(n, \gamma)^{82}Br$	liquid	34.7	—	0.7	1.7	17.1	1.8	3.1	2.8	2.7	1.5
	solid	88.4	—	2.7	3.4	26.9	2.4	6.0	6.0	17.8	12.1

increase with increase in the recoil energy, as predicted by Willard's theory, but this increase is too small compared with the change in the recoil energy. For a change in the recoil energy by a factor of 10^3, the retention changes by a factor of only 1.5 (see Table 1). Thus some other factor, not the recoil energy, influences the retention. Moreover, according to Willard's views, there should be no differences in retention in the solid phase, but Rowland and Libby[7], and later Milman[10,11], observed that the yields of organic compounds in the secondary reactions of recoil atoms with the medium depend on whether the substance irradiated exists in the crystalline or vitreous state. In the vitreous state, the size of the "liquid drop" will be greater, and the retention less, than in the crystalline state. This is due to the fact that fusion of a substance in the vitreous state requires less energy than fusion of the same substance in the crystalline state. The volume of the resulting "liquid drop" will in this case be greater in the vitreous substance, so that the retention and isotopic effect will be less. The retention data for ^{80}Br in solid ethyl bromide[10,11], obtained for different times of freezing of an ethyl bromide–bromine mixture, indicate a considerable (up to 10%) decrease in the retention for the vitreous state of C_2H_5Br. This result to some extent confirms Libby's theory.

The problem of the difference in the behaviour of recoil atoms in the crystalline and vitreous states can, however, be approached from another viewpoint. As already noted[12], the radiation yield of elementary iodine in the irradiation of ethyl iodide with γ-rays depends on its structure. In the vitreous state the radiation yield of iodine is three times that [for bromine ? (Ed. of Translation)] in the irradiation of ethyl bromide in the crystalline state. Thus it is not the size of the "liquid drop" which is the chief determining factor in the irradiation of vitreous or crystalline substances, but the orientation of the molecules relative to one another, and the related difference in the secondary reactions. As a result, isotopic effects may be produced.

Let us summarise briefly. With increase in the recoil energy an increasing quantity of fragment radicals appears in the track of the hot atom. In the subsequent reactions this gives an increase in the yield of labelled organic substances. This increase is slight compared with the increase in the recoil energy. Thus the isotopic effect (as defined above) is not directly related to the recoil energy. Experimental data show that the isotopic effect is not observed in the presence of radical acceptors, so that this type of isotopic effect should be referred to as an "apparent isotopic effect". Impurities and the accompanying γ-radiation (which cannot be excluded on irradiation in a reactor) can also produce an isotopic effect (as a result of differences in the half-lives of the isotopes). Willard[2], contrary to Capron, claims that the latter factor is of decisive importance and relates it to the isotopic differences accompanying the irradiation of substances in the liquid phase; this is apparently correct. As far as experiments on the irradiation of vitreous and crystalline structures are concerned, it is necessary, before final conclusions are reached, to carry out more detailed experiments with the addition of radical acceptors, since in the solid phase diffusion reactions are not completely blocked.

2. THE BEHAVIOUR OF RECOIL ATOMS IN INORGANIC SYSTEMS

A difference in the behaviour of isotopes as a result of the formation by them of unequal quantities of fragments is predicted by Maddock's theory[13], which is used to describe the processes taking place in the thermal annealing of substances irradiated by γ-rays, neutrons, protons, and other particles. In the irradiation of crystalline potassium chromate with, for example, neutrons, the radioactive chromium atoms obtained by the (n, γ) reaction are stabilised in the form of CrO_3, CrO_2^{2+}, and CrO^{4+} (possibly Cr^{6+}) fragments as a result of the loss of oxygen atoms along the path of their movement. The yield of the mother compound (retention) containing radioactive chromium increases during the subsequent annealing as a result of recombination processes, whose rate depends on the temperature of the experiment. Maddock obtained an expression for the dependence of the rate of recombination of recoil atoms on the distance between them:

$$dR/dt = e^{-A/kT} e^{V/kTX},$$

where X is the least distance between the fragments at time t (between CrO_2^{2+} and O^{2-} for example), T the absolute temperature, k the Boltzmann constant, and V a constant taking account of the charge, dielectric constant, etc.

It follows that since different isotopes of a given element can form different quantities of fragments, the appearance of an isotopic effect is possible after thermal annealing. The thermal annealing of specimens of $NaBrO_3$ and $RbBrO_3$ [14] irradiated by thermal neutrons gave for the two bromine isotopes ^{82}Br and ^{80m}Br, data (Table 3) which show that the initial retention is the same for the two isotopes, but that when the irradiated salt specimens are heated, the values of the retention become different. It was considered[14] that the magnitude of the recoil energy does not influence the retention, but since a difference is shown as a result of the processes of recombination between the fragments and recoil atoms during subsequent heating, it must be assumed that the quantities of these fragments are not the same. The quantity is possibly greater for ^{82}Br, and this gives an increase in the retention for this isotope relative to ^{80m}Br as a result of annealing, despite the fact that the initial energy of the ^{80m}Br recoil atom is slightly higher. The difference in the quantities of fragments obtained during deceleration of the ^{82}Br and ^{80m}Br recoil atoms may be due to a difference in their chemical states after the radiation capture of a neutron.

The results given in Table 3 cannot be interpreted in terms of the influence of the recoil energy on the retention. In fact, when the bromates are annealed, the retention for the ^{82}Br isotope increases more rapidly than that for the ^{80m}Br isotope, but the recoil energy of the ^{82}Br isotope is not greater than that of ^{80m}Br. The initial recoil energy

TABLE 3. The influence of thermal annealing on the retention of bromates irradiated with neutrons (t = 200°).

Duration of annealing, min	Retention, %			
	$NaBrO_3$		$RbBrO_3$	
	^{80m}Br	^{82}Br	^{80m}Br	^{82}Br
0	11	11	13	13
10	22	17	—	—
20	23	30	—	—
30	25	33	31	40
90	31	40	35	45
180	34	41	38	49
360	37	45	40	50

thus has no significant influence on the secondary reactions of the recoil atoms, as has been established not only for halogen recoil atoms but also for ^{14}C,[15] tritium,[16] ^{60}Co,[18] and a number of others. The recoil atoms evidently begin to react with the molecules of the medium to form intermediate or stable compounds after preliminary loss of energy. The isotopic effect which has been observed during the thermal annealing of bromates is apparently the result of a difference in the chemical states of the ^{82}Br and ^{80m}Br recoil atoms after the radiation capture of a neutron.

Differences in the behaviour of the isotopes of a given element have also been observed in the study of the (n,γ) reaction in certain metal compounds. Thus a considerable difference was observed in the values of the retention for ^{65}Zn and ^{69}Zn isotopes, obtained by the reactions $^{64}Zn(n,\gamma)^{65}Zn$ and $^{68}Zn(n,\gamma)^{69}Zn$, in the study of the complex formed by zinc with phthalocyanine[17]. The authors erroneously assume, however, that the reason for the production of the isotopic effect is the difference in the initial recoil energy†, which in their opinion leads to a difference in the probability of return to the original molecule. The probability of return to the original molecule for ^{65}Zn recoil atoms, with a recoil energy of 477 eV, is less than that for ^{69}Zn atoms with a kinetic energy of 238 eV. It is assumed[17] that this results in a difference in the values of the retention for the two zinc isotopes (29.4% for ^{65}Zn, 38.2% for ^{69}Zn). It has now been established, however, that the return of the recoil atoms to the original mother molecule is impossible. The recoil atoms form the mother compound in subsequent secondary reactions with other molecules, as a result of the excess energy which they possess, or during subsequent thermal annealing, as a result of recombination with fragments formed during deceleration. Other work[18] has shown that the retention in metal complexes is independent of the initial recoil energy and is determined only by the type of nuclear reaction and the nature of the complex compound. In the case of the two cobalt isotopes ^{58}Co and ^{60}Co obtained by the reactions $^{59}Co(\gamma,n)^{58}Co$ and $^{59}Co(n,\gamma)^{60}Co$ when bisindenylcobalt nitrate is irradiated with γ-quanta or neutrons, the values found for the activity in the form of the original compound were 16.2 ± 1.2% and 2.5 ± 0.2%. These results do not agree with data obtained in the study of the retention in complex compounds of zinc. The recoil energy after the (γ,n) reaction in the cobalt complexes is greater by several powers of ten than that after the (n,γ) reaction. If the above hypothesis were correct, the retention after the (γ,n) reaction should be less than that after the (n,γ) reaction, due to the lower probability of return to the original molecule. The results were contradictory, however. The magnitude of the recoil energy does not influence the retention in metal complexes, as has been proved for organic compounds. The recoil atoms evidently react with the medium to form stable or intermediate compounds in the last stages of the "cooling" process, when their energy decreases to values of the order of 10–100 eV.

Table 4 gives data on the retention for ^{122}Sb and ^{124}Sb isotopes after the (n,γ) reaction in crystalline triphenylantimony, obtained by Hall and Sutin[19]. They consider that the reason for the difference in the values of the retention for the antimony isotopes is to be found in the difference in the recoil energies after the (n,γ) reaction. Making use of the theories developed by Libby, they suggest that the ^{122}Sb recoil atom has apparently a smaller recoil energy, which leads to a greater retention for this isotope, as a result of the higher local concentration of fragments. There are, however, no data for the recoil energies of ^{122}Sb and ^{124}Sb, so that this explanation of the isotopic differences is not convincing. The isotopic effect may be the result of a difference in the degree of conversion of the electron clouds of the ^{122}Sb and ^{124}Sb isotopes formed after isomeric transition in 3.5 min from ^{122m}Sb and in 21 min and 1.3 min from the two isomers of ^{124m}Sb. As a result of isomeric transition, the antimony atoms acquire a positive charge and leave the mother molecule due to coulombic repulsion. The internal conversion coefficients are different for the isomeric transitions $^{122m}Sb \rightarrow {}^{122}Sb$ and $^{124m}Sb \rightarrow {}^{124}Sb$, and this may lead to a difference in the number of ^{122}Sb and ^{124}Sb atoms leaving the molecules in which they are stabilised directly after the (n,γ) reaction. The quantity of ^{122m}Sb and ^{124m}Sb excited states produced is only 1%, however,[19] so that this cannot significantly influence the distribution of ^{122}Sb and ^{124}Sb isotopes among the individual products.

According to Maddock's data[17,20], the difference in the values of the retention for the ^{122}Sb and ^{124}Sb isotopes, and also for the isotopes ^{186}Re and ^{188}Re, may be related to the difference in the degree of conversion of the soft γ-rays of the capture radiation of thermal neutrons. This is a probable explanation of the production of isotopic differences, since it has been confirmed experimentally that a relationship exists between the internal conversion coefficients and the retention[21]. In a study of the removal of the chemical species C_6H_5Pb(ThB, RaD)Cl, as a result of the β-decay of the lead isotopes ThB and RaD and their conversion to the bismuth isotopes ThC and RaE, it was found that the ratio

TABLE 4. Yields of products containing the radioactive isotopes ^{122}Sb and ^{124}Sb during the irradiation of crystalline triphenylantimony with neutrons.

Products	^{122}Sb, %	^{124}Sb, %	$^{122}Sb/^{124}Sb$
$(C_6H_5)_3Sb$	4.4	3.2	1.37±0.02
$(C_6H_5)_2SbO(OH)_2$	13.9	13.8	1.01±0.05
$(C_6H_5)SbO$ and $(C_6H_5)SbO(OH)_2$	32.7	30.7	1.06±0.04
Sb	29.7	33.8	0.88±0.01

† The reader is advised to consult Ref.17, p.499, however (Ed. of Translation).

of ThC and RaF in the original compound is equal to $1 - k_1/1 - k_2$, where k_1 and k_2 are the internal conversion coefficients for the β-decay of the ThB and RaD isotopes. In fact for the β-decay of heavy isotopes, the recoil energy is insufficient to rupture a chemical bond, and the probability of removal from the mother compound is determined by the degree of conversion of the electron cloud. The marked isotopic effect in the β-decay of ThB and RaD (retention 50 ± 2% and 19 ± 1% respectively) indicates that the state of the electron cloud of the recoil atoms is the decisive factor influencing the magnitude of the retention.

3. THE INFLUENCE OF THE CHEMICAL STATE OF THE RECOIL ATOMS ON SUBSEQUENT REACTIONS IN WHICH THEY TAKE PART

Considerable attention has recently been paid to the possibility of ion–molecule reactions during the stabilisation of recoil atoms activated by nuclear reactions. This possibility is based on the fact, first observed by Wexler and Davies[22,23], that the recoil atoms obtained by an (n, γ) reaction have a positive charge. It was found that approximately 25% of the ^{82}Br recoil atoms, 18% of ^{82m}Br atoms, 12% of ^{80}Br atoms, 45% of ^{128}I atoms, and 21% of ^{38}Cl atoms are obtained with positive charges and can be collected at a negative electrode in the gas phase. The average charge on the ^{80}Br atoms (18 min) is +10, and that on the ^{38}Cl atoms +4.[23] The quantity of charged ^{82}Br atoms is greater than the quantity of ^{80m}Br atoms, so that the fragmentation of the molecules is greater for the ^{82}Br recoil atoms. Some authors[14] have tried to explain the difference in the values of the retention for ^{82}Br and ^{80m}Br isotopes from this viewpoint. Others[24-28] suggest that the isotopic effect is a direct result of ion–molecule reactions between the recoil atoms and the molecules of the medium.

It is known[29] that chlorine atoms readily remove hydrogen from hydrocarbon molecules with the formation of HCl. The activation energy for this process is less, the longer the hydrocarbon chain. Aditya and Willard[30], found, however, that the retention for ^{38}Cl obtained by the reaction $^{37}Cl(n, \gamma)\,^{38}Cl$ in CCl_4 diluted with various hydrocarbons is constant and independent of the nature of the solvent or the chain length of the hydrocarbon molecule. This unexpected feature of the retention cannot be satisfactorily explained in terms of the existing theory of stabilisation of recoil atoms and cannot be attributed to reaction between the "cooled" chlorine recoil atoms and the hydrocarbon molecules. The value of 21% found experimentally for the retention[30] shows remarkable agreement with the proportion of positively charged ^{38}Cl atoms (21%) obtained after the (n, γ) reaction, as shown by Wexler and Davies. This suggests the possibility of ion–molecule reactions involving charged chlorine atoms. When C_3H_7Cl was diluted with methane in the gaseous phase, the retention for ^{38}Cl resulting from the (n, γ) reaction was found to be 17%;[31] for dilution with ethane the retention was 10%[16] and for dilution with butane 7%.[16] The fact that in these cases the retention was found to be less than the 21% found in Aditya and Willard's experiments indicates that the nature of the solvent has a certain influence, but this is not surprising from the viewpoint of the ion–molecule reaction theory, since the rates of loss of charge may be different in different media. The yields of C_2H_5Cl and $C_2H_4Cl_2$, obtained during the irradiation of methyl chloride with neutrons [(n, γ) reaction], show that the CH_3Cl molecule is able to react with another CH_3Cl molecule to form a C–C bond. The possibility of the formation of chains in the reactions of the recoil atoms with the medium exists in principle. Willard[32] suggested the following mechanism of chain formation resulting from the secondary reactions of tritium recoil atoms with methane in the gas phase:

$$T^+ + CH_4 \rightarrow CH_3T^+ + H_2, \quad (1)$$
$$CH_3T^+ + CH_4 \rightarrow C_2H_4T^+ + H_2. \quad (2)$$

There are strong objections to this mechanism of chain formation, however, as Willard himself pointed out[31]. These arise from the fact that the tritium atoms are assumed to be neutralised before their energy decreases to ~100 eV, *i.e.* to a value which is still sufficiently high for the formation of stable products by inelastic collisions.

Studies by Wolfgang and coworkers help to resolve this contradiction. They have shown[33-35] that the relative kinetic energy of the most probable reactions of tritium with methane molecules,

$$T + CH_4 \rightarrow T^+ + CH_4 + e^-$$
$$T + CH_4 \rightarrow T^- + CH_4^+$$
$$T^- + CH_4 \rightarrow T + CH_4 + e^-$$
$$T^+ + CH_4 \rightarrow T + CH_4^+$$

has the values (eV) 30 000, 25 000, 90, and 30 respectively. From this it can be seen that tritium atoms with an initial kinetic energy greater than 30 000 eV [^{6}Li (n, α)T reaction] are gradually slowed down and become able to ionise or be ionised, and at lower velocities of 100 eV and below they effectively neutralise one another. This, however, is the upper kinetic energy limit where reactions of inelastic collision between the tritium recoil atoms and the molecules become possible. It is therefore possible that ion–molecule reactions of charged tritium recoil atoms can take place, so that Willard's initial assumption is correct.

The reactions of the ions of radioelements dispersed in high-tension fields have recently been studied, in order to obtain a model for processes taking place after nuclear reactions. Wolfgang[33] has obtained data on the distribution of tritium between different compounds during reactions of tritium ions, dispersed at 100 eV, with organic substances. Analogous experiments by Lemmon[36,37] on the reaction of dispersed $^{14}C^+$ ions with benzene have shown that the ion–molecule reactions taking place when the charged $^{14}C^+$ ions collide with benzene molecules lead to the formation of the following compounds, labelled with carbon-14: carbon dioxide, benzene, cycloheptatriene, and hydrocarbons from propane to pentane. The ratio of the yields of these products changes with change in the energy of the moving $^{14}C^+$ ions. The preparation of labelled compounds by means of the reactions of artificially dispersed ions is of considerable theoretical importance in explaining the regular features of the secondary reactions of recoil atoms obtained as a result of nuclear reactions. Work in this direction is undoubtedly of practical importance for the synthesis of various compounds containing radioactive atoms.

Willard *et al.*[38-40] have shown that ~50% of the ^{128}I atoms obtained by the reaction $^{127}I(n, \gamma)\,^{128}I$ in a mixture of iodine and methane are stabilised (at pressures of 0.2 mm Hg and 400 mm Hg respectively) in the form of organic compounds, whereas during photochemical dissociation under the same conditions, less than 1% of the iodine enters the organic compounds. The authors discuss the possibility of the introduction of iodine into organic compounds by reactions of the type

$$I + CH_4 \rightarrow CH_3I + H \quad (3)$$

or

$$I^+ + CH_4 \rightarrow CH_3I + H^+. \quad (4)$$

Both reactions are endothermic, the first requiring the expenditure of ~50 kcal mole^{-1} and the second 100 kcal × × mole^{-1}. The ratio of the masses of methane and iodine is such that the proportion of the energy which can be transferred by the iodine atom in one collision with a methane molecule is 40%. On the average, 20% of the initial kinetic energy is used up in one collision. Assuming that when a neutron is captured by the atom, one γ-quantum is emitted with an energy of 8 MeV, we find that the initial energy of the ^{128}I recoil atom is 268 eV. Since reaction (3) requires an activation energy of 50 kcal mole^{-1} or ~2 eV, the number of collisions necessary to decrease the initial energy of the iodine recoil atom to this value is

$$n = \ln \frac{268}{2} \Big/ \eta = 2.3 \log (134)/0.4 \simeq 12,$$

where η is the logarithmic decrement of the loss in energy when an iodine atom collides with a methane molecule.

Despite the fact that the ^{128}I recoil atom undergoes ~12 collisions with methane molecules and at each collision has an energy greater than the activation energy of reaction (3), the formation of methyl iodide as a result of these collisions is impossible, for the following reasons. The maximum proportion of the kinetic energy which can be possessed by the activated complex and can hence be used for the rupture of the C–H bond is equivalent to the ratio of the mass of the methane molecule to the sum of the masses of the methane molecule and iodine atom

$$\frac{M_{CH_4}}{M_{CH_4} + M_I},$$

and has the value ~0.1.

Thus the iodine atom should have an energy of not less than 20 eV if it is to transfer, on collision with a methane molecule, an amount of energy sufficient to dissociate a C–H bond. In this case the activated complex will have an energy of 460 kcal mole^{-1} (20 × 23 = 460). It is unlikely that the C–I bond in such a molecule will be preserved on collision with other molecules. As a result, the formation of methyl iodide according to reaction (3) is impossible. The ionisation potential of the methane molecule is 14.4 eV, and that of iodine 10.6 eV, so that the iodine atom collides with methane molecules without losing its positive charge. In the presence of iodine the following reaction is possible:

$$^{128}I^+ + I_2 \rightarrow I_2^+ + {}^{128}I \quad (5)$$
$$^{128}I^+ + I_2 \rightarrow I^{128}I^+ + I, \quad (6)$$

since the ionisation potential of the I_2 molecule is lower than that of the iodine atom (10.1 eV and 10.6 eV respectively), so that subsequently, as suggested by Willard, a reaction may take place between the iodine molecules, which acquired an excitation energy in reactions (5) and (6), and methane molecules:

$$I^{128}I + CH_4 \rightarrow CH_3{}^{128}I + HI$$
$$I^{128}I + CH_4 \rightarrow CH_3I + H^{128}I.$$

Developing Willard's initial hypothesis of ion–molecule reactions in the iodine–methane system, let us assume that charge transfer takes place according to the following scheme:

$$II^+ + CH_4 \rightarrow CH_3I^+ + HI \quad (7)$$
$$II^+ + CH_4 \rightarrow CH_3I + HI^+. \quad (8)$$

The heat of the reaction can be calculated from the formula

$$Q = A - B + P_1 - P_2,$$

where Q is the heat, A the energy of formation of the new bonds, B the dissociation energy of the old bonds, and P_1 and P_2 the ionisation potentials of the newly formed ionised molecule and the original compound.

A reaction of type (4) is impossible for the same reasons as those which apply to reaction (3), and also because the ionisation potential of the hydrogen atom is 4.59 eV greater than the ionisation potential of the I atom, leading to an increase in the activation energy of reaction (4), calculated by Polyani's rule, by several kcal mole^{-1}. For reactions (5) and (6), we obtain Q = 0.5 eV, *i.e.* the heat of ion–molecule reactions of types (5) and (6) is equal to the difference in the ionisation potentials of the iodine atom and molecule. In the comparison of the heats of reactions (7) and (8) only the ionisation potentials are taken into account, since the nature of the products obtained by these reactions is the same:

$$Q(7) = (A - B) + 0.33,$$
$$Q(8) = (A - B) - 1.71,$$

where $(A-B)$ is the heat of the reaction without allowance for the ionisation potentials. Reaction (7) is more probable, since the heat is higher.

In the absence of added elementary iodine, it is possible that the determining reaction is the introduction of charged iodine atoms into the methane molecule according to the scheme

$$^{128}I^+ + CH_4 \rightarrow CH_3{}^{128}I^+ + H, \quad (9)$$

which is energetically more favourable than the corresponding reaction with uncharged atoms.

Experiments[39] carried out by Willard on the activation, by thermal neutrons, of a mixture of iodine and methane in the presence of substances with higher ionisation potentials than that of iodine (He 24.58 eV, Ar 15.76 eV, and Xe 12.13 eV) and substances with lower ionisation potentials (CH_3I 9.67 eV, C_2H_5I 9.47 eV, and C_3H_7I 9.41 eV) indicated the absence of any effect when the inert substances were added and a marked decrease in the retention when substances with lower ionisation potentials were added. These data provide very significant evidence in support of the hypothesis that ion–molecule reactions take place.

For the three radioactive bromine isotopes ^{80}Br, ^{80m}Br, and ^{82}Br, obtained by (n,γ) reactions from the natural mixture of isotopes, the ratio of the retentions for the isotopes should be 1.5 : 1 : 2, as postulated by Willard *et al.*[40], if it is assumed that positively charged bromine atoms take part in the reaction. They carried out experiments on the neutrons of bromobenzene, of a mixture of benzene and bromine, and of n-propyl bromide. The data are given in Table 5. They concluded that there is no difference in the behaviour of the three bromine isotopes. The ionisation potentials of the substances which they used are in all cases lower than the ionisation potential of bromine (C_6H_6 9.5 eV, C_6H_5Br 9.4 eV, Br 11.8 eV, Br_2 10.9 eV), so that if some of the reactions occurred through positively charged bromine atoms, this would be clearly shown for the ^{82}Br isotope. The negative result of these experiments indicates that ion–molecule reactions do not take place in the systems chosen. The benzene molecule has a lower ionisation potential than the bromine atom, so that the bromine recoil atom loses its charge in the earliest stages of the

TABLE 5. Retention for the bromine isotopes ^{80}Br, ^{80m}Br, and ^{82}Br during slow-neutron irradiation of compounds mixed with bromine.

Mixture irradiated	Retention, %		
	^{80}Br	^{80m}Br	^{82}Br
C_6H_5Br + 3 mole % Br_2	5.56	5.89	5.40
C_6H_5Br + 0.1 mole % Br_2	16.6	17.4	16.5
C_6H_6 + 5 mole % Br_2	1.77	1.77	2.32
C_6H_6 + 2 mole % Br_2	2.68	2.64	2.75
n-C_3H_7Br + 0.5 mole % Br_2	5.28	5.74	5.43

"cooling" process. At the moment when super-thermal reactions become possible, it no longer possesses a charge. Ion–molecule reactions can be expected only in a system where the ionisation potentials of the substances are greater than the ionisation potentials of the recoil atoms and the products obtained have a lower ionisation potential. Then, in the first place, the recoil atom has not lost its charge up to the moment when super-thermal inelastic interactions begin to take place, and secondly, reactions will take place with the formation of products whose ionisation potentials are lower than those of the original substances and the ion–molecule reactions may compete with ordinary radical reactions. From this viewpoint the latest experiments[40] cannot be considered successful.

4. THE ISOTOPIC EFFECT REGARDED AS THE RESULT OF SUPER-THERMAL ION–MOLECULE REACTIONS

In the study of the reactions of "hot" bromine atoms activated by (n, γ) reactions in mixed liquid chlorobromomethanes an isotopic effect was observed[24-27] for ^{82}Br and ^{80m}Br in the case of the following compounds: CCl_3Br, CCl_2Br_2, CH_2ClBr, $CHCl_2Br$, and $CHClBr_2$. The retention for ^{82}Br was greater than that for ^{80m}Br and was independent of both the duration of irradiation and the addition, before irradiation, of elementary bromine over a wide concentration range. An analogous result was obtained for fluorobromomethanes in the liquid phase[28]. To explain the isotopic effect, Nesmeyanov and Filatov put forward a theory of ion–molecule reactions in the super-thermal energy range according to the scheme

$$\overset{+}{Br}{}^{*} + RClBr \longrightarrow \begin{cases} \overset{+}{R}ClBr^{*} + Br^{\cdot} & (6) \\ \overset{+}{R}BrBr^{*} + Cl^{\cdot} & (7) \\ RCl^{\cdot} + \overset{+}{Br}Br^{\cdot} & (8) \end{cases}$$

These reactions are possible because the ionisation potentials of the compounds formed in the reactions are less than the ionisation potential of the bromine so that the activation energy of the reactions is less than usual. The introduction of a radioactive bromine atom into the organic compounds will be greater for the ^{82}Br isotope, since the number of positively charged ions is greater for $^{82}Br^{+}$ than for $^{80m}Br^{+}$, and inorganic radiobromine will appear in the form of Br–Br, and not Br–Cl, since the ionisation potential of the latter is greater. (The reactions occur in the direction of substances with the lower ionisation potentials.)

In iodobromomethane the isotopic effect is opposite to that observed for the chlorobromomethanes[26]. The effect of elementary iodine on the retention was studied, but over a wide concentration range the iodine had no influence on the isotopic effect. The influence of polar and non-polar solvents on the retention for ^{82}Br and ^{80m}Br was also studied. It was observed that when polar solvents are added, the retention for ^{82}Br decreases more rapidly than for ^{80m}Br; the isotopic effect decreases; for CH_2BrI the opposite effect is observed. Thus the polarity of the solvent influences the isotopic effect, but the polarity of the compound being irradiated has no significant influence on the magnitude of the retention, since, for example, the values of the retention for ^{82}Br and ^{80m}Br in 1,2-chlorobromoethane and bromopicrin were found to be identical.

An apparent isotopic effect has been observed[25] in the irradiation of bromoform with neutrons at an elementary bromine content of less than 10^{-3} mole. When specimens containing more than 10^{-3} mole of Br_2 were irradiated, the isotopic effect disappeared, and it was also absent when the irradiation was of short duration (at a bromine content of less than 10^{-4} mole), indicating that in this compound the isotopic effect results from diffusion–recombination reactions. In chlorobromomethanes the isotopic effect does not change with change in the duration of irradiation from 4 h to 120 h, indicating that the isotopic effect in these compounds is due to high-energy reactions.

An interesting fact is that the isotopic effect (ΔR) is related to the fraction of diffusion reactions (R_D) in the compounds studied (Table 6). It was found that for all the compounds, except $CHCl_2Br$, the isotopic effect was smaller, the greater the part played by diffusion–recombination reactions in the stabilisation of the recoil atoms. This indicates that the isotopic effect in the substances studied cannot be due to diffusion reactions of the recoil atoms, since otherwise the isotopic effect would increase with increase in the proportion of the diffusion reactions, as a result of the greater average lifetime of the ^{82}Br isotope compared with the ^{80m}Br isotope.

When substances with ionisation potentials lower than that of bromine (benzene, toluene) are added, the retention remains unchanged for both ^{82}Br and ^{80m}Br. This agrees with Willard's data on the neutron irradiation of $C_6H_6 + Br_2$ mixtures (Table 5).

In all the mixed halogenobromomethanes, in which an isotopic effect was observed on irradiation in the liquid phase, no difference in the behaviour of ^{82}Br, ^{80m}Br, and ^{80}Br was observed in the solid phase[28]. This can apparently be attributed to an increase in the rate of neutralisation of the charge of the bromine recoil atoms in the solid medium because of the higher forces of adhesion between the molecules in the molecular crystal. In a liquid medium the isotopic effect had the greatest value in non-polar substances (CCl_3Br, CCl_2Br_2, and CBr_3F). In polar substances it was generally absent ($CHBr_3$, CBr_3NO_2, and CH_2Br_2). This also confirms the assumption that neutralisation of the charge of the recoil atoms is possible during deceleration

TABLE 6. Retention, isotopic effect, and proportion of diffusion reactions in halogenobromomethanes in the liquid phase.

Substance	R_D	$R_{^{82}Br}$	$R_{^{80m}Br}$	$R_{^{80}Br}$	ΔR
CCl_3Br	14	48.0	38.0	—	10
CCl_2Br_2	18	54.0	450	—	9
$CHBr_2F$	20	54.0	48.0	49.0	9
$CHBr_2Cl$	24	63.3	57.5	—	9
$CHCl_2Br$	30	64	53.1	—	11
CH_2BrCl	30	58.9	57.7	—	3
CBr_3F	—	67.2	56.8	55.5	10

in the solid phase. It is not yet clear, however, why the isotopic effect was observed specifically in mixed halogenobromomethanes.

The isotopic effect observed in mixed halogenobromomethanes differs significantly from the "apparent isotopic effect" considered earlier (Section 1). The "apparent isotopic effect" is associated with the last stage of the "cooling" of the recoil atoms — with diffusion–recombination reactions. The small quantities of impurity, which cannot be controlled, or the accompanying γ-radiation, play a significant part at this stage. To eliminate the influence of these last factors, the experiments on halogenobromomethanes were carried out with the addition of bromine. The isotopic effect did not disappear, which means that the reactions producing the isotopic differences in this case take place in the high-energy stage. It is possible that these processes are ion–molecule reactions of the recoil atoms with the molecules of the medium.

The problem of the origin of the isotopic effects in the secondary reactions of recoil atoms is still unsolved. The available experimental data do not agree with the theories of Libby and Willard. According to Libby's theory, the difference in the kinetic energy of the recoil atoms should be revealed as a difference in the size of the "liquid drop" in the solid substance and should thus lead to a difference in the proportion of organic products for isotopes with different recoil energies, as a result of the difference in the local concentration of radicals. Evidence against this theory is provided, however, not only by the experimental data considered above, but also by certain fundamental considerations, which may be summarised as follows.

1. With smaller "liquid drop" in a solid body for recoil atoms with a lower kinetic energy of recoil, there is an increase in the local concentration not only of the organic fragments, but also of the inorganic fragments, so that a decrease in the size of the "liquid drop" should not lead unambiguously to an increase in the retention (in the form of organic compounds).
2. The temperature inside the "liquid drop" is too high (10 000°K). No reactions other than intense dissociation of the molecules can take place in it.
3. With increase in the initial recoil energy of the atom from 100 eV to 1 MeV the change in the size of the "liquid drop" should lead to a considerable change in the yield of organic products, but this is not observed.

The "chance fragmentation" (or "pocket of radicals") theory of Willard assumes that the isotopic differences, which depend on the energy of recoil (or charge), are produced as a result of subsequent diffusion–recombination reactions between the recoil atoms and the fragments in the track of the "hot" atom. In this case, however, a change in the recoil energy by several powers of ten should lead to a considerable change in the yield of organic products. Experiments show that there is no clear significant relationship between the recoil energy and the yield of organic products.

On the basis of Brinkman[41,42] and Seitz's[43] theory of radiation damage in solids, Harbottle[5,44] suggested a mechanism for the reaction of the recoil atoms with the medium, involving the formation, by the recoil atom, of a "hot zone" with non-uniform heating from the centre of the zone to the periphery. An advantage of this theory is its more definite character and the possibility of using the fundamental hypotheses and mathematical apparatus of solid state physics. Harbottle also points out that chemical super-thermal and thermal reactions may play an important part in the stabilisation of recoil atoms. The "hot zone" theory predicts the possibility of isotopic effects, the mechanism of their production being assumed to be the same as in Willard's "chance fragmentation" theory, *i.e.* diffusion–recombination reactions between the recoil atoms and the radicals and organic fragments created in the "hot zone". As already pointed out, however, there is no definite relationship between the recoil energy and the isotopic effects, so that the "hot zone" theory cannot explain the production of the isotopic differences. The isotopic differences may possibly be explained by the widely circulating theory of ion–molecule reactions, whose existence, in the gas phase at any rate, is accepted by most workers[45]. As already pointed out, considerable success in the treatment of the results obtained in experiments on the activation of halogens and tritium in different media has been achieved by the ion–molecule reaction theory. If this theory is adopted, deceleration and charge transfer by the recoil atom can be represented as follows. The recoil atoms leaving the mother molecules generally have a recoil energy which is insufficient to lead to ionisation of the atoms during movement. If the recoil atoms are to be able to ionise during movement, they must have the energy[5]

$$E = \frac{M}{m_e} P,$$

where M is the mass of the recoil atom, m_e the mass of the electron, and P the ionisation potential of the recoil atom.

Thus the ^{11}C recoil atom, whose ionisation potential is 11.26 eV, should have an initial kinetic energy of at least 228 keV if it is to ionise during movement. It is known[15] that the ^{11}C atoms obtained by the reaction $^{12}C\ (n, 2n)\ ^{11}C$ with fast neutrons have a recoil energy of about 1 MeV, *i.e.* they are able to ionise and subsequently react in the form of charged ions. For the ^{14}C atoms obtained by the reaction $^{14}N(n, p)\ ^{14}C$, the recoil energy is 45 000 eV and is thus insufficient for ionisation. For heavier recoil atoms such as ^{82}Br and ^{128}I, the values of E are 1740 eV and 2440 eV respectively, so that the ^{82}Br and ^{128}I recoil atoms obtained as a result of the capture of thermal neutrons have a recoil energy of ~100 eV and cannot ionise. As already pointed out, however, some of the recoil atoms such as ^{82}Br, ^{128}I, ^{38}Cl, etc. are obtained in ionised form after an (n, γ) reaction.

Let us assume that the ionisation potential of the surrounding molecules is lower than the ionisation potential of the recoil atoms. The recoil ions then rapidly lose their charge before they are able to take part in super-thermal ion–molecule reactions. In this case an isotopic effect may appear for isotopes with different quantities of charged recoil atoms as a result of diffusion–recombination reactions, since the ionised molecules dissociate at any of the bonds and give a much greater quantity of fragments in the track of the charged recoil atom. If the ionisation potential of the molecules surrounding the recoil atom is greater than the ionisation potential of the recoil atom, the latter, on collision, will not lose its charge and subsequently, when the energy decreases to super-thermal values, it may take part in ion–molecule reactions. Moreover, if the compounds obtained by these reactions have ionisation potentials lower than that of the recoil atom, the process by which the compound is obtained may compete successfully with ordinary radical reactions and produce an isotopic effect.

This hypothesis obviously requires confirmation. Ordinary chemical methods of study may be insufficient, and it is possible that solution of the problem of the mechanism of the secondary reactions of recoil atoms requires detailed study (for example by mass-spectrometry) of the chemical state and subsequent reactions of the recoil atoms with molecules. An important contribution may be made by the study of the reactions of accelerated ions.

The problem of the mechanism of the reactions of "hot" atoms is not distinct from the solution of other chemical problems (despite the specific features of their behaviour). This apparently is the main difficulty for workers in this field; the chemistry of "hot" atoms is evidently closely interwoven with such fields of chemistry as reaction kinetics and reactivity of atoms and radicals, radiochemistry, and high-temperature chemistry.

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ORGANOSILICON COMPOUNDS CONTAINING A CYANO-GROUP

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I. INTRODUCTION

Alkylated (or arylated) siloxane polymers have long been used industrially as lubricants, hydraulic liquids, rubbers, coatings, and other materials. At the present time, however, typical polysiloxane materials cannot fully satisfy the growing demand of technology. A promising and important method for the controlled modification of the special properties of siloxane polymers† is the introduction of polar substituents into the hydrocarbon radicals surrounding the siloxane chains. The problem of synthesising organosilicon compounds containing functional groups is therefore now one of the most important tasks in the organic chemistry of silicon.

One of the most polar functional groups is the cyano--group[2,3]. When introduced into other polymers, it conferred on them several valuable technical properties; examples are provided by the acrylonitrile rubbers[4]. Furthermore, nitriles are convenient starting materials for the preparation of organic compounds with various functional groups[5]. These are probably the main reasons for the rapid expansion of research on the synthesis and properties of organosilicon nitriles.

Although the first organosilicon nitriles were obtained twenty years ago, their systematic investigation began only in 1955, both in the USSR[6,7] and abroad[8-10]. General methods have now been worked out for the synthesis of silicon-containing nitriles, and their properties have been studied in detail. Several cyanoalkyl derivatives of silicon are already produced on a large scale, and materials obtained from them are finding use in important branches of technology.

Polysiloxanes containing 2-cyanoethyl and 3-cyanopropyl groups have good stability to thermal oxidation together with high resistance to oils, petrol, and frost. This fact is of fundamental importance, since it contradicts the widely held view that the only thermostable alkylpolysiloxanes are those in which the surrounding alkyl groups are small (preferably methyl).

Organosilicon compounds containing two nitrile groups will probably have many uses. These compounds, like their organic analogues, can be readily converted into

† The specific properties of siloxanes are largely determined by the low "barrier" to rotation about the Si–O bond and the extraordinarily small intermolecular forces[1].

$\alpha\omega$-dibasic acids, diamines, diesters, and other bifunctional compounds suitable for the preparation of silicon-containing polyamides, polyesters, polyurethanes, etc. It can be expected that among such organosilicon polymers, which are fundamentally different from polysiloxanes, materials having valuable technical properties will be obtained[11].

We shall consider in this review the cyanoalkyl and cyanoaryl derivatives of silicon as well as compounds of silicon with cyanoalkoxy radicals and silanes in which the cyano-group is directly linked to a silicon atom, Si[CN]. The latter compounds are now attracting attention as interesting materials for theoretical investigations, owing to the ease with which they undergo tautomeric change.

II. COMPOUNDS CONTAINING A CYANO-GROUP ATTACHED DIRECTLY TO SILICON

1. Methods of Synthesis

As early as 1941 Emeléus obtained a silicon-containing nitrile by the reaction of SiH_3I with AgCN.[12] The product was given the nitrile structure $H_3Si-C\equiv N$ without proof. Subsequently alkylsilyl cyanides, in particular $CH_3SiH_2[CN]$, were obtained from alkylsilyl iodides, and also by exchange reactions with metal cyanides[13,14].

Eaborn obtained a series of alkylsilyl cyanides[15], which boiled at lower temperatures than the corresponding iodides; on this basis he ascribed an isocyano-structure to them: $(C_2H_5)_3Si-N=C$, $(n\text{-}C_3H_7)_3Si-N=C$, $(C_2H_5)_2Si(-N=C)_2$. At the same time he found that $(n\text{-}C_3H_7)_3SiCl$ does not react with silver cyanide under the conditions of reaction (I)

$$R_n Si I_m + m\,AgCN \rightarrow R_n Si(CN)_m + m\,AgI\,. \qquad (I)$$

It was later found[16] that the corresponding $R_3Si[CN]$ compounds are formed by the reaction of silver cyanide with trialkylsilyl bromides and with $(CH_3)_3Si-S-Si(CH_3)_3$.

McBride and Beachel considered Eaborn's arguments regarding the structure of his compounds unconvincing, and made a thorough investigation of the problem[17]. They prepared the required compounds from tri- and di-methylsilyl halides and silver cyanide. They found that $SiBr_4$ and CH_3SiBr_3 do not react with silver cyanide in boiling benzene. The characteristic frequencies which they discovered in the infra-red spectra of the preparations could equally well be assigned to the structure $Si-C\equiv N$ or to a mixture of the nitrile and isocyano-structures. Several of the chemical reactions [(II), (III)] supported, in the opinion of these workers, the isocyano-structure of the preparations:

$$(CH_3)_3Si-N=C+S \xrightarrow{\text{boiling}} (CH_3)_3Si-N=C=S, \qquad (II)$$

$$(CH_3)_3Si-N=C \xrightarrow{H_2} (CH_3)_3Si-N=CH_2 \xrightarrow{H_2} (CH_3)_3SiNH_2+CH_4,$$
$$2(CH_3)_3SiNH_2 \longrightarrow (CH_3)_3Si-\underset{\displaystyle H}{N}-Si(CH_3)_3+NH_3. \qquad (III)$$

They were unable to effect the thermal rearrangement of the isocyanide into the normal nitrile, which was explained by the peculiar thermodynamic stability of the Si–N=C group.

On the basis of this work the iso-structure was accepted up to 1958 for the cyano-group linked to silicon[8,18]. In that year Bither *et al.* published a careful spectroscopic investigation[19] at various temperatures of compounds containing the Si[CN] group. Analysis of the infra-red spectra led them to conclude that a tautomeric equilibrium is present in compounds containing such groups:

$$2R_3Si-C\equiv N \rightleftarrows \left[\begin{matrix} R_3Si-C\equiv N \\ N\equiv C-SiR_3 \end{matrix}\right] \rightleftarrows 2R_3Si-N=C\,.$$

At 20° the normal form predominates, whereas at 80° the iso-form does so. Seyferth[20] has recently reported the presence of tautomerism even in the case of trimethylcyanogermane: $(CH_3)_3Ge-N=C \rightleftharpoons (CH_3)_3Ge-C\equiv N$. These conclusions agree well with experimental data on the chemical properties of these nitriles. The structure of the Si[CN] group has also been discussed in several other papers[14,21-25].

New exchange reactions (IV)–(VI) have recently been proposed for the synthesis of compounds containing Si[CN] groups[19]:

$$2R_3SiCl + K_2Hg[CN]_4 \rightarrow 2R_3Si[CN] + 2KCl \rightarrow Hg(CN)_2\,, \qquad (IV)$$

$$R_3Si-\underset{\displaystyle H}{N}-SiR_3 + 3HCN \rightarrow 2R_3Si[CN] \rightarrow NH_4[CN], \qquad (V)$$

$$R_3SiOCH_3 + (CH_3)_3C(CO)C\equiv N \xrightarrow{AlX_3} R_3Si[CN] + (CH_3)_3C(CO)OCH_3\,, \qquad (VI)$$

where R = alkyl. The compound $(CH_3)_3Si[CN]$ can be obtained from HCN, $(CH_3)_3SiCl$, and metallic lithium[14].

Existing methods have also been improved; in particular the yield of $(CH_3)_3Si[CN]$ from $(CH_3)_3SiCl$ and AgCN can be increased if the reaction is carried out under pressure[18,19] or if the AgCl formed in the reaction is removed from the reaction mixture[14].

Anderson and his coworkers[26-29] used exchange reactions to synthesise compounds of the type $R_nM[CN]_m$, where $m + n = 4$ and M = Si, Ge, Sn; no proof was given of the structure of the resulting compounds.

McBride prepared arylsilyl and alkylarylsilyl cyanides from AgCN and the corresponding arylsilyl [and alkylarylsilyl? (Ed. of Translation)] halides[23].

Prober discovered that trimethylsilyl cyanide is formed by reaction (VII):

$$(CH_3)_3SiCH_2I + AgCN \rightarrow (CH_3)_3Si[CN] + \text{other products}, \qquad (VII)$$

but he did not discuss the mechanism of this unexpected reaction. Later he noted that $(CH_3)_3Si[CN]$ is also formed by the reaction of $(CH_3)_3SiCl$ and Na with CH_3CN in ether. Petrov and Vdovin[31] showed this observation to be an example of the general reaction (VIII) for a series of trialkylsilyl halides and nitriles:

$$R(CH_3)_3SiX + R'CH_2CN + Na \xrightarrow{\text{ether}} R(CH_3)_3Si[CN] + \text{other products}, \qquad (VIII)$$

It is interesting that with $(CH_3)_2RSiCl$ and acetonitrile the yields of trialkylsilyl cyanides increased as R became larger, being 25%, 37%, and 51% when R = CH_3, C_2H_5, and C_4H_9 respectively. Since the difficultly accessible trialkylsilyl iodides or bromides and silver cyanide have usually been required in order to obtain trialkylsilyl cyanides, this last method, using readily available reagents, is of interest for such preparations.

Prober[18] suggested the following scheme for the formation of trimethylsilyl cyanide from acetonitrile:

$$2CH_3CN + 2Na \rightarrow CH_4 + NaCN + (CH_2CN)^-Na^+\,, \qquad (IX)$$

$$NaCN + (CH_3)_3SiCl \longrightarrow (CH_3)_3Si[CN] + NaCl.$$

He assumed that NaCN formed "in the nascent state" is more active than powdered NaCN, which does not interact with $(CH_3)_3SiCl$ under these conditions. However, this scheme was criticised[31], since it was inconsistent with several experimental data. The formation of compounds of the type $R_3Si[CN]$ in this case is probably the result of the decomposition of α-nitriles, $R_3SiCHRCN$, formed initially in the reaction, which are known to be unstable under the influence of various reagents (see Section III, 2).

2. Properties

Emeléus[12] found that cyanosilane is very unstable, decomposing in air with the formation of hydrogen cyanide. It was subsequently discovered[15,17,23] that trialkylsilyl (and triarylsilyl) cyanides split off the cyano-group under the influence of water, Grignard reagents, and mercuric oxide:

$$2R_3Si[CN] + H_2O \rightarrow R_3SiOSiR_3 + 2HCN, \quad (I)$$

$$R_3Si[CN] + R'MgX \rightarrow R_3SiR' + [CN]MgX, \quad (II)$$

$$2R_3Si[CN] + HgO \rightarrow R_3SiOSiR_3 + Hg[CN]_2. \quad (III)$$

where R and R′ = alkyl and aryl.

Analogous reactions take place in the presence of silver salts[16]:

$$(C_2H_5)_3Si[CN] + AgNCO \rightarrow (C_2H_5)_3SiNCO + AgCN, \quad (IV)$$

$$(C_2H_5)_3Si[CN] + AgNCS \rightarrow (C_2H_5)_3SiNCS + AgCN. \quad (V)$$

Not only trialkylsilyl halides (VI) but also chlorides of other elements (VII) can undergo double decomposition with $R_3Si[CN]$:[19]

$$(CH_3)_3Si[CN] + R_3SiCl \rightarrow (CH_3)_3SiCl + R_3Si[CN]^{\ddagger}, \quad (VI)$$

where R = aryl or a higher alkyl group,

$$x(CH_3)_3Si[CN] + MCl_x \rightarrow x(CH_3)_3SiCl + M[CN]_x, \quad (VII)$$

where M = As, Sb, Bi, Pb, Ge, and x is the valency of the metal.

Exchange reactions take place still more readily with cyanosilane derivatives containing the $Si[CN]_2$ group[15,23]:

$$n R_2Si[CN]_2 + n H_2O \rightarrow (R_2SiO)_n + 2n HCN, \quad (VIII)$$

$$R_2Si[CN]_2 + 2R'MgX \rightarrow R_2SiR'_2 + 2XMg[CN]. \quad (IX)$$

These reactions as well as a series of other exchange reactions[14,26-30] are characteristic of organometallic compounds containing an M[CN] group (M = Si, Sn, Ge, etc.).

Several reactions undergone by the Si[CN] group without splitting off the cyano-group have been mentioned in Section I. It is interesting that hydrogenation of $(CH_3)_3Si[CN]$ in the presence of an Adams catalyst or Raney nickel[17] leads to the formation of the silazane $(CH_3)_3Si-NH-Si(CH_3)_3$, whereas reduction of $(CH_3)_3Si[CN]$ with $LiAlH_4$ yields $(CH_3)_3SiH$.[19]

The polymerisation of $CH_3SiH_2[CN]$ has been investigated[13]: above 40° it polymerises rapidly in the absence of catalysts, it remains unchanged in the presence of $Ni(CO)_4$ at 20°, and with a catalytic quantity of BF_3 it is converted even at 0° into a polymeric mass containing no BF_3.

‡ This reaction occurs so smoothly that Bither[19] regards it as the most convenient method for preparing the higher trialkylsilyl and triarylsilyl cyanides.

The following reaction has been studied[30]:

$$(CH_3)_3M[CN] + Fe(CO)_5 \xrightarrow{65°-110°} (CH_3)_3M-N=C-Fe(CO)_4, \quad (X)$$

where M = Si, Ge, Sn. High yields of adducts are obtained even at 65°–75° if M = Si (93%) or Ge (69%). When M = Sn, the yield of adduct is negligible, even after heating at 110°.

Evers and his collaborators studied the reaction of $(CH_3)_3SiCN$ and H_3SiCN with diborane and dibutylboron chloride[14,32]. At temperatures between -196° and +20° the solid complexes (A) and (B) were formed:

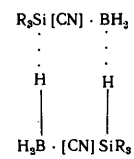
$$2H_3Si[CN] + B_2H_6 \rightarrow \underset{(A)}{2H_3Si[CN]\cdot BH_3} \quad (XI)$$

and similarly $(CH_3)_3Si[CN]$ yielded $(CH_3)_3Si[CN].BH_3$ (B). Above 70° complex (A) decomposes:

$$H_3SiCN\cdot BH_3 \rightarrow H_2B[CN] + SiH_4. \quad (XII)$$

Complex (B) decomposes similarly, but under more severe conditions, with the formation of $(CH_3)_3SiH$ and $H_2B[CN]$.

The ease with which $R_3Si[CN]$ is reduced to R_3SiH is explained by the presence of vacant 3*d* orbitals in the silicon atom, reduction probably occurring in a new complex (AA) or (BB):



where R = H, CH_3. Exchange with a dialkylboron chloride is effected in an analogous manner:

$$(n\text{-}C_4H_9)_2BCl + (CH_3)_3Si[CN] \rightarrow (n\text{-}C_4H_9)_2B[CN] + (CH_3)_3SiCl. \quad (XIII)$$

The following reactions of complex (B) have been studied:

$$B \xrightarrow{H_2O/KOH} [(CH_3)_3Si]_2O + KBO_2 + KCN + H_2O,$$

$$B \xrightarrow[[-H_2]]{HCl} (CH_3)_3Si(CN)\cdot BH_2Cl \longrightarrow (CH_3)_3SiCl + H_2B(CN)$$

$$B \xrightarrow{(CH_3)_3Si(CN)} (CH_3)_3SiH + (CH_3)_3Si(CN)\cdot BH_2(CN).$$

Several physical properties of compounds containing Si[CN] groups, including their infra-red and Raman spectra, molecular refraction, etc., have been described[14,17,19,21-25]. A sharp, unpleasant odour is a characteristic property of these organosilicon compounds. Substances containing Si[CN] groups dissolve readily in the usual organic solvents.

Since a [CN] group directly linked to a silicon atom is readily split off, polysiloxanes containing the Si[CN] group have not yet been prepared. Such materials would hardly be of interest, because of the instability of the Si–[CN] bond. Nevertheless, as a result of the great reactivity of the [CN] group, these compounds may be useful as starting materials for the synthesis of polymers consisting of silicon–nitrogen–carbon chains. At present such polymers are attracting considerable interest both on their own account and as components in the preparation of chelate polymers[33,34].

III. ORGANOSILICON COMPOUNDS CONTAINING CYANOALKYL OR CYANOARYL GROUPS ATTACHED TO SILICON

1. Methods of Synthesis

(*a*) Substitution by the cyano-group of halogen in halogenoalkyl and halogenoaryl derivatives of silicon. The double decomposition of alkyl and aryl halides with metal cyanides is the classical method for preparing alkyl and aryl cyanides. This method was, of course, tried in the first attempts to obtain organosilicon nitriles. Thus as early as 1946 Krieble and Elliott treated chloromethylpentamethylcyclotrisiloxane with sodium cyanide[35]. However, when the mixture was boiled in aqueous–alcoholic solution, the substituted methyl radical was cleaved from the silicon atom. Hauser and Harles studied the reaction of α-halogenomethyl derivatives of silicon with potassium cyanide in boiling methanol[36]. $(CH_3)_3SiCH_2Br$, $(CH_3)_3SiCHBrC_6H_5$, and $(CH_3)_3SiCBr(C_6H_5)_2$ reacted with potassium cyanide, but the normal exchange products were not isolated. The presence of trimethylmethoxysilane and of nitriles not containing silicon led these workers to suggest that α-cyanomethylated silicon derivatives are formed initially and then decompose

$$(CH_3)_3SiCHBr \xrightarrow[65^\circ]{KCN} [(CH_3)_3SiCHCN] \xrightarrow[65^\circ]{CH_3OH} (CH_3)_3SiOCH_3 + C_6H_5CH_2CN. \quad (I)$$

Formation of α-cyanomethylated silicon compounds in these cases is supported also by the fact that α-halogenomethylated silicon compounds are extremely reactive in bimolecular nucleophilic substitutions (see for example Refs. 37–40).

Prober[8] heated $(CH_3)_3SiCH_2Cl$ with NaCN in the absence of solvent at 200°, but the expected cyanomethyltrimethylsilane was obtained in low yield; $(CH_3)_3SiOSi(CH_3)_2CH_2X$, where X = Cl, I, did not react at all with NaCN under these conditions. Chloromethylated silicon compounds reacted neither with AgCN nor with CuCN at 150°–200°, whereas $(CH_3)_3SiCH_2I$ under similar conditions formed the anomalous reaction product $(CH_3)_3Si[CN]$. Klebanskii and Ponomarev report[41] that chloro(and bromo)methylheptamethylcyclotetrasiloxane reacted neither with CuCN nor with $Hg(CN)_2$ below 170°, above which considerable resinification of the products began.

In contrast to the α-halogenomethylated products, *p*-halogenophenyl compounds of silicon were successfully used for the synthesis of the corresponding cyanophenylated silanes and siloxanes[42–44] by reactions (II) and (III):

$$[p\text{-}Br{-}C_6H_4Si(CH_3)_2]_2O + CuCN \mid NaCN \xrightarrow[10\ h]{275^\circ-300^\circ} [p\text{-}CN{-}C_6H_4Si(CH_3)_2]_2O, \quad (II)$$

$$[p\text{-}Br{-}C_6H_4]_3Si(CH_3)_3 + CuCN \xrightarrow[4\ h]{250^\circ} [p\text{-}CN{-}C_6H_4]_3Si(CH_3)_3. \quad (III)$$

In reaction (II) a 24% yield of the dinitrile was obtained, and in reaction (III) an 82% yield. Prober succeeded in preparing α-cyanomethylated derivatives by reaction (IV):[8]

$$\equiv SiCH_2MgCl + [CN]_2 \longrightarrow \equiv SiCH_2CN + ClMgCN. \quad (IV)$$

The reaction was carried out between -40° and -50°, and 38–52% yields of the α-nitriles — cyanomethyltrimethylsilane, cyanomethylpentamethyldisiloxane, and cyanomethylheptamethylcyclotetrasiloxane — were obtained from the corresponding halogenomethyl derivatives. Although the yields indicated by Prober for the last of the above α-nitriles could not be reproduced subsequently[41], replacement of the original chloromethylated cyclic tetrasiloxane by the bromomethyl derivative gave 85% yields of this α-nitrile[41].

(*b*) Silico-alkylation (silylation) of nitriles by halogenosilanes. Prober[18] tried to synthesise α-cyanomethyl derivatives of silicon by the following reaction:

$$(CH_3)_3SiCl + CH_3CN + Na \xrightarrow{ether} (CH_3)_3SiCH_2CN + NaCl.$$

However, the yield of the expected organosilicon nitrile was only 2%. Nevertheless, among the products were found the disilylated acetonitrile derivatives $[(CH_3)_3Si]_2CHCN$ (7%) and $(CH_3)_3SiCH{=}C{=}NSi(CH_3)_3$ (25%) as well as several others. The appearance of a ketenimine was explained by resonance of the anions (A) and (B) of the organosodium derivative $[(CH_3)_3SiCHCN]^-Na^+$:

$$[(CH_3)_3Si\overline{C}H] \longleftrightarrow [(CH_3)_3Si{-}CH{=}C{=}\overline{N}].$$
$$\quad\quad C{\equiv}N \qquad\qquad\qquad (A) \qquad\qquad\qquad (B)$$

Owing to a definite steric effect, the $(CH_3)_3SiCl$ molecule reacts mainly with form (B) (ketenimine). Under the influence of basic catalysts (H_2O, $C_6H_5NH_2$) the ketenimine readily isomerises to the nitrile. This isomerisation is probably a consequence of a molecule of the base attacking the central carbon atom, after which the $(CH_3)_3Si$ group migrates from the nitrogen to the carbon according to the scheme:

$$(CH_3)_3SiCH{=}C{=}N{-}Si(CH_3)_3 + H_2O \longrightarrow (CH_3)_3Si{-}\overset{\delta-}{C}H{-}\overset{\delta-}{C}{=}N{-}Si(CH_3)_3 \longrightarrow$$
$$\longrightarrow (CH_3)_3Si{-}CH(Si(CH_3)_3){-}C{\equiv}N + H_2O \quad (IV)$$

In the alkylation of benzyl cyanide with trimethylsilyl chloride in the presence of sodamide the expected compound, $C_6H_5CH(C{\equiv}N)Si(CH_3)_3$, was not obtained[18].

Shaw[45] made a detailed study of the alkylation of benzyl cyanide with trialkylsilyl fluorides and chlorides, and concluded that it takes place according to scheme (V) with the formation of *N*-silylated dimers of benzyl cyanide:

$$R_3SiX + 2C_6H_5CH_2CN \xrightarrow{NaNH_2} C_6H_5CH_2{-}C{=}C[CN]C_6H_5 \quad (V)$$
$$\quad\quad\quad

of the trialkyl-2-cyanoethylsilane was obtained with X = I and R = CH_3. Later these workers used the silico-alkylation of nitriles to synthesise $\alpha\omega$-bis-(trimethylsilyl)alkanes having a CN group in the hydrocarbon chain[47]:

$$(CH_3)_3Si(CH_2)_nCH_2CN + XCH_2Si(CH_3)_3 \xrightarrow[\text{ether}]{Na} (CH_3)_3Si(CH_2)_nCHCH_2Si(CH_3)_3 \quad \text{(VII)}$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad CN$$

where n = 1, 2 and X = Cl, Br, I.

The best yields of nitrile were obtained using iodomethyltrimethylsilane, whereas with the chloromethyl compound considerable quantities of byproducts, dimers of ω-cyanoalkyltrimethylsilanes, were formed.

The anomalous behaviour of 3-(2-cyanoethoxy)propyltrimethylsilane in this reaction is interesting. As with other nitriles, an organosodium derivative is probably formed, but it is readily decomposed in the same manner as organometallic compounds containing reactive centres in the 1,4-position[48]:

$$(CH_3)_3Si(CH_2)_3O-\overset{1}{C}H_2-\overset{2}{C}H_2-\overset{3}{C}H(C\equiv N)-\overset{4}{C}H_2-H \xrightarrow[\text{ether}]{Na} \left[(CH_3)_3Si(CH_2)_3O-\overset{1}{C}H_2-\overset{2}{C}H_2-\overset{3}{C}H(C\equiv N)-\overset{4}{C}H_2(Na)\right] \longrightarrow \text{(VIII)}$$

$$\longrightarrow \begin{cases} (CH_3)_3Si(CH_2)_3ONa \xrightarrow{H_2O} (CH_3)_3Si(CH_2)_3OH \\ \left[CH_2=CH(C\equiv N)\right] \longrightarrow \text{polymer.} \end{cases}$$

Several halogenomethylated silicon derivatives have been condensed with cyanoacetic ester, also under the influence of sodium[49]. De Benneville and his collaborators have reported[50,51] the alkylation of cyanoacetic ester in the presence of organic bases according to scheme (IX):

$$(CH_3)_3SiCl + CH_2(COOC_2H_5)(CN) + (C_2H_5)_3N \longrightarrow (CH_3)_3SiCH(COOC_2H_5)(CN) + (C_2H_5)_3N\cdot HCl \quad \text{(IX)}$$

Later they concluded[52] that the isomeric alkylation product $(CH_3)_3SiOC(OC_2H_5)=CHCN$ is formed according to scheme (VIII).

The possibility of condensing isobutyronitrile with methyltrichlorosilane in the presence of sodium to yield the α-nitrile $CH_3SiCl_2C(CH_3)_2CN$ has been mentioned in a patent[53].

Thus, in most cases the alkylation of nitriles with halogenosilanes R_3SiX does not yield the expected silicon-containing α-nitriles. Nevertheless, the silico-alkylation of nitriles with halogenomethyl (and probably other halogenoalkyl and halogenoaryl) derivatives of silicon can serve for the preparation of silicon-containing nitriles in which a cyano-group is attached to a carbon atom in the β-position to (or more remote from) the silicon atom. Silicon-containing α-nitriles $\gtrless Si-\overset{\alpha}{C}(CN)-$, in contrast to the β-nitriles $\gtrless Si-\overset{\alpha}{C}H_2-\overset{\beta}{C}(CN)-$, are unstable to heat. Their preparation is also unimportant, since they readily split off the α-cyanoalkyl group from the silicon atom under the influence of various reagents (see Section III, 2).

(*c*) Direct synthesis of cyanoalkylhalogenosilanes from ω-halogenonitriles and silicon. Petrov, Sadykh-Zade, and Vdovin studied the interaction of 2-cyanoethyl halides with silicon–copper alloys[6,31,54-56]:

$$NCCH_2CH_2X + Si \xrightarrow{Cu} X_3SiCH_2CH_2CN, \quad \text{(I)}$$

where X = Cl, Br. The reaction was carried out on a technical Si–Cu alloy under static conditions in a glass tube, and took place within a narrow temperature range (usually 370°–380°), which shifted somewhat, however, with variation in the composition of the alloy. Below 370° mainly unchanged $ClCH_2CH_2CN$ was recovered, whereas above 380° a different reaction predominated:

$$ClCH_2CH_2CN \xrightarrow[>380^\circ]{Si/Cu} \begin{cases} HCl \xrightarrow{Si/Cu} SiCl_4 + HSiCl_3 \\ + \\ CH_2=CHCN \end{cases} \quad \text{(II)}$$

The yields of $X_3SiCH_2CH_2CN$ when X = Cl and Br reached 20% and 17% respectively based on the weight of condensate obtained, and in both cases ~40% based on the halides used. By carrying out the reaction between 3-chloropropionitrile and silicon using a fluidised-bed technique, Golubtsov and his collaborators[56] were able to improve the yield to 40% of the condensate and 57% with respect to the chloride used. Chloroacetonitrile does not react with the Si–Cu alloy up to 450° (nor does it decompose appreciably under these conditions)[54].

It is interesting that 2-cyanoethyltrichlorosilane was first obtained by direct synthesis: it is an important industrial monomer which is now produced by the catalytic addition of trichlorosilane to acrylonitrile.

(*d*) Cyanoethylation of organosilicon compounds. The addition of organic compounds in general to acrylonitrile forms one of the most important methods for obtaining nitriles. This method has been successfully applied in the chemistry of organosilicon compounds as well.

Petrov *et al.*[7] and also Sommer[57] carried out cyanoethylation of silicon-containing alcohols according to the general scheme (I):

$$R_3Si(CH_2)_nOH + CH_2=CHCN \xrightarrow{\text{catalysts}} R_3Si(CH_2)_nOCH_2CH_2CN, \quad \text{(I)}$$

where R = alkyl and n = 1–3. The catalysts used were sodium methoxide, alkoxides of the initial silicon-containing alcohols, and Trilon B§, the reaction occurring even in the cold with 80–90% yields of the silicon-containing ω-cyanoalkyl ethers. Unsaturated silicon-containing alcohols of the type $R_3SiCH=CHCH_2OH$ have also been successfully cyanoethylated[58,59].

A study has been made of the cyanoethylation of amines and thiols containing silicon[60-62]:

$$(CH_3)_3SiCH_2\underset{R}{NH} + CH_2=CHCN \rightarrow (CH_3)_3SiCH_2\underset{R}{N}CH_2CH_2CN, \quad \text{(II)}$$

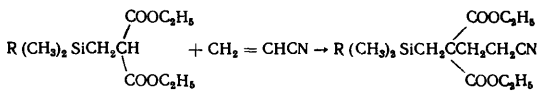
$$R_3Si(CH_2)_nSH + CH_2=CHCN \rightarrow R_3Si(CH_2)_nSCH_2CH_2CN, \quad \text{(III)}$$

where n = 1, 3 and R = alkyl.

When R = C_2H_5, reaction (II) took place in the absence of catalysts, whereas with R = C_6H_5, acetic acid acted as catalyst. When a functional group containing "active hydrogen" is directly linked to silicon (Si–OH, Si–NH_2), cyanoethylation takes place either very slowly or not at all[62-64].

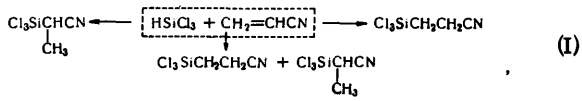
§ Tetrasodium salt of ethylenediaminetetraacetic acid (Ed. of Translation).

Examples are also known in which the cyanoethylation of organosilicon compounds takes place at a C–H bond[65-67]:



(*e*) Addition of Si–H compounds to unsaturated nitriles. This method of synthesising silicon-containing nitriles has hitherto been studied more thoroughly than others, since it is possible to obtain important industrial monomers more rapidly and more simply in this way than by other methods.

The addition of trichlorosilane to acrylonitrile was first accomplished by Petrov *et al.*[68] and independently by Japanese chemists[9,10]. These compounds can be made to react in any of three ways:



(I)

depending on the catalysts employed and the reaction conditions.

When an equimolar mixture of acrylonitrile and trichlorosilane is heated in sealed glass tubes to 180°, the β-isomer is formed, but in low yield (up to 10%)[9]. With peroxide catalysts at 160°, also in glass, the yield of the β-isomer is raised to 46%.[9] Use of Raney nickel as catalyst enables 3-trichlorosilylpropionitrile to be obtained, also in low yield[68]. Platinised asbestos or carbon at 100°–200°, either in a glass or metal apparatus[69,70], favours the formation of the β-isomer in yields of 40–60%.

Organic bases are efficient catalysts for the addition of $SiHCl_3$ to CH_2=CHCN.[9]

Table 1 gives results for the interaction of an equimolar mixture of acrylonitrile and trichlorosilane when heated in sealed glass tubes for 5 h (only the β-isomer was obtained). When the same reaction was carried out with pyridine as catalyst in an autoclave, a mixture of the α- and β-isomeric adducts was obtained. The actual catalyst here was found to be complexes of pyridine and nickel chlorides formed from the walls of the autoclave. In fact, when $NiCl_2.C_5H_5N$. .HCl, $NiCl_2.C_5H_5N$, and $NiCl_2.4C_5H_5N$ were used as catalysts in sealed glass tubes, the α-adduct was obtained.

Catalysts proposed subsequently[71,72], tributylamine and diethylaniline, were effective enough to enable the reaction to be carried out by boiling a mixture of the reactants in flasks, resulting in the formation solely of the β-adduct in yields of 50% and above. According to Saam and Speir[73,74], high catalytic activity (formation of the β-isomer) is exhibited by *N*-substituted amides such as *NN*-dimethylformamide, *NN*-diethylformamide, *NN*-dibutylacetamide, *NN*-diethyldecanoamide, and *N*-acetyl-*p*-toluidine, etc. (yields of adducts 38–43%). Acetanilide is a somewhat less active catalyst (yield of addition product 21%). It is interesting that the corresponding amine hydrochlorides possess no catalytic activity. Dialkylcyanamides and higher phenols[75-78] are effective catalysts.

Pike and his collaborators[77-82] employed several organoelemental compounds as catalysts for the addition of $SiHCl_3$ to acrylonitrile. Table 2 gives data on the catalytic activity of some of these compounds, and Table 3 data on the effect of temperature and catalyst concentration on the yield of adducts[80]. Table 3 shows that temperature is of decisive importance in this reaction, whereas catalyst concentration and duration of heating have little effect on its extent.

The addition of alkyldichlorosilanes and of some other silicon hydrides to acrylonitrile has been considerably less studied than the cyanoethylation of trichlorosilane. It has not yet proved possible to obtain by this method a satisfactory yield of the industrially important β-adduct of CH_3SiHCl_2 to CH_2=CHCN¶. Petrov and Vdovin[83] and also Goodman *et al.*[69,70] studied the latter reaction, and found that, with both pyridine and platinised carbon, the expected $CH_3SiCl_2CH_2CH_2CN$ is formed in low yield, accompanied by the α-isomer.

TABLE 1.

Catalyst*	Reaction temp., °C	Yield of $SiCl_3CH_2CH_2CN$, %
Pyridine	185	67
Pyridine	160	69
Pyridine	130	14
Triethylamine	160	76
Piperidine	160	69
Quinoline	160	40
Dimethylaniline	160	0
Pyridine hydrochloride	190	35
Benzyltriethylammonium chloride	160	70

* Equal relative weights of the catalysts were used, with respect to the weight of the reactant mixture.

TABLE 2*

Catalyst	Conversion, %	Adducts
No catalyst	42	α
$(n\text{-}C_4H_9)_3P$	55	β
$(C_6H_5)_2PCl$	47	β
$C_6H_5PCl_2$	39	β
$(C_6H_5)_3P$	56	β
$(C_6H_5)_3N$	29.8	mixture of α and β
$(C_6H_5)_3N$	30.7	β
$(C_6H_5)_3As$	25.8	mainly α, little β
$(C_6H_5)_3B$	10.5	mixture of α and β
$(C_6H_5)_3Sb$	traces	mixture of α and β

* An equimolar mixture of the reactants was used, with 2 mole % of the catalyst; heating was carried out in a steel autoclave at 200° for 2 h.

¶ During the printing of this review Bluestein[153] described the synthesis of the β-adduct $CH_3SiCl_2CH_2CH_2CN$ from acrylonitrile and methyldichlorosilane using the ternary catalyst $(CH_3)_2NCH_2$. . $CH_2N(CH_3)_2$–$N(C_4H_9)_3$–Cu_2Cl_2, which is quite effective when a mixture of the reactants is boiled at atmospheric pressure (yield up to 80%).

TABLE 3.

Catalyst wt. %*	Temp., °C	Duration of heating, h	Conversion, %
2	200	2	56
2	150	2	65
1	150	2	67
0.5	150	2	59
1	100	0.5	71
1	100	2	70
1	75	2	13

* The catalyst was $(C_6H_5)_3P$; reaction of an equimolar mixture of $SiHCl_3$ and CH_2=CHCN was carried out in a steel autoclave.

Speir was unable to effect the addition of CH_3SiHCl_2 to acrylonitrile in the presence of chloroplatinic acid[84], or of phenylsilanes to acrylonitrile (or to allyl cyanide) in the presence of peroxides[85]. The possibility of adding CH_3SiHCl_2, $CH_3SiH(OC_2H_5)_2$, and $C_2H_5SiHCl_2$ to acrylonitrile in the presence of organophosphorus catalysts is reported in a patent[81], which also describes the preparation (II) of the interesting bifunctional compound $CH_3SiCl(CH_2CH_2CN)_2$:

$$(CH_3)H_2SiCl + 2\,CH_2{=}CHCN \xrightarrow{(C_6H_5)_3P} CH_3SiCl(CH_2CH_2CN)_2. \qquad (II)$$

Freidlina *et al.* showed[86] that CH_3SiHCl_2 and $SiH(C_2H_5)_3$ add smoothly to acrylonitrile in the presence of the catalyst $Fe(CO)_5.NiCl_2$, only the α-adducts being formed (yields up to 70%).

Trichlorosilane adds to methacrylonitrile in the presence of the catalysts used for addition to acrylonitrile[71,81]. Under the influence of H_2PtCl_6 or Pt/C catalysts various incompletely substituted silanes add smoothly to olefines containing a CN group which is not conjugated with the double bond. Thus Sommer *et al.* carried out the reaction[87]:

$$CH_3SiCl_2H + CH_2{=}CH(CH_2)_n CN \xrightarrow{Pt/C\ (20\%)} CH_3Si(Cl_2)(CH_2)_{n+2}CN, \qquad (III)$$

where n = 1, 2, and established the direction of addition of the silyl group. Allyl cyanide and 2-cyanoethyl ether react with $SiHCl_3$ and alkyldichlorosilanes in the presence of platinum catalysts even at atmospheric pressure[72,84,88-90]. Reaction with allyl cyanide slows down appreciably on passing from alkyldichlorosilanes to dialkylchlorosilanes, while with tetraalkyldisiloxanes $SiHR_2OSiHR_2$ such reaction does not take place at atmospheric pressure[72].

Alkoxysilylalkyl ω-cyanides suitable for hydrogenation to the corresponding amines can be conveniently prepared by the reaction[88]:

$$R'(RO)_2SiH + CH_2{=}CHCH_2X \xrightarrow{Pt/C\ \text{or}\ H_2PtCl_6} R'(RO)_2SiCH_2CH_2CH_2X, \qquad (IV)$$

where R' = alkyl or alkoxy-group, R = lower alkyl, and X = CN or OCH_2CH_2CN. Trichlorosilane adds on to allyl cyanide with lower yields and under more severe conditions if organophosphorus compounds[81] or $NiCl_2.4C_5H_5N$[91] are used as catalysts, the latter yielding a mixture of two isomeric adducts:

$$CH_3CH(Cl_3Si)CH_2CN \text{ and } Cl_3SiCH_2CH_2CH_2CN.$$

The addition of cyanocyclohexene to silanes has been studied[90]. Addition takes place selectively when silanes react with vinylethynyl compounds containing a cyano-group[92,93]:

$$(R')_2RSiH + CH_2{=}CH-C{\equiv}C-C(CH_3)_2OCH_2CH_2CN \xrightarrow{60°-80°;\ H_2PtCl_6} CH_2{=}CH-\underset{\displaystyle SiR(R')_2}{\underset{|}{C}}{=}CH-C(CH_3)_2OCH_2CH_2CN \qquad (V)$$

where R' = alkyl or Cl, and R = alkyl. The resulting dienes are of interest as monomers for polymerisation and copolymerisation. The addition of trichlorosilane to allyl cyanide under the influence of γ-rays has been reported[94].

The mechanism of the addition of silanes to acrylonitrile and its analogues is discussed in several papers. Goodman[70] assumes that in the presence of platinised carbon addition of silicon hydrides to acrylonitrile (and to other olefines) takes place by an ionic mechanism. He supports this view by the following arguments: (a) the reaction occurs in the presence of inhibitors of radical polymerisation; and (b) replacement of unconjugated by conjugated olefines results in a change in the orientation of addition. In Goodman's view the role of platinum consists in polarising the Si–H bond in the direction $\overset{\delta+}{\text{Si}}-\overset{\delta-}{\text{H}}$.

With unconjugated olefines electrophilic addition takes place:

$$\bar{H} - R_3Si^+ + CH_2{=}CH-R' \rightarrow [R_3\overset{+}{Si}\cdot CH_2{=}CHR']^+ H^- \rightarrow R_3SiCH_2CH_2R. \qquad (VI)$$

In conjugated systems, where the double bond is polarised by a neighbouring electronegative group, conditions are favourable for reaction by a nucleophilic mechanism:

$$\bar{H} - R_3\overset{+}{Si} + CH_2^+{=}\bar{C}HCN \rightarrow [\bar{H}\cdot CH_2{=}CH-C{\equiv}N]^-\cdot\overset{+}{Si}R_3 \rightarrow H_3C-\underset{\displaystyle SiR_3}{\underset{|}{CH}}C{\equiv}N. \qquad (VII)$$

However, Goodman himself noted that, as the negative charge on the hydrogen atom in the Si–H group increases, both reactions (VI) and (VII) should be accelerated, which was not observed on passing from $SiHCl_3$ to CH_3SiHCl_2†. Later, Goodman's views encountered still more serious objections[75,95,96].

Nozakura and Konotsune[9,10] also regard the addition of trichlorosilane to acrylonitrile in the presence of organic bases as taking place by an ionic mechanism:

$$\begin{aligned} &Cl_3SiH + B \rightarrow Cl_3\bar{Si} + HB^+, \\ &Cl_3\bar{Si} + CH_2{=}CHCN \rightarrow Cl_3SiCH_2C\bar{H}CN, \\ &Cl_3SiCH_2\bar{C}HCN + HB^+ \rightarrow Cl_3SiCH_2CH_2CN + B, \end{aligned} \qquad (VIII)$$

where B represents a basic catalyst.

This mechanism is supported by the arguments that the reaction is catalysed by bases, telomers of acrylonitrile nitrile are not formed, and polar solvents (acetonitrile)

† Goodman used nuclear magnetic resonance experiments to show that from $SiHCl_3$ to CH_3SiHCl_2 and $(CH_3)_3SiH$ there is an increase in the electronegativity of the hydrogen atom attached to silicon (owing to the decrease in the inductive effect of the Si–Cl groups).

activate the reaction appreciably. These workers are forced to explain the change in the orientation of the addition of $SiHCl_3$ to $CH_2=CHCN$ in the presence of the catalyst $4C_5H_5N.NiCl_2$ by a change in the mode of dissociation of $SiHCl_3[Cl_3Si^+ + H^-]$ under the influence of this catalyst. An ionic mechanism is also assumed by Freidlina[86] for the addition of CH_3SiHCl_2 and $(C_2H_5)_3SiH$ to acrylonitrile [with $Fe(CO)_5.NiCl_2$ as catalyst].

In the presence of peroxides[9] the cyanoethylation of $SiHCl_3$ (the β-adduct is formed) undoubtedly proceeds by a radical mechanism, as shown particularly by the formation of telomeric products.

Saam and Speir[73] assume that trichlorosilane forms complexes with compounds containing nitrogen, and in particular with *NN*-substituted amides, by means of the vacant *d* orbitals of the silicon and that these complex compounds are active intermediates in the reaction with acrylonitrile. In our view such a concept provides a more correct approach to the problem of the mechanism of this reaction, although it does not answer directly whether rupture of the Si–H bond then takes place homolytically or heterolytically. Actually, if the role of the catalysts were merely to increase the polarisation of the Si–H bond, it would be expected that only the α-isomeric products would be obtained from $Cl_3\overset{+}{S}i-\overline{H}$ and $^{+}CH_2=\overline{C}HCN$. In fact, the β-adducts are formed.

The role of organic derivatives of phosphorus, arsenic, and bismuth as catalysts[73,74,80] is probably also to form active intermediates with silanes. Such an intermediate acts as a kind of carrier of trichlorosilane in the reaction with acrylonitrile. A similar reaction mechanism has been suggested in the chemistry of the cyanoethylation of compounds not containing silicon[97]. Thus it is suggested that in the cyanoethylation of aromatic amines (with acids or copper and nickel salts as catalysts) the amines form complexes with the catalysts, the complexing agent being displaced by the acrylonitrile, after which the cycle is repeated.

The fact that reaction takes place with the intermediate formation of complex compounds, and not by the formation of kinetically independent species, affects, of course, the process as a whole. In studying the reaction mechanism, therefore, we can hardly utilise the criteria which serve as arguments in support of typical radical or ionic processes.

It is interesting that germanium and tin hydrides, whose complexing power is greater than that of organosilicon derivatives, add to acrylonitrile in the absence of any catalyst[98–100].

(*f*) Preparation of organosilicon compounds containing a cyano-group by copolymerisation. A considerable amount of detailed work has been done on the copolymerisation of acrylonitrile with silicon-containing olefines[101–104]. With the aid of radical initiators, acetyl and benzoyl peroxides, copolymers have been obtained of acrylonitrile with siloxanes, of the type

$$CH_2=CHSi[OSi(CH_3)]_m(CH_3)_n,$$

where $m + n = 3$, and the constants for the copolymerisation of the original compounds have been calculated. Increase in the concentration of the silicon-containing olefine in the monomeric mixture diminishes the rate of polymerisation and lowers the molecular weight of the polymer. A study has been made of the behaviour of olefines of the types $R_3SiCH=CH_2$ and $RSi(OR')_3$ (where R = alkenyl, for example $CH_2=CH-$ and $CH_2=CHCH_2-$, or cycloalkenyl, and R' = = lower alkyl) on copolymerisation with acrylonitrile.

The preparation of silicon-containing nitriles by the γ-irradiation (^{60}Co) of solutions of acrylonitrile in polydimethylsiloxanes[105] is of fundamental interest, the kinetic features of this case of γ-initiated graft polymerisation having been investigated.

A promising line of investigation in the chemistry of organosilicon compounds is opened up by work on bivalent silicon, which is obtainable, for example, by the reaction[106,107]

$$SiX_4 + Si \xrightarrow{>1000^\circ} 2SiX_2 \quad , \qquad (I)$$

where X = halogen.

There is an indication in a patent[106] that acrylonitrile reacts at low temperatures with difluorosilylene to form polymers in which the unit is probably

$$\left[-(SiF_2)_n-CH_2-\underset{\displaystyle CN}{\underset{|}{CH}}-\right].$$

Silicon-containing butadienes readily react with acrylonitrile[108]

$$R_3SiCH=CH-CH=CH_2 + H_2C=CHCN \rightarrow R_3Si-\underset{\displaystyle CH=CH}{\overset{\displaystyle CH_2-CH-CN}{\overset{\diagup\quad\diagdown}{CH}}}-CH_2 \quad . \qquad (II)$$

(*g*) Other methods of preparation. Trialkylsilylalkyl ω-cyanides can be obtained by dehydrating the corresponding ω-amides by means of phosphorus pentoxide, for example[109,110]. Jex mentions in a patent[111] the possibility of obtaining 2-cyanoethyltrichlorosilane from chloropolysilanes ($Cl_3SiSiCl_3$, $SiCl_3SiCl_2SiCl_3$) and acrylonitrile.

2. Chemical Properties

(*a*) Conversion of the cyano-group into other functional groups. The following example[6] demonstrated the hydrolysis of the cyano-group in an organosilicon compound:

$$(CH_3)_3SiCH_2CH_2CN \xrightarrow{KOH/C_2H_5OH} (CH_3)_3SiCH_2CH_2COOH. \qquad (I)$$

The reaction took place, with a high yield of the acid, on boiling the compound in 40% KOH solution. Elimination of the cyanoalkyl group was not observed.

Other work[42–44,49,65–67,91,154] established that simple nitriles of the type $R_3Si[CHR]_nCN$ (R = H or CH_3, $n \geq 2$) or silicon-containing dinitriles with ω-cyanoalkyl or *p*-cyanoaryl group are also hydrolysed without appreciable cleavage of the Si–C bond. With α-nitriles ($n = 1$, R = H or CH_3) attempts to hydrolyse the cyano-group involved elimination of the cyanoalkyl group[8,10,86]. Table 4 gives data on the stability of cyanomethyl groups[8], which show that, as Si–O–Si links accumulate in the molecule, the stability of the compound increases somewhat, although it remains low in acid and especially in alkaline media.

This difference in behaviour between α- and β-nitriles is explained by the inductive ($-I$) effect of the CN group,

TABLE 4. Cleavage of Si–C bond after the mixture has been boiled for 24 h (in %).

Nitrile	H_2O	5% HCl/H_2O	5% NaOH/H_2O
Cyanomethyltrimethylsilane	100	100	100
Cyanomethylpentamethyldisiloxane	58	86	100
Cyanomethylheptamethylcyclotetrasiloxane	0	38	100

which is particularly strong in the case of α-nitriles. This effect produces an increase in the positive charge on the silicon atom, and preferential nucleophilic attack on the silicon atom becomes possible:

$$(CH_3)_3\overset{+}{S}iCH_2\overset{-}{C}N + O\overset{-}{H} \longrightarrow (CH_3)_3SiOH + C\overset{-}{H}_2CN,$$
$$^-CH_2CN + {}^+H \longrightarrow CH_3CN,\ 2(CH_3)_3SiOH \longrightarrow (CH_3)_3SiOSi(CH_3)_3 + H_2O. \quad (II)$$

The mechanism of cleavage in acid medium is represented by the scheme

$$(CH_3)_3SiCH_2C{\equiv}N + H^+ \rightarrow CH_3SiCH_2C{\equiv}N{:}H^+,$$
$$H_2O + (CH_3)_3SiCH_2C{\equiv}N{:}H^+ \rightarrow (CH_3)_3SiOH_2^+ + CH_2{=}C{=}NH, \quad (III)$$
$$CH_2{=}C{=}NH \rightarrow CH_3C{\equiv}N,\ (CH_3)_3SiOH_2^+ \rightarrow (CH_3)_3SiOH + H^+.$$

A β-cyano-group can be hydrolysed when it occurs in polymeric compounds, both three-dimensional[8,80,112] and linear[112,113] siloxanes:

$$O_{3/2}SiCH_2CH_2CN \xrightarrow{NaOH/H_2O} O_{3/2}SiCH_2CH_2COONa \xrightarrow[\downarrow\ HCl/H_2O]{} O_{3/2}SiCH_2CH_2COOH. \quad (IV)$$
$$\xrightarrow[HCl/H_2O]{}$$

In the case of a linear silicon polymer $[-OSi(CH_3).(CH_2CH_2CN)-]_n$ sulphuric acid is used as catalyst for the hydrolysis. According to a patent[114], products of the partial hydrolysis of cyanoalkylated silicon compounds can be prepared. In this case the polymer $\{-OSiR([CH_2]_k.CHR'CN)-\}_n$ is treated with concentrated sulphuric acid and then ice, when the polymer $\{-OSiR([CH_2]_kCHR'CONH_2)-\}_n$ is obtained (in both cases R and R′ are lower alkyls and $k \geq 1$). A polymer containing 1-cyanoethyl group $\{-OSi.(CH_3)[CH(CH_3)CN]-\}_n$ completely eliminates the 1-cyanoethyl group on treatment with concentrated alkalis[86].

In the presence of Grignard reagents α-cyanoalkylated silicon compounds eliminate the CN-containing group[10,83,86], whereas organosilicon compounds containing the cyano-group in the β-position (or more remote) react in the usual way[6,9,46,87,91]:

$$(CH_3)_3Si\underset{\underset{R'}{|}}{(CH)_n}CN + RMgX \longrightarrow (CH_3)_3Si\underset{\underset{R'}{|}}{(CH)_n}\overset{\overset{O}{\|}}{C}R, \quad (V)$$

where R = CH_3, C_6H_5; R′ = H, CH_3; $n \geq 2$.

Whereas reaction (V) takes place at room temperature, heating at 100° is required to obtain ketones from nitriles of the type $(CH_3)_3Si[CH_2]_nCH(CN)CH_2Si(CH_3)_3$ ($n \geq 1$)[47].

Several papers[44,88,109,115-118] have dealt with reduction of the cyano-group. The compound $(CH_3)_3SiCH_2CH_2CN$ is smoothly reduced to the amine by $LiAlH_4$ [109] or on hydrogenation over metallic catalysts[117]. Di-(cyanophenyl)dimethylsilane is hydrogenated in the presence of ammonia on a Raney nickel catalyst at 130°, but, in spite of the severe reaction conditions, the corresponding diamine is obtained in low yield[35]. Dinitriles of the type $O(R_2Si[CH_2]_nCN)_2$ with $n = 2, 3$ and R = CH_3, C_2H_5 are smoothly reduced to the corresponding diamines even at 75°–100° in the presence of Raney Co and Ni catalysts[115,116], the yields of the diamines reaching 92%.

Petrov, Friedlin, and their collaborators were the first to show the possibility of hydrogenating ω-cyanoalkylsilanes containing alkoxyl groups attached to the silicon atom[115]. This line of investigation was later extended by these workers[88,116,117] and by American[118] and Japanese[155] investigators.

The hydrogenation has been studied of nitriles of the types $NC[CH_2]_kSiR_n(OR')_{3-n}$ and $NCCH_2CH_2O[CH_2]_3SiR_n.(OR')_{3-n}$, where $k \geq 2$, and R and R′ are lower alkyl radicals. Yields of up to 85% of the corresponding amines are obtained.

Raney cobalt catalysts have the most selective effect in the formation of primary amines by hydrogenation; platinum catalysts result in the formation of considerable quantities of secondary and tertiary amines. With the cobalt catalysts the yield of primary amines is increased very slightly if hydrogenation is carried out in the presence of dry ammonia[88]. Japanese investigators achieved the best results by using a Raney Ni–Pt catalyst[155].

Synthesis of one of the amines, 3-triethoxysilylpropylamine, which is now produced industrially[132], can be accomplished by three methods, (VI),[88,116-118] (VII),[119] and (VIII):[120,155]

$$(C_2H_5O)_3SiCH_2CH_2CN \xrightarrow[Raney\ Co]{H_2} (C_2H_5O)_3SiCH_2CH_2CH_2NH_2, \quad (VI)$$

$$CH_2{=}CHCH_2NH_2\cdot(CH_3)_3SiCl \xrightarrow[H_2PtCl_6]{HSi(OC_2H_5)_3}$$
$$\rightarrow (C_2H_5O)_3SiCH_2CH_2CH_2NH_2\cdot(CH_3)_3SiCl \xrightarrow{C_2H_5OH} (C_2H_5O)_3SiCH_2CH_2CH_2NH_2, \quad (VII)$$
$$(C_2H_5O)_3SiCH_2CH_2CH_2Cl + NH_3 \rightarrow (C_2H_5O)_3SiCH_2CH_2CH_2\mathbf{NH_2}, \quad (VIII)$$

method (VI) successfully competing with the other two.

Interaction of acrylonitrile with methyldichlorosilane in the presence of catalysts in steel autoclaves has been found to yield unstable products whose composition was close to that of adducts of one mole of $CH_2{=}CHCN$ and two or three moles of the silane[83]. This was explained by reaction of the silanes not only at the C=C bond but also at the C≡N bond of the acrylonitrile. It was subsequently confirmed[121] that the cyano-group reacts with silanes in the presence of metal chlorides, for example, in the following manner:

$$C_6H_5CN + HSi(C_2H_5)_3 \xrightarrow{NiCl_2} C_6H_5{-}CH{=}N{-}Si(C_2H_5)_3. \quad (IX)$$

Conditions have been determined[80] for the conversion of the CN into an ester group:

$$(C_2H_5O)_3SiCH_2CH_2CN \xrightarrow{abs.\ C_2H_5OH/HCl} (C_2H_5O)_3SiCH_2CH_2COOC_2H_5 \quad (X)$$

The α- and β-isomers of cyanoethyltrimethylsilane interact differently with thioglycollic acid[9,10]:

$$(CH_3)_3SiCH_2CH_2CN \xrightarrow{HSCH_2COOH/HCl} (CH_3)_3SiCH_2CH_2\underset{\underset{NH\cdot HCl}{\|}}{C}SCH_2COOH, \quad (XI)$$

$$(CH_3)_3SiCHCN \xrightarrow{HSCH_2COOH/HCl} (CH_3)_3SiCl + CH_3CH_2\underset{\underset{NH.HCl}{\|}}{C}SCH_2COOH.$$
$$\underset{CH_3}{|}$$

Dimerisation of cyanoalkyltrimethylsilanes takes place in the presence of sodium:

$$(CH_3)_3SiCH_2CH_2CN \xrightarrow{Na} (CH_3)_3SiCH_2CH(Na)CN \xrightarrow{(CH_3)_3SiCH_2CH_2CN} \rightarrow (CH_3)_3SiCH_2CH_2C(NH_2)C{\equiv}N-CH_2Si(CH_3)_3 \quad (XII)$$

(b) Reactions of cyanoalkylsilanes in which the cyano-group is preserved. In the case of reaction (I) it has been found that the Si–X bond is more reactive than the C≡N bond towards Grignard reagents[6]:

$$Cl_3SiCH_2CH_2CN + 3\,CH_3MgX \longrightarrow (CH_3)_3SiCH_2CH_2CN. \quad (I)$$

Later this method was used to obtain from various cyanoalkylhalogenosilanes a wide variety of CN-containing silico-hydrocarbons, siloxanes, and alkylhalogenosilanes[9,31,47,72,87,91]. It is interesting that, with a Grignard reagent[10,86], an Si–Cl group in the α-nitriles $SiCl_3CH(CH_3)CN$ and $CH_3SiCl_2CH.(CH_3)CN$ can be replaced by Si–R without the cyano-group being affected.

As mentioned above, satisfactory yields of the industrially important $RSiCl_2CH_2CH_2CN$ could not be obtained by the addition of $RSiHCl_2$ to $CH_2{=}CHCN$. These bifunctional nitriles were prepared by the action of the Grignard reagent on $SiCl_3CH_2CH_2CN$.

An attempt to obtain $CH_3SiCl_2CH_2CH_2CN$ using CH_3MgX at room temperature was unsuccessful, a mixture of products $(CH_3)_nSiCl_{3-n}CH_2CH_2CN$ (n = 1–3), which were difficult to separate, being formed; the bifunctional compound was isolated in 25% yield[73,74,122]. If, however, this reaction is carried out in tetrahydrofuran at low temperatures, it takes place more selectively (see Table 5)[123].

When cyanoalkyl derivatives (from CH_3I and Zn–Cu) were made to react with $SiCl_3CH_2CH_2CN$, only $(CH_3)_3SiCH_2CH_2CN$ could be isolated from the reaction products, although equimolar proportions of the reactants were taken[113]. Yields of the bifunctional compound up to 90% are obtained by the action of $(CH_3)_2Cd$ on $SiCl_3CH_2CH_2CN$.[71,122] In this reaction the yield of $CH_3SiCl_2CH_2CH_2CN$ can be increased if alkylation is effected with CH_3MgX in the presence of tertiary amines[124,125].

Since it is difficult to isolate the dialkylmonochlorosilylalkyl ω-cyanides obtained by the alkylation of trichlorosilylalkyl or alkyldichlorosilyl alkyl ω-cyanides, the following technique has been proposed for the preparation of αω-dinitriles, which does not require the isolation of the chlorides[72,156]:

$$2\,NC(CH_2)_nSiRCl_2 \xrightarrow{R'MgX} \xrightarrow{H_2O} [NC(CH_2)_nSiRR'-]_2O, \quad (II)$$

where R and R′ are lower alkyls, and n = 2, 3.

There are several studies of the hydrolysis of cyanoalkylsilanes containing functional groups attached to the silicon atom[6,9,10,31–41,80,84,112,113]. That of 2-trichlorosilylethyl cyanide has been investigated in detail by Pike *et al.*[80] Table 6 gives comparative data on the hydrolysis of $SiCl_3.CH_2CH_2CN$ and other silicon chlorides, which show the exceptional reactivity of this compound.

The ease with which the chlorine atoms attached to silicon in $SiCl_3CH_2CH_2CN$ are replaced by OH groups is a result of the inductive effect (–*I*) of the cyano-group, owing to which an additional positive charge is induced on the silicon atom, and favourable conditions are created for nucleophilic attack on this atom:

$$NCCH_2CH_2Si^{\delta+}Cl_3 \cdots O(H)H \longrightarrow \left[NCCH_2CH_2Si(Cl)_2(OH)\right]^{-} + HCl. \quad (III)$$

The inductive effect is still greater in the case of the α-isomer, so that it is possible to obtain $\{O_{3/2}Si[CH(CH_3).CN]\}_n$ only under mild conditions, otherwise decomposition occurs at the Si–C bond (IV):[10,80]

$$NCCHSiCl_3 \xrightarrow[0^\circ]{H_2O/ether} \left[NCCHSiO_{3/2}\right]_n, \quad (IV)$$

$$NCCHSiCl_3 \xrightarrow[20^\circ]{H_2O/ether} [SiO_2]_n + CH_3CH_2CN. \quad (V)$$

The linear polysiloxane from $CH_3SiCl_2CH(CH_3)CN$ also can be obtained only under mild conditions[86]. The polymer prepared from 2-methyldichlorosilylethyl cyanide[113] is a thick oil, insoluble in the usual organic solvents but soluble in dimethylformamide; the polysiloxane from $CH_3SiCl_2CH_2.CH_2CH_2CN$ also is only partly soluble in benzene[41].

Cyanoalkylsilanes having hydrolysable groups attached to the silicon atom, in particular $SiCl_3CH_2CH_2CN$, can be cohydrolysed with other alkylsilicon chlorides, for example with $(CH_3)_3SiCl$ and $(CH_3)_2SiCl_2$.[112] A rubberlike polymer has been prepared by condensing $CH_3SiCl_2CH_2CH_2CH_2CN$ with $(HO)(CH_3)_2SiOSi(CH_3)_2(OH)$.[41] Even under mild conditions of hydrolysis it was not possible to obtain the silanediol from $CH_3SiCl_2CH_2CH_2CN$, since it immediately undergoes polycondensation to an oily polymeric product[113].

TABLE 5*

RMgX	Conversion (mole %) into $RSiCl_2CH_2CH_2CN/R_2SiClCH_2CH_2CN$		
	at –50°	at –30°	at +5°
CH_3MgCl	73/7	61.6/10.6	52.4/16.1
C_2H_5MgCl	69/9		

* Equimolar proportions of RMgX and $SiCl_3CH_2CH_2CN$ were used.

TABLE 6. Relative rate of hydrolysis of the first chlorine of alkylchlorosilanes in dimethylcellosolve*.

$RSiCl_3$	At –51°	At –20°	At 0°
$C_2H_5SiCl_3$	1.0	1.0	1.0
CH_3SiCl_3	2.2	0.59	0.3
$C_6H_5SiCl_3$	4.1	2.0	1.4
$NCCH_2CH_2SiCl_3$	62.0	116.0	153.0

* Ethylene glycol dimethyl ether (Ed. of Translation).

In the presence of 2 wt.% of concentrated H_2SO_4 at 20°, CN-containing siloxanes undergo rearrangement at the Si–O–Si bonds[8]:

$$2\,(CH_3)_3Si{-}O{-}Si(CH_3)_2CH_2CN \rightarrow [NCCH_2(CH_3)_2Si]_2O + [(CH_3)_3Si]_2O. \quad \text{(VI)}$$

However, 4 wt.% of H_2SO_4 was sufficient for the cyanoalkyl group to be split off from the silicon atom when an attempt was made to obtain a linear polysiloxane from hexamethyldisiloxane and cyanomethylheptamethylcyclotetrasiloxane. In the similar reaction

$$NC(CH_2)_nSi(CH_3)_2{-}O{-}(CH_3)_2Si(CH_2)_nCN + x[(CH_3)_2SiO]_4 \xrightarrow[20^\circ]{H_2SO_4} \rightarrow$$

$$\rightarrow NC(CH_2)_nSi(CH_3)_2[OSi(CH_3)_2]_{4x}O(CH_3)_2Si(CH_2)_nCN,$$

where $n = 2, 3$ and $x = 1-4$, carried out under the influence of 2–6 wt.% of H_2SO_4, β- and γ-cyanoalkyl groups are not eliminated[156].

According to Sommer[126], it was not possible to demethylate $(CH_3)_3SiCH_2CN$ (with sulphuric acid), because in this case the cyanoalkyl group was eliminated with the formation of $(CH_3)_3Si{-}O{-}Si(CH_3)_3$.

All cyanoalkylhalogenosilanes are smoothly alkoxylated[9,10,31,46,47,73,74,80,88,115,117,124] by anhydrous alcohols, including allyl alcohol. The reaction is carried out in the presence of substances (pyridine, ammonia) which will combine with the HCl evolved, and also in their absence, but in the latter case the yields of alkoxy-derivatives are somewhat lower, since the cyano-group also reacts to some extent with the alcohols (the HCl evolved acting as catalyst for this reaction)[80].

Acetic anhydride reacts according to (VII), the yields of the desired products exceeding 90%:[46]

$$NCCH_2CH_2SiCl_3 + 3\,CH_3CO{-}O{-}OCCH_3 \longrightarrow NCCH_2CH_2Si(OCOCH_3)_3 + 3CH_3COCl\,. \quad \text{(VII)}$$

Acyloxylation of $SiCl_3CH_2CH_2CN$ can also be effected with salts of organic acids, but lower yields are then obtained.

3. Physical Properties

Organosilicon compounds containing cyanoalkyl groups are strongly polar liquids[8,113]. Table 7 gives quantitative data enabling the properties of cyanomethyl compounds to be compared with those of analogous substances not containing cyano-groups.

The dielectric constants and dipole moments of cyanomethyl compounds in Table 7 also characterise them as polar substances. The polysiloxane $[-OSi(CH_3)(CH_2CH_2CN)-]_n$ behaves as a polar liquid[113].

As noted in parts 1 and 2 of this Section, α-nitriles, $Si{-}\overset{|}{\underset{|}{C}}{-}C{\equiv}N$, in contrast to β-, γ-, etc. nitriles, possess anomalous chemical properties. These are mainly due to the inductive effect of the cyano-group, but in some cases probably also to a steric effect or other peculiarities of molecular structure. The spectra of α-cyanoalkyl compounds also show characteristic features. Thus the infra-red absorption spectra of the first member of the series of compounds of general formula $(CH_3)_3Si[CH_2]_nCN$ (where $n = 1-3$) have the characteristic frequency of the cyano-group about 10–15 cm^{-1} below that in the β- and γ-nitriles,

TABLE 7.

Compound	Activation energy of viscous flow, kcal mole^{-1}	Heat of evaporation, kcal mole^{-1}	Entropy of evaporation, kcal mole^{-1} × × deg^{-1}
Cyanomethyltrimethylsilane	—	10.8	24.9
Tetramethylsilane	3.1	5.8[11]	19.4
Cyanomethylpentamethyldisiloxane	3.2	12.0	25.4
Hexamethyldisiloxane	2.2[9]	8.3[9]	22.2
Cyanomethylheptamethylcyclotetrasiloxane	4.5	14.0	27.6
Octamethylcyclotetrasiloxane	3.4[10]	10.0[9]	24.8

the frequency being considerably more intense than in the β-nitrile‡.[8,18,31,47]. However, in the series of nitriles

$$(CH_3)_3SiCH_2CN > (CH_3)_3SiCHCN > (CH_3)_3SiCHCN\,,$$
$$\qquad\qquad\qquad\quad (CH_3)_3Si \qquad\qquad\quad CH_3$$

the frequency of the cyano-group falls, its respective values being 2240,[8,18,31] 2218,[18] and 2205 cm^{-1}.[86]

The characteristic frequencies of the CN group which have been reported[127] for nitriles not containing silicon are 2250 ± 8 cm^{-1} (unconjugated nitriles) and 2255 ± 10 cm^{-1} (conjugated nitriles). The characteristic frequency of a cyano-group attached to a β-carbon atom is also lower when the latter is a secondary carbon atom. In nitriles of the type $(CH_3)_3Si[CH_2]_nCH(CN)CH_2Si(CH_3)_3$ ($n = 1$ or 2), for example, it is 2240 cm^{-1}, whereas in $(CH_3)_3Si[CH_2]_nCN$ ($n = 2$ or 3) it is 2249 cm^{-1}.[47]

The stability of silicon polymers to thermal oxidation has been studied[80,122] (Table 8). The instability of the 1-cyanoethylsiloxane is consistent with the above results. The stability of the 2-cyanoethylsiloxane, however, is unexpected, since it is a substituted analogue of the unstable

TABLE 8. Comparison of resistance of silicone polymers to thermal oxidation in air at 250°.

Siloxane	% of initial content of carbon after 100 h
Diphenyl-	98.4
Methyl-	96.7
2-Cyanoethyl-	88.3
Dimethyl-	81.5
1-Cyanoethyl-	12.6*
1-Cyanoethyl-	1.0
3-Cyanopropyl-	94.4
2-Cyanopropyl-	75.6
Ethyl-	6.7

* After 25 h.

‡ This fact enables infra-red analysis to be used for the identification of isomeric silicon-containing α-and β-nitriles. Pike[80] also recommends analysis of mixtures of isomeric 1-and 2-cyanoethyltrichlorosilanes by infra-red spectroscopy, but his method is based on the different absorption bands of the CH and CH_2 groups in the region of the stretching vibrations.

ethylsiloxane. It is supposed that the stability of $[(NCCH_2CH_2)SiO_{3/2}]_n$ is due to the presence in the polymer molecules of intermolecular or intramolecular bonds involving the polar cyano-group.

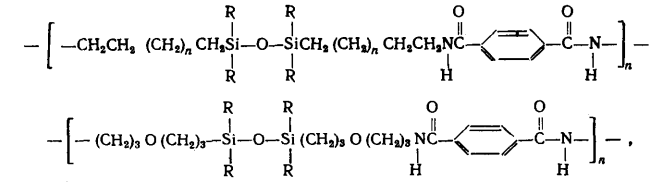
Individual cyanoalkyl compounds of silicon are soluble in the usual organic solvents, whereas the polymeric compounds are sparingly soluble in them but dissolve in dimethylformamide.

4. Practical Uses of Cyanoalkyl Compounds of Silicon

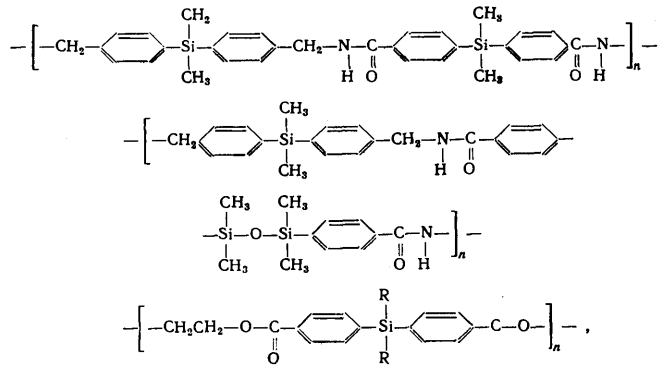
Several papers[122,128-131] show that American industry started the production of nitrile-containing siloxane rubber as early as 1958. Thanks to its valuable technical properties, this type of rubber is especially promising in the aircraft, petroleum, automobile, and radio and electrical industries[128,129]. The information in these publications deals mainly with the properties of the rubbers. The materials are dimethylpolysiloxane rubbers in which some of the methyl groups have been replaced by $[CH_2]_nCN$, the influence of the nitrile group on the properties of the rubber diminishing with increase in n.[128] Such rubbers resist the action of fuels, oils, and solvents, and are used over the temperature range from -73° to +260°.[122,128] The CN-containing groups in the rubber are apparently[122,129] 2-cyanoethyl and 3-cyanopropyl.

Table 9 and the diagram give data indicating the remarkable properties characteristic of these cyanoalkylated materials. Although the stability of nitrile-siloxane rubber to the action of petrol is about equal to that of a nitrile rubber, the advantages of the former are undisputed for work at high temperatures.

Diamines and dibasic acids obtained from $\alpha\omega$-dinitriles containing silicon have been used for the preparation of silicon-containing polyesters and polyamides, especially those having siloxane groups in the main polymer chain. For example, polymers of the following types have been obtained[43,44,115]:



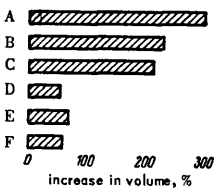
where n = 0, 1 and the R's are the same or different — CH_3 and C_2H_5.



where R = CH_3 and C_6H_5.

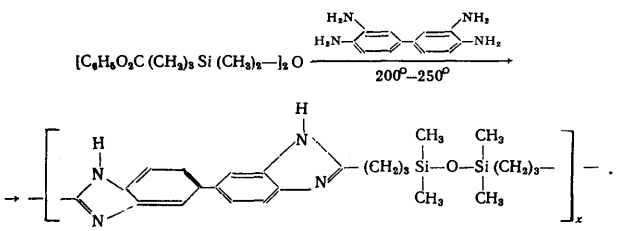
TABLE 9. Principal properties of nitrile–siloxane rubbers[129].

Property	NSR–x8701	NSR–x4803	NSR–x5602 a	NSR–x5602 b
Vulcanisation time, h	16	16	1	3
Temperature of vulcanisation, °C	232	204	149	204
Shore hardness	70±5	80±5	55±5	60±5
Tensile strength, kg cm^{-2}	45.5	59.5	77.0	70.0
Relative elongation, %	125	125	300	240
Tear strength, kg cm^{-1}	8.9	13.4	16.1	13.4
Residual shrinkage, %	55	45	—	50
Brittle point, °C	−68	−73	−73	−73
Specific gravity	1.25	1.4	—	1.121
After aging at 232° for 70 h				
Shore hardness	70±5	8025	—	65±5
Tensile strength, kg cm^{-2}	42	49	—	56.0
Relative elongation, %	100	100	—	190



Swelling of rubbers in aviation spirit:
A - natural rubber;
B - butadiene–styrene rubber;
C - general-purpose silicone rubber;
D - nitrile rubber;
E - chloroprene rubber;
F - nitrile–siloxane rubber.

Some polymers of this type will, perhaps, find future application as elastic and frostproof fibres and elastomers. Derivatives of silicon-containing dinitriles have been used to introduce the siloxane group into a benzoimidazole polymer chain[154]:



The siloxane group introduces several new properties into this new class of polymers, which are interesting because of their exceptional thermal stability; its primary effect is to increase the solubility of the polymer compared with that of benzoimidazole polymers not containing silicon[157].

The production of trialkoxy(and alkyldialkoxy)silylalkyl--ω-amines§ was mastered by industry a few years ago[132]. According to patent information[118,120] these amines possess a strong fungicidal action, and are also successfully used in the preparation of glass fabrics. For example, treatment of glass fibre with a water-soluble polymer from $NH_2CH_2CH_2CH_2Si(OC_2H_5)_3$, with subsequent application to it of a melamine–formaldehyde resin, makes it possible to obtain materials of high mechanical strength and resistance to water[120]. Glass laminates based on glass fibres finished with a γ-aminoalkyltriethoxysilane possess enhanced short--period thermal stability[133].

ω-Aminoalkyl derivatives of silicon have been patented[134-138] as intermediates for several other important technical materials.

We shall not deal in the present review with work on compositions based on CN-containing polymers and silicon--containing substances. It must be borne in mind, however, that this provides a line of research of great practical promise. Thus, for example, the introduction of silicon dioxide into a polyacrylonitrile fibre[139], or of sodium silicate into a nitrile rubber[140], substantially improves the properties of these materials.

IV. CYANOALKOXY-DERIVATIVES OF ORGANOSILICON COMPOUNDS

1. Methods of Synthesis

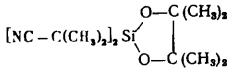
In a series of alkoxy-derivatives of silicon, →Si–[OAlk], the resistance of the Si—O bond to hydrolysis increases as Alk changes in the sequence primary, secondary, tertiary¶. In order to obtain hydrolytically stable cyanoalkoxy derivatives of silicon, therefore, investigators have usually employed secondary and tertiary alcohols, cyanohydrins of aldehydes and ketones.

Hahn[141] obtained cyanoalkoxy-derivatives of silicon by the reaction

$$NC—CRR'—OH + SiCl_4 \longrightarrow [NC—CRR'—O]_mSiCl_{4-m}, \qquad (I)$$

where R′ = CH_3, and R = C_2H_5, CH_3, cyclohexyl.

Successive treatment of silicon tetrachloride with pinacol and with acetone cyanohydrin enabled him to obtain the mixed ester



Frish and Wolf[142,143] synthesised derivatives of acetone cyanohydrin and methylchlorosilanes using pyridine and tertiary amines to combine with the hydrogen chloride evolved in the reaction. Later a thorough investigation was made of the interaction of acetone cyanohydrin with various alkyl-, aryl-, and alkenyl-chlorosilanes[144-146]. The size, structure, and number of the organic radicals attached to the silicon were found[145] to have a substantial influence on the rate of conversion of Si–Cl into $Si–O–C(CH_3)_2CN$: in the series

$$RHSiCl_2 > RSiCl_3,\ R'RSiCl_2 > R''SiCl_3,$$

where R and R′ = alkyl, while R″ = aryl, the reactivity of the Si–Cl bond decreases.

The compound $Si[O–C(CH_3)_2CN]_4$ is readily obtained by the interaction of equimolar amounts of $SiCl_4$ and acetone cyanohydrin[144]. It is interesting that for a long time the structurally analogous tetra-t-butoxysilane could not be obtained at all owing to steric hindrance; this problem was later solved only by replacing $(t\text{-}C_4H_9O)_3SiCl$ and $t\text{-}C_4H_9OH$ by the more reactive $(t\text{-}C_4H_9O)_3SiBr$ and $t\text{-}C_4H_9ONa$.[147]

Acetone cyanohydrin also proved to be considerably more reactive than $t\text{-}C_4H_9OH$ towards the Si–H bond. Whereas with R = CH_3 reaction (II) requires prolonged heating in an autoclave with catalysts (alkalis),[148] with R = CN it took place even under mild conditions of esterification of the Si–Cl bond, without catalysts[146]:

$$\equiv SiH + HOC(CH_3)_2R \longrightarrow \equiv SiOC(CH_3)_2R + H_2, \qquad (II)$$

where R = CH_3, CN.

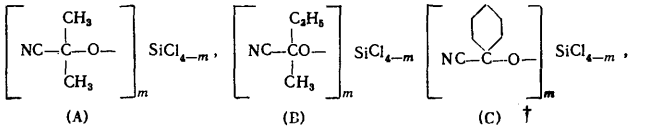
Products formed by the interaction of silicon tetrachloride cyanohydrins of aldehydes and ketones have also been described in patents[149,150].

The CN-containing ester $(t\text{-}C_4H_9O)_2Si(OCH_2CH_2CN)_2$ has been obtained from di-t-butoxydichlorosilane and 3-hydroxypropionitrile, whereas it could not be obtained from di-t--butoxysilanediol and acrylonitrile[64].

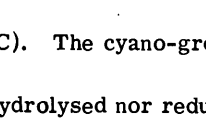
2. Properties

Individual cyanoalkoxy-derivatives of silicon are readily soluble in inert organic solvents; polymeric silicon compounds containing cyanoalkoxy-groups are considerably less soluble or do not dissolve at all in them.

Hahn[141] prepared the three series of derivatives



(A) (B) (C) †

and noted their ready hydrolysability even in moist air. The hydrolytic stability increases in the sequence (A) < < (B) < (C). The cyano-group in  could be neither hydrolysed nor reduced[141].

Cyanoalkoxy-compounds in which some of the silicon valencies are occupied by alkyl or aryl groups possess considerably hydrolytic stability[142,145]. Compounds containing no Si–Cl bonds are particularly stable, for example $C_6H_5Si[O–C(CH_3)_2CN]_3$, $C_6H_5Si[O–C(CH_3)_2CN)]_2CH_3$, $(CH_3)_3SiOC(CH_3)_2CN$, etc.; they are stable on prolonged contact with water, and are only partly hydrolysed by 5%

§ As indicated p.401 a good method for obtaining them is to hydrogenate ω-cyanoalkyl compounds of silicon.

¶ With increase in the degree of branching of the alkoxy-groups, however, it becomes difficult to attach them to the silicon atom because of steric factors.

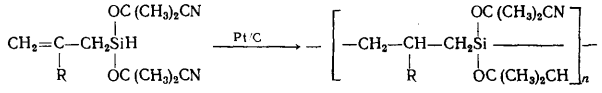
† Compound (C) is derived from cyclohexanone cyanohydrin (Ed. of Translation).

aqueous HCl or NaOH. It proved possible under mild conditions of hydrolysis to obtain the siloxanes $NCC(CH_3)_2.OSiR_2OSiR_2OC(CH_3)_2CN$ and the diol $CH_3Si(OH)_2OC(CH_3)_2CN$ from $R_2ClSiOC(CH_3)_2CN$ and $CH_3SiCl_2OC(CH_3)_2CN$ respectively[142,145].

Hydrolysis of $C_2H_5SiCl_2OC(CH_3)_2CN$ in the presence of pyridine in benzene at 0° yields a polysiloxane of low molecular weight, $\{C_2H_5SiO[O-C(CH_3)_2CN]\}_n$.[142]

Cohydrolysis of the dichlorides $RSiCl_2OC(CH_3)_2CN$ with dimethyldichlorosilane was accompanied by partial elimination of the cyanoalkyl groups[151].

Polyakova *et al.*[55,152] studied the polymerisation of alkenyl- and dialkenyl-siloxydimethylacetonitriles with peroxide catalysts[31,55]. The following reaction was also studied[55,152]:



where R = CH_3, H.

In both cases solid or oily polymeric substances are obtained, sparingly soluble in the usual organic solvents, but soluble in dimethylformamide.

With alcohols and Grignard reagents and alkylchlorosiloxydimethylacetonitriles, reaction takes place at both Si–Cl and $SiOC(CH_3)_2CN$ groups[145,146].

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ORGANIC CHARGE-TRANSFER COMPLEXES

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INTRODUCTION

Organic molecular complexes have been known for a long time, but their systematic study which has resulted in the appearance of special monographs[1,2], is comparatively recent. During the past few years research on molecular complexes has been carried out particularly intensively not only by chemists but also by physicists and biophysicists. These complexes are formed as a result of donor–acceptor interaction between molecules, the so-called charge-transfer complexes, on which many papers have been published during the past decade, including some reviews[3-6]. The search for organic semiconductors has aroused especial interest in charge-transfer complexes. The present paper deals mainly with work on the electrical conductivity of such complexes, and on the probably related magnetic properties.

I. NATURE OF CHARGE-TRANSFER COMPLEXES

Charge-transfer complexes are those formed by molecules or ions, or both, without a covalent bond participating in complex formation. A feature of such complexes is the transfer of an electron from one component (the donor) to the other (the acceptor). The extent of electron transfer can in principle vary from zero to complete transfer, the latter case involving the conversion of neutral molecules to radical-ions The ground state of charge-transfer complexes containing one donor molecule combined with one acceptor molecule is approximately represented by the wave function[7-13]

$$\psi_n(D,A) = a\psi_0\ (DA) + b\psi_1\ (D^+A^-)\ldots, \qquad (1)$$

where D is the donor and A the acceptor; ψ_0 is the wave function for the non-ionic state of D and A, in which they may be linked either by a hydrogen bond, by dipole–dipole interaction forces, or by any others forming part of the classical "van der Waals forces"; ψ_1 is the wave function of the combined state, corresponding to complete transfer of one electron from D to A, and a and b are coefficients. The excited state is represented by the equation

$$\psi_e(D,A) = a^*\psi_1\ (D^+A^-) - b^*\psi_0(DA). \qquad (2)$$

With complexes having a weakly ionic bond, $a \gg b$, $|a| \simeq 1$, and $|b| \simeq 0$, so that

$$\psi_n \simeq \psi_0(DA), \text{ and } \psi_e \simeq \psi_1(D^+A^-),$$

i.e. the excited state is almost completely a diradical-ion. In complexes having a stable ionic bond between the D and A species, $b > a$. Table 1 indicates the relation between the coefficients a and b for several complexes, expressed in terms of the quantity $100b^2/(a^2 + b^2)$. It follows from these data that a is nearly always greater than b.

TABLE 1. Values of $100b^2/(a^2 + b^2)$ for some complexes.

Donor	Acceptor	$\frac{100\,b^2}{a^2+b^2}$	References
Hexamethylbenzene	trinitrobenzene	3.8	14
Stilbene	»	3.5	14
Naphthalene	»	2.8	14
1,2,4,5-Tetramethylbenzene	»	2.1	14
Hexamethylbenzene	chloranil	4.4	14
Benzene	iodine	2.8	9
Benzene	»	8.2	15
Pyridine	»	25	16

When A and D are weak donors and acceptors,

$$\psi_n(D, A) = a\psi_0(D\,A) + b\psi_1(D^+A^-) + c\psi_2(D^-A^+), \qquad (3)$$

where usually $c \ll b$.

With the so-called "self-complexes", which may be formed from identical molecules of aromatic hydrocarbons, $b = c$, since donor and acceptor possess identical properties. The general expression thus obtained is similar to that for the ground state of the hydrogen molecule.

This quantum-mechanical treatment of charge-transfer complexes was developed by Mulliken with reference to their state in solution. The application of these ideas to such complexes in the solid state may suffer certain restrictions or additional conditions. It is clear, however, that the smaller intermolecular distances occurring in the solid state result in greater coulombic forces, and hence in stabilisation of the ionic structure. The deep colour characteristic of many charge-transfer complexes is associated with the presence of excited ionic structures.

The energetics of charge-transfer complexes has been discussed in detail[3]. It is quite obvious that the process of complex formation itself and its energy characteristics depend on the ionisation potential of molecule D and the electron affinity of molecule A. Thus the energy required to raise the complex to an excited state can be written[17]

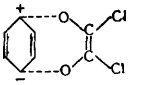
$$h\nu = I - E_a - W,$$

where h is Planck's constant, ν the transition frequency corresponding to charge transfer, I the ionisation potential of the donor, E_a the electron affinity of the acceptor, and W the dissociation energy of the excited state of the complex.

The above views on the nature of charge-transfer complexes are closely related on the one hand to their treatment as purely ionic compounds[18,19], and on the other as resonance hybrids[20] located between the uncombined state D : A and the ionic state $D^+ : A^-$. The possibility has also been considered[21,22] that a condition for the linking of the D and A molecules by free π electrons from the donor is that they should penetrate the potential barrier by a tunnel effect.

The energy of formation of charge-transfer complexes varies from hundreds to several thousand calories per mole.

With regard to the mutual arrangement of D and A molecules in the complex, the superposition of two coplanar molecules suggested for aromatic (including quinonoid) structures has been confirmed in several cases by crystallographic investigations[23-27]. Frequently, however, a different arrangement has been found. Thus, for example, the complex of 1,3,5-trinitrobenzene and anthracene provides an example of such superposition of coplanar D and A molecules[28], whereas the complex of trinitrobenzene with *p*-iodoaniline contains, besides the overlapping layers, alternating D and A molecules arranged in a single layer[29]. In the "self-complex" of *p*-nitroaniline the proximity of the O atom of the nitro-group to a C atom of a neighbouring ring (2.66 Å)[30] led to the hypothesis that acceptor centres may be localised in the substituents, with the formation of chains of "head-to-tail" type. On the other hand, a spectrophotometric investigation of quinhydrone[31] gave no indication of any substantial influence of the hydrogen bond formed here on the transfer of charge or the relative positions of the nuclei. It is very probable that, where the uniform distribution of electron density about the C atoms of the benzene ring is considerably disturbed, there is a tendency for quinonoid structures to be formed with localisation of the active (donor or acceptor) centres. For example, the following structure has been suggested[32] for the complex of benzene with oxalyl chloride:



A linear structure $\geqslant N-Hal-Hal$ has been demonstrated[33,34] for the so-called "onium" complexes formed between a tertiary nitrogen atom and a halogen molecule. Thus both charge-transfer structures in which A and D molecules are superposed and other structures can probably occur.

II. DONORS

The donors in organic charge-transfer complexes are almost exclusively aromatic compounds. With benzene and its derivatives the donor properties of the molecule, and hence the stability of the complex formed with a given acceptor, are determined by the nature of the substituent. The relative stabilities of complexes of benzene derivatives with the silver ion were found to be as follows[35-37] (the numbers in parentheses are relative to the stability of the complex obtained from iodobenzene taken as 5.0): NO_2 (0.19), F (0.46), $COCH_3$ (0.54), $COOC_2H_5$ (0.56), Cl (0.69), Br (0.97), OH (2.19), H (2.41), OCH_3 (2.50), CH_3 (2.63), I (5.00), and $CH=CH_2$ (18.2). With the exception of the last two cases, in which the silver ion apparently gravitates towards the substituent, the stability of the complex is directly linked with the inductive effect of the substituent. The following series has been obtained[38] for the relative stabilities of complex of benzene derivatives with tetranitromethane: H (0.05), CH_3 (0.90), $OCOCH_3$ (1.68), OH (12.28), OC_6H_5 (15.87), OCH_3 (20.41), and OC_2H_5 (20.62). Alkylbenzenes are good donors, and the relative stabilities of the complexes which they form with various acceptors are given in Table 2.

It is seen from Table 2 that accumulation of methyl groups strengthens the donor properties of the benzene ring. In the opinion of several workers[42] introduction of larger alkyl groups weakens the complex by preventing donor and acceptor from coming together.

The donor properties and the capacity for complex formation of aromatic nitrogen compounds of the amine type, pyridine, quinoline, and their derivatives are well known.

Polycyclic aromatic hydrocarbons are active donors. Stilbene and diphenylpolyenes[43,44] give 1 : 2 complexes with

TABLE 2. Relative stabilities of complexes of alkylbenzenes with various acceptors (benzene = 1.00).

Donor	Acceptor				
	Ag^+ [35,37,39,40]	iodine [39]	tetranitromethane [38]	HF [41]	tetracyanoethylene [42]
Benzene	1.00	1.00	1.00	1.00	1.00
Toluene	1.09	1.09	20.0	7.0	1.87
o-Xylene	1.31	1.82	143	12.2	—
m-Xylene	1.36	2.09	143	290	—
p-Xylene	1.09	2.09	143	12.2	3.80
1,2,4-Trimethylbenzene	—	—	—	700	—
1,2,3-Trimethylbenzene	—	—	—	770	—
1,3,5-Trimethylbenzene	0.74	5.50	465	145000	8.65
1,2,4,5-Tetramethylbenzene	0.93	4.25	590	1560	27.1
1,2,3,4-Tetramethylbenzene	—	—	—	4450	—
1,2,3,5-Tetramethylbenzene	—	—	—	178000	—
Pentamethylbenzene	—	5.90	800	320000	61.5
Hexamethylbenzene	—	9.10	1120	1080000	—
Ethylbenzene	1.22	—	26	—	—
Hexaethylbenzene	—	0.88	—	—	—
Propylbenzene	1.31	—	—	—	—
Isopropylbenzene	1.26	—	18.5	—	—

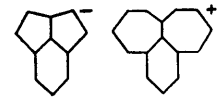
1,3,5-trinitrobenzene, which suggest that the benzene rings act in this case as independent donors; however, the donor properties of such systems become stronger as the polyene chain becomes longer. The ionisation potential of fused-ring hydrocarbons falls, and hence their capacity for complex formation increases, not with increase in the total number of fused rings but as quinonoid rings accumulate in the molecule [45]. Thus the ionisation potential falls from 9.24 eV for benzene to 4.39 eV for graphite, the latter substance showing an extremely great capacity for complex formation [46]. The ionisation potentials of several donors are given in Table 3.

The importance of the ionisation potential of the donor was confirmed by the fact that, in a series of complexes of iodine with various donors, the frequency of the electronic absorption band corresponding to charge transfer varies linearly with this ionisation potential [50]. Since in polycyclic aromatic systems the fall in ionisation potential is accompanied by an increase in electron affinity, when such systems react with alkali metals as donors they also exhibit the properties of acceptors, forming negatively charged radical-ions. Many alkali-metal complexes can initiate anionic polymerisation [51]. Metals like magnesium, aluminium, zinc, and even copper can act as donors with sufficiently strong acceptors, such as tetracyanoethylene, for example [52].

TABLE 3. Ionisation potentials of some donors.

Donor	Ionisation potential, eV	References
Benzene	9.24	47
Naphthalene	8.12	47
Anthracene	7.4	48
Naphthacene	7.0	48
Toluene	8.82	47
1,3,5-Trimethylbenzene	8.39	47
1,2,4,5-Tetramethylbenzene	8.3	47
Hexamethylbenzene	7.85	48
Aniline	7.70	47
NN-Dimethylaniline	7.3	48
NNN'N'-Tetramethyl-*p*-phenylenediamine	6.5	48
Pyridine	9.23	47
Trimethylamine	7.82	47
Potassium	4.34	49
Sodium	5.14	49
Copper	7.72	49

Aromatic structures which cannot exist as neutral molecules, of the type



etc., should show a very strong tendency to form charge-transfer complexes [53].

III. ACCEPTORS

Many inorganic substances are known as acceptors in charge-transfer complexes, among them being notably chlorine [54], bromine [55-58], iodine [55,57-67], hydrogen halides [41,68-71], aluminium chloride [72,73], ferric chloride [46,74,75], and the chlorides of antimony [74,76,77], tin [74,76], and titanium [78,79]. Other compounds which must be mentioned are sulphur dioxide [80-82], sulphuryl chloride [82,83], and water [84].

Among organic compounds used are anhydrides of di- and poly-carboxylic acids, *e.g.* maleic [20,83,85-87], phthalic [83], and mellitic [88] anhydrides, as well as acid chlorides such as oxalyl [32,83], fumaroyl [83], and phthaloyl [83] chlorides.

TABLE 4. Electron affinity of some acceptors [128].

Acceptor	Electron affinity, eV
Maleic anhydride	0.5
Trinitrobenzene	0.6
Iodine	0.8
Chloranil	1.35
Tetracyanoethylene	1.6

Halogenated derivatives have also been investigated, for example, chloroform [89,90], carbon tetrachloride and tetrabromide [91-93], and chloromaleic [85] and tetrachlorophthalic [94,95] anhydrides.

Among nitro-derivatives we must mention tetranitromethane [20,38], nitrobenzene and dinitrobenzenes [96-100], 1,3,5-trinitrobenzene [15,19,26,101-108], picric acid [101,103,108-109], picryl chloride [102,110-112], and styphnic acid [76]; among nitriles are 1,3,5-tricyanobenzene [96], tetracyanoethylene [42,52,113-115], and 7,7,8,8-tetracyanoquinodimethane [116-118].

An important group of acceptors are the quinones: *o*-[119] and *p*-benzoquinones [23,103,111,112,119-123] and their derivatives – chloranil [20,23,31,111,112,119,124], bromanil [23,113,119], and iodanil [113,119], – and also naphthaquinones [23] and substituted anthraquinone and phenanthraquinone [125].

Substituents in the benzene ring affect the properties of acceptors, as in the case of donors. In substituted quinones the tendency to complex formation varies [126] in the following sequence: chloroquinone > benzoquinone > > toluquinone > xyloquinone > duroquinone. Among the 4-substituted 1,3-dinitrobenzenes the acceptor strength decreases in the order [127] Cl > Br > OH > H > CH_3 > NH_2. The inductive effect of the substituent is quite evident in all cases.

The approximate electron affinities of several acceptors are given in Table 4.

IV. METHODS OF INVESTIGATING CHARGE-TRANSFER COMPLEXES AND SOME OF THEIR PROPERTIES

The following methods are generally used both to establish the actual fact of complex formation and to study the properties of the resulting complex: investigation of solubility in and distribution between various solvents, measurement of vapour pressure, plotting of melting point–composition curves for mixtures of donor and acceptor, spectrophotometric measurements, determination of dipole moments, viscosity measurements, radiofrequency spectroscopy, investigation of electrical conductivity both of solutions of the complexes and of the solid complexes themselves. We shall consider briefly optical methods, which are most often employed, and which have so far been the most important in research on charge-transfer complexes.

1. Optical Studies on Charge-Transfer Complexes

Spectrophotometry is an extremely convenient method for ascertaining the formation of a complex and also for determining its composition and the equilibrium constant of the reaction

$$D + A \rightleftharpoons \text{charge-transfer complex.}$$

The displacement of electron density accompanying the formation of such a complex corresponds to a considerable bathochromic change in the absorption and also to an increase in its intensity. Measurements of the shift in the absorption maxima in the electronic spectra and also of the optical density of solutions of the complexes are widely used for the investigation of such systems, notably of the picrates[129,130], complexes of stilbene and diphenylpolyenes with trinitrobenzene[44], complexes of aromatic nitro-compounds with hydrocarbons and amines[131-136], complexes of maleic anhydride[124,137] and of tetracyanoethylene[42]. Izmail'skii and his coworkers have made an extensive investigation of the optical properties of aromatic systems containing donor and acceptor groups, both insulated from one another and linked together by a system of conjugated bonds[138-146]. It is quite obvious that charge-transfer complexes are formed in these cases. The formation of such complexes is very probable in the so-called aggregation of dyes[147,148], and also in several cases of solvatochromism[149-154].

Infra-red spectroscopy has been employed to investigate the donor–acceptor interaction of aromatic compounds with halogens[151-157] and hydrogen halides[158-160], of pyridine with iodine[106], and also of aniline[161], dimethylaniline, and acenaphthene[162] with aromatic nitro-compounds.

The infra-red spectra, Raman spectra, and also X-ray structure analysis indicate that the formation of a charge-transfer complex involves some weakening of the interatomic bonds both in the donor molecule and in the acceptor molecule[3].

The luminescence spectra of such complexes show[163-165] that the resulting D....A bond affects the character of the luminescence by the donor.

2. Investigations of the Magnetic Properties of Charge-Transfer Complexes

Determinations of magnetic susceptibility by the static method have shown that the diamagnetism of many complexes is even greater than the additive value[105,122,166].

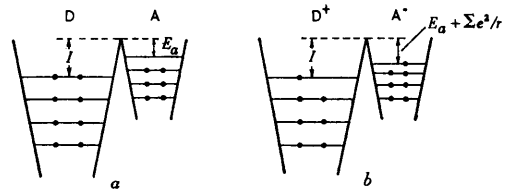


Fig.1.

The increase in the diamagnetism of the charge-transfer complexes with trinitrobenzene corresponds to the fall in the ionisation potential of the donor in the series naphthalene–phenanthrene–anthracene[96]. This fact is probably connected with the increasing delocalisation of the electrons in complexes of non-ionic type. For such charge-transfer complexes, $a \gg b$ in Eqn. (1).

With complexes of predominantly ionic type, D^+A^-, the energy required for excitation to the triplet level should be small, and the charge-transfer complex may be paramagnetic even at room temperature. A sharp fall in diamagnetism has been noted in the formation of charge-transfer complexes of bromine and iodine with polycyclic aromatic hydrocarbons.

The presence of temperature-independent paramagnetism has been established in such charge-transfer complexes by the method of electron spin resonance. The calculations showed that, for the complex of violanthrene with iodine, the faster contribution of the diradical-ion state is ~ 14%.[167] The presence of paramagnetism has been shown in this way in the complexes of *NNN'N'*-tetramethyl-*p*-phenylenediamine with *p*-benzoquinone and its tetrahalogeno-derivatives and also with tetrabromo-*o*-benzoquinone[119,168]. Paramagnetism had been detected previously[169] in the complex of *NN*-dimethylaniline with chloranil. According to Bijl *et al.*[119], the complex of *NNN'N'*-tetramethyl-*p*-phenylenediamine with chloranil contains 0.4% of the diradical form, while that with tetrabromo-*o*-benzoquinone, which has a considerably higher redox potential, contained 80%. Over the temperature range 6°–300°K the paramagnetism of the resulting complexes satisfies the Curie law, which suggests that the diradical state is in this case, as in several others[161], not an excited but the ground state.

More recent work[170] has shown that the contribution of the diradical-ion form in the charge-transfer complexes of dimethylaniline and *NNN'N'*-tetramethyl-*p*-phenylenediamine with chloranil, bromanil, and iodanil reaches 17%. However, the integral intensity of the electron spin resonance signal of these complexes, and also its form and width, change when the complexes are stored either in air or in an inert atmosphere. These changes are supposed to be due to the decomposition and reformation of the complexes during storage. A change with time in the concentration of the paramagnetic species, and in the colour of the charge-transfer complexes, has also been noted in other work[171]. Furthermore, it has been found that the form of the electron spin resonance signals depends on the mode of preparation and isolation of the specimens of the complex investigated.

The various states of a charge-transfer complex can be represented diagrammatically as in Figs. 1 and 2, in which D represents the donor, A the acceptor, *I* the ionisation

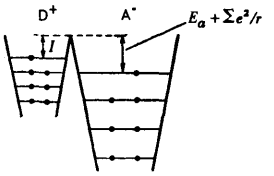


Fig.2.

potential, E_a the electron affinity, and $\Sigma e^2/r$ the coulombic interaction forces. In cases involving unpaired electrons the contribution of the diradical-ion state may actually be less than 100% owing to partial overlapping of the wave functions of D^+ and A^-.

Since in principle the two components of a charge-transfer complex in the radical-ion state, *i.e.* D^+ and A^-, have different g-factors, the spectrum may be expected to show two separate peaks, corresponding to each of the components. This has been found with the complex of p-phenylenediamine with chloranil, and thus the relative weakness of the electronic interaction between the components has been demonstrated[171]. For different ratios of the coefficients a and b in Eqn. (1), it is possible to have charge-transfer complexes which are diamagnetic between wide temperature limits (when $a \gg b$), complexes which can be relatively easily excited to a paramagnetic diradical-ion state (when $a \leqslant b$), and finally those in which the diradical-ion form represents the ground state. Unfortunately, the papers which have been quoted do not always give the precise conditions under which the complexes have been prepared, which makes it difficult to compare the results of the investigations.

Study of the temperature dependence of the electron spin resonance spectra of the ionic complexes of tetracyanoquinodimethane[118] led to the conclusion that their singlet ground state is so easily depopulated thermally that even at -100° about 4% of the substance has passed into the triplet state.

The paramagnetism of several polycyclic aromatic hydrocarbons, as also the form of the electron spin resonance signals which they give, is greatly dependent on the presence or absence of oxygen, and is presumably connected with the formation of a charge-transfer complex between the O_2 molecule as acceptor and the hydrocarbon molecule as donor[172]. The close link between the paramagnetism and the electrical conductivity of such systems suggests the presence of a common mechanism governing both phenomena[173].

In some cases, in particular with the charge-transfer complexes of pyrene and perylene with iodine, the intensity of the electron spin resonance signal shows an exponential dependence on temperature (over the range 77°–350°K), which is very close to that of the conductivity[69]. This suggests that in these cases the unpaired electrons are also the conduction electrons.

3. Investigations of the Electrical Conductivity of Charge-Transfer Complexes

This part of the review deals solely with the electrical conductivity of charge-transfer complexes in the solid state. It has already been suggested[174] that the magnetic, electrophysical, and catalytic properties of such highly ordered structures as nucleic acids, nucleoproteins, and also polymers containing conjugated bonds may be linked with the formation of charge-transfer complexes within these structures. It is assumed that the ordered group in the molecules (or macromolecules), the latter being mostly arranged in piles, *i.e.* packed one on the other, can transmit electrons thus producing a long-range oxidation–reduction process[175]. With charge-transfer complexes an alternating arrangement of D and A is envisaged.

The following mechanism has recently been suggested[176] for conduction in charge-transfer complexes. In the first stage one of the π electrons, having acquired the energy E, passes from a higher filled electronic level to the lowest of the unfilled levels. The ease of excitation determines the "activation energy" of conduction. In the second stage the unpaired electron passes through the intermolecular potential barrier by a tunnel effect. Decrease in intermolecular distances greatly facilitates this process. The ease of transfer determines the mobility of the charge carrier and the magnitude of the preexponential factor σ_0 in Eqn. (4).

The conductivity of polycyclic aromatic hydrocarbons with fused rings is considerably higher than that in saturated systems, and it satisfies the equation

$$\sigma = \sigma_0 \exp\left(-\frac{E}{kT}\right). \qquad (4)$$

The "activation" energy of conduction E varies linearly with the energy of excitation to the triplet state[177] and falls as rings of quinonoid structure accumulate in the molecule[45]. These relations are shown most clearly in the naturally ordered arrangement of crystals of aromatic hydrocarbons which is obtained on evaporation of the solvent from a solution[45]. It is known that in crystals coplanar molecules of polycyclic hydrocarbons are arranged mainly on top of one another with some lateral displacement[28]. All this cannot but suggest that in these cases a charge-transfer "self-complex" is formed, which results in a relatively high conductivity in these systems. It has even been suggested that ionic conduction may occur in aromatic hydrocarbons, with the formation of Ar^+ and Ar^- ions[178]. Self-complexes of aromatic systems have been often discussed[9,21,22]. The close connection between the activation energy of conduction and the triplet excitation energy indicates that either an excited or (where possible) a ground triplet state is probably responsible for conduction. Polycyclic aromatic systems containing quinonoid rings[45] are not distinguished by an evenness of electron density but contain local active centres[179], which are the most probable regions of charge transfer. Many conductivity measurements on polycyclic aromatic hydrocarbons and related systems have been published and intercompared[180–183]. The values given for the activation energy of conduction [E in Eqn. (4)] vary between 2.0 and 0.2 eV. The excitation energies are about the same. The conduction is of p-type[184–186].

Semiconductor properties have been confirmed in such coplanar aromatic systems as the phthalocyanines[187] and polyphthalocyanines[188], and also chlorophylls contained in the layered particles of chloroplasts[189]. Research on energy transfer processes in aromatic hydrocarbons[190], graphite (which is related to the former in structure)[191], and also in charge-transfer complexes[192] is being actively pursued.

The conduction of organic dyes and their photoelectric properties have recently been reviewed[193], the author paying special attention to the possibility of electron transfer by pairs of oppositely charged ions.

Table 5 gives published data on the electrical resistivity of specially synthesised charge-transfer complexes. The striking variation in the results is partly due to incidental factors. Firstly it may be doubted whether the results ascribed to complexes of *p*-phenylenediamine and diaminopyrenes with chloranil, bromanil, and iodanil, do actually relate to charge-transfer complexes. Amines are known to react readily with halogenated benzoquinones. In particular, diamines yield with such derivatives polymers which both possess increased conductivity and give electron spin resonance spectra[204]. Unfortunately, it was on these complexes that quantitative investigations of the Seebeck effect were made[200].

TABLE 5. Electrical resistivity of charge-transfer complexes.

Acceptor	Donor	Molar ratio A : D	Resistivity at 300 °K, ohm cm	Temp. range, °K	E^*, eV	References
Br_2	perylene	2,2 : 1	7,8	103—253	0.065	194—196
	pyranthrene	1,7 : 1	220	103—253	0.10	194—196
	violanthrene	2,3 : 1	66	103—253	0.10	194—196
	3,4-benzoquinoline	1,19 : 1	10^7		0.45	197
	2,3-benzoquinoline	4,9 : 1	$10^{15,4}$		2.09	197
I_2	pyrene	2 : 1	75		0.11;0.068	66, 198
	perylene	3 : 2	8		0.015; 0.019	66, 198
	violanthrene	2 : 1	45	103—253	0.07	194—196
	violanthrene	2 : 1	45	283—388	0.07	194—196
	perylene	—	10			199
	coronene	—	10^9			199
	acridine	—	$10^{1\,2}$			199
ICl	acridine	—	10^{12}			199
1,3,5--Trinitrobenzene	coronene	—	10^{13}			199
	NN-dimethylaniline	—	10^8,10^{11}			199
Picric acid	coronene	—	10^{12}			199
Trinitrofluorenone	coronene	—	10^{12}			199
Chloranil	pyrene	—	$10^{1\,1}$			199
	perylene	—	10^8			199
	hexamethylbenzene	—	10^1			199
	NN-dimethylaniline	1-1	$8\cdot10^9$		0.23	176
	p-phenylenediamine	—	10^7			119
	p-phenylenediamine	—	10^6	263—293	0.25	119
	p-phenylenediamine	3 : 5	10^7	250—330	0.57	200
	NN-dimethylaniline	—	10^9,10^{10}		0.22	169, 199
	naphthylene-1,5-diamine	—	10^{11}			199
	naphthylene-1,8-diamine	—	10^{11}			199
	p-aminodiphenylamine	—	10^{10}			199
	NNN'N'-tetramethyl-*p*-phenylenediamine	—	10^9			199
	ditto	1 : 1	$2\cdot10^4$		0.26	176
	3,8-diaminopyrene	—	10^4			199
	3,10-diaminopyrene	—	10^8			199
	p-anisidine	—	10^{11}			199
	acenaphthene	1 : 1	10^{15}		2.9	203
Bromanil	*NN*-dimethylaniline	—	10^9		0.22	169, 199
	ditto	1 : 1	$1.5\cdot10^9$		0.22	176
	p-phenylenediamine		10^{10}			199
	NNN'N'-tetramethyl-*p*-phenylenediamine	1 : 1	$1.3\cdot10^8$		0.28	176
	3,8-diaminopyrene		10^3			199
Iodanil	*NN*-dimethylaniline	—	10^8		0.22	169, 199
	ditto	1 : 1	$1.7\cdot10^9$		0.21	176
	p-phenylenediamine		10^{11}			199
	NNN'N'-tetramethyl-*p*-phenylenediamene	1 : 1	$1.5\cdot10^6$		0.29	176
	3,8-diaminopyrene	—	10^6			199
p-Benzoquinone	quinol	—	10^{11}			199
Tetracyanoethylene	pyrene	—	10^9,10^{10}			199
	perylene	—	10^8,10^{11}			199

TABLE 5 (contd.)

Acceptor	Donor	Molar ratio A : D	Resistivity at 300 °K, ohm cm	Temp. range, °K	E^*, eV	References
Tetracyanoethylene	hexamethylbenzene	—	10^{11}			199
	dimethoxybenzene	—	10^{11}			199
	naphthalene	1 : 1	$3.2\cdot10^{15}$		1.24	115
	phenanthrene	1 : 1	$2.2\cdot10^{12}$		0.76	115
	pyrene	1 : 1	$4.5\cdot10^{15}$		0.85	115
	perylene	1 : 1	$2.4\cdot10^{12}$		0.72	115
	anthanthrene	1 : 1	$1.1\cdot10^{10}$		0.57	115
	violanthrene	1 : 1	$5.2\cdot10^8$		0.18	115
	pentamethylbenzene	1 : 1	$4.4\cdot10^{12}$		0.56	115
	hexamethylbenzene	1 : 1	$4.1\cdot10^{13}$		0.58	115
	acenaphthene	1 : 1	$5.3\cdot10^{12}$		1.02	115
	azulene	1 : 1	$4.7\cdot10^{10}$		0.38	115
Tetracyanoquinodimethane	quinolinium	2 : 1	10^{-2}		<0.01	117
	trimethylammonium	2 : 1	0,25		0.14	117
	K	2 : 2	$5\cdot10^3$		0.34	117
Anthracene	Li	1 : 1.16	10^{11}	300—350	1.36	201
	Na	1 : 1.08	10^9	300—350	1.20	201, 202
	K	1 : 1.18	10^{11}	300—350	1.13	201
3,4--Benzoquinoline	Na	1 : 1.11	10^{21}		2.34	202
		1 : 1.49	10^{10}		0.35	202

* From the equation $\rho = \rho_0 \exp(E/kT)$.

Secondly, some of the complexes[176,199] were obtained by crystallisation from solution, while several others were obtained directly by interaction between the components. Such a difference in methods of preparation can lead to marked differences in conductivity.

In spite, however, of these reservations, it is clear that the charge-transfer complexes of aromatic hydrocarbons with halogens have outstandingly high conductivity. This may be linked with their structure, *i.e.* with the alternation of hydrocarbon planes, both atoms of the halogen molecule being located between the planes on the same axis of symmetry as the latter[33,34].

Complexes of chloranil, bromanil, and iodanil with *NN*-dimethylaniline and with *NNN'N'*-tetramethyl-*p*-phenylenediamine[205], which are also distinguished by relatively high conductivity, have a similar structure, with alternating donor and acceptor molecules, of the type ADAD... In the purely organic complexes steric and other factors may prevent donor and acceptor from coming sufficiently close together, but the highest conductivity is in fact shown by ionic organic complexes of 7,7,8,8-tetracyanoquinodimethane. Discussion continues on the relation between the crystal structure of charge-transfer complexes and their conductivity.

Existing data do not permit the conductivity parameters to be directly linked with the ionisation potential of the donor. One cause of this is undoubtedly that the conductivity measurements were usually made on tablets pressed out of microcrystalline preparations. With this mode of preparation of the specimens, the measurements cannot reveal the anisotropy of conductivity which is undoubtedly characteristic of the charge-transfer complexes, and yield a mean result which is too low.

The conductivity of tetracyanoquinodimethane complexes and of graphite and its lamellar compounds, in particular those with potassium, $(C_8K)_n$, and with bromine, $(C_8Br)_m$,

exhibits a marked anisotropy (it can differ by a factor of 10^4); there is also an increase in the conductivity of graphite when either a donor or an acceptor is introduced into it[208]. Graphite itself, in which the ionisation potential, 4.39 eV, is equal to the electron affinity, can act either an an acceptor or as a donor, depending on the properties of the second component. The Hall effect could not be observed with any of the charge-transfer complexes: *i.e.* the mobility of the current carriers is low. Measurements of the thermoelectric power have been made on the tetracyanoquinodimethane complexes[117]. The few data available on the magnitude of the preexponential factor σ_0 and the activation energy of conduction E do not, in most cases, permit the steepness of the conductivity–temperature curve for charge-transfer complexes to be assessed. Now, however, it is already clear that the conductivity of such complexes is always greater than that of their organic components, and also that charge-transfer complexes can be obtained having either low or high values of σ_0 and E. These two important facts open up wide theoretical possibilities for the utilisation of such complexes as organic semiconductors having various specified properties. In the solid state charge-transfer complexes are, of course, polymeric complexes. If the hypothesis[174] should prove correct that the conductivity and the magnetic properties of polymers having conjugated bonds, many of which have been described[182,207-210], result from the formation of charge-transfer complexes, such an approach will enable us to speed up the production not only of synthetic polymeric semiconductors but also of synthetic polymeric catalysts[211-213], including those which simulate biological catalytic systems[214].

Several charge-transfer complexes[169], in particular those of *NN*-dimethylaniline with chloranil, catalyse the ortho–para conversion of hydrogen. Sometimes, however, this catalytic activity did not appear. Its presence or absence is probably associated with differences in the method of preparing the complexes[176].

The synthesis of polymeric donor and polymeric acceptor systems should be of considerable interest from the point of view of conductivity and magnetic and catalytic properties. The charge-transfer complexes formed by such systems should be characterised by stability, high conductivity, and stable paramagnetism. The effects may be expected to be especially marked when both donor and acceptor are polymers having an extensive system of conjugated bonds.

V. CHARGE-TRANSFER COMPLEXES AND THE MECHANISM OF CHEMICAL REACTIONS

Starting from the idea that the first stage in many organic reactions is a sudden shift in electron density from one reactant to another, whereas movement of the nuclei to new fixed positions corresponding to the reaction products is a secondary process, we readily conclude that the first reaction complex is actually a charge-transfer complex. Consideration of the effect of the polarity and polarisability of the reactants on the reaction mechanism leads to the same conclusion[215,216].

Table 6 shows clearly that the rate of halogenation of various aromatic hydrocarbons[217] and the stability of the charge-transfer complexes formed by these hydrocarbons with such acceptors as Br_2 [218] and HF [41] can be correlated. In these cases the tendency of the hydrocarbon to form a charge-transfer complex and the stability of the complex are probably the factors governing the rate of halogenation. Such complexes of aromatic hydrocarbons with bromine are unstable, forming brominated derivatives on storage.

TABLE 6. Relative stabilities of charge-transfer complexes and rates of halogenation of aromatic hydrocarbons (benzene = 1).

Hydrocarbon	Stability of charge-transfer complex with		Rate of halogenation
	Br_2	HF	
Benzene	1.00	1.00	1
Toluene	1.43	7	$3 \cdot 10^2$
o-Xylene	2.4	12.2	$4 \cdot 10^3$
m-Xylene	2.08	290	$4 \cdot 10^5$
p-Xylene	2.16	12.2	$2 \cdot 10^3$
1,2,4-Trimethylbenzene		700	$6 \cdot 10^5$
1,2,3-Trimethylbenzene		770	$8 \cdot 10^5$
1,3,5-Trimethylbenzene		145000	$1.6 \cdot 10^8$
1,2,4,5-Tetramethylbenzene		1560	$3 \cdot 10^6$
1,2,3,4-Tetramethylbenzene		4450	$4 \cdot 10^6$
1,2,3,5-Tetramethylbenzene		178000	$5 \cdot 10^8$
Pentamethylbenzene		320000	$7 \cdot 10^8$

The formation of charge-transfer complexes has also been suggested[85] in reactions of diene synthesis between maleic anhydride and other acceptors — between dienophiles on the one hand and donors (dienes) on the other.

The view that charge-transfer complexes are important intermediates in many reactions has been used to systematise a large number of facts[219]. The formation of unstable charge-transfer complexes in chemical reactions could be confirmed experimentally in actual cases by investigation of the reaction mechanism using such modern physical methods as conductimetric measurements and radiofrequency spectroscopy.

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STRUCTURE AND REACTIVITY OF CYCLOPROPANE AND ITS DERIVATIVES

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I. INTRODUCTION

In certain physical and chemical properties cyclopropane and its derivatives differ markedly from alicyclic compounds with a larger number of carbon atoms in the ring and are more similar to alkenes. The anomalous behaviour of compounds containing a three-membered carbon ring, including their typical unsaturation, has for a long time been interpreted solely by the assumption that considerable strain, in the original Baeyer sense, exists in this ring.

The criterion of unsaturation in organic chemistry is the capacity of a compound to take part in addition reactions. This is certainly characteristic of multiple bonds. The three-membered carbon ring also exhibits unsaturation towards reagents which unite with alkenes. It should, however, be stressed that unsaturation in the cyclopropane series is less pronounced than in alkenes.

The analogy between the three-membered ring and the double bond is clearly brought out in cases where this ring is adjacent to a double bond. In their properties such systems are similar to conjugated ones of the π,π-type rather than to σ,π-systems.

With the accumulation of the experimental evidence for the unsaturation of the three-membered ring it became obvious that the explanation of this property does not reside in strain but in the peculiar electronic structure of cyclopropane. Since 1945, a great deal of work has been devoted to this subject.

There is a series of reviews dealing with the synthesis and properties of cyclopropane derivatives[1-3]. In the present review an effort has been made to present the current views on the structure of cyclopropane and the most interesting work on the reactivity of these compounds, and also to elucidate the reactivity and certain other properties of systems in which the three-membered ring is adjacent to unsaturated groups. Unsaturation, and especially the ability of the three-membered ring to conjugate, can only by understood in terms of the modern concept of the structure of cyclopropane, and are inexplicable in terms of the classical theory.

II. STRUCTURE OF CYCLOPROPANE

Before discussing work on the cyclopropane structure the following well-known facts may usefully be reiterated.

Pauling[4] introduced the theory that bonds are formed in the direction of the greatest concentration of electronic clouds. This allows maximum overlapping of electron clouds derived from two atoms, *i.e.* maximum overlap of the orbitals of the two electrons forming the bond. The electron-pair (covalent) bond is formed through the interaction of two electrons of opposite spins derived from two atoms, forming one stable orbital around them. The valence shell of carbon atom consists of four such stable orbitals, one 2*s* orbital and three 2*p* orbitals. As a result, carbon can form four covalent bonds.

The *s* orbital (Fig. 1) is spherically symmetrical and can form a bond in any direction.

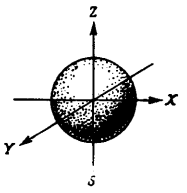


Fig.1.

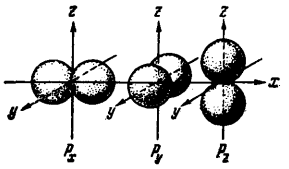


Fig.2.

The three 2*p* orbitals (Fig. 2) are directed along mutually perpendicular axes and form bonds in these directions. In view of the directional property of the *p* orbital, if only its angular distribution is considered, its magnitude will be $\sqrt{3}$ times that of an *s* orbital. The value of the angular contribution to a bonding orbital is termed its "strength"; and is unity for an *s* orbital, 1.732 for a *p* orbital. In other words *p* orbitals can overlap more strongly with the orbitals of another atom than *s* orbitals of the same shell, and bonds formed from *p* orbitals are stronger than those from *s* orbitals†.

However, these orbitals are not employed as such in bonds between two atoms. The orbital used for bonding is formed by linear combination of *s* and *p* orbitals of definite numerical coefficients, and is twice as strong as *s* or *p* orbitals taken separately; it is called a hybrid orbital (Fig. 3).

Strongly concentrated in the direction of the bond, the hybrid orbital is well-adapted for overlapping with the orbital of another atom, and can therefore produce a stronger bond.

In saturated compounds, a carbon atom forms four such hybrid orbitals, mutually inclined at 109°28', that is, directed to the corners of a regular tetrahedron. Such hybridisation, yielding maximum bond energy, is termed sp^3 hybridisation.

In ethylene, carbon atoms are in a state of sp^2 hybridisation. Here, three hybrid orbitals lie in a plane at angles of 120°, and a fourth orbital, which is a pure *p* orbital, has its symmetry axis perpendicular to that plane. This type of hybridisation is termed trigonal.

† This is right if the radial functions of *s* and *p* orbitals are assumed to be equal. Strictly speaking this is not the case in real atoms, and the Pauling theory should therefore be regarded as an approximation.

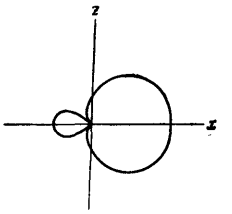


Fig.3.

Cyclopropane, formally a saturated compound, should belong to the type of compound in which the carbon atom is in a state of sp^3 hybridisation. The peculiarity of its structure, however, lies in the fact that the angles between carbon atoms are distorted and are not tetrahedral, which is in contradiction with the strict orientation of sp^3 hybrid orbitals in saturated open-chain carbon compounds. For this reason the structure of cyclopropane could not be interpreted by the Pauling theory of directed bonds and demanded further refinement of that theory.

Duffey was one of the first to study a suitable model for a non-tetrahedral carbon atom[5]. He attempted to calculate the external valence angles in some alicyclic compounds bearing in mind that the internal valency angles are predetermined by the geometry of the molecule. He obtained the value 111°1' for the H–C–H angles in cyclopentane, and 180° for those in cyclobutane and cyclopropane. In the author's own words, these values are only rough approximations. Kilpatrick and Spitzer[6] continued along the same lines of investigation and calculated not only the values of H–C–H angles for several values of C–C–C angles, but also bond strengths in corresponding compounds. They assumed that in compounds with distorted valence angles, the so-called "strained" compounds, the maxima of hybrid orbitals do not necessarily coincide with the direction of the bonds, as postulated by Pauling. Their results are collected in Table 1.

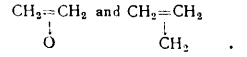
According to Kilpatrick and Spitzer the bond strength is proportional to the value of the orbital in the desired direction, whether or not the maximum of the orbital lies in this direction. When the maximum coincides with the direction of the bond, the bond strength is at its highest (angle 109°28'). In cyclopropane the C–C bond strength is small and differs from that of the C–H bond.

TABLE 1.

C–C bond angle	C–C bond strength	C–H bond angle	C–H bond strength
0°	1.414	126°52'	1.982
60°	1.887	121°58'	1.989
90°	1.984	115°23'	1.995
108°	2.000	109°58'	2.000
109°28'	2.000	109°28'	2.000
120°	1.996	105°50'	1.998
180°	1.932	90°	1.732

This work was very important for the further study of the cyclopropane structure. The applicability of *sp* orbital hybridisation to cyclopropane, with its requirements for strict orientation of four atomic orbitals and location of attached groups along the lines of maximum electron density, was questioned for the first time.

To account for the unsaturation of the three-membered rings Walsh[7] suggested the so-called unsymmetrical π complex formulae for ethylene oxide and cyclopropane, instead of the conventional cyclic ones:

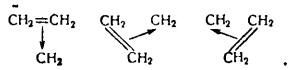


In his opinion two carbon atoms in cyclopropane are in trigonal, and the third in tetrahedral state. He imagines cyclopropane as having a disturbed ethylene structure, where two electrons of the ethylenic bond form bonds with three carbon atoms.

Robinson[8] strongly criticised Walsh's formula for cyclopropane, mainly because it did not reflect the symmetry of the cyclopropane molecule, which is that of an equilateral triangle. Robinson preferred the conventional formula for cyclopropane, and interpreted its peculiar properties by means of quantum mechanical treatment of the linkage of atoms and electron distribution in the molecule.

In his criticism of Walsh's work, McDowell[9] considers that if the double bonds in structures suggested for cyclopropane and ethylene oxide do in fact have the properties ascribed to those bonds, it should be reflected in the Raman spectra of these compounds. However, absorption in the 1600 cm^{-1} region, characteristic of the double bond vibration in ethylene, is absent from both cyclopropane and ethylene oxide.

In reply to these criticisms by McDowell and Robinson, Walsh published another paper[10], in which he contends that the symmetry of the cyclopropane molecule is by no means destroyed if three equivalent resonance formulae are considered:



However, when these are superimposed they are still not equivalent to the classical cyclic formula, since they are based on trigonal, not tetrahedral carbon atoms. As for McDowell's argument, Walsh considers that the ethylene structure is so greatly upset in cyclopropane that its spectra cannot be expected to display frequencies characteristic of the double bond in ethylene. Later on Walsh[11] renounced his formulae for ethylene oxide and cyclopropane, but the basic idea in his work, that the hybridisation of carbon atoms in these compounds resembled that in ethylene, was further developed in his subsequent investigations.

In his second paper Robinson[12] sharply criticised Walsh's concept: in his opinion, the carbon atoms in cyclopropane are not trigonal but tetrahedral, the tetrahedral angles being distorted. A number of publications at that time, mainly reporting experimental data, made possible a more precise representation of the structure of a three-membered ring. Thus, it followed from spectrographic data that cyclopropane molecule is a fully symmetrical planar ring, with the three carbon atoms at the vertices of an equilateral triangle, and the CH_2 planes bisecting the corresponding C–C–C angle in the ring[13].

Assuming that the cyclopropane molecules is built in the form of an equilateral triangle, and that H atoms are located at tetrahedral angles outside the ring plane, Saksena[14] calculated the stretching force constant of the C–C bond as 4.04×10^5 dynes cm^{-1} (a value indicating a weakening of the bond compared with that in ethane), and the stretching force constant of the C–H bond as 4.91×10^5 dynes cm^{-1}, similar to that in ethylene. By cruder methods, Bonner[15] obtained the same value for the C–C stretching force constant. Basing his calculation on infra-red and Raman spectra, Linnett[16] obtained the value 5.05×10^5 dynes cm^{-1} for the C–H stretching force constant in cyclopropane. The stretching force constant of the C–H bond in ethylene[17] is 5.1×10^5 dynes cm^{-1}, and that of the methylene group in paraffins[18] is 4.6×10^5 dynes cm^{-1}. The force constant data thus indicate a similarity between the C–H bonds of cyclopropane and those of ethylene. It was therefore assumed that the H–C–H angle is approximately trigonal, namely 120°, as in alkenes.

These assumptions were confirmed in 1946 by the studies of Bastiansen and Hassel[19] on the electron diffraction of the cyclopropane molecule. The significance of their work is considerable, for they were the first to establish that the H–C–H angle in cyclopropane is 118.2° ± 2°and thus larger than tetrahedral; it is indeed closer to the trigonal (120°) than to the tetrahedral angle (109°28'). These authors also determined the distance between the carbon atoms in cyclopropane as 1.54 Å, and the H–C–C angle as 116.4°.

Somewhat later, Bastiansen and Hassel's data for H–C–H angles in cyclopropane were confirmed by Günthard *et al.*[20], who calculated this angle from infra-red spectra, and by Goldsmith *et al.*[21], who obtained it from the dipole moments of cyclopropane derivatives.

Bastiansen and Hassel's value for the distance between carbon atoms in cyclopropane (1.54 Å) corresponds to that found for alkanes. For this reason Skinner[22] considered that there was very little similarity between the bonds in cyclopropane and double bonds. Nonetheless, thermochemical data indicate a marked weakening of C–C bonds of cyclopropane as compared with diamond and ethane.

At the same period Sugden[23] attempted to apply the method of non-localised molecular orbitals to cyclopropane. He considered CH_2 orbitals as formed by a linear combination of H 1*s* and C 2*s* and $2p_{x,y,z}$ orbitals, and used these for constructing $(CH_2)_3$ orbitals.

The most conclusive evidence that the valence state of carbon atoms with respect to hydrogen in cyclopropane is nearer to sp^2, as it is in ethylene, was obtained from the study of the dipole moment of cyclopropyl chloride. Rogers and Roberts[24] showed that its dipole moment (1.75 *D*) is 0.3 *D* below that for isopropyl chloride and cyclopentyl chloride. The low dipole moment of cyclopropyl chloride may be interpreted by assuming that the C atom linked with the chlorine is trigonal. Such an atom has a higher electronegativity in its *p* valency than the tetrahedral one in its sp^3 hybridisation. For that reason vinyl chloride and phenyl chloride have lower dipole moments than the corresponding alkane analogues.

At this time, Murray and Stevenson[25] synthesised spiropentane. Donohue *et al.*[26], by electron diffraction, confirmed the presence of two three-membered, mutually perpendicular rings in the spiropentane molecule, with H–C–H angles of 120° ± 8°.

New data obtained in the above investigations became the basis for considerable generalisations. Therefore it was quite proper that two fundamental studies devoted to the

cyclopropane structure should appear in 1949 by Walsh[27] and by Coulson and Moffitt[28].

Walsh's paper is the further development of his own ideas on cyclopropane structure, discussed above, based on the assumption that the valence state or the hybridisation of carbon atoms in cyclopropane resembles the hybridisation of carbon in ethylene. He considers that the electronic structure of cyclopropane is based on the union of three ethylenic CH_2 bonds. As in ethylene, each carbon atom forms three hybrid sp^2 valencies, which are in one plane and make an angle of 120° with one another, and one pure p valency, having its symmetry axis normal to this plane, as in Fig. 4.

Fig. 5 shows Walsh's representation of the combination of three CH_2 groups in cyclopropane: the molecular orbitals of the hypothetical cyclopropane ring are formed by the mutual overlap of $2p$ orbitals whose symmetry axes lie in the plane of the ring, as well as by the overlap of hybrid sp^2 orbitals, whose symmetry axes also lie in the ring plane. In Fig. 5 the planes AB, CB, and DB of the C–H bonds lie at 90° to the plane of the diagram. According to Walsh the electron distribution in that system is the following: if it assumed that the CH orbitals are localised, but the molecular orbitals, formed by overlapping of the corresponding atomic orbitals (ψ_1, ψ_2, ψ_3) of each carbon in the ring, are non-localised, then according to Mulliken[29] molecular orbitals are given by:

$$\frac{1}{\sqrt{3}}(\psi_1 + \psi_2 + \psi_3), \quad (1)$$

$$\frac{1}{\sqrt{2}}(\psi_1 - \psi_2), \quad (2)$$

$$\frac{1}{\sqrt{6}}(\psi_1 + \psi_2 - 2\psi_3), \quad (3)$$

where (2) and (3) are degenerate orbitals.

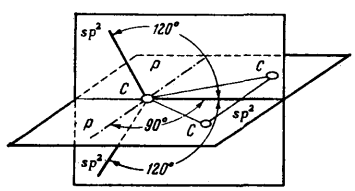


Fig. 4.

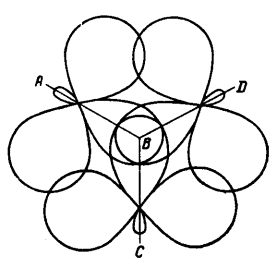


Fig. 5.

Fig. 5 shows two types of overlapping of atomic orbitals. For each type there are three possible molecular orbitals, (1), (2), and (3). In the first type ψ_1, ψ_2, and ψ_3 are hybrid sp^2 orbitals, and in the second they are $2p$ orbitals.

In the type consisting of sp^2 orbitals, (1) will give rise to bonding between carbon nuclei (the bonding orbital), while (2) and (3) are anti-bonding. Of the $2p$ orbitals lying in the plane of the ring, the orbital (1) is anti-bonding and the two degenerate orbitals (2) and (3) are bonding. Here two electrons occupy orbital (1), where ψ_1, ψ_2, and ψ_3 represent hybrid sp^2 orbitals. Their probability pattern is the area a in Fig. 6. Four electrons occupy the two degenerate orbitals (2) and (3), where ψ_1, ψ_2, and ψ_3 represent $2p$ orbitals in the plane of the ring. Their probability pattern is the three-lobed area b,d,e. Walsh points out that in this treatment he assumed non-localised orbitals in the ring but there can also be some localised bond character, and in addition that the overlap between any pair of $2p$ orbitals is neither what it is in the case of a π bond (sideways), nor what it is in a σ bond (endwise). The author himself thus stressed the fact that his treatment of the cyclopropane structure is not sufficiently rigorous.

Nonetheless, the nature of the cyclopropane molecule could be qualitatively understood as formed from three ethylenic CH_2 groups. The resulting orbitals, as shown in Fig. 5, display a certain tendency to form localised bonds in the C–C direction. This structure would account for the stability of cyclopropane, since it is based on three bonding orbitals involving six electrons.

The stability of cyclopropane is in its turn taken to explain the stability of spiropentane and certain other molecules. The most characteristic feature of the overlap of atomic orbitals in cyclopropane is that each carbon atom has a $2p$ orbital with the axis lying in the plane of the ring, and a hybrid orbital directed towards the centre of gravity of the ring. This characteristic must be preserved if one of the carbon atoms changes its state of hybridisation from trigonal to digonal. The hybrid orbital directed towards the centre of the ring must in this case be an sp orbital, two hydrogen atoms must be replaced by another $2p$ orbital with the symmetry axis perpendicular to the plane of the ring, and another sp orbital formed at an angle of 180° with the first. In other words, the second ring must form an angle of 90° with the first (Fig. 7).

The existence of spiropentane, with its two rings at 90° to one another is, in the author's opinion, the most important evidence for the correctness of his views. It should be noted that on classical theory the spiropentane molecule is highly strained.

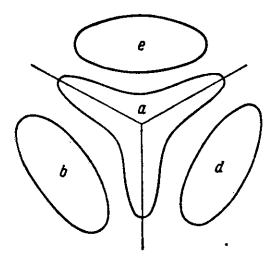


Fig. 6.

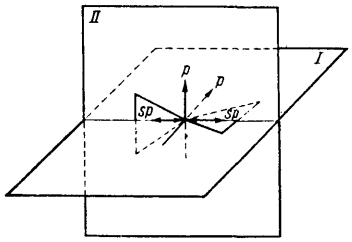


Fig.7.

The characteristic overlap pattern (Fig.5) must be preserved when two carbon atoms change their state of hybridisation from trigonal to digonal. In this case, the $2p$ orbitals, with their axes in the plane of the ring, and the hybrid orbitals directed to the centre of gravity of the ring remain fundamentally as in Fig.5, but each of two carbon atoms should have additional $2p$ orbitals with axes forming an angle of 90° with the plane of the ring. A genuine π bond, and a compound with such structure can in this case be formed:

compounds of this type were later described in a number of papers [30-33].

It should be noted that Walsh's hypothesis on the structure of the three-membered ring is based on much experimental evidence supporting the author's basic idea about the trigonal nature of carbon atoms in cyclopropane. The most important confirmation of this idea, the conjugation of the cyclopropane ring with π bonds, is an indication of the existence of almost pure $2p$ orbitals for the carbon atoms of cyclopropane. Conjugation occurs if there is an overlap of the $2p$ orbital in cyclopropane with the $2p$ orbital in a neighbouring unsaturated group, with their axes parallel to each other.

The positive feature of Walsh's theory is therefore its ability to account for a series of characteristic properties of the three-membered ring, mainly its unsaturation and conjugating capacity.

In this connection mention may be made of the recent publication by Dyatkina and Syrkin [34]. Their view on cyclopropane structure is very close to that of Walsh, but they suggest a somewhat different electron distribution in the molecule (Fig.8).

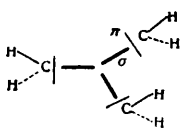


Fig.8.

It is assumed that each cyclopropane carbon atom used two hybrid atomic orbitals to form two C–H bonds. Therefore, for the bonds in the ring there remains one hybrid σ orbital directed from a carbon atom towards the centre of the ring, and a p orbital located in the plane of the ring. The described σ orbitals are fully suited to form ordinary three-centre orbitals of the "central" type. Two lowest orbitals (bonding and anti-bonding) can be occupied by four electrons. The remaining two electrons can occupy the lower one of the three-centre orbitals of the second type, formed from three carbon π orbitals whose axes are located in one plane and form angles of 120° with each other. This is a molecular orbital which overlaps all three carbon atoms along a circumference described around the C–C–C triangle. This interaction is much weaker than the one leading to the formation of a regular three-centre σ orbital of the central type. For this reason only one lower three-centre π orbital seems to be filled.

In the usual model of two-centre σ bonds in cyclopropane, electrons are distributed along the triangular perimeter while in the representation proposed by these authors a considerable part of the electron density appears not in the perimetric region, but inside the triangle, owing to the presence of central three-centre orbitals filled by four electrons.

Conjugation of a cyclopropane ring with double bonds, in their opinion, is caused by the presence of a three-centre π orbital which interacts with the π orbitals of the double bond.

Somewhat later than Dyatkina and Syrkin, Coulson and Moffitt approached the problem of cyclopropane structure from an attitude different from that of Walsh. They first published a short paper [35] in which they elaborated on ideas proposed by Kilpatrick and Spitzer [6] regarding compounds with non-tetrahedral carbon atoms, and briefly presented the results of quantum mechanical calculations of bonds in cyclopropane. Their main work, concerned with the structure and properties of strained hydrocarbons, followed later [28]. They started from the premise that since compounds which possess Baeyer strain do not have tetrahedral valence angles, the hybridisation in these compounds must differ from that found in compounds with undistorted valence angles.

The hybridisation, which is responsible for maximum bond strengths, that is, for the minimum energy in a system, was regarded by these authors as the unknown parameter, which they calculated. They did this bearing in mind a very important fact: since the H–C–H and C–C–C angles in cycloalkanes are different, hybridisations of C–H and C–C bonds in these compounds must also differ. They therefore treated separately the respective hybridisation ratios for C–C and C–H bonds. On the basis of their calculations they arrived at a model of cyclopropane in which each carbon atom is at a vertex of an equilateral triangle and hybridisation is such that two orbitals from any one carbon lie in the plane of the ring forming an angle of ~104° with one another. Less overlapping of orbitals is thus more than compensated by a decrease in strain energy at the carbon atom. Since the C–C bonding orbitals are not directed at one another, the authors describe them as "bent".

According to Coulson and Moffitt's calculations the energy of the system is at a minimum when the H–C–H angle is 116°. This value is in excellent agreement with the experimentally found value for the internal angle in cyclopropane. Results of their calculations for various

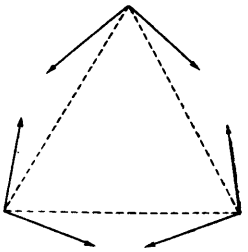


Fig.9.

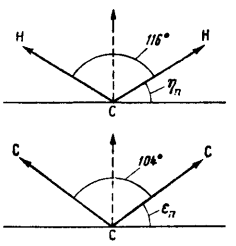


Fig.10.

cycloalkanes and ethylene are collected in Table 2. Values λ and μ in Table 2 are the hybridisation ratios of the C–C and C–H bonds. In order to illustrate their meaning it may by mentioned that by suitably varying μ one can run through the whole range of known types of hybrids: $\mu = 1$, H–C–H = = 180° (digonal); $\mu = \sqrt{2}$, H–C–H = 120° (trigonal); $\mu = \sqrt{3}$, H–C–H = 109°28' (tetrahedral); and $\mu = \infty$, H–C–H = 90° (pure p). The values of angles ϵ_n, η_n, and θ_n given in Table 2, are shown in Fig. 10.

The data of Table 2 show cyclopropane to differ considerably from other hydrocarbons. Thus, λ is considerable higher for the three-membered ring than for cyclobutane or cyclopentane. This indicates the predominantly p character of bonds in this ring (C–C bonds), in contrast to normal tetrahedral bonds, where $\lambda = 1.73$. On the whole, C–H bonds are further away from the p orbital type, which is apparent in the lower value for μ. This effect is less pronounced in cyclobutane, and is completely absent in cyclopentane, where angles and hybridisation are both tetrahedral.

The differences in the hybridisation ratios λ and μ from the mean value 1.73 corresponds to an increase of H–C–H angle, an effect which is slight in cyclobutane but considerable in cyclopropane.

θ is the angle between the direction of the C–C bond and the hybrid orbital. If the hybrid orbital coincides with the direction of the bond $\theta = 0$; here the bonds may be described as direct. If all the bonds are equivalent, as in methane, the angle between them $\pi - 2\epsilon$ is tetrahedral (109°28'). In cycloalkanes, the C–C bonds are strained ($\pi - 2\epsilon \neq 109°28'$) and bent ($\theta \neq 0$). The difference between $E_{(\epsilon,\theta)}$ and $E_{(\epsilon)}$ is a measure of the energy of a strained system.

Judging by the hybridisation ratio μ, C–H bonds in cyclopropane are more akin to those in ethylene than to those in ethane. In cyclobutane they are more like those in ethane or cyclopentane.

Using data from Table 3 the authors drew a curve (Fig. 11) which enables us to predict the force constant for the three cycloalkanes shown at the top of the table. The constants shown in parentheses have been used to draw the curve relating force constant and hybridisation ratio μ.

The values for force constants obtained by Coulson and Moffitt are in good agreement with those given by Linnett[16-17] and Wilson[36] for cyclopropane and cyclobutane.

If the behaviour of C–H bonds with varying hybridisation ratio applies also to C–C bonds, they should be expected to have lower force constants in the strained systems than in normal unstrained (direct) tetrahedral C–C bonds.

In view of the fact that strained bonds are energetically less stable than their unstrained counterparts, their length should be appreciably greater than that in ethane (1.55 Å). However, the investigations mentioned earlier revealed a bond shortening. Coulson and Moffitt think that one should distinguish between internuclear distance and the bond lengths, namely between the length r of the straight line CC and the length of the arc CDC', which is equal to $r\theta \operatorname{cosec}\theta$, and longer than r (Fig.12). When $\theta = 22°$, $\theta \operatorname{cosec}\theta = 1.025$.

This means that the length of the strained (bent) bond may be greater than 1.55 Å, although the internuclear distance between carbon atoms may be less than this. This can easily be understood if hybrid orbitals can be considered to be impenetrable; in this case, the orbitals of an unstrained bond would necessitate a longer interatomic distance than would a strained bond set at an angle (Fig. 13): *i.e.* in the latter case the atoms approach each other more closely than in the former.

Coulson and Moffitt's paper gives contours of equal electron density for strained and unstrained bonds (Fig.14).

As shown in Fig. 14, for strained bonds the lines of equal electron density are distorted. The arrows show the

TABLE 2.

Compound	n	ϵ_n	η_n	θ_n	H H \ C / ($\pi = 2\eta_n$)	λ	μ
Cyclopropane	3	38°	32°	22°	116°	2.03	1.51
Cyclobutane	4	36°	34°30'	9°	111°	1.80	1.67
Cyclopentane	5	35°15'	35°15'	0°	109°30'	1.73	1.73
"Ethylene"	2	40°	28°30'	50°	123°	2.40	1.36

TABLE 3.

Hydrocarbon	H–C–H angle	C–H force constant, dynes cm^{-1}	μ
Cyclopropane	116°	$5.0 \cdot 10^5$	1.51
Cyclobutane	111°	4.85	1.67
Cyclopentane	109.5°	4.8	1.73
Ethane	109.5°	(4.8)	1.73
Ethylene	120°	(5.1)	1.41
Acetylene	180°	(6.0)	1.00
CH radical	90°	(4.1)	—

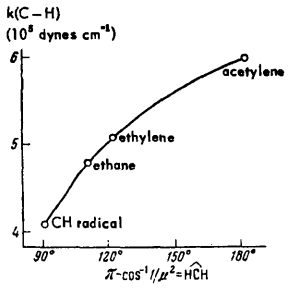


Fig.11.

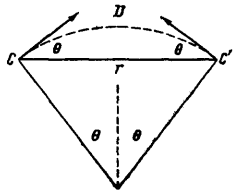


Fig.12.

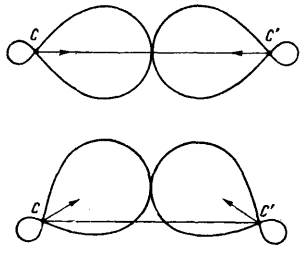


Fig.13.

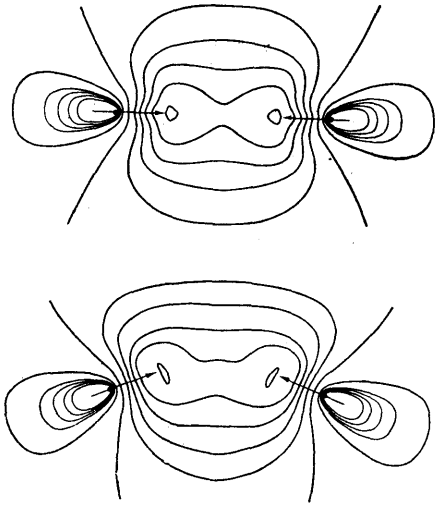


Fig.14.

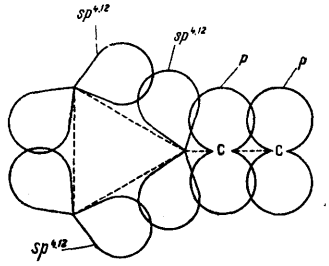


Fig.15.

direction of hybrid orbital maxima. In unstrained bonds these coincide with the direction of the bonds, while in cyclopropane they make an angle $\theta = 60° - 38° = 22°$ with the direction of the bonds. The bent character of the C–C bonds in cyclopropane is demonstrated well here.

Using the Coulson and Moffitt's representation of bent *endo*-orbitals in a three-membered ring Ingraham[37] calculated that these ring orbitals are now $sp^{4.12}$ orbitals instead of the usual tetrahedral sp^3 orbitals formed at a valence angle of 109°28'. The high p character of the *endo*-orbitals results in a high s character of the $sp^{2.28}$ *exo*-bonds in cyclopropane. These bonds are at 116° to each other.

This structure, in Ingraham's opinion, affects the properties of three-membered ring compounds. The most important effect is the result of the fact that these $sp^{4.12}$ bonds are well placed for overlap with adjacent p orbitals of the double bond, as in vinylcyclopropane (Fig. 15).

Cromwell and Graff[38] have a somewhat different concept of the conjugation of similar systems. Taking the ethyleneimine and ethylene oxide rings as examples, they consider conjugation to take place between *endo*-bonds and π bonds, as in Fig. 16.

In this case, to form endocyclic bent bonds in a three-membered ring two carbon atoms use their hybrid orbitals ($2s - 2p\delta$) (angle 104°), while O or N atoms use their $2p_x$ and $2p_y$ orbitals (angle 92°). This type of bond is intermediate between π and σ bonds.

When an atom containing π electrons is linked with a carbon atom from any ring system with bent bonds (ethyleneimine, ethylene oxide, cyclopropane) a degree of interaction or overlap is observed between these bent bonds and the π or p orbitals (see broken lines in Fig. 16).

In conclusion it may be stated that Walsh, and also Coulson and Moffitt interpret the peculiarities of a three-membered ring by a characteristic of the valence state of the ring carbon atoms. In both concepts the valence state or hybridisation is assumed to differ from tetrahedral sp^3. Walsh describes this state as sp^2 hybridisation, but admits

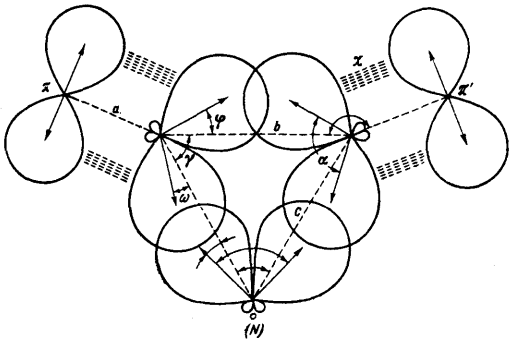


Fig.16.

that it is somewhat of a special type. For example, he assumes a certain amount of localisation of bonds in a three-membered ring.

Coulson and Moffitt's concept of hybridisation in cyclopropane is more concrete. They consider that hybridisation is different for the C–C and the C–H bonds in cyclopropane and that neither is sp^3 or sp^2 hybridisation, which are characteristic of tetrahedral and trigonal carbon atoms, respectively. This means that a new type of bond exists in cyclopropane, different from bonds in saturated molecules and unsaturated ones with undistorted valence angles. In his monograph[39] Coulson termed C–C bonds in cyclopropane "banana" bonds, and this term is gradually gaining ground in the chemical literature.

Although the concept of cyclopropane structure as proposed by Coulson and Moffitt is more rigorous than that of Walsh, they are basically very similar. Thus, although they differ in their description of the endocyclic bonds in cyclopropane, they agree about the delocalisation and the p character of bonding molecular orbitals. It is precisely in terms of these that a series of properties of three-membered rings can easily be understood, in particular their capacity to conjugate with adjacent π bonds.

III. REACTIONS OF CYCLOPROPANE AND ITS DERIVATIVES WITH EMPHASIS ON THE ANALOGY BETWEEN THE THREE-MEMBERED RING AND THE DOUBLE BOND

The characteristic reactivity of the three-membered ring and the deep analogy between the behaviour of cyclopropane derivatives and alkenes can be more readily understood in the light of the above views on cyclopropane structure. Bonds in the three-membered ring differ from those in alkanes or higher alicyclic compounds with undistorted valence angles, their properties resembling more the bonds in alkenes than the σ bonds of saturated compounds. The properties of cyclopropane and its derivatives are therefore understandably dissimilar from those of alkanes or higher alicyclic compounds, and this is no longer to be considered anomalous.

The complex chemistry of cyclopropane has long been attracting the attention of the most prominent Russian and foreign scientists, including Gustavson, Perkin, Willstätter, Kishner, Dem'yanov, Robinson, and others. The literature abounds with data on the reactivity of cyclopropane compounds. The present review deals only with the most interesting reactions which illustrate similarities and discrepancies between the behaviour of a three-membered ring and that of a double carbon–carbon bond. In our opinion these reactions are consistent with the theoretical concepts discussed in the previous section, and can be taken as evidence confirming the hypotheses of Walsh and Coulson and Moffitt on cyclopropane structure.

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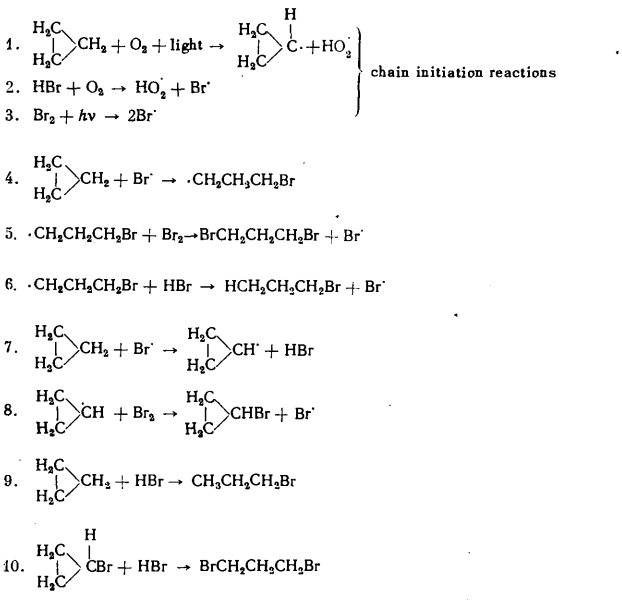
The reactions of a three-membered ring with halogens and with hydrogen halides were first studied in 1900 by Gustavson[40]. Ogg and Priest[41] later made a more thorough study of these reactions. They found that at room temperature and in strong light a rapid photochemical reaction took place between cyclopropane and bromine vapour, consisting exclusively of addition to give 1,3-dibromopropane. In the dark, bromine and cyclopropane react only at 220°, but here a considerable amount of substitution occurs as well as the addition.

Ogg and Priest also found that at 250° cyclopropane readily reacts with iodine forming 1,3-diiodopropane. Light has no appreciable effect on this reaction rate. Later, these authors investigated in detail the kinetics of the vapour-phase reaction of cyclopropane and iodine[42].

Kharasch *et al.*[43] made a detailed study of the reaction of cyclopropane with bromine, including the effects of light and oxygen. They found that pure cyclopropane and pure bromine do not react appreciably in the dark, and do so only slightly in light. For that reason they suggested a chain mechanism for bromination, according to the scheme below:



The dots denote unpaired electrons.

The reaction of cyclopropane with chlorine was studied by Gustavson[44], and later in more detail by Stevens[45]. In contrast to bromine and iodine, chlorine is unable to open the three-membered ring, and substitution occurs, mainly forming 1,1-dichlorocyclopropane.

The work by Roberts and Dirstine[46], on the photochemical chlorination of cyclopropane, is of interest. Here also the reaction is slow, and since chlorine attacks hydrogen rather than carbon, results in substitution, not ring-opening. Brown and Borkowski[47] discovered that in the chlorination of methylcyclopropane, despite the presence of a tertiary carbon atom, only the methyl hydrogen atoms undergo substitution.

Freed and Sancier[48] found that, in the temperature range from -43° to -196°, iodine reacts with cyclopropane forming a molecular compound (1 : 1). The composition of the adduct was established from ultra-violet absorption spectra. These authors had earlier obtained similar adducts from a series of alkenes, *e.g.* propene, 2-butenes (*cis* and *trans*), and butadienes. In all cases, the adducts were molecular compounds of molar ratio 1 : 1. The energies of activation were determined.

Ogg and Priest[41] found that cyclopropane is almost completely resistant towards gaseous hydrogen chloride, bromide, and iodide, even at 300°. Freund[49], Gustavson[40], and later Kishner[50], and Kohler and Conant[51], found that cyclopropane and its alkyl derivatives readily react with aqueous solutions of these acids. Alkylcyclopropanes react according to the Markownikow rule, which is evidence in favour of an ionic reaction mechanism. Addition of hydrogen bromide to unsymmetrical alkenes containing alkyl substituents can be represented in the following manner:

$$CH_3-\overset{+\delta}{C}H=\overset{-\delta}{C}H_2+H^+Br^- \rightarrow CH_3-CHBr-CH_3.$$

With alkylcyclopropanes this reaction proceeds as below:

$$CH_3-\overset{+\delta}{\underset{\diagdown\,\diagup}{CH}}-\overset{-\delta}{CH_2}+H^+Br^- \rightarrow CH_3-\underset{Br}{CH}-CH_2-CH_3,$$
$$\qquad\quad CH_2$$

and the cyclopropane ring opens between those carbon atoms which are united with the greatest and the smallest number of alkyl residues, the bromine atom attaching itself to that carbon atom which carries most alkyl radicals. The addition of hydrogen bromide to cyclopropane was studied by Kharasch *et al.*[43] In the presence of an excess of cyclopropane this reaction is greatly accelerated by oxygen, and only slightly by light. In the presence of an equivalent amount of cyclopropane neither oxygen nor light appreciably affect the reaction rate, but an acceleration by peroxides is observed.

Kuivila *et al.*[52] studied the interesting reaction of *N*-bromosuccinimide with 1-phenyl-2-isopropylcyclopropane[53]. This reagent reacts with alkenes to form the corresponding dibromides in good yields. With cyclopropane derivatives, instead of the expected substitution products (isomeric bromides), a small yield of an open-chain dibromide was obtained, formed by ring opening between the two substituted carbon atoms:

$$C_6H_5-\underset{\diagdown\,\diagup}{CH}-\underset{\diagdown\,\diagup}{CH}-CH \begin{matrix} CH_2 & CH_3 \\ & \\ & CH_3 \end{matrix} + 2\,\begin{matrix} CH_2-CO \\ \\ CH_2-CO \end{matrix}\!\!>NBr \rightarrow C_6H_5-\underset{Br}{CH}\ \underset{Br}{CH}-CH \begin{matrix} CH_2 & CH_3 \\ & \\ & CH_3 \end{matrix}$$

This reaction is yet another example of the far-reaching analogy between the behaviour of a three-membered ring and a double bond.

One of the most characteristic addition reactions in the cyclopropane series is catalytic hydrogenation involving ring opening (hydrogenolysis).

Although the catalytic hydrogenation of cyclopropane hydrocarbons has been the subject of numerous investigations, it has not been possible until recently to form a clear picture of the conditions and direction of the opening of the three-membered ring in this case.

Willstätter and Bruce[54] found that, over nickel on pumice, cyclopropane undergoes partial hydrogenation at 80°, and is completely hydrogenated at 120°. With the same catalyst, Bond and Sheridan[55] found that hydrogenation commenced at 129°. In the presence of platinum or palladium on pumice, hydrogenation did not start until 50° and 72°, respectively.

Corner and Pease[56] hydrogenated cyclopropane in the presence of nickel on kieselguhr and found that ring opening occurred at 0°. Boeseken and his associates[57] pointed out that the rate of the hydrogenation of cyclopropane over platinum black in acetic acid solution at 25° is the same as that for the hydrogenation of ethylene. On the other hand, Kazanskii *et al.*[58,59] repeatedly observed that in the presence of platinum and palladium blacks in alcoholic solution at room temperature hydrogen does not react with alkylcyclopropanes, while alkenes readily undergo hydrogenation under these conditions. Bond and Sheridan[55] also consider that the hydrogenation of a three-membered ring requires harsher reaction conditions than does the olefinic double bond.

Views also differ as regards the direction of the opening of a three-membered ring on hydrogenation. Rozanov[60] (nickel on asbestos), Kishner[61] (nickel), Kazanskii *et al.*[62,63] (Pt on carbon), and Slabey[64] (platinum oxide) found that alkylcyclopropanes are hydrogenolysed by rupture of the bond between those two ring carbon atoms which carry the greatest number of hydrogen atoms. A different direction of the ring opening was observed by Slobodin *et al.*[65] (Ni on kieselguhr), and by Boord and his coworkers[66,67] (Ni on kieselguhr). They found that, in all the cases studied, the cyclopropane ring was opened at the bond between those two carbon atoms which are united with the greatest and the smallest number of hydrogen atoms.

These contradictory results stimulated Lukina *et al.*[68-70] to undertake a thorough investigation of the behaviour of alkylcyclopropanes under conditions of hydrogenation and they found that in the presence of many substances a three-membered ring readily undergoes isomerisation into open-chain alkenes. This reaction was shown to be caused by carriers used in the preparation of hydrogenation catalysts, particularly silica gel[71], aluminosilicate, kieselguhr, aluminium oxide, and (at relatively higher temperatures) pumice and activated carbon[70]. The result is that, depending on the conditions and the nature of the catalyst, two different reactions proceed concomitantly during the hydrogenation of cyclopropane hydrocarbons: hydrogenolysis, *i.e.*, addition of hydrogen to the three-membered ring, and isomerisation to alkenes, which is followed by the addition of hydrogen to the double bond[68,72,73].

These reactions involve different C–C bonds of the three-membered ring and yield products of different structure.

$$\begin{matrix} R \\ | \\ CH \\ \diagup\ \diagdown \\ CH_2-CH_2 \end{matrix} \xrightarrow[H_2]{\text{catalyst}} CH_3-\underset{R}{CH}-CH_3 \qquad \text{hydrogenolysis}$$

$$\begin{matrix} R \\ | \\ CH \\ \diagup\ \diagdown \\ CH_2-CH_2 \end{matrix} \xrightarrow[H_2]{\text{catalyst}} R-CH_2-CH_2-CH_3 \qquad \begin{matrix} \text{isomerisation} \\ \text{followed by} \\ \text{hydrogenation} \end{matrix}$$

The characteristic isomerisation of the three-membered ring under relatively mild conditions has not been taken into account in studies of catalytic hydrogenation so that the two reactions are taken as one, hence the discrepancies as regards the direction of the ring opening and the reaction conditions. In all cases where nickel on kieselguhr was used as a catalyst[65,66,67] the reaction involved mainly or exclusively isomerisation, kieselguhr being very active in catalysing this reaction. The resulting alkene immediately underwent hydrogenation in the presence of nickel, yielding the corresponding alkane. The cleavage of the ring occurred between those two carbon atoms which were united with the greatest and smallest number of hydrogen atoms. This explains the readiness in the opening of the three-membered ring observed by Corner and Pease[56], who used nickel on kieselguhr as hydrogenation catalyst. Direct hydrogenolysis of the ring proceeds readily in the presence of platinum on activated carbon or pumice, since those carriers, at relatively low temperatures used in this reaction, are not very active as isomerising agents. Certain catalysts, for instance palladised carbon[72], catalyse both reactions simultaneously.

Bond and Sheridan[55] studied the kinetics and the mechanism of the hydrogenolysis of cyclopropane in the presence of platinum, palladium, and nickel on pumice. In contrast to alkenes, the hydrogenation of cyclopropane in the 100°–200° temperature range is of first order with respect to cyclopropane, and of zero with respect to hydrogen. This is an evidence that during the hydrogenation of cyclopropane, in the studied range of hydrogen pressure, the catalyst's surface is completely covered by adsorbed hydrogen and the reaction rate is independent of its concentration [in the gas phase (Ed. of Translation)].

Bond and Turkevich[74] studied the deuteration of cyclopropane over platinum and found that the reaction order in this case is the same as in hydrogenation, and depends on temperature. On the basis of their results they dispute the various versions of the mechanism of hydrogenolysis suggested earlier by Bond and Sheridan[55]. In their opinion[74] the most probable mechanism is that whereby a molecule of gaseous cyclopropane unites with two hydrogen atoms after an intermediate formation of an adsorbed radical. The mechanism whereby cyclopropane is first isomerised to propene is excluded, since according to Bond and Turkevich the distribution of deuterium in the propane from the catalytic deuteration of propene differs from that in the propane formed from cyclopropane[74].

The reaction of cyclopropane with deuterium over palladium was studied by Addy and Bond[75]. Hydrogenation of cyclopropane in the presence of platinum and palladium proceed according to the same mechanism, although platinum is more active.

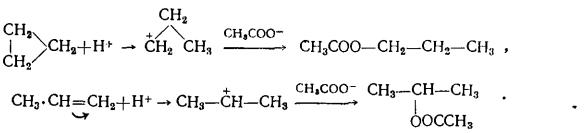
Addy and Bond[76] established that the hydrogenation of cyclopropane in the presence of rhodium and iridium catalysts follows the same reaction mechanism as in the case of platinum or palladium.

In their study of the hydrogenation of cyclopropane in the presence of commercial nickel–aluminosilicate catalyst at 75°, Benson and Kwan[77] obtained a kinetic equation different from that proposed by Bond and Sheridan[55]. Irrespective of that, they believe that the reaction mechanism proposed by Bond and Sheridan is correct. The validity of their results may be questioned, as they studied the isomerisation of cyclopropane into propene under the action of the aluminosilicate carrier, and not its hydrogenolysis. In the presence of nickel, propene undergoes hydrogenation to propane. Hayes and Taylor[78] described the same reaction in the presence of a catalyst prepared by melting magnetite ore with potash, which they termed Fe-catalyst. In this case both the kinetic equation and the suggested reaction mechanism differ from that given by Bond and Sheridan. The authors interpret this by the lower activity of Fe-catalyst in the hydrogenation of cyclopropane owing to the fact that its surface is incompletely covered by hydrogen. The remaining free surface, in their opinion, catalyses the isomerisation of cyclopropane.

Hydrogenolysis is specific not only for a three-membered, but also for four- and five-membered rings. It is only natural to suppose that in the cyclopropane series it should proceed under milder conditions. It is nevertheless difficult to form a clear picture from the literature regarding the differences in the stability of various rings in this reaction.

Comparative hydrogenolysis of three hydrocarbons of molecular formula C_5H_{10}, containing different rings, was studied by Lukina *et al.*[79] In the presence of platinised carbon of low activity ethylcyclopropane is completely converted into the corresponding alkane at 50°, methylcyclobutane is hydrogenated on this only at 250°, while with cyclopentane at 250° only the breaking of the carbon–carbon bonds is beginning.

No less interesting are the reactions in which the three-membered ring, like an alkene, may be represented as a nucleophilic reagent. For instance the reaction of cyclopropane with acids, studied for many examples, belongs to this category. Thus, Dorris and Sowa[80] established that cyclopropane reacts with acetic acid in the presence of boron fluoride forming 65% n-propyl acetate. Under the same conditions propene yields the isopropyl ester. The authors suggested the following scheme for those two reactions:



Like the lower alkenes, cyclopropane is absorbed by concentrated sulphuric acid to form esters. Davis and Schuler[81], and later Rathman[82], studied the absorption rate of cyclopropane and propene. Sulphuric acid absorbs cyclopropane more rapidly than propene, the absorption rate depending on acid concentration. Rathman based his method for analysing mixtures of alkenes and cyclopropane on this difference in the absorption rate.

Somewhat later Lawrence and Tipper[83] studied the reactions of cyclopropane and propene with various acids and found that the kinetics are similar in both cases although the reaction rate is different. The authors interpret this as indicating similar reaction mechanisms represented as follows:

(1) $C_3H_6+H^+ \rightarrow C_3H_7^+$,

(2) $C_3H_7^+ \rightarrow C_3H_6+H^+$,

(3) $C_3H_7^+ + HX\,(acid) \rightarrow C_3H_7X+H^+$.

It can be assumed that reaction (1) is slow, reaction (2) very rapid, and reaction (3) moderately rapid. The first reaction stage, the addition of a proton, proposed by

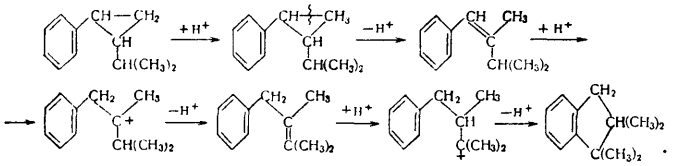
Dorris and Sowa[80], proceeds as shown above. The rate is five times faster for cyclopropane than for propene, which in agreement with the above scheme, is interpreted by the fact that proton can attack any one of the three equivalent carbon atoms in cyclopropane, and only one in propene.

Almost all the investigations of the reactivity of the three-membered ring include comparative studies of the behaviour of cyclopropane derivatives and alkenes of analogous structure. Thus, Davidson and Feldman[84] studied the action of sulphuric acid on monophenylalkenes and monophenylcyclopropanes. Under the conditions employed, alkenes either undergo polymerisation or form indanes and tetralins.

By the action of 90% sulphuric acid 2-isopropyl-1-phenylcyclopropane forms small amounts of 1,1,2-trimethylindane, while 2-methyl-1-phenyl- and 2-ethyl-1-phenyl-cyclopropane form resinous polymers and traces of volatile oils.

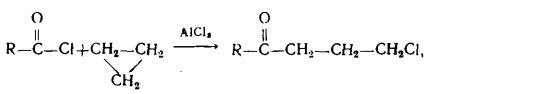
In the opinion of the authors, the attack of sulphuric acid on a 2-alkyl-1-phenylcyclopropane starts by the opening of the cyclopropane ring following the addition of a proton to the least substituted carbon atom. As in the case of alkenes, the resulting carbonium ion may subsequently undergo the following specific reactions: addition to an unsaturated molecule (polymerisation), decomposition to form other carbonium ions or unsaturated compounds with a smaller number of carbon atoms (depolymerisation), isomerisation into other carbonium ions (rearrangement), or decomposition into an alkene and a proton.

These authors found that these reaction types only proceed in the case of isopropyl derivatives, where the conditions for cyclisation are especially favourable. In other cases only polymerisation takes place:



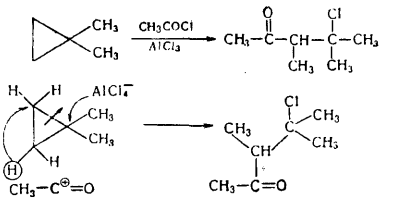
Similar behaviour of the three-membered ring and the double bond has been confirmed by Hart and Curtis[85] in a study of the reaction of cyclopropane with $RCOCl.AlCl_3$ in chloroform (a reaction catalysed by a Lewis acid). Similar reaction with alkenes yields β-chloro-ketones.

Cyclopropane and an acyl halide were expected to form a γ-halogeno-ketone:



where R = CH_3; C_2H_5; C_3H_7; i-C_3H_7; Δ; C_6H_5. This reaction course is probable since the reverse reaction, cyclisation of β-chloro-ketones in the presence of alkali, yields cyclopropyl ketones. In fact, the reaction was accompanied by unexpected rearrangement leading to a mixture of products consisting mainly of the β-chloro-ketone $RCOCH(CH_3)CH_2Cl$ and to a lesser extent of the γ-chloro-ketone $RCOCH_2CH_2CH_2Cl$.

Hart and Levitt[86] studied this reaction with a series of other compounds, and each time they obtained β-chloro-ketones. Using dimethylcyclopropane as an example, they suggested the following reaction mechanism:

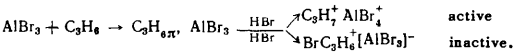


A great deal of work has been done on the action of aluminium halides on the three-membered ring, and a close analogy in the behaviour of alkenes and cyclopropane derivatives was observed.

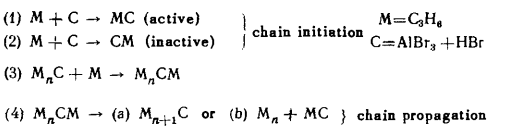
Schmerling[87] alkylated benzene by passing cyclopropane into a solution of aluminium chloride in nitromethane and benzene at 20°–50°. The reaction product was n-propylbenzene. Later, Tipper and Walker[88] studied the kinetics of this reaction.

In 1953 Ipatieff *et al.* studied the reaction of cyclopropane hydrocarbons with aluminium chloride[89]. They found that under their conditions cyclopropane homologues underwent polymerisation. They interpreted this by invoking the olefinic character of the three-membered ring.

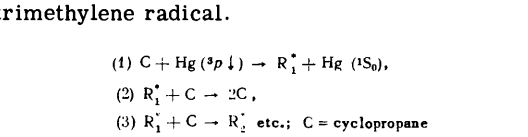
According to Tipper and Walker[90] cyclopropane polymerises in the presence of aluminium bromide and hydrogen bromide (in heptane solution), from 0° to -78°, forming polymers of low molecular weight. These polymers, whose molecular weight is inversely proportional to temperature, appear to be long-chain alkenes with a terminal double bond. The proposed reaction mechanism consists of the initial interaction of cyclopropane, aluminium bromide, and hydrogen bromide leading to two complexes, one of which initiates the reaction, while the other, which is inactive, forms a precipitate:



The first step may possibly consist of complex formation. The mechanism can be represented as follows:

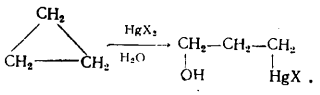


In their study of cyclopropane spectra, Harris *et al.*[91] observed that cyclopropane polymerised on irradiation by ultra-violet light. The polymer is a colourless oil of high boiling point. Gunning and Steacie[92] later made a thorough study of this phenomenon and suggested a mechanism for it which is based on the preliminary formation of an energy-rich trimethylene radical.

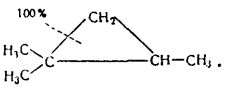


Breaking of the chain takes place when the polymer biradical is no longer able to supply energy for the cleavage of the C–C bond of cyclopropane. In that case the radical is stabilised by a proton shift. Reaction (2) is 43 times faster than reaction (3)‡.

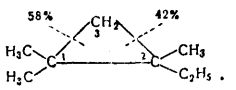
Of considerable interest is the reaction of a three-membered ring with mercuric salts, investigated by Levina and coworkers[93]. Mercuric salts are known to react with the double bond of many alkenes[94] and alkadienes[95]. Cyclopropane hydrocarbons readily react (usually on shaking at room temperature) with mercuric salts at the point where the ring is normally opened, forming γ-hydroxyalkylmercury salts, *i.e.* alcohols mercurated in the γ position:



The three-membered ring in substituted cyclopropane always opens at the bond lying between the two carbon atoms which carry the smallest and the largest number of hydrogen atoms[96]:



If two bonds are equivalent in this respect, a mixture of both possible reaction products is obtained:

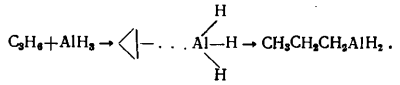


Formation of a somewhat greater amount of the product resulting from the cleavage of the 1–3 bond is accounted for by greater polarisation of that bond as compared with the 2–3 bond[97]. There can be no preliminary isomerisation of the three-membered ring, for then acetate would attach itself at the double bond forming a β-hydroxyalkylmercury acetate. This reaction has been studied so frequently that it could be used for the identification of cyclopropane hydrocarbons.

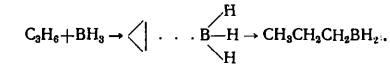
According to Tipper[98], cyclopropane (liquid), in contrast to alkenes, does not form complexes with silver, copper, and mercury salts at low temperatures. Nevertheless, with chloroplatinic acid in acetic anhydride it forms a brown precipitate of the complex $(PtCl_2C_3H_6)_2$. A cold aqueous solution of potassium cyanide decomposes this complex, rapidly liberating cyclopropane. This is evidence that the three-membered ring remains unchanged in the complex. Under these conditions alkenes also form complexes with chloroplatinic acid. Formation of complexes may be taken as evidence supporting the views of Walsh and of Coulson and Moffitt on the unsaturated character of the three-membered ring.

‡ See, however, K.Ivin, J.Chem.Soc., 2241 (1956), in which an alternative mechanism is proposed (Ed. of Translation).

The work by Tipper and Walker[99] on the reaction of cyclopropane with lithium hydroaluminate is also of interest. This reagent reacts with lower alkenes forming the corresponding alkylaluminium compounds. Cyclopropane similarly yields tri-n-propylaluminium. The authors think that the first stage of this reaction consists of the coordination of cyclopropane with AlH_3, which is followed by the shift of hydrogen and the opening of the ring:



This process is subsequently repeated and the reaction results in tri-n-propylaluminium. Graham and Stone similarly observed the formation of a carbon–boron bond in the reaction of cyclopropane with diborane at 80°–100°.[100] Reactions of that type, involving a shift of hydrogen, also take place with alkenes. The authors consider that the "banana" bonds of cyclopropane possess sufficient electron density to permit a reaction of this type:



Graham and Stone consider that the addition of BH_3 or AlH_3 to cyclopropane proceeds through the intermediate formation of a π complex, similar to that formed by ethylene. Sometimes, however, organometallic compounds are formed in which the cyclopropane ring is preserved intact. For example, Hart and Sandri[101] found that boiling finely divided lithium with cyclopropyl chloride in pentane solution yields cyclopropyllithium.

Reynolds *et al.*[102] obtained dicyclopropylmercury in 64% yield. They similarly obtained divinyl- and dipropenyl-mercury in 60 and 75% yield, respectively. In contrast to divinylmercury, dicyclopropylmercury does not decolorise potassium permangante solution.

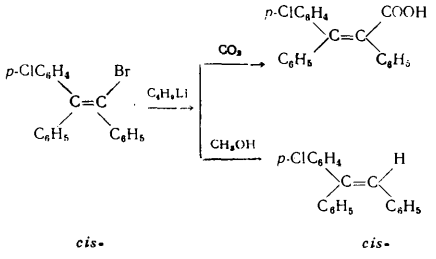
Shatenshtein *et al.*[103] studied the deuterium exchange between liquid deuterated ammonia and cyclopropane hydrocarbons in the presence of potassium amide. In this experiment the cyclopropane compounds act as electrophilic reagents, while most of the other work was concerned with their nucleophilic reactivity with electrophilic reagents (halogens, acids, etc.). The unsaturated character of the cyclopropane ring is manifested in a higher rate of hydrogen exchange as compared with saturated hydrocarbons.

It may be noted that in certain cases the behaviour of cyclopropane differs from that of alkenes. Hammond and Todd[104] found that in contrast to their olefinic analogues, some cyclopropane derivatives, including cyclopropyl cyanide and cyclopropyl methyl ketone did not react with various free radicals. Phenylcyclopropane completely resists polymerisation in the presence of benzoyl peroxide. Alkenes are known to undergo radical-initiated polymerisation with great ease.

Walborsky and Hornyak[105,106] compared certain properties of the cyclopropyl carbanion with those of the carbanions formed at trigonal carbon atoms (alkenyl anions).

According to Curtin and Harris[107], *cis*- and *trans*-1-bromo-2-*p*-chlorophenyl-1,2-diphenylethylenes on treat-

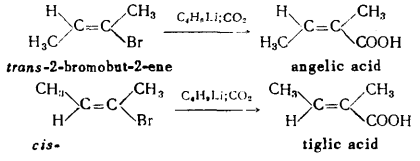
ment with n-butyllithium at -20° and subsequent carboxylation (or reaction with methanol) yield the corresponding *cis*- and *trans*-derivatives, respectively:



cis- *cis*-

All three reactions investigated, *i.e.* substitution of halogen by lithium, carboxylation, and substitution of lithium by hydrogen, are stereospecific. It was thus shown that the intermediate vinyllithium derivative preserves its configuration at -20°.

Somewhat later Dreiding and Pratt [108] confirmed this in another case:

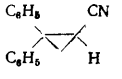


trans-2-bromobut-2-ene angelic acid

cis- tiglic acid

It was hereby shown that the alkenyl anion is capable of keeping its steric configuration.

Walborsky's experiments with an optically active nitrile showed that in this respect the analogy between the three-membered ring and the double bond breaks down:



since the cyclopropyl carbanion is unable to preserve its steric configuration§. On treatment with bisisopropylaminelithium at room temperature, the above cyano-compound is completely racemised. Alkenes and cyclopropanes also differ in their behaviour towards potassium permanganate. Cyclopropane does not react in the cold, while alkenes do so instantaneously. This is well illustrated by the reaction studied by Dem'yanov and Doyarenko [109]:

§ See, however, H.M.Walborsky, A.A.Youssef, and J.M.. Motes, J.Amer.Chem.Soc., 84, 2465 (1962).

Moreover, cyclopropane and its homologues do not react with dilute anhydrous bromine solution, and in contrast to alkenes, are not oxidised by air, and almost fail to react with ozone.

IV. CONJUGATION OF THE THREE-MEMBERED RING WITH UNSATURATED GROUPS

As already noted, the analogy between the three-membered ring and the double bond is especially clearly manifested in the capacity of cyclopropane for conjugation with unsaturated groups. This was first observed by Kishner [110], and later by Robinson [111]. Numerous publications are devoted to this interesting phenomenon.

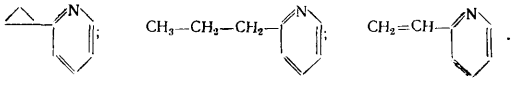
Conjugation of a three-membered ring has been studied in great detail by spectrographic methods, mainly ultra-violet absorption. Conjugation is measured by the bathochromic shift of the long-wavelength absorption band. For instance, the absorption maximum of ethylene in the ultra-violet region at 1750 Å shifts to 2170 Å in $CH_2=CH-CH=CH_2$, and to 2190 Å in $CH_2=CH-CO-CH_3$. A similar shift is observed in cyclopropane compounds conjugated with neighbouring unsaturated groups, although it is less pronounced than in dienes.

Many three-membered ring compounds of varied type were studied. Rogers [112] compared the spectra of simple cyclopropane derivatives with those of similar compounds in which the cyclopropane ring was substituted by an allcenyl or an allcyl group. The absorption band of compounds of type ▷−C=C occupies an intermediate position between the corresponding bands displayed by compounds of type R−C=C and C=C−C=C.

By spectrographic studies Roberts and Green [113], and later Hawthorne [114], established the presence of conjugation of the ring with the carbonyl group in the 2,4-dinitrophenylhydrazones of cyclopropane ketones.

Conjugation of the three-membered ring with the benzene nucleus in phenylcyclopropane was established from ultra-violet spectra by Carr and Burt [115] and later by Rogers [112]. Levina *et al.* [116] recently found that on going from phenylcyclopropane to tolyl- and anisyl-cyclopropane the absorption maximum is shifted bathochromically. They interpret this as increased conjugation of the cyclopropane ring with the aromatic nucleus containing nucleophilic substituents.

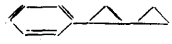
Mariella *et al.* [117] examined 2-cyclopropyl-, 2-n-propyl-, and 2-vinyl-pyridine by the same method and found the absorption maximum of the cyclopropane derivative to occupy an intermediate position between those of the conjugated and the unconjugated systems:



The work of Klotz [118] on steroid compounds containing a three-membered ring and on terpenes is noteworthy.

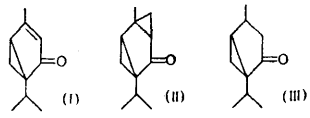
In their comparison of the ultra-violet spectra of chlorocyclopropane and cyclopropane, Eberlin and Pickett [119] observed a considerable bathochromic shift in the former, which they interpreted as indicating conjugation of the *p* orbital of chlorine with the three-membered ring.

The still unsolved problem of the possible transmission of conjugation by a three-membered ring has been discussed in a series of investigations which are discussed below. In 1951 Smith and Rogier[120] first synthesised 2-cyclopropyl-1-phenylcyclopropane:



Conjugation in 2-cyclopropyl-1-phenylcyclopropane was found to be no greater than it is in phenylcyclopropane, which may be interpreted by the absence from the former compound of a chain of conjugation involving both cyclopropyl rings. These authors therefore suggested that a cyclopropane ring is able to take part in a conjugation chain only as its terminal member, and is unable to transmit conjugation if located between two unsaturated groups.

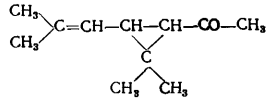
Eastman[121] made a spectroscopic study of the three compounds:



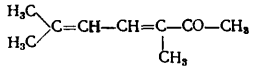
(I) (II) (III)

and observed that the spectra of compound (I) exhibited a pronounced conjugation effect, while those of compounds (II) and (III) did not differ essentially from one another. This was taken as evidence that in the tricyclic ketone (II) a chain of conjugation including both rings does not exist, while separately both rings are conjugated with the carbonyl group. However, such a chain of conjugation is found in compound (I).

Later Eastman and Freeman[122] synthesised and investigated the ketone of the following structure:

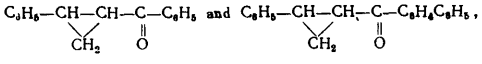


The combination of the double bond and the carbonyl group separated by a three-membered ring has very little similarity with the combination of two double bonds and a carbonyl group in the ketone of structure:



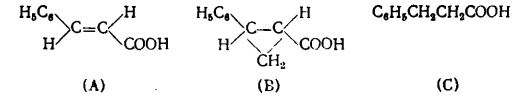
This was taken as evidence for the inability of the three-membered ring to transmit conjugation.

On the basis of their spectrographic studies of the ketones:



Mohrbacher and Cromwell[123] reached a different conclusion. A phenyl group in the β position of the cyclopropane ring shifts the absorption maximum in the ultra-violet bathochromically, which effect they ascribed to the ability of the three-membered ring to transmit the unsaturation of the phenyl group to the aroyl chromophore. Their point of view is shared by Cannon *et al.*[124]

Trachtenberg and Odian approached this problem using another, non-spectroscopic, method[125]. They studied the relative capacity of various substituents to affect the acidity of the carboxyl group in *trans*-cinnamic, *trans*-2-phenylcyclopropane-1-carboxylic, and β-phenylpropionic acids:



(A) (B) (C)

From the dissociation data of each acid series they calculated Hammett's constant (ρ) as: (A) 0.466; (B) 0.182; and (C) 0.204–0.212. Hammett's ρ constant for the cyclopropane series is very close to that for saturated analogues, so they concluded that the three-membered ring cannot transmit the conjugation effect, and that, like a saturated group, it isolates the carboxyl group from the influence of the phenyl ring.

This result, however, must not be taken as definite, since the comparison of Hammett's ρ constants for the alkaline hydrolysis of esters of the above acids led Fuchs and Blumfield[126] to an opposite conclusion. In their opinion the three-membered ring transmits conjugation, but much less so than the double bond.

Increase of the integral intensities of certain lines in Raman spectra is a far more sensitive criterion of the existence of conjugation than the bathochromic shift of the long-wavelength ultra-violet absorption bands. The absorption intensity for a double bond sharply increases (10–15 times) on conjugation with another double bond. This method is therefore well suited for the study of cyclopropane compounds, where conjugation is less pronounced. A systematic study of the conjugation of a three-membered ring by Raman spectra was carried out by Aleksanyan and his coworkers[127–130], and by Levina *et al.*[116,131,132]. From the spectrographic studies of systems such as vinylcyclopropane, isopropenylcyclopropane, and phenylcyclopropane, Aleksanyan and Sterin derived conclusive evidence of the existence of conjugation between a three-membered ring and a double bond or a benzene ring¶. The integral intensities of certain spectral lines of cyclopropane hydrocarbons and the corresponding model compounds are collected in Table 4. The intensities of the double bond lines of

TABLE 4.

Compound	Frequency, cm^{-1}		
	~1200	~1600	1640–1650
Pent-1-ene	—	—	340
Ethylcyclopropane	290	—	—
Vinylcyclopropane	430	—	660
2-Methylpent-1-ene	—	—	290
Isopropylcyclopropane	260	—	—
Isopropenylcyclopropane	410	—	620
Toluene	220	290	—
Isopropylbenzene	190	330	—
Phenylcyclopropane	800	1150	—

¶ This work was presented at the 10th All-Union Conference on Spectroscopy, 6th July 1956, and published in 1957 in the Report of the Conference. In 1957 there appeared in Vestnik Moskov. Gos. Univ., a paper by Levina *et al.*, in which, using the same method, they established the existence of conjugation between the three-membered and the benzene ring in arylcyclopropanes, particularly phenylcyclopropane.

vinyl- and isopropenyl-cyclopropane are nearly twice that of pent-1-ene and 2-methylpent-2-ene. The intensity of the lines in the ~1200 and 1600 cm^{-1} regions of phenylcyclopropane is even higher compared with that of alkylbenzenes of similar structure. The intensity of the lines in the ~1200 cm^{-1} region, which are due to the breathing frequency of the three-membered ring, are considerably higher in vinyl- and isopropenyl-cyclopropane than in alkylcyclopropanes, which emphasises the unsaturated character of the ring.

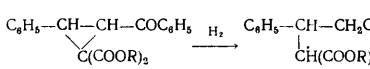
Aleksanyan and Sterin also studied the spectra of diphenyl- and phenylcyclopropyl-cyclopropanes and cyclopropane ketones. The reactivity of these compounds was studied simultaneously by Kazanskii, Lukina, and their coworkers, whose results will be discussed later in this review.

Levina, Treshchova, and their coworkers studied the Raman spectra of various arylcyclopropanes [116,131,132]. As mentioned earlier, this study included the ultra-violet spectra of these systems [116].

The presence of conjugation in a molecule can also be detected from other properties. Thus Rogers and Roberts [42] used dipole moments, and Kierstead *et al.* [133] and Kishner [110] the exaltation of molecular refraction. However, the validity of the latter method is controversial, since according to Jeffery and Vogel [134], and Slabey [135], exaltation of molecular refraction in the cyclopropane series may depend not only on conjugation, but also on the structure of the compound in question.

Kozina, Skuratov *et al.* [136] recently determined the heats of combustion of cyclopropane hydrocarbons, including phenylcyclopropane. This constant is also affected by conjugation.

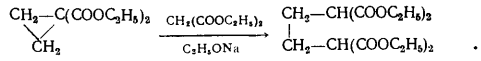
There is relatively little information in the literature on the reactivity of compounds in which the cyclopropane ring is adjacent to unsaturated groups. One of the first investigations in this field was carried out by Robinson [111], who interpreted several reactions in the terpene series by the conjugation of the three-membered ring with the double bond. In a number of examples Kohler and Conant [137] also stressed the analogy between α,β-unsaturated compounds and the cyclopropane derivatives containing a neighbouring C=O group. They carried out the reduction of a cyclopropane compound with nascent hydrogen which resulted in the opening of the three-membered ring:



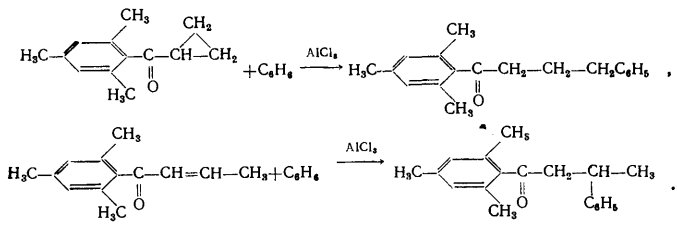
This reaction, one of the most specific for conjugated diene compounds may be taken as conclusive chemical evidence of the similarity between conjugation involving a three-membered ring and $\pi\pi$ conjugation. Nevertheless, attempts to add hydrogen in the 1,4-position of similar systems by reduction with metals in liquid ammonia were unsuccessful.

Greenfield *et al.* [138] observed that the action of sodium in liquid ammonia on vinylcyclopropane homologues resulted in the reduction of the double bond only. On reducing phenyl- and *p*-tolyl-cyclopropanes under similar conditions, Levina *et al.* [139] found that only the phenyl nucleus adds hydrogen. In both those cases the three-membered ring remained intact.

Bone and Perkin [140] showed that, like α,β-unsaturated esters, the diethyl ester of cyclopropane-1,1-dicarboxylic acid can add ethyl malonate, which contains a mobile hydrogen atom:

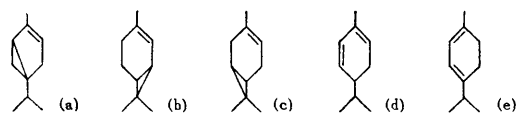


Fuson and Baumgartner [141] compared the behaviour of cyclopropyl mesityl ketone with that of mesityl propenyl ketone. Both ketones undergo condensation with aromatic hydrocarbons forming the corresponding butyromesitylenes:



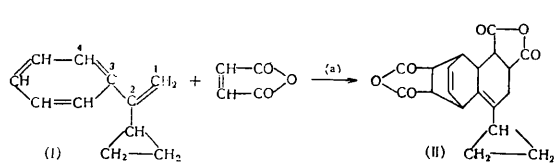
Cyclopropyl ketone does not, however, react with ethyl malonate or Grignard reagents, although α,β-unsaturated compounds do so.

In 1940 Gascoigne [142] reported that α-thujene, Δ^4-carene, and Δ^3-carene can take part in the Diels–Alder reaction with maleic anhydride or benzoquinone, forming adducts derived from α-phellandrene and α-terpinene:

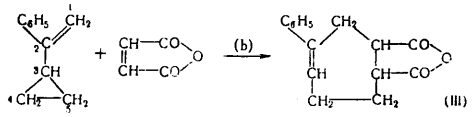


However, Trachtenberg and Odian [143] showed in 1958 that the above reaction is not a reaction of the Diels–Alder type involving systems of type (a), (b), and (c), since under the reaction conditions used (a), (b), and (c) undergo isomerisation to (d) and (e). Attempts to carry out the Diels–Alder reaction with vinylcyclopropane [144] or 1-phenyl-2-cyclopropylcyclopropane [120] were unsuccessful.

Sarel and Breuer [145] recently showed that vinylcyclopropane activated by a phenyl group is in fact an active conjugated system capable of taking part in the Diels–Alder reaction. For instance, on boiling for a long time with maleic anhydride in anhydrous benzene α-cyclopropylstyrene (I) reacts in two ways. The first yields 12% of the bis-adduct (II), in which the cyclopropane ring remains intact but the exocyclic double bond behaves as if conjugated with the aromatic nucleus. Addition takes place in the 1,4-position:

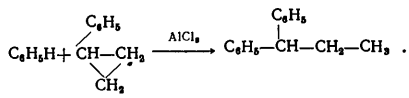


Another reaction simultaneously yields 40% of the adduct (III):

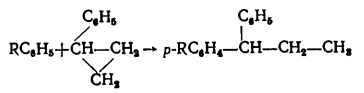


In the latter case the addition takes place in the 1,5-position and involves the exocyclic double bond and the cyclopropane ring, while the phenyl group remains intact.

Levina, Shabarov, and Shanazarova[146] studied the reaction of phenylcyclopropanes with benzene in the presence of aluminium chloride. Nenitzescu and coworkers[147] and Tsukervanik and Gar'kovets[148] had shown earlier that under those conditions styrene yields 1,1-diphenylethane. In this case also the double bond and the three-membered ring behave very similarly. Phenylcyclopropane yields 52% 1,1-diphenylpropane:



The yield of 1,1-diarylpropane is increased in the case of toluene (61.5%) and anisole (72.5%):



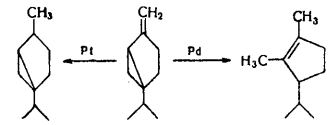
where R = CH_3; CH_3O. Alkylation proceeds only in the *para*-position of toluene and anisole, owing to the greater reactivity of the hydrogen atoms in that position.

Alkylation of benzene by *p*-tolyl- and *p*-anisylcyclopropane does not proceed as readily as that of phenylcyclopropane, and is accompanied by much polymerisation.

Levina and her coworkers[149] studied the reactivity of phenylcyclopropane in acylation by acetic anhydride in the presence of phosphoric acid and compared it with that of non-conjugated hydrocarbons of the cyclopropane series. Under the conditions employed, phenylcyclopropane underwent isomerisation, while the unsaturated hydrocarbons were acetylated.

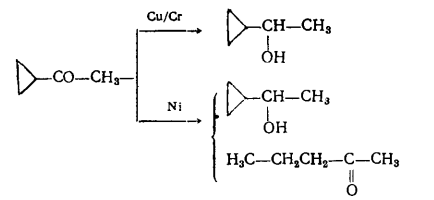
In their study of deuterium exchange in cyclopropane hydrocarbons in which the three-membered ring is conjugated with a multiple bond, Shatenshtein *et al.*[103] found that these systems are more reactive than alkylcyclopropanes in exchange reactions of this type.

The similarity between the behaviour of cyclopropane hydrocarbons containing unsaturated groups and that of conjugated systems is also observed in catalytic reductions. Richter *et al.*[150] found that the reduction of sabinene† by platinum black in ether solution at room temperature yields thujane, while reduction under the same conditions with palladium black yields an unsaturated hydrocarbon of the cyclopentane series. The authors think that in the latter case hydrogen is added on in the 1,4-position of the conjugated system ▷—C=C:



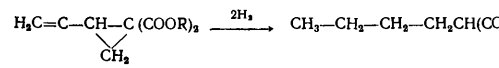
Later Short and Read[151] obtained the same results on hydrogenating sabinol with Adams catalyst.

In the hydrogenation of vinylcyclopropane and isopropenylcyclopropane over Raney nickel, Boord and his colleagues[144,152] discovered that besides alkylcyclopropanes the reaction product also contained alkanes. They think that this may be the result of addition of hydrogen in the 1,4-position of the starting hydrocarbons, assuming conjugation between the ring and the double bond. Hydrogenation of cyclopropyl methyl ketone led Slabey and Wise[153] to the same conclusion. They observe that, depending on the catalyst, hydrogen is added either entirely to the double bond of the carbonyl group (copper–chromium catalyst), or simultaneously to the carbonyl group and the three-membered ring (Raney nickel):



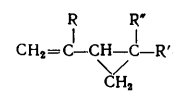
The same authors[154] found that hydrogenation of 2-cyclopropylalk-1-enes in the presence of copper–chromium catalyst yields the corresponding cyclopropylalkanes. Hydrogenated under the same conditions, 2-cyclopropylalk-2-enes gave, however, only small amounts of alkanes. The authors think that here also hydrogen is added in the 1,4-position.

The work of Kierstead *et al.*[133] is worthy of note. They found that under identical conditions of hydrogenation conjugated cyclopropane rings undergo opening, while non-conjugated ones do not. Unfortunately, their results are not very clear, since they used a rather complex starting compound:



where the three-membered ring is one of several unsaturated groups.

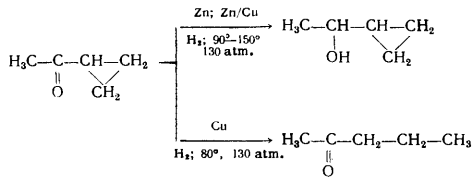
Nickl[155] succeeded in opening the three-membered ring of compounds of type



where R = CH_3; R′ and R″ = $COOC_2H_5$; or R = CH_3; R′ = CN; and R″ = $COOC_2H_5$, by hydrogenation under similar conditions. The two last groups of authors assumed that the first stage of hydrogenation consists of the addition of hydrogen in the 1,4-position of the conjugated system formed by the three-membered ring and the double bond.

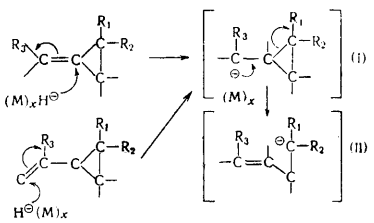
† I.U.P.A.C. name for compound shown is thuj-4(10)-ene (Ed. of Translation).

Freidlin *et al.*[156] studied the hydrogenation of cyclopropyl methyl ketone in the presence of Zn, Zn/Cu, and Cu catalysts and found that depending on the catalyst the reaction could proceed along different pathways:



Freidlin *et al.*[157] had shown earlier that during the hydrogenation of α,β-unsaturated ketones in the presence of zinc or zinc–copper catalyst, hydrogen is added to the carbonyl group, while in the presence of copper the double bond is hydrogenated first. The behaviour of cyclopropyl methyl ketone in this reaction is therefore very similar to that of α,β-unsaturated ketones.

In 1959 Ullman[158] expressed a different view of the hydrogenation mechanism for alkenylcyclopropanes. On the basis of the existing information that certain alkylidenecyclopropanes[159,160], like alkenylcyclopropanes, may undergo ring opening during hydrogenation under mild conditions, he suggested that the hydrogenation of both types of compounds proceeds *via* a common intermediate. Hydrogenation is preceded by the chemisorption of the organic molecule by the catalyst, which is followed by the attack of the hydride ion at the catalyst on the double bonds of vinyl- or alkylidene-cyclopropane. The result is the formation of the carbanion–metal complex (I). The carbanion may subsequently ring open to yield (II), or add a proton from the catalyst (or solvent) to form the "normal" 1,2-addition product:



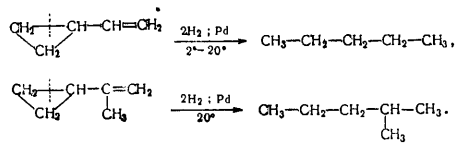
Protonisation of the decomposition product (II), and the concomitant saturation of the double bond must yield acyclic compounds. Taking as evidence his own results on the hydrogenation of certain alkylidenecyclopropanes, and published data on the hydrogenation of alkenylcyclopropanes, the author concluded that identical substituents had the same effect on the reaction course of both types of compounds, and thus confirmed his hypothesis on the mechanism of hydrogenation of alkenyl- and alkylidene-cyclopropanes. Unfortunately the author's own experiments were conducted under a different set of conditions and in the presence of various catalysts, so that they cannot be taken as reliable evidence of the effect of substituents. Ullman's hypothesis concerning the hydrogenation mechanism thus still remains to be proved.

As noted earlier, the catalytic hydrogenation and isomerisation of cyclopropane hydrocarbons has been long investigated by Kazanskii, Lukina, and their coworkers.

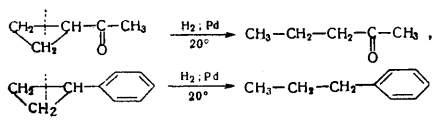
Since they used simple compounds and strictly standard reaction conditions they were able to compare the behaviour of various compounds. They observed that the principles underlying the behaviour of a great many alkylcyclopropanes do not hold for compounds in which the three-membered ring is adjacent to an unsaturated group. The reactivity of these systems is completely different, and can only be interpreted in terms of a unique type of conjugation.

The enhanced reactivity of such systems in catalytic reactions might not be sufficiently conclusive of conjugation had these investigations not been supported by studies of Raman spectra[127–130], by studies of reactivity and of deuterium exchange with potassium amide in liquid ammonia[103], and by the determination of heats of combustion[136]. The results of all these investigations accord well with the data on reactivity in catalytic hydrogenation.

In the presence of palladium black and hydrogen at room temperature, conditions which leave saturated cyclopropanes unaffected, conjugated cyclopropanes readily undergo hydrogenation and concomitant ring opening at the bond adjacent to the substituent. Alkenylcyclopropanes (vinyl-[161] and isopropenyl-cyclopropane[58]) react with two moles of hydrogen forming the corresponding alkanes:



Cyclopropyl methyl ketone[162] and phenylcyclopropane[163] react with one mole of hydrogen forming 2-butanone and n-propylbenzene, respectively.



Thus, on hydrogenation in the presence of palladium black, conjugated cyclopropane hydrocarbons and ketones show high reactivity, which is manifested in the readiness of the three-membered ring to open with the addition of hydrogen under conditions where a non-conjugated ring stays intact.

Palladium is a specific catalyst for this reaction. In the presence of other metals hydrogenation of conjugated cyclopropane compounds is very slow and non-specific. For instance, in the presence of platinum black, phenylcyclopropane[163] undergoes hydrogenation at one-ninetieth the rate in the presence of palladium, and the composition of the reaction mixture obtained shows that besides the cyclopropane ring, the benzene nucleus has also been hydrogenated.

Of special interest in these studies was the hydrogenation of diphenylcyclopropanes[164]. Here conjugation is only possible if the axes of the π clouds in the ring and the substituent are parallel or nearly so, that is, conjugation depends on the mutual orientation of the benzene and cyclopropane rings[128,163], as shown in Fig. 17.

Owing to steric effects, in disubstituted cyclopropane hydrocarbons the mutual orientation of these rings may assume different forms. Simple calculations show that not all conformations are possible in the *cis*-isomer because of the vicinity of the hydrogen atoms of different benzene rings (Fig. 18). In the *trans*-isomer, all conformations are possible since these rings are separated (Fig. 19). As a result, one of the substituents, or to a less extent both,

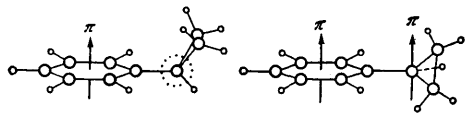


Fig.17.

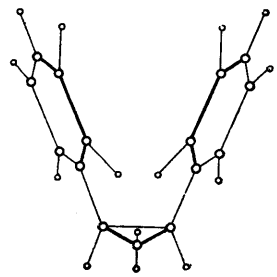


Fig.18.

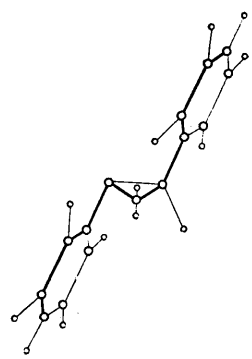
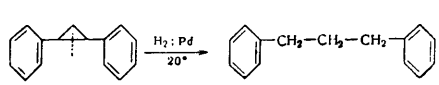


Fig.19.

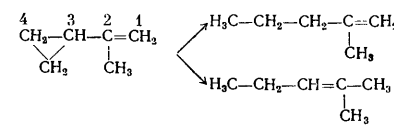
can be prevented from taking up a position suitable for conjugation. On these considerations it was possible to predict that conjugation could not take place in 1,1-diphenylcyclopropane, since the only possible spatial arrangement of the two phenyl groups is the one where the axes of their π clouds are not parallel with the plane of the three-membered ring.

All these considerations were confirmed by spectrographic studies [128,129] and later by catalytic hydrogenation [161]. In the latter reaction, 1,1-diphenylcyclopropane behaved as a non-conjugated hydrocarbon and did not combine with hydrogen, whereas 1,2-diphenylcyclopropane was hydrogenated:



The hydrogenation of *trans*-1,2-diphenylcyclopropane is considerably faster than that of the *cis*-isomer, and the latter is slower than the hydrogenation of phenylcyclopropane. This indicates that in the *cis*-isomer the optimum conditions for conjugation are disturbed for both phenyl rings. The reactivity of diphenylcyclopropanes therefore depends on the position of substituents in space, which accords well with the theoretical representations of the structure of a three-membered ring, which require the π electron cloud of this ring to be in the ring plane.

To explain the mechanism of hydrogenation of conjugated cyclopropane compounds in the presence of palladium black, partial hydrogenation of isopropenylcyclopropane was carried out in the presence of less than stoichiometrical amounts of hydrogen. In addition to unreacted isopropenylcyclopropane and 2-methylpentane, the reaction products also contained 2-methylpent-1-ene and 2-methylpent-2-ene.



2-Methylpent-1-ene may be formed by the addition of hydrogen in the 3,4-position, and 2-methylpent-2-ene as a product of 1,4 addition. However, it was established in a separate experiment that in the presence of palladium both hexenes are interconvertible, and form an equilibrium mixture. Each may therefore be considered as a secondary reaction product formed by the shift of the double bond. Nevertheless, experiments on incomplete hydrogenation showed that the three-membered ring undergoes hydrogenation first, and not the double bond in the substituent, otherwise the reaction product would contain isopropylcyclopropane. This indicates the special lability of a three-membered ring conjugated with an unsaturated group, as under the conditions employed in these experiments unconjugated three-membered rings resist hydrogenation, and double bonds are readily hydrogenated.

To conclude, the conjugation effect of the three-membered ring with unsaturated substituents during hydrogenation in the presence of palladium is manifested in the fact that the C–C bonds of cyclopropane are considerably weaker and affect the ring stability.

It was noted earlier [68-70] that the opening of the three-membered ring at the bond between carbon atoms carrying the largest and the smallest number of hydrogen atoms is typical of hydrogenation. However, it was not possible to study isomerisation in the presence of palladium, since in the absence of hydrogen, palladium caused no change in compounds under investigation, while in the presence of even small amounts of hydrogen it caused hydrogenation. Therefore, kieselguhr was used to study conjugated compounds under isomerisation conditions. A new interesting phenomenon was observed; in the presence of kieselguhr at 120° vinyl- [165] and isopropenyl-cyclopropane [166] are rapidly polymerised, *i.e.* they undergo a reaction most characteristic for conjugated systems. In addition to polymer, the catalysate also contains non-conjugated and conjugated diene hydrocarbons. In fact, under identical conditions the transformations of a conjugated hydrocarbon (isomerisation and polymerisation) are considerably more rapid than the transformations of the corresponding alkylcyclopropane (isomerisation).

Thus, this reaction also shows that the presence of conjugation considerably enhances the reactivity of a three-membered ring by lowering its stability.

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It is evident from this review of published information that the three-membered ring undoubtedly possesses unsaturated character, similar to that of the double bond. The unsaturation, however, is less pronounced in the cyclopropane series than in alkenes, as is brought out by the fact that the majority of reactions typical of alkenes are less marked in the cyclopropane series.

Investigations of systems in which the three-membered ring is conjugated with neighbouring unsaturated groups now being carried out by a great many methods (absorption and Raman spectra, dipole moments, heats of combustion, reactivity), show conclusively the existence of a similarity between these and conjugated systems. This is the most telling evidence in favour of the similarity of the three-membered ring and the double bond.

The experimental data discussed above are in good agreement with theoretical representations of the structure of a three-membered ring and give support to the basic ideas in the hypotheses of Walsh and Coulson and Moffitt.

It follows from the above considerations of their electron structure and properties that cyclopropane and its derivatives cannot be classified as cycloalkanes, a term used for alicyclic hydrocarbons. In fact cyclopropanes can only formally be classified with other polymethylene compounds (including cyclobutanes) in which the small distortions of the valence angles in the ring cause considerably less important changes in the hybridisation at the carbon atoms.

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ORGANIC COMPOUNDS OF BERYLLIUM, CALCIUM, STRONTIUM, AND BARIUM

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INTRODUCTION

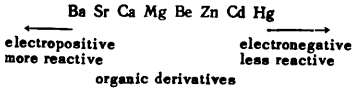
The immense part played by magnesium compounds in modern organic chemistry is well known. The number of papers on methods of obtaining organomagnesium compounds, their structure, properties, and especially their use in organic synthesis is continually increasing and has reached many thousands[1]. Such intensive development of the chemistry of these compounds is explained by their extraordinarily high reactivity, which enables numerous derivatives of the most varied classes of compounds to be readily obtained.

In contrast to magnesium, the remaining elements of its subgroup received little attention, and it is only recently that the chemistry of the organic compounds of beryllium, calcium, barium, and strontium has begun to be developed. It therefore seems useful to make a short survey of the present position in this field, especially as its literature is scattered among various journals, which are often not readily available. The review by Jones and Gilman[2] considers very briefly only methods for obtaining these organometallic compounds, and the review published by Novoselova *et al.*[3] in 1958 deals only with organic compounds of beryllium.

The present review examines only compounds containing a carbon–metal bond. Thus it is not concerned with salts of organic acids, metal alkoxides, or similar compounds, nor with many complex compounds.

Since there are only a small number of publications we divide the review according to the metals. Each section includes methods of preparation, physical and chemical properties, and also (where information is available) the fields of application of the organometallic compounds.

The organic compounds of both subgroups of metals in Group II show a clear connection between reactivity and change in electronegativity of the elements[4].



Organic compounds of the more electropositive elements — calcium, strontium, and barium — are quite like those of lithium and sodium in their ability to add to ethylenic bonds and in metallations, although in general they are some somewhat less reactive. Beryllium, like magnesium, forms organic compounds which are essentially covalent in structure and are relatively reactive, although inferior to organomagnesium compounds in this respect.

ORGANIC COMPOUNDS OF BERYLLIUM

Formally, the chemistry of organoberyllium compounds is entitled to celebrate its centenary, since the earliest publications date from 1860–1861. However, this work was not fully confirmed subsequently, and it can hardly be doubted that the pioneers of the organic chemistry of beryllium were not dealing with individual compounds.

Interest in the chemistry of beryllium has grown especially during the past 10–15 years. This is due both to general progress in the chemistry of organometallic compounds and to the importance which beryllium has acquired in modern technology: its uses in the form of the especially heat-resistant beryllium bronzes, and in the production of atomic energy[5] as radium–beryllium neutron sources and also as moderators in nuclear reactors[6], are well known. The heat and corrosion resistance of beryllium are important in the construction of nuclear reactors. However, the brittleness of metallic beryllium and its oxide restrict their application.

Modern technology requires in many instances extremely pure metals. In this respect the organic chemistry of beryllium may be of interest even to metallurgists, since conversion of a metal into an organic compound may provide a method of purifying the metal.

Beryllium compounds are toxic, the resulting poisoning being known as "berylliosis". In the acute form the symptoms are similar to those of chlorine poisoning. Chronic forms of beryllium poisoning have been described, in which the characteristic signs of the illness develop over several years[6].

The number of organic compounds of beryllium known to date is small. They can all be included in one of two classes of compounds, symmetrical beryllium dialkyls or diaryls R_2Be, and mixed organoberyllium compounds RBeX, where X represents a halogen or an amino-group; unsymmetrical compounds RBeR′ have not yet been described.

The observation by Cahours[7] of the reaction of beryllium with ethyl iodide on being heated in a sealed tube must probably be regarded as the first mention of the formation of an organoberyllium compound. Under these conditions a solid product was formed, which on distillation gave a liquid that vigorously decomposed water with the evolution of a flammable gas. Frankland[8] in his review points out the analogy between this reaction and the action of aluminium on ethyl iodide, but emphasised that formation of diethylberyllium was not confirmed by analysis.

It was shown much later that reaction of metallic beryllium with alkyl halides leads not to beryllium dialkyls but to mixed organoberyllium compounds RBeHal.[9]

At the present time the following methods are available for obtaining organoberyllium compounds.

1. Reaction of metallic beryllium with dialkyl[10-12] or diaryl[13] derivatives of mercury in a sealed tube heated to 130°–150° (with the dialkyls) or 225° (with the diaryls). In order to obtain a purer product, it is advisable to remove the resulting metallic mercury with gold foil[14]. Traces of mercuric chloride act as catalyst in the preparation of beryllium diaryls[13].
2. Beryllium dialkyls are readily obtained by a Grignard reaction, by the interaction of anhydrous beryllium chloride or bromide with the corresponding alkylmagnesium halide[13,15]. The process must be carried out in anhydrous ether in an atmosphere of dry nitrogen or hydrogen. A disadvantage of this method is that the substance is isolated in the form of an addition compound with ether, from which it is very difficult to remove the ether. Therefore all workers who have used this method describe in detail procedures for obtaining the purest products; their methods will be noted in describing the preparation of individual beryllium dialkyls.

A related method is the synthesis of diphenylberyllium by the reaction of beryllium chloride with phenyllithium in ethereal solution[16].

Apart from these two main methods of synthesis, dialkylberyllium compounds are formed when alkylberyllium halides are cautiously heated[9], and also by the interaction of free methyl or ethyl radicals with metallic beryllium[17].

In the early 1930s a method was patented[18] for obtaining organoberyllium compounds by fusing beryllium oxide with carbon compounds which do not contain oxygen (saturated and unsaturated, and also cyclic and acyclic, hydrocarbons, nitro-compounds, primary and secondary amines, etc.). The reaction can be carried out in an inert organic solvent; metal oxides or salts of inorganic acids can be used as catalysts. In the case of benzene, the reaction is written as follows

$$2C_6H_6+BeO \rightarrow Be(C_6H_5)_2+H_2O.$$

No confirmatory results have appeared during recent years, and one agrees with Novoselova[3], who stresses that this mode of synthesis seems very improbable owing to the extreme sensitivity of organoberyllium compounds to moisture.

Comparatively recently a patent has been granted for the preparation of organoberyllium compounds of general formula BeR_2 by the addition of alkenes to BeH_2. The resulting compounds, containing a carbon–beryllium bond, can be used as catalysts for the polymerisation of alkenes and as intermediates. Thus diethylberyllium at 100° for 82 h adds to 2-methylpent-1-ene $C_3H_7.C(CH_3):CH_2$ to form the dialkylberyllium $C_3H_7.C(CH_3)(C_2H_5).CH_2.Be.C_2H_5$.[19]

The preparation of beryllium analogues of Grignard reagents, alkylberyllium halides, is difficult. All these compounds, like the magnesium derivatives, are extremely reactive, and are not isolated as pure substances, so that their formation can be demonstrated only indirectly, on the basis of various reactions.

In Gilman and Schulze's method[9] alkylberyllium halides are obtained by the prolonged heating (at 150°), in a sealed

tube, of finely divided metallic beryllium with the corresponding alkyl or aryl halide in the presence of ether and a catalyst ($HgCl_2$, free bromine, $BeCl_2$).

At room temperature dimethylberyllium is a solid, the remaining beryllium dialkyls being liquids which can be distilled *in vacuo*. They are soluble in most organic solvents and are associated in solution, the extent of association depending on the nature of the solvent and the time during which the solution has been allowed to stand[20].

The organic compounds of beryllium are quite reactive, in this respect approaching lithium derivatives in several reactions, and magnesium derivatives in some cases.

Beryllium dialkyls are extremely sensitive to moisture, some of them reacting extremely vigorously, even explosively, with water; hydrolysis results in the formation of the corresponding hydrocarbons. Beryllium dialkyls react with hydrogen peroxide in ether solution to form beryllium peroxide[21]. Reaction with phenyl isocyanate in ethereal solution yields the corresponding anilides[13].

In their reaction with ethylene[22,23] beryllium dialkyls resemble more closely aluminium and lithium compounds than those of magnesium, since the last do not show the stepwise addition of the alkene characteristic of the alkyl derivatives of the other three metals:

$$RM + CH_2{=}CH_2 \rightarrow RCH_2CH_2M \qquad (M = \text{metal})$$

$$RCH_2CH_2M \xrightarrow{C_2H_4} R(CH_2CH_2)_2M \xrightarrow{C_2H_4} R(CH_2CH_2)_3M.$$

Ziegler mentions in his review[22] that the beryllium dialkyls react with the higher alkenes, but these reactions have not been investigated in greater detail.

Reactions of beryllium derivatives resulting in the formation of hydrides have been quite fully studied; beryllium hydride is obtained in particular by the pyrolysis of beryllium dialkyls.

The considerable electronic unsaturation of the beryllium dialkyls readily leads to the formation of coordination compounds with electron-donating substances[24]. This electron deficit, caused by the fact that the total number of electrons is less than double the number of bonds present[25], also explains the strong association of organoberyllium compounds and the ease of formation of spiro-compounds, like the complexes described by Bähr and Thiele[26].

Beryllium dialkyls give an immediate positive reaction with Michler's ketone[13]; diaryl derivatives do not give satisfactory results with this colour reaction[27].

The compounds of mixed type, RBeX, are in general less reactive than the corresponding R_2Be derivatives[9]. They are decomposed by water with formation of the corresponding hydrocarbons. Their ethereal solutions do not fume in air, but if the ether is removed and the liquid residue heated, white fumes are evolved, probably of beryllium oxide. Cautious heating converts alkylberyllium halides into beryllium dialkyls. In contrast to the latter, which give an immediate colour reaction with Michler's ketone, the halides give a positive result only after 10–15 min.[9]

The elementary analysis for carbon and hydrogen in organoberyllium compounds is difficult because of their peculiar properties, and requires the application of special techniques[28].

Very little information is available on the practical applications of organic beryllium derivatives. According to the patent literature[29-31] organoberyllium compounds R_2Be, where R is an alkyl or an aryl group, may be used as initiators for the dimerisation and the polymerisation of individual alkenes and alkene mixtures. In particular, it is claimed that diethylberyllium, diphenylberyllium, and sodium triethylberyllate may be used to activate the dimerisation of propene[32]. The use of mixed catalysts of $(C_2H_5)_2Be$ and $TiCl_4$ for the polymerisation of propene has been patented. The molar ratios of these compounds determine the length of the induction period in the polymerisation[33].

In 1931 a method was patented for obtaining metallic beryllium from its organic compounds[18], and in 1957 Wood and Brenner[16] described the electrodeposition of beryllium and its alloys from solutions of its inorganic and organic compounds in various solvents. The best results (beryllium contents up to 95%) were obtained by electrolysis of a mixture of dimethylberyllium and beryllium chloride in ethereal solution. Solutions of diphenylberyllium are electrically conducting, but, in contrast to dimethylberyllium, the metal cannot be electrodeposited from them.

Dimethylberyllium $(CH_3)_2Be$

Dimethylberyllium was first obtained by Lavrov[11,12] in 1884, by the reaction of dimethylmercury and metallic beryllium. This method has recently been found[14] to give a high degree of purity (97%) and a quantitative yield. It has been used to prepare radioactive dimethylberyllium containing ^7Be.[34] Schulze[35] prepared dimethylberyllium by the reaction of beryllium with dimethylmercury containing traces of mercurous iodide. It has also been obtained by a Grignard reaction[13,35]. In order to obtain the compound free from ether, the distilled reaction product is heated at 100°–125°, when most of the ether is expelled and the whole of the solution is suddenly converted into a mass of white needles containing some ether, which can be removed by heating to 200°. At this limiting temperature the compound begins to sublime rapidly; the yield of dimethylberyllium is 85–90%.[13] In order to remove the ether more effectively, it is advisable to pass a current of dry nitrogen through the reactants[36]. Changes in the conditions of the Grignard reaction have no great effect on the yield of dimethylberyllium[16].

At room temperature dimethylberyllium is a solid. It crystallises from hot ether solution as snow-white crystals, and forms similar crystals on sublimation[13].

X-Ray structural analysis suggests[37,38] that dimethylberyllium has a chain structure in which the CH_3-groups are arranged tetrahedrally about the beryllium. The C–Be–C angle, 114°, is rather greater than the tetrahedral angle, while the Be–C–Be angle is 66°. The Be–C distance in the electron-deficient bond is 1.93 Å. This structure is consistent with the rule that electron-deficient bonds arise because metals having fewer valency electrons than low-energy orbitals utilise the latter for bond formation.

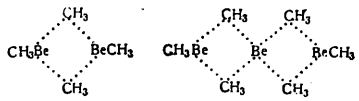
The body-centred orthorhombic unit cell of dimethylberyllium is characterised by the constants $a_0 = 6.13$, $b_0 = 11.53$, and $c_0 = 4.18$ Å, and is of the SiS_2 type[37,39].

Coates *et al.*[40] measured the vapour pressure and vapour density of dimethylberyllium and determined its degree of association and several physical constants. Above 200° the compound shows signs of thermal decomposition. The vapour pressure can be represented by the equation

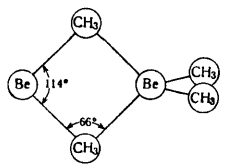
$\log p$ (mm) = 12.530 - 4771/T over the range 100°–155°, and by $\log p$ (mm) = 13.292 - 5100/T over the range 155°–180°. An equilibrium between monomer and dimer is established in the vapour; a certain amount of trimer is also present. At 180° the saturated vapour consists of 41% of monomer +44% of dimer +14% of trimer; at 160° the corresponding percentages are 27, 50, and 23%.

The heat of sublimation of dimethylberyllium is 23.5 kcal × × mole^{-1}, and the extrapolated sublimation point 217°. The heat of formation of the dimer from the monomer is 24 kcal × × mole^{-1}, and that of the trimer 45 kcal mole^{-1}. The entropy changes accompanying formation of the dimer and the trimer are 50 and 93 e.u. respectively[40].

The following structures have been suggested for the dimer and the trimer in the vapour state[40].



Dimethylberyllium is sparingly soluble in benzene, and is readily polymerised in solution. Polymerisation probably takes place by a chain mechanism, which can be represented as follows[20]: the dimer, having the structure



would add a further $(CH_3)_2Be$ molecule at the beryllium atom possessing an incomplete electron octet. The resulting trimer adds the next dimethylberyllium molecule, and polymerisation continues in this manner. The fact that true polymerisation is taking place follows from the observation that the molecular weight is independent of the concentration of dialkyiberyllium in solution.

From the net charge on the methyl group (-0.250) dimethylberyllium occupies an intermediate position between the methyl derivatives of magnesium and of aluminium[41].

Dimethylberyllium ignites spontaneously in air, especially in a moist atmosphere. It reacts with CO_2 in ether solution, yielding (after hydrolysis) acetic acid[13]; with phenyl isocyanate it forms the corresponding anilide, with 1-naphthyl isocyanate *N*-naphth-1-ylacetamide, with benzophenone 1,1-diphenylethanol, and with benzoyl chloride it yields 1-methyl-1-phenylethanol. Dimethylberyllium reacts vigorously with iodine, probably forming methylberyllium iodide[13].

Like the Grignard reagents, dimethylberyllium does not react with diphenylethylene or with diphenyl sulphone, but it does react with azobenzene[42]. The reaction was carried out in ethereal solution in a sealed tube at room temperature. After the reaction mixture had been allowed to stand for 7 days, analysis showed that two molecules of azobenzene had reacted with one molecule of dimethylberyllium, and the following equation was suggested

$$2C_6H_5N{=}NC_6H_5+(CH_3)_2Be \rightarrow \begin{matrix} C_6H_5N(CH_3)NC_6H_5 \\ | \\ Be \\ | \\ C_6H_5N(CH_3)NC_6H_5 \end{matrix}.$$

The reaction of dimethylberyllium with lithium tetrahydroaluminate in ethereal solution can be used to obtain beryllium hydride[36], but the product is contaminated with ether. In an attempt to prepare BeH_2 free from ether, the reaction was carried out with liquid $(CH_3)_2AlH$ in the absence of solvent. Although trimethylaluminium was formed, as indicated by the equation

$$2(CH_3)_2AlH+(CH_3)_2Be \rightarrow 2Al(CH_3)_3+BeH_2,$$

a product free from methyl groups was not obtained, perhaps owing to the intermediate occurrence of the reversible reaction:

$$(CH_3)_2AlH+(CH_3)_2Be \rightleftarrows CH_3BeH+Al(CH_3)_3.$$

Burg and Schlesinger showed[43] that dimethylberyllium reacts with diborane, the reaction taking place in several stages. Initially a vitreous mass is formed, containing a high percentage of methyl groups, which then changes into a mobile, non-volatile liquid. When this is further treated with diborane, an unstable solid is obtained which sublimes readily, and which analysis shows to correspond to the formula CH_3BeBH_4. This substance reacts vigorously with diborane yielding the final product, a volatile beryllium hydroborate BeB_2H_3 with a certain amount of a non-volatile substance, probably $(BeBH_5)_x$. In addition, trimethylboron and a methylated diborane are formed. These workers represent the overall reaction by the scheme

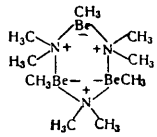
$$[Be(CH_3)_2]_x \xrightarrow{B_2H_6} (CH_3)BeBH_4 \xrightarrow{B_2H_6} HBeBH_4 \xrightarrow{B_2H_6} (BH_4)Be(BH_4),$$

with the reservation that it does not claim to represent the reaction mechanism or the structure of the products.

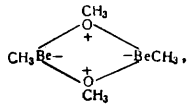
The considerable electron deficiency of dimethylberyllium results in its readily forming coordination complexes, as Coates and Huck[24] have shown, with trimethylamine, trimethyl phosphite, and dimethyl and diethyl ethers. The stability of these complexes diminishes in the sequence N > P > O. The affinity of trimethylamine for dimethylberyllium is sufficient to break down the polymeric structure of the latter, and it therefore yields a volatile substance to which can be assigned the structure $(CH_3)_2Be^- - N^+(CH_3)_3$, whereas the weak donor properties of trimethyl phosphite result in its forming a series of coordination compounds with different Be : P ratios. The formation of an unstable compound $[(CH_3)_2Be]_2[N(CH_3)_3]_3$ [24] has also been demonstrated. Dimethylberyllium does not form coordination complexes with trimethylphosphine or with dimethyl sulphide[24].

Dimethylberyllium reacts with methylamine, dimethylamine, dimethylphosphine, methanol, methanethiol, and

also HCl to give methane and dimeric, trimeric, or polymeric products. Dimethylamine yields a trimeric compound $[CH_3BeN(CH_3)_2]_3$, to which may be assigned the cyclic structure:



Methyl alcohol gives the dimer $(CH_3Be.OCH_3)_2$



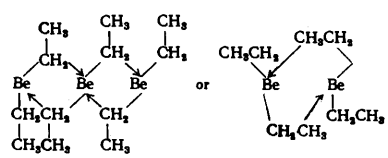
which readily disproportionates into dimethylberyllium and beryllium dimethoxide. The other substances mentioned yield non-volatile or relatively non-volatile products which undoubtedly have a polymeric structure[44].

The reaction of dimethylberyllium with an ethereal solution of hydrogen peroxide yields a gelatinous precipitate of beryllium peroxide[21].

Diethylberyllium $(C_2H_5)_2Be$

In 1873 Cahours[10] published a synthesis of diethylberyllium by means of an organomercury compound, the product being distilled in an atmosphere of carbon dioxide. Later, however, Gilman and Schulze[13] were unable to repeat this synthesis, and they prepared diethylberyllium by a Grignard reaction. Their product was a colourless liquid boiling at 93°–94°/4 mm, and at 110°/15 mm; under atmospheric pressure it distils between 180° and 240° with considerable decomposition. Some of the purest material solidifies in a solid CO_2/ether mixture to form white crystals melting between -13° and -12°.[13] Goubeau[45] obtained diethylberyllium by carrying out the reaction with excess of ethylmagnesium bromide in nitrogen. The purest product, containing only 2% of ether, was obtained by leaving diethylberyllium for 6 days after separating most of the ether, and then distilling at 0.3–0.5 mm; the yield was 80–90%.

Diethylberyllium containing ~2% of ether boils at 63°/0.3 mm and sets to a glass at -80°.[45] Its high boiling point compared with those of diethylzinc and diethylmercury, and also the fact that the pure substance boils at a higher temperature than its ether complex, indicate strong association This explains the formation of a glass on setting and the stable link with ether. Goubeau suggests the following structures for the associated molecules



and points out that, since such molecules terminate in a beryllium atom with coordination number 3, which means that it is coordinatively unsaturated, it is able to add ether, the ratio of ether to diethylberyllium depending on the different lengths of the polymer chain and varying between 1 : 2 and 1 : 50.

Diethylberyllium is monomeric in dioxan, but is associated in cyclohexane and in benzene[20], its molecular weight in these two solvents being 160 and 140 respectively two days after preparation of the solution, and 212 and 224 after 240 days (the molecular weight of the monomer is 67.1).

The dipole moment of diethylberyllium in various solvents is intermediate between that of the corresponding derivatives of magnesium and of zinc. Its moment is 1.0 D in heptane (the monomer is not present), 1.69 D in benzene, and 4.3 D in dioxan[46,47].

Diethylberyllium is a very reactive compound[45]. It reacts with water extremely violently, sometimes even explosively. Methyl and isopropyl alcohols react with it at -80° extremely vigorously with formation of fumes; with ethyl alcohol the reaction takes place more smoothly. At the temperature of liquid air HCl reacts forming beryllium chloride, but the reaction does not proceed to completion, since the resulting $BeCl_2$ envelops the particles of diethylberyllium and prevents further reaction. With diethylamine the reaction goes smoothly with the evolution of ethane; this substitution occurs to the extent of 75%, and it is only on heating that it can with difficulty be made complete. With triethylamine neither heat nor gas is evolved, but some of the amine probably reacts, since it cannot all be recovered. Reaction of diethylberyllium in ethereal solution with CO_2 yields triethylmethanol, the anilide being obtained with phenyl isocyanate, and diphenylmethanol with benzophenone[13]. This last reaction is supposed to involve the intermediate formation of free radicals. Diethylberyllium reacts vigorously with iodine, and also with excess of an ethereal solution of beryllium chloride, probably yielding the corresponding ethylberyllium halides[13].

Pyrolysis of diethylberyllium[45] at 190°–200° evolves ethylene, ethane, and but-2-ene in the proportions 1 : 2 : 1.5 and ether†; the Raman spectrum indicates that hex-3-ene, cyclohexa-1,3-diene, and benzene are also present. From one molecule of diethylberyllium about 0.9 ethyl group is involved in the formation of gaseous products, the residue being a mixture of a viscous oil boiling at 95°–100°/0.1–0.2 mm having the composition $(HBeCH_2CH_2BeH)_x$ and a crystalline deposit of $[HBe_2(CH_2)_3]_x$ or $[Be_2(CH_2)_3]_x$.

Diethylberyllium reacts readily with diphenylamine in benzene with the evolution of ethane and the formation of bisdiphenylamideberyllium $Be[N(C_6H_5)_2]_2$.[48]

Addition of hydrogen peroxide to an ethereal solution of diethylberyllium first causes the appearance of a brown coloration, and then the precipitation of a solid deposit of beryllium peroxide[21].

Dipropylberyllium $(n\text{-}C_3H_7)_2Be$

The only reference to the synthesis of this compound occurs in the paper by Cahours[10], who, on heating metallic beryllium with dipropylmercury in a sealed tube at 130°–150°, observed the rapid disappearance of the metal and the appearance of metallic mercury. After distilling twice in an atmosphere of carbon dioxide (?), a colourless liquid was obtained boiling at 244°–246°. It fumed strongly in air, but did not ignite. On being cooled to -17° it became a thick oily liquid, but did not solidify. It was violently

† Present in the original compound as an impurity (Ed. of Translation).

decomposed by water with evolution of gas and formation of a deposit of beryllium hydroxide on the walls of the vessel.

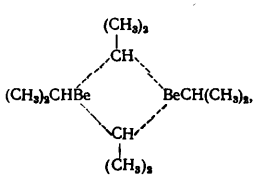
Diisopropylberyllium (iso-$C_3H_7)_2Be$

This compound has been obtained by the Grignard method[49]. It retains ether very strongly, for distilling twice and treatment in a vacuum for two days yields a product containing 16% of ether; complete elimination requires refluxing for two days with continuous removal of ether in a vacuum. The product melts at -9.5° and has a b.p. of 280° (extrapolated value). The vapour pressure is 0.17 mm at 20°, and 0.53 mm at 40°; it can be represented by the equation $\log p = 7.01 - 2280/T$. The heat of vaporisation, ΔH, is 10.45 kcal mole^{-1}. When diisopropylberyllium is distilled *in vacuo*, slow decomposition with the evolution of propene is observed even at 40°; at 200° pyrolysis takes place rapidly according to the equation:

$$n\ (\text{iso-}C_3H_7)_2Be \rightarrow 2/n\ (\text{iso-}C_3H_7BeH)_n + 2C_3H_6.$$

Isopropylberyllium hydride is a colourless, non-volatile, viscous oil, which hydrolyses [pyrolyses? (Ed.of Translation)] to beryllium, propane, and hydrogen, and is obviously polymeric. Pyrolysis of this hydride at 220°–250° does not yield beryllium hydride: the substance decomposes into metallic beryllium, hydrogen, propane, propene, and an organic residue.

Diisopropylberyllium dissolves readily in benzene, in which it is dimeric, the degree of association being independent of the concentration. The structure of the dimer is represented[49] as



i.e. as being analogous to the structure of dimethylberyllium in the vapour state. The Be–C–Be bond is formed by the sp^2 orbitals of the beryllium and the sp^3 orbitals of the carbon, so that each Be–C bridge may be regarded as a half-bond. The decrease in the degree of association on passing from a methyl to an isopropyl derivative of beryllium is probably associated not only with a steric effect but mainly with a decrease in the electronegative character of the alkyl group.

Like dimethylberyllium, diisopropylberyllium forms a 1 : 1 addition compound with trimethylamine, which is somewhat more volatile and thermally stable than the dialkyl itself; the addition compound is monomeric in benzene, and decomposes on being heated to 100°.

Although uncontrolled hydrolysis of diisopropylberyllium occurs explosively, the reaction with methanol involves the smooth evolution of one mole of propene and the formation of isopropylberyllium methoxide, which consists of crystals melting at 133°. Reaction with dimethylamine is accompanied by the evolution of propane and the formation of dimethylaminoisopropylberyllium, a colourless liquid which at 100° loses propene with the formation of the vitreous polymeric dimethylaminoberyllium hydride‡. Diisopropylberyllium reacts with excess of dimethylamine to form the crystalline beryllium bisdimethylamide together with two molecules of propane.

Di-n-butylberyllium (n-$C_4H_9)_2Be$

Gilman and Schulze[13] were unable to obtain this compound *via* dibutylmercury, but synthesised it by a Grignard reaction in an atmosphere of dry nitrogen. Dibutylberyllium is a colourless liquid with a mercaptan-like odour; it can be distilled in a vacuum, boiling point 170°/25 mm. It does not ignite in air, but is rapidly oxidised with the evolution of heat. It reacts vigorously in ethereal solution with phenyl isocyanate, yielding the corresponding anilide.

Di-t-butylberyllium (t-$C_4H_9)_2Be$

This compound was first obtained by Coates and Glockling[50] by the Grignard reaction. However, their product contained a large quantity of ether (up to 30%), and a special method was subsequently worked out for preparing pure di-t-butylberyllium from its ether addition compound by treating the latter with anhydrous beryllium chloride[51]; the ether addition compound of t-butylberyllium chloride is apparently formed as a by-product.

The ether complex of di-t-butylberyllium, containing 51–52 mole % of the beryllium dialkyl, is a colourless transparent liquid of density 0.78 g cm^{-3}. It is stable on storage[51].

The ether-free di-t-butylberyllium is a colourless, transparent, mobile liquid, of density 0.65 g cm^{-3}, freezing at -16°. The vapour pressure of the freshly prepared material is ~35 mm at 25°. At room temperature it slowly decomposes with the evolution of isobutane and apparently polymerisation of the remaining liquid[51].

Hydrolysis of di-t-butylberyllium gives complete decomposition into isobutane and isobutene in the molar ratio 60 : 1, whereas hydrolysis of the ether adduct yields 36.1% of ether and isobutane and isobutene in the molar ratio 4 : 1.[51]

In contrast to diisopropylberyllium, the di-t-butyl derivative does not yield the half-hydride $(CH_3)_3CBeH$ on thermal decomposition, but smoothly forms isobutene and beryllium hydride, in which, however, some butyl groups remain, since hydrolysis of this hydride yields a little isobutene[50]

$$[(CH_3)_3C]_2Be \rightarrow BeH_2 + 2(CH_3)_2C{=}CH_2.$$

The ratio of t-butyl groups to hydrogen atoms in the product decreases with increase in the temperature of pyrolysis: at 150° the product contains 89 mole % of beryllium hydride, whereas on pyrolysis at 210° the proportion is 96 mole %.

Vacuum pyrolysis of di-t-butylberyllium containing no ether gave beryllium hydride in yields up to 80%.[51]

Trimethylamine displaces ether from its addition compound with di-t-butylberyllium[50] with the formation of a readily volatile crystalline compound, which is probably a highly symmetrical di-t-butylberyllium–trimethylamine.

‡ Presumably dimethylamidoberyllium hydride, $(Me_2N.BeH)_n$ (Ed. of Translation).

Diphenylberyllium $(C_6H_5)_2Be$

Diphenylberyllium has been synthesised by heating metallic beryllium with an equivalent quantity of diphenylmercury in the presence of traces of mercuric chloride as catalyst[13] in a sealed tube at 225°. Wood and Brenner suggested a method for obtaining this compound by the reaction of beryllium chloride with phenyllithium in ethereal solution[16].

The dipole moment of diphenylberyllium is 1.64 D in benzene and 4.33 D in dioxan[46]. This compound, just like diethylberyllium, is acting here as an electron-acceptor in the intermolecular exchange interaction with solvents which act as electron-donors. In heptane, which possesses no electron-donor properties, the dipole moment of diphenylberyllium is zero[47].

Data have been published on the infra-red spectrum of diphenylberyllium[52].

In its addition reactions with benzylideneacetone and with *p*-(dimethylamino)benzylideneacetone, diphenylberyllium, like the magnesium, aluminium, zinc, and manganese compounds, shows almost exclusively 1,4-addition, giving respectively a 90% yield of ββ-diphenylpropiophenone§ and a 71% yield of β-dimethylaminophenyl-β-phenylpropiophenone¶[53]. Diphenylberyllium reacts symmetrically with azobenzene, the metal adding at the azo-bond, and ultimately forming hydrazobenzene in 55.4% yield[54]. The presence of diphenylberyllium changes the course of the reaction between triphenylmethylsodium and isoprene, with the predomination of 1,4-addition (not 1,2) and the formation of 3-methyl-5,5,5-triphenylpent-2-ene[55].

Wittig has shown[56,57] that diphenylberyllium reacts in ethereal solution with phenyllithium to give lithium triphenylberyllate $Li[Be(C_6H_5)_3]$. This is a solid which crystallises from dioxan with four molecules of the solvent, and from xylene without solvent molecules; in the latter case it is quite stable to heat and remains unchanged up to 200°, whereas diphenylberyllium starts to decompose at 160°.[57] In the light of these results, the possibility of obtaining pure diphenylberyllium by Wood and Brenner's method is open to doubt. Lithium triphenylberyllate is not in equilibrium with its ligands, since it does not form a fluorenyllithium complex with fluorene, and does not yield phenylacetic acid after carboxylation[56,57]. It is less stable than its aluminium analogue, and reacts slowly with benzophenone, giving a 31% yield of triphenylmethanol[57]. In the reaction of the addition compound with benzylideneacetophenone the yield of the diphenylpropiophenone† was 41%, whereas diphenylberyllium itself gave a yield of 58%.[57] The stability of the complexes decreases in the sequence $Li[Al(C_6H_5)_4]$, $Li[B(C_6H_5)_4]$, $Li[Zn(C_6H_5)_3]$, and $Li[Be(C_6H_5)_3]$.[58]

Cyclic ethers have been cleaved by the action of pairs of antagonistic Lewis bases and acids — triphenylmethylsodium with triphenylboron, diphenylberyllium, or triphenylaluminium[59]. The action of the pair triphenylmethylsodium–diphenylberyllium on benzofuran gave an 83% yield of 1-[*o*-hydroxyphenyl]-3,3,3-triphenylpropane. The reactivity of the complexes falls in the sequence $Na[(C_6H_5)_3.AlC(C_6H_5)_3]$, $Na[(C_6H_5)_3BC(C_6H_5)_3]$, and $Na[(C_6H_5)_3BeC.(C_6H_5)_2]$. This sequence agrees neither with that of the electrophilic character of the complexes nor with that for their activity as polymerisation initiators.

Fusion of diphenylberyllium with lithium hydride yields lithium diphenylhydroberyllate $Li[BeH(C_6H_5)_2]$,[60] which can be recrystallised from ether. This hydride reacts vigorously with water with the evolution of hydrogen, and has therefore been used as a reducing agent for phenylnonatetraenoylcarbazole, giving a 37% yield of 9-phenylnonatetraenal.

Di-*p*-tolylberyllium $(p\text{-}CH_3C_6H_4)_2Be$

This compound is readily obtained by reaction between metallic beryllium and di-*p*-tolylmercury[13].

Dicyclopentadienylberyllium $(C_5H_5)_2Be$

This compound was prepared in 1959 in 74% yield by reaction between beryllium chloride and cyclopentadienylsodium in ether[61]. Initially an attempt had been made to obtain the dicyclopentadienyl derivative by passing cyclopentadiene over metallic beryllium under various conditions (150°–550°, at atmospheric pressure and *in vacuo*), but without success. A very low yield of dicyclopentadienylberyllium is formed by reaction between beryllium chloride and cyclopentadienylpotassium under almost completely heterogeneous conditions.

Dicyclopentadienylberyllium consists of colourless crystals, which sublime in a high vacuum at 25°–60°.[61] It dissolves in benzene, ether, and in petroleum ether, from which it can be recrystallised on cooling to -60°. In such solvents as carbon disulphide, carbon tetrachloride, methylene chloride, and tetrahydrofuran, slow decomposition ensues with the formation of yellow solutions. If a solution of $(C_5H_5)_2Be$ in tetrahydrofuran was left for not more than 15 min, a good yield of unchanged dicyclopentadienylberyllium could be recovered unchanged after removal of the solvent and sublimation of the residue, but if the solution was left for a long period, a yellowish gel was formed, from which the substance could not be isolated. This explains the previous unsuccessful attempts to prepare dicyclopentadienylberyllium in tetrahydrofuran. $(C_5H_5)_2Be$ is extraordinarily sensitive to the presence of oxygen; water decomposes it rapidly with the formation of beryllium hydroxide.

The physical properties of dicylopentadienylberyllium have been studied in detail[61]. In an atmosphere of nitrogen or in a high vacuum it melts at 59°–60°; the boiling point is 233° (by extrapolation). The vapour pressure obeys the equation $\log p = 8.2242 - 2671/T$ over the range 110°–190°. Cryoscopic measurements in benzene indicate the absence of association between $(C_5H_5)_2Be$ molecules.

The following values have been obtained for the magnetic susceptibility of dicyclopentadienylberyllium[61]

$$\chi_M^{291°K} = (-107 \pm 4) \times 10^{-6} \text{ cm}^3 \text{ mole}^{-1},$$

$$\chi_M^{190°K} = (-99 \pm 4) \times 10^{-6} \text{ cm}^3 \text{ mole}^{-1},$$

$$\chi_M^{77°} = (-86 \pm 4) \times 10^{-6} \text{ cm}^3 \text{ mole}^{-1}.$$

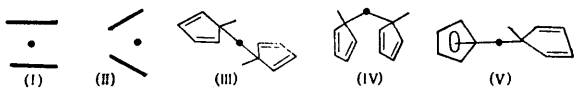
§ Presumably benzyl 2,2-diphenylethyl ketone is intended (Ed. of Translation).

¶ Presumably benzyl 2-*p*-(dimethylamino)phenyl-2-phenylethyl ketone is intended (Ed. of Translation).

† Phenyl 1,2,2-triphenylethyl ketone? (Ed. of Translation).

In contrast to the analogous compounds of magnesium and iron, which possess no dipole moment, the $(C_5H_5)_2Be$ molecule is unsymmetrical, having a dipole moment at 25° of 2.46 ± 0.06 D in benzene, and 2.24 ± 0.09 D in cyclohexane[62]. The infra-red spectrum of solid $(C_5H_5)_2Be$ contains many intense bands in the region of the C–C bond, at 1524, 1610, 1669, 1715, and 1773 cm^{-1}, the spectrum differing substantially from those of ferrocene and dicyclopentadienylmagnesium[61]. Thus a purely organometallic structure for dicyclopentadienylberyllium is evidently excluded. The suggestion has been made[61] that the bond between beryllium and the cyclopentadienyl rings involves π electrons, but it is stressed that a structure with non-parallel rings, analogous to that accepted for $(C_5H_5)_2Pb$ and $(C_5H_5)_2Sn$, cannot be excluded. The latter hypothesis has been confirmed by the nuclear magnetic resonance spectrum of dicyclopentadienylberyllium, which contains only one proton line[63].

Fritz and Schneider have investigated the far infra-red spectra of dicyclopentadienyl compounds, and found[64] with $(C_5H_5)_2Be$ a weak band at 662 cm^{-1}, a very weak band at 587 cm^{-1}, and a band of medium intensity at 414 cm^{-1}. They have considered the spectra and the values found for the force constants in relation to the various possible positions of the cyclopentadienyl rings with respect to the metal atom, and also conclude that, of the possible structures (I)–(V) for dicyclopentadienylberyllium, the structure (II) is the most probable, the angle between the rings being ~90°.

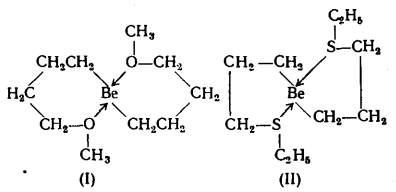


Reaction between $(C_5H_5)_2Be$ and ferrous chloride in tetrahydrofuran gives a 19% yield of ferrocene; if ferric chloride is used in the presence of iron powder, the yield of ferrocene is 76%.[61]

There is mention of the existence of a bismethylcyclopentadienylberyllium $(CH_3.C_5H_4)_2Be$, which is liquid at room temperature[61].

Spiro-Compounds of Beryllium

Bähr and Thiele[26] have synthesised di-(4-methoxybutyl)-beryllium (I) and di-(3-ethylthiopropyl)beryllium (II):



The first compound can be obtained in 45% yield by the reaction of beryllium chloride with $CH_3O[CH_2]_4MgCl$ in ether; alternatively, beryllium chloride can be treated with $CH_3O[CH_2]_4Cl$ (the process is strongly exothermic), and then magnesium added to the intermediate complex, but the yield is then considerably lower (22%). The second substance is obtained by the Grignard method according to the equation

$$2C_2H_5S(CH_2)_3MgCl+BeCl_2 \rightarrow II+2MgCl_2.$$

The reaction can be carried out in dimethyl sulphide or in ether, the yields being 35% and 60% respectively.

Di-(4-methoxybutyl)beryllium and di-(3-ethylthiopropyl)-beryllium are liquids which are completely miscible with isooctane (2-methylheptane), ether, and benzene, and possess comparatively low boiling points, in the first case 108°/4 mm and 222°–224°/765 mm, and in the second 122°–123°/2 mm and 220°–225° at 760 mm, the latter compound being so stable to heat that in an atmosphere of nitrogen it boils without appreciable decomposition (*cf.* diethylberyllium, which boils at 93°–95°/4 mm)[26]. On being cooled to -60° and -80° respectively, the two substances first set to a glassy mass, but when the temperature is raised to -40° and -30° they pass into a crystalline state. The first substance melts at 7.5°–7.8°, and the second at 7°–8°. The compounds fume in air and even ignite. On contact with water they strongly deflagrate. However, they are less reactive than the lower beryllium dialkyls. They are monomeric in benzene[26].

Alkylberyllium and Arylberyllium Halides RBeHal

As stated above, these compounds are known only in the reaction mixture, their formation being demonstrated by analysis of the decomposition products and by their participation in various reactions, in particular the test with Michler's ketone.

In 1923 Gilman reported an unsuccessful attempt to prepare alkylberyllium halides by the interaction of metallic beryllium with methyl and ethyl iodides, phenyl bromide and chloride, tolyl bromide, and finally 1-bromonaphthalene[65]. Reaction was carried out in various solvents at temperatures up to 245°–250°, the duration of heating being varied from 12 h to 2 weeks. Formation of RBeHal was checked by the colour test with Michler's ketone, but in no experiment was any evidence obtained of reaction between the beryllium and the alkyl or aryl halide. In the same paper Gilman, referring to private communications, enumerated a series of equally unsuccessful attempts by other workers (Grignard and others) to obtain compounds of the type RBeHal. The use as catalyst of free bromine, iodine, dimethylaniline, or even a freshly prepared Grignard reagent was also unsuccessful[65].

In 1926 Durand[66] reported the synthesis of methylberyllium iodide by heating metallic beryllium with methyl iodide in the presence of mercuric chloride; a grey mass was formed, which was insoluble in ether, and which on treatment with HCl evolved a gas which burned in oxygen to carbon dioxide. However, Durand's results were soon disputed by Gilman and Schulze[9], who obtained a series of alkylberyllium and arylberyllium halides (CH_3BeI, C_2H_5BeI, $n\text{-}C_4H_9BeBr$, and C_6H_5BeI) by heating metallic beryllium with the corresponding alkyl or aryl halide in the presence of a catalyst and ether in a sealed tube. Phenylberyllium iodide is formed particularly readily on heating to 150°–170° in the presence of mercuric chloride or beryllium chloride as catalyst. t-Butyl chloride and bromide probably react with metallic beryllium when heated (at 80°–90°) for 15 h, but the reaction mixture does not give the colour test with Michler's ketone[67]. Under similar conditions benzyl bromide and n-butyl chloride showed no signs of

reaction[9]. The use of ether as solvent is probably not essential, since methylberyllium iodide was successfully prepared by heating a mixture of beryllium, mercuric chloride, and a large excess of methyl iodide in a sealed tube‡[35].

In contrast to magnesium, metallic beryllium does not react with alkyl halides under the influence of ultrasonic vibrations[68].

The ether addition compound of t-butylberyllium chloride was probably obtained by Head *et al.*[51] on treating the di-t-butylberyllium–ether with beryllium chloride; it is a volatile white solid melting at 50° and subliming in a vacuum at a considerably lower temperature.

There are indications of the formation from beryllium chloride and chloroform of CCl_3BeCl at 25° and of $(CCl_3)_2Be$ at a higher temperature, but neither of these compounds has been isolated. With bromoform beryllium chloride yields Br_3CBeCl.[69]

From the facts of the formation of beryllium dialkyls by the cautious heating of alkylberyllium halides, and of the formation of the latter when beryllium dialkyls are treated with beryllium halides, it was suggested that the following equilibrium can exist[9,34]

$$2AlkBeHal \rightleftarrows Alk_2Be + BeHal_2.$$

Until quite recently alkylberyllium halides were assigned the structure RBeHal, but in 1960 Dessy[70] showed, by using $^7BeBr_2$, that no isotopic exchange occurs in the $(C_6H_5)_2Be$–$BeBr_2$ system, and hence that an equilibrium of the Schlenk type

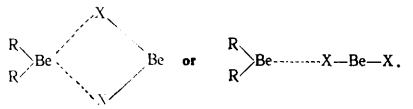
$$R_2M + MX_2 \rightleftarrows 2RMX,$$

where M = metal and X = halogen, is absent.

Thus true organoberyllium compounds of mixed type do not exist; such compounds must be assigned a complex structure $R_2Be.BeX_2$, and the existence of the following equilibrium assumed

$$R_2Be + BeX_2 \rightleftarrows R_2Be \cdot BeX_2.$$

In Dessy's work the presence of the complex $(C_6H_5)_2Be.BeBr_2$ follows also from the fact that beryllium bromide gives a two-phase system in ether, which is converted into a single phase on the addition of diphenylberyllium. The structure of this complex has not yet been determined, but it can be presumably represented[70] as



The alkylberyllium halides are decomposed by water with the formation of the corresponding hydrocarbons[35]; their reaction with Michler's ketone is slow at room temperature, but becomes rapid on heating; they do not react with carbon dioxide, but with phenyl isocyanate they give the corresponding anilides[35]. It is concluded[35] that, on the whole, the alkylberyllium halides are less reactive than the beryllium dialkyls or the corresponding organomagnesium compounds.

‡ It has been shown recently that alkylberyllium halides can actually be obtained by boiling alkyl halides with metallic beryllium in the complete absence of catalysts; L.I. Zakharkin, O. Yu. Okhlobystin, and B. N. Strunin, Izv. Akad. Nauk SSSR, Otd. Khim. Nauk, 2254 (1961).

ORGANIC COMPOUNDS OF CALCIUM

Organic compounds of calcium are still less readily available and less well known than those of beryllium, most of the work in this field being concerned with the preparation of calcium analogues of Grignard reagents: only a few representatives of symmetrical compounds, R_2Ca, are known. The methods employed for preparing dialkyl and diaryl derivatives of beryllium are probably of little use for the preparation of the corresponding calcium compounds. Thus, for example, Schulze[35] obtained no evidence of the formation of calcium compounds when the metal was heated with the diethyl, di-n-butyl, diphenyl, and di-*p*-tolyl derivatives of mercury in a sealed tube. However, the search for methods of preparing organocalcium compounds may be expected to continue, since such compounds are of interest for synthetic purposes since an unusual orientation of the substituent occurs in addition reactions[53,71].

Dimethylcalcium $(CH_3)_2Ca$

Jones and Gilman[2], referring to the Rices' book[72], report that free methyl radicals react readily with metals, including calcium to form the corresponding methyl derivatives. In 1958 dimethylcalcium was prepared by the reaction of metallic calcium with methyl iodide in pyridine in an atmosphere of helium[73]. An insoluble dark precipitate first separates, from which iodine is removed by continuous extraction with fresh pyridine, and then the pyridine in a vacuum at 20°. A pale yellow residue is obtained containing up to 95% of dimethylcalcium. This deposit remains unchanged when heated in a vacuum to 400°; it is rapidly decomposed by water.

Diethylcalcium $(C_2H_5)_2Ca$

A 52.8% yield of this compound has been obtained by the action of calcium on diethylzinc in benzene[74]. Early work had indicated that a solution of diethylcalcium obtained by heating calcium with diethylzinc did not conduct electricity[75].

Diethylcalcium gives no colour reaction with benzylamine or dibenzylamine in petroleum ether, whereas diethylstrontium, diethylbarium, and diphenylbarium give such a reaction[76].

Calcium Acetylide $[Ca(C_2H)_2$ (Ed. of Translation)]

This compound can be obtained either by passing acetylene into a solution of calcium in ammonia, or else by adding the calcium solution to an ammoniacal solution of acetylene[77], the second method giving the more satisfactory results.

Diethyl sulphate reacts vigorously with calcium acetylide in liquid ammonia, giving the theoretical yield of pure but-1-yne; pentyl chloride and bromide also react well, as does butyl bromide, the yields of the corresponding acetylenes being 56%, 31%, and 45% respectively[77].

Dicyclopentadienylcalcium $(C_5H_5)_2Ca$

Ziegler and coworkers[78,79] reported that a suspension of calcium chloride in decalin reacts with a solution of cyclopentadiene in liquid ammonia to form $(C_5H_5)_2Ca.2NH_3$. The

very strongly held ammonia can be removed by heating in a high vacuum to 170°, or by prolonged refluxing in decalin. The ammonia-free dicyclopentadienylcalcium reacts with carbon dioxide yielding a dicyclopentadienedicarboxylic acid. In the presence of ammonia the carbamic acid which is first formed decomposes the $(C_5H_5)_2Ca$, so that cyclopentadiene and calcium carbamate result. The ammonia used in the preparation of $(C_5H_5)_2Ca$ can be replaced by diethylamine or ethylenediamine; in the latter case reaction can also be effected between dicyclopentadiene at 160° and calcium carbide[78]. The dicyclopentadienylcalcium obtained in this way is a yellowish-black powder contaminated with CaC_2, CaO, and other impurities; it smoulders in air. Its solubility is negligible.

Ziegler has also patented[79] the preparation under the above conditions of dicyclopentadienylcalcium in the form of a pale yellow powder which smoulders in air. Quite recently its preparation has been reported, in ~17% yield, by the action of metallic calcium on cyclopentadiene in tetrahydrofuran heated in an atmosphere of nitrogen[80]. A reddish 1 : 2 complex $(C_5H_5)_2Ca.2C_4H_8O$ is formed at first, but is unstable and loses tetrahydrofuran in a high vacuum at 110°. The product sublimes at 265° with partial decomposition and the formation of colourless crystals of pure $(C_5H_5)_2Ca$. The method[80] of obtaining dicyclopentadienylcalcium from calcium hydride and cyclopentadiene at 400° is less valuable for preparative purposes, since the yield is only 9.3%.

The spectrum in the far infra-red[64] confirms the ferrocene-like structure (I, see above) of dicyclopentadienylcalcium, and reveals the electrostatic nature of the bonds between the rings and the central metal atom. In contrast to the beryllium and magnesium derivatives, homopolarity of the bonds is not observed in the calcium derivative, and the salt-like character of the compounds is intensified[80].

Alkylcalcium and Arylcalcium Halides RCaHal

Beckmann[81] observed the formation of an amorphous white deposit when metallic calcium was heated with ethyl iodide in ether, and on the basis of an analysis assumed that it was an ether addition compound of ethylcalcium iodide $(C_2H_5)_2O.C_2H_5CaI$. However, Gilman and Schulze[27] showed later, using the colour test with Michler's ketone, that only traces of ethylcalcium iodide are formed in the solution in Beckmann's reaction, the precipitate being an ether complex of calcium iodide.

Gilman and Schulze[27] obtained butylcalcium iodide by the interaction of metallic calcium with butyl iodide in ether; the reaction started after 10 h, a considerable amount of an insoluble deposit being formed. After two days the reaction mixture was hydrolysed with dilute HCl, and n-octane was isolated from the ether layer, its amount indicating a 59% yield of the organocalcium compound.

The same workers observed a reaction between equimolecular quantities of calcium and octyl iodide in ether. After 24 h a heavy white deposit was formed, while the supernatant liquid gave a positive colour reaction for the presence of octylcalcium iodide; hydrolysis of the ether layer gave a 17.8% yield of hexadecane[27].

The course of the reaction between alkyl iodides and metallic calcium is very dependent on the grade of the calcium and on its state of division, as well as on whether the metal had been in contact with air and with traces of moisture. Greater amounts of iodine are required to catalyse the reaction than in the preparation of the corresponding Grignard reagents[27].

The technique for preparing the iodides was then improved[82] by introducing a seed, either RMgHal or previously prepared RCaHal. In addition, the condenser was closed by a tube immersed in mercury, which enabled the boiling point to be raised and the reaction to be accelerated somewhat. Under these conditions the following compounds react readily with metallic calcium (the use of shavings of size 0.2–0.5 mm is recommended): CH_3I, C_2H_5I, C_3H_7I, C_4H_9I, C_6H_5I, $CH_2:CHCH_2I$, iso-$C_5H_{11}I$, n-$C_8H_{17}I$, and m-$CH_3C_6H_4I$. The iodides $CH_3CHIC_2H_5$ and CH_3CHICH_3 do not react very well, while $C_2H_5CI(CH_3)_2$ and $(CH_3)_3CI$ do not react at all.

Bryce-Smith and Skinner[83] showed, from an investigation of the reaction between metallic calcium and alkyl halides, that the following factors facilitate the formation of alkylcalcium halides: activation of the calcium by heating (preferably in argon) at 150° with a few atomic per cent of mercury, the presence of a few atomic per cent of magnesium in the calcium, use of an ether as medium (in particular tetrahydrofuran), and finally the choice of a suitable temperature, which is different for different preparations, and in particular may be considerably below 0°. The catalytic effect of magnesium is explained[83] by the formation of traces of a Grignard reagent. Thus if the reaction is carried out between n-butyl iodide and calcium not containing magnesium as impurity (this is usually present in commercial calcium), traces of n-butylmagnesium iodide catalyse this reaction. The presence of traces of sodium in the calcium is undesirable, since this diminishes the yield of organocalcium compounds.

An attempt to prepare alkylcalcium halides by the action of ultrasonic vibrations on a mixture of metallic calcium and an alkyl halide was unsuccessful[68].

To prepare phenylcalcium iodide, iodobenzene is heated with metallic calcium in anhydrous ether, with addition of traces of iodine as catalyst[61]. Phenylcalcium iodide and also calcium dialkyls give a positive reaction with Michler's ketone[27,67].

In an assessment of the prospects for the use of organocalcium compounds for preparative purposes, Gilman and Schulze[27] considered that attempts to use these compounds like Grignard reagents were doomed to failure. The main defects of substances of the RCaHal type were regarded as the following: (*a*) the formation of RCaHal is probably confined to the iodides; (*b*) only primary alkyl iodides react with calcium, and by no means all of these do so, benzyl iodide, for example, not reacting; (*c*) reaction between alkyl iodides and calcium is extremely slow and is accompanied by numerous side reactions, resulting in a low yield of the organocalcium derivative; and (*d*) alkylcalcium halides are in general less reactive than the corresponding magnesium compounds.

Further work, however, compelled a change in this opinion, and the recognition that phenylcalcium iodide is more reactive than the phenylmagnesium halide. This assertion is based on the following three reactions[84]: phenylcalcium iodide reacts more rapidly than phenylmagnesium bromide with benzonitrile; it metallates dibenzofuran in a similar manner to the organic compounds of lithium, sodium, and potassium, whereas the Grignard reagent does not react; and finally phenylcalcium iodide, like phenyllithium but in contrast to phenylmagnesium

bromide, adds to several double bonds, yielding, for example, triphenylmethylaniline with benzophenone-anil.

Compounds of the type RCaI are more convenient than the corresponding bromides or chlorides for synthetic purposes, since the latter react considerably more slowly[83]. Although preparations proceed more rapidly in tetrahydrofuran than in diethyl ether, the solution obtained in the former solvent is less stable owing to the greater rate of cleavage. Organocalcium compounds are closer to organolithium than to organomagnesium compounds in reactivity. This closeness appears, for example, in the cleavage of ethers and in the reactions with pyridine and with CO_2.[83] Phenylcalcium iodide reacts readily with pyridine at 5° and above, forming 2-phenylpyridine. With carbon dioxide the n-butylcalcium halide gives mainly di-n-butyl ketone and tri-n-butylmethanol: very little n-valeric acid is formed, even with a high rate of carboxylation. Phenylcalcium iodide and bromide, on the other hand, yield principally benzoic acid, in a similar manner to the organomagnesium compounds[81,83]. Like the corresponding magnesium compounds, n-butylcalcium and phenylcalcium iodides do not give a colour reaction with benzylamine or dibenzylamine in petroleum ether[76].

The reaction of benzaldehyde with methyl-, ethyl-, n-propyl-, and isopentyl-calcium iodides gave the corresponding α-alkylbenzyl alcohols in 30–40% yield[82].

Ethylcalcium iodide reacts with nitriles, giving ethyl phenyl ketone (yield 30%) with benzonitrile, and ethyl methyl ketone with acetonitrile[82]. With ethyl formate and ethyl acetate, ethylcalcium iodide forms the corresponding alcohols, pentan-3-ol and 3-methylpentan-3-ol, in 20% yield[82].

Reaction of butylcalcium iodide with ethyl methyl ketone gives a 40% yield of 3-methylheptan-3-ol.[82] It reacts with naphth-1-yl isocyanate forming *N*-naphth-1-ylvaleramide[27]. Phenylcalcium iodide reacts analogously with phenyl isocyanate to yield benzanilide[27]. An attempt to synthesise the imidic ester $C_6H_5.C(:N.C_6H_5).OC_2H_5$ by treating phenylcalcium iodide with phenyl isocyanate and then adding excess of diethyl sulphate was unsuccessful[27]. Phenylcalcium iodide reacts vigorously with benzoyl chloride, but greatly varying yields of triphenylmethanol are reported, from 1%[27] to 94%.[83] Triphenylmethanol is formed also by the reaction of phenylcalcium iodide with benzophenone (yield 16%) and with ethyl benzoate (yield 26%)[82]. Addition of benzaldehyde to an ethereal solution of phenylcalcium iodide results in the formation of diphenylmethanol by the reaction[81]

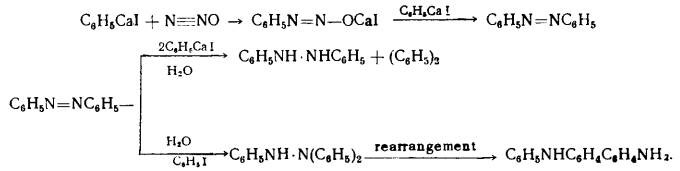
$$C_6H_5CaI + C_6H_5CHO \rightarrow C_6H_5CH(C_6H_5)OCaI,$$
$$C_6H_5CH(C_6H_5)OCaI + H_2O \rightarrow C_6H_5CH(C_6H_5)OH + ICaOH.$$

Dibenzofuran-4-carboxylic acid has been obtained by the action of phenylcalcium iodide on dibenzofuran, the resulting calcium derivative being treated with carbon dioxide[84].

Used of an organocalcium compound as metallating agent leads in some cases to an unusual orientation of the substituent. Whereas dibenzothiophen is metallated by diethylcalcium[85], as by butyllithium and potassium[86], in position 4, with phenylcalcium iodide metallation takes place in the 3-position, resulting in the formation on subsequent carboxylation of dibenzothiophen-3-carboxylic acid[71,85]. Phenylcalcium iodide adds to phenyl styryl ketone in the 1,2-position, with the formation of αα-diphenylcinnamyl alcohol[57]. The yield of this carbinol reaches 45%,[53] and with *p*-dimethylaminostyryl phenyl ketone 64% of *p*-dimethylamino-αα-diphenylcinnamyl alcohol is formed, *i.e.* 1,2-addition takes place in both cases[53].

In contrast to phenylmagnesium bromide, phenylcalcium iodide does not reduce azobenzene[87]; as in the case of phenylpotassium, unsymmetrical addition takes place, resulting in the formation of an 18.5% yield of triphenylhydrazine, 64.4% of the azobenzene being recovered unchanged[54].

Phenylcalcium iodide reacts with nitrous oxide[88]: biphenyl, azobenzene, *N*-phenylbenzidine, and benzidine have been isolated from the reaction mixture by means of chromatography, which enables the following scheme of reactions to be suggested



Dufford *et al.*[89] observed a feeble chemiluminescence during the oxidation of phenylcalcium iodide with oxygen, and the product of this oxidation also showed a weak fluorescence.

In conclusion we may mention the formation of organocalcium compounds by the action of metallic calcium on some phenylated alkenes in liquid ammonia[90]. Thus calcium adds to the ethylenic bond of 1,1-diphenylethylene, the solution turning red; after ammonolysis, 1,1-diphenylethane (70%) and 1,1,4,4-tetraphenylbutane (14%) were isolated from the reaction mixture. Addition of calcium to 1,1,2-triphenylethylene yields after ammonolysis 1,1,2-triphenylethane (40%).

ORGANIC COMPOUNDS OF BARIUM AND STRONTIUM

The first attempts to obtain dialkyl and diaryl compounds of barium and strontium were made as early as 1933. However, these compounds could not be obtained by reaction of the metal with the corresponding organomercury compounds[35]. The formation of organometallic compounds by the action of strontium and barium on 1,1-diphenylethylene in liquid ammonia was noted by Gilman and Bailie[90], since 1,1-diphenylethane and 1,1,4,4-tetraphenylbutane were isolated from the reaction mixture after ammonolysis. The analogous addition of strontium and barium to 1,1,2-triphenylethylene yields 1,1,2-triphenylethane; barium reacts also with triphenylmethane with the formation of traces of triphenylmethylbarium[90].

Dimethylbarium and dimethylstrontium were obtained only in 1958, in a similar manner to dimethylcalcium, by reaction of the metal with methyl iodide in anhydrous pyridine in an atmosphere of helium[73]. After extraction of iodine with fresh pyridine and removal of the latter in a vacuum, preparations of 95% purity were obtained, stable on heating in a vacuum to 400°, but unstable in the presence of moisture, oxygen, and carbon dioxide.

Diethylstrontium was obtained in the form of a complex with diethylzinc by heating metallic strontium filings with diethylzinc in benzene in an atmosphere of nitrogen in a

sealed tube[91]. A 51% yield of the complex $(C_2H_5)_2Sr.(C_2H_5)_2Zn$ was obtained as brown crystals which decomposed at 170° with the formation of a metallic mirror, the liberation of diethylzinc, and the evolution of a considerable quantity of gas. The complex is readily soluble in benzene.

In a similar manner diethylbarium and dibutylbarium were obtained by the reaction of barium with diethylzinc and dibutylzinc respectively[85]. Diphenylbarium could not be obtained by this method, but it was prepared from diphenylcadmium and barium[85].

Barium and strontium dialkyls and diaryls, and also phenylbarium iodide, give a positive reaction with Michler's ketone[27,67]. When a solution of diethylstrontium, diethylbarium, or diphenylbarium is shaken up with benzylamine or dibenzylamine in petroleum ether, a cherry-red coloration appears[76]. A similar reaction is given by alkyl and aryl derivatives of the alkali metals, but not by organocalcium or organomagnesium compounds.

Diethylstrontium and diethylbarium add to the olefinic bond in 1,1-diphenylethylene with the formation of organostrontium and organobarium compounds, which have been identified by carboxylation to the corresponding acid $(C_6H_5)_2C(C_3H_7)COOH$.[85,91] Diethylstrontium metallates anisole in the *ortho*-position with the formation of di-(*o*-methoxyphenyl)strontium; dibenzofuran and dibenzothiophen are metallated in position 4.[91] Diethylbarium also metallates anisole in the *ortho*-position[85]. The action of diethylbarium or diethylstrontium on methyl phenyl sulphide results in *ortho*-metallation in the ring with the formation of o-$CH_3SC_6H_4COOH$ after carboxylation[85].

Diethylbarium does not add to stilbene (in contrast to butyllithium and $\alpha\alpha$-dimethylbenzylpotassium)[85]. Diethylbarium and ethyllithium (but not diethylstrontium) to a limited extent add to styrene, yielding after carboxylation 2-phenyl-n-valeric acid[85]. Diethylstrontium and diethylbarium add to diphenylmethyleneaniline with the formation of the secondary amine $(C_6H_5)_2C(C_2H_5)NHC_6H_5$.[85] Addition to azobenzene results in 1-ethyl-1,2-diphenylhydrazine, which rearranges to *N*-ethylbenzidine[85].

With 1-bromonaphthalene an exchange reaction takes place with both metal diethyls and naphthoic acid can be isolated after carboxylation[85]. The following reaction also takes place in low yield[85]:

$$(C_6H_5)_3PbC_6H_4Br\text{-}p + (C_2H_5)_2Ba \xrightarrow[H_2O]{CO_2} (C_6H_5)_3PbC_6H_4COOH\text{-}p.$$

Exchange of the metals occurs in the reaction between tetraphenyltin and diethylbarium and diethylstrontium with the formation after carboxylation of benzoic acid in yields of 32% and 11% respectively[85]. Exchange reactions do not take place with tetraphenylsilane, tetraphenylgermanium, or tetraphenyllead. Triphenyltin chloride and diethylbarium give a good yield of ethyltriphenyltin[85]. Triphenyllead chloride yields not only ethyltriphenyllead but also an appreciable quantity of tetraphenyllead[85].

The preparation of barium acetylide has been mentioned, its formula in liquid ammonia being $Ba(C_2H)_2.4NH_3$.[92]

Just recently dicyclopentadienylstrontium has been prepared by the reaction of metallic strontium with cyclopentadiene in dimethylformamide at 50°. The resulting addition compound, a reddish substance, is heated at ~250° for 1 h, and a 4.1% yield of colourless crystals of $(C_5H_5)_2Sr$ is obtained by sublimation at 360°–440°. The yield of dicyclopentadienylstrontium obtained from strontium hydride and cyclopentadiene was ~1.4%.[80]

Dicyclopentadienylbarium has been obtained with great difficulty only by the action of barium hydride on cyclopentadiene at 400°.[80] Extraction with dimethylformamide and sublimation at 420°–460° gave a 0.2% yield of colourless crystals of $(C_5H_5)_2Ba$.

From the far infra-red spectra of these dicyclopentadienyls it has been concluded that their structure is analogous to that of dicyclopentadienylcalcium[64].

Attempts to prepare organostrontium and organobarium compounds by reaction of the metal with alkyl iodides were unsuccessful[35]. However, the reaction mixture obtained with ethyl iodide and barium gave a positive colour reaction, indicating formation of ethylbarium iodide[93].

Phenylbarium iodide is prepared from iodobenzene and barium[93], only the electrolytic metal being suitable. Several reactions of phenylbarium iodide have been studied[93]: carboxylation gives benzoic acid, naphthyl isocyanate yields *N*-1-naphthylbenzamide, and with ethyl benzoate triphenylmethanol is obtained. It is stressed[93] that it is more difficult to obtain phenylbarium iodide than phenylcalcium iodide, and that the former compound cannot compete with a Grignard reagent.

In 1936 Gilman *et al.*[84] suggested that organostrontium compounds should be more reactive than organocalcium compounds, but less reactive than the organobarium compounds. This postulate was later tested[74] in the case of the reaction between the phenylethynyl derivatives and benzonitrile:

$$(C_6H_5C{\equiv}C)_2M + C_6H_5CN \xrightarrow{H_2O} C_6H_5C{\equiv}CCOC_6H_5,$$

where M = Ba, Sr, Ca, Mg, and Be. The following reactivity sequence was established: $R_2BA > R_2Sr > R_2Ca > R_2Mg > R_2Be$. This sequence correlates with the ionisation potentials of the corresponding metals: Ba 5.19, Sr 5.67, Ca 6.09, Mg 7.61, and Be 9.28 eV. A decrease in the ionisation potential of a metal in this group results in greater reactivity of its simple organic compounds.

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Thus the general progress in the chemistry of organometallic compounds during recent years has made the organic compounds of the alkaline-earth metals more readily available. At the present time they are still unable to compete with the organomagnesium compounds; nevertheless, the possibility of using them in some syntheses is not excluded.

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PROGRESS IN THE CHEMISTRY OF LOCAL ANAESTHETICS IN THE LAST DECADE

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INTRODUCTION

It is now more than 80 years since the Russian doctor Vasili Konstantinovich Anrep† administered cocaine subcutaneously as an anaesthetic and thus initiated the use of local anaesthetics in surgery. Since that time, local anaesthesia has, of course, undergone a great evolution. In the search for new anaesthetics, less toxic than cocaine, many organic compounds of the most diverse kind have been synthesised and tested, and a large amount of valuable factual knowledge has accumulated on the relation between molecular structure and anaesthetic activity; many attempts have been made to elucidate the mechanism of anaesthetic action, and the methods of anaesthesia themselves have been perfected. Nevertheless, the problem of local anaesthetics remains important, because no single available preparation meets all modern clinical requirements.

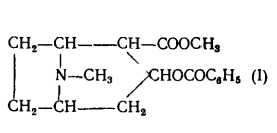
Progress in synthetic chemistry is so great and increasing so rapidly from day to day that it might be thought the time is not far off when the problem of synthesising the "ideal" local anaesthetic will be solved by the combined efforts of chemists and pharmacologists.

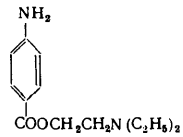
† Strange as it may seem, some authors outside the Soviet Union[1,2] still give priority for this discovery to Koller on the basis of a telegram he sent to the Congress of Ophthalmologists in Vienna in 1884. Not only was this report five years late, but Koller recommended a surface paint for the mucous membrane of the eye, whereas as early as 1879 Anrep first used a subcutaneous injection[3,4]; this was of fundamental importance in the practice of local anaesthesia[5].

In planning future developments, it is useful from time to time to review the past and to evaluate the present state of a problem under investigation. This review is devoted to the progress in the chemistry of anaesthetics over the past decade.

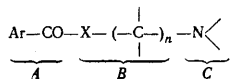
I. SOME THEORETICAL PRINCIPLES

The disadvantages of cocaine stimulated the search for new local anaesthetics, and at first the work was directed towards simplifying the cocaine molecule (I) to give norcocaine, eucaine A, eucaine B, and procaine (novocaine) (II)[6]:


(I)


(II)

Several active anaesthetics were synthesised. The presence of a common structure in all these compounds gave rise to the idea of a special "anaesthesiophore grouping" (III) responsible for the anaesthetic function, and made up of three component parts, acid *A*, alkyl *B*, and amine *C*.


(III)

where X = O, NH, S.

Cocaine, the eucaines, procaine, and also cinchocaine and amethocaine, which were discovered later, do in fact contain this grouping. However, there are many compounds with local anaesthetic activity in which it is not present. Amino-alcohols, amino-ketones, simple amines, and even compounds containing no nitrogen have been found to be more active than the well-known preparation; this shows that the principle of an essential anaesthesiophore grouping is clearly unsatisfactory. We estimate that in the past ten years more than 60% of the papers on the synthesis of new local anaesthetics have been concerned with compounds that do not contain this grouping. The compounds synthesised show great variations in physicochemical and physiological properties, such as the rate of penetration through the tissues, the duration of action because of differences in tissue fixation, the distribution coefficient between aqueous and non-polar phases, and side reactions of the tissues[2].

A large amount of experimental material has now accumulated on anaesthetics and this has resulted in efforts being made to set up a theory to explain the mechanism of their action and to provide a guide for chemists to useful synthetic approaches.

It is still not clear on what links of the reflex arc of the body local anaesthetics act. Many workers[7-9] consider that anaesthetics destroy the conduction of nerve fibre, either by prolonged depolarisation of the membrane, or by the opposite process of steady polarisation. In both cases, the transmission of the nerve impulse, which according to modern concepts[10] is related to temporary reversible polarisation of the cell membrane with corresponding changes in permeability, becomes impossible. It has been shown experimentally by several workers[11-14] that local anaesthetics do affect the permeability of the membrane to Na^+ and K^+ ions.

Other workers[15-16] consider that anaesthetics destroy nerve conductivity not in the fibre itself but in the cell synapses. It is now accepted that the synaptic transmission of an impulse is effected by special compounds called mediators (these include acetylcholine, adrenaline, and noradrenaline) that act directly on the receptors[17-20], or through certain enzyme cycles[21,22]. The anaesthetics may interfere with the production or the adsorption of the mediator[23,24], but their effect is more probably due to intervention in the enzyme cycle, which is thus interrupted[25]. This is confirmed by the action of local anaesthetics on many enzyme reactions[26-28] and also by the relation between anaesthetic and anticholinesterase effects[29,30]. The most likely hypothesis is that different local anaesthetics react by different mechanisms, depending on their structures and physicochemical properties. This is supported, on the one hand, by the great diversity of anaesthetics, and on the other hand, by the fact that the regularities in structure, physicochemical properties (dissociation constant[32,33], rate of hydrolysis[34,35], penetrating power[36-38], and others[39,40]), and activity established for some homologous series do not hold when applied to other classes of anaesthetics[31,41,42]. This appears to be related to a change in the mechanism of action of the anaesthetic, that is, a change in the way the nerve impulse is interrupted or inhibited, or in the site at which this occurs.

II. PROCAINE-TYPE COMPOUNDS‡

Although procaine is one of the most popular preparations, it has several great disadvantages, the main ones being its low surface anaesthetic activity, its depressor properties, and the short duration of its action; it must therefore be used in combination with adrenaline, which produces several side effects, especially complications in wound healing. For this reason, more and more work is done every year on the synthesis of procaine analogues with improved properties.

As already mentioned, the procaine molecule may be considered to consist of three component parts:

$$\underbrace{p\text{-}NH_2C_6H_4CO}_{A}\text{—}\underbrace{OCH_2CH_2}_{B}\text{—}\underbrace{N(C_2H_5)_2}_{C}$$

acid *A*, alkyl *B*, and amine *C*. Research on the effect of modifying different parts of the molecule on the activity of the compound has accordingly taken three main directions.

1. The Acid Component

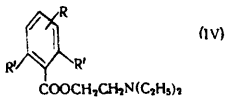
The problem that arose in the first instance concerning the part played by the aromatic radical may be considered to be largely solved. Notwithstanding isolated cases in which anaesthetic properties are shown by esters of cycloalkylcarboxylic acids[43-48], these properties are in the main characteristic of the aromatic series. Esters of aliphatic acids are virtually inactive§.

‡ Although, as will be clear from the foregoing, the division of anaesthetics into those having an anaesthesiophore grouping and those that have not is purely arbitrary, this division is used here for convenience of arrangement.

§ This applies to esters of monocarboxylic acids. Bisdialkylaminoalkyl esters of the aliphatic dicarboxylic acids, and even such derivatives as diethylaminoethyl ethyl malonate show considerable activity, although in these only one carboxyl is esterified by an amino-alcohol residue[52,53].

The nature and positions of the substituents in the phenyl radical of the acid greatly influence the activity. The introduction of alkyl groups such as isopropyl, or t-butyl into the *p*-position to increase the lyophylic properties of the molecule retards hydrolysis and enhances the infiltration activity[49,50], but at the cost of increased irritancy. The activity of the alkylamino-esters of the 2,3,5,6-tetraalkylbenzoic acids, which is much superior to that of procaine in duration[51], can be explained in the same way.

Recently the (trimethylsilyl)benzoates of some amino-alcohols[54] have been found to show pharmacological activity, the first to be observed in the organosilicon compounds. Several of the alkoxybenzoates having the general formula (IV):



(IV)

where R = *p*-AlkO—[55, 56, 59], *m*-CH_3O—[59], 3, 4-(CH_2O_2)[57, 58], *p*-$C_6H_5OCH_2CH_2O$—[59], 3, 4-$(CH_3O)_2$,[61] C_2H_5S,[62, 63] R′ = CH_2,[58] H,[57—63] CH_3O.[60].

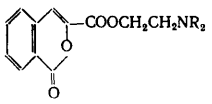
have been found to have therapeutic value.

The anaesthetic action of these compounds depends on the alkoxy-radical, reaching a maximum in the *p*-hexyloxybenzoates (see Table 1)[55]. The introduction of the *p*-phenoxyethoxy-groups into the benzoic acid nucleus prolongs the activity up to six weeks or more; in the words of the authors[59], after this time "muscular control is lost over the injection area and the animal is completely insensitive to stimulation in this area". The *p*-alkylthio-derivatives[62,63] are of great interest in this class of compounds; the diethylaminoethyl ester of *p*-ethylthiocinnamic acid is five times as effective as procaine intravenously and 20 times as effective as cocaine topically[63]; also of interest are the dialkoxybenzoates, in which the increase in activity is related to an increase in the distribution coefficient between a non-polar and an aqueous phase[61].

Recently, most work has been devoted to the aminobenzoic acid esters, as the most closely related to procaine. A survey of the work done shows that alkylation of the amino-group and introduction of hydroxy- and alkoxy-residues or halogens into the aminobenzoic acid nucleus leads to compounds some of which are superior to procaine and cocaine. Japanese workers[64] have made the important observation that electron-donor groups are more effective in the *o*-position of *p*-aminobenzoic acid, and electron-acceptor groups in the *m*-position. This has been confirmed in many ways: it has been shown, for example, that the 4-amino-2-chlorobenzoates have valuable pharmacological properties; in particular, the diethylaminoethyl ester is 10 times as active as procaine with two-thirds its toxicity[65,66]. Of the hydroxyamino-derivatives[67-72] the 2-alkoxy-4-aminobenzoates are also the most active; as with the compounds described above, the anaesthetic activity and toxicity increase with the size of the alkyl group, but here the maximum therapeutic effect is observed with the C_2H_5O- and C_3H_7O-groups[68,72]. In the 3-alkoxy-4-aminobenzoates, the C_4H_9O-group confers the greatest activity[69,70]. All these facts show that electronic structure has an important influence on anaesthetic activity.

Other substituted benzoic acids have also been found active, including mono- and di-halogen-substituted[73-76], *m*- and *o*-aminobenzoic acids[77-81], etc. Of recent work on the replacement of the amino-group, that of French workers[82] on the carbalkoxylation of procaine is of greatest interest. It has been shown that when the hydrogen of the amino-group is replaced by ROOC, the activity increases to a maximum with the compound having R = C_7H_{15}; this compound is 10–12 times as active as cocaine and 4–7 times as toxic. The simultaneous introduction of a hydroxy-group into position 2 reduces the toxicity without affecting the high activity.

If, as has already been mentioned, the question of the necessity of an aromatic radical can be regarded as settled, the second question on the role of conjugation of the carbonyl group with the double bond of the benzene nucleus still remains undecided. Up to now there has been no agreement as to whether such conjugation is necessary or whether unsaturation of the carbon adjacent to the carbonyl group (on the principle of "vinylogy") is sufficient. It is also not clear whether anaesthetic activity in general is related to the conjugated system. On the one hand, reduction of the duration of anaesthesia by a factor of 2–4 when the esters of $\beta\beta$-diarylacrylic acid[83] are hydrogenated, and the absence of anaesthetic activity in the alkylaminoesters of isocoumarinic--3-acid (V) (in which the nature of the double bond is changed because of the adjacent oxygen[84]), tend to confirm the role of the system of conjugated bonds in anaesthetic



(V)

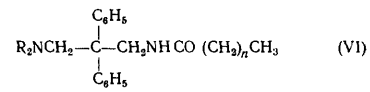
activity and justify the conclusion of Shilov and Kanevskaya[84] that "destruction of conjugation leads to loss of anaesthetic activity". However, on the other hand, many workers have found significant local anaesthetic activity in the esters of such acids as diarylacetic[85,86], benzilic[87,90], mono-, di- and tri-arylpropionic[91-93] and others, in which the chain of conjugated bonds is interrupted by one or even several methylene groups. Many of these compounds are superior to the corresponding unsaturated derivatives. Nazarov and Cherkasova[94-96], Shapiro *et al.*[73], and others have shown that the phenoxyacetates of various amino-alcohols are not inferior to the benzoates in activity, and some of them are superior. These facts cast doubt on the necessity for a conjugated system of double bonds in local anaesthetics. Obviously the question may be answered in different ways, according to the mechanisms by which different groups of compounds act.

In addition to the esters of benzoic acids, the alkylaminoesters of heterocyclic- and naphthalene-carboxylic acids have also been examined for activity; Sergievskaya[97,98] found that some naphthalene compounds were superior to the corresponding benzene derivatives. The activity of most esters of acids with heterocyclic nuclei[99-114] is comparatively low; according to Burger[115], it decreases in the order: phenyl > 2-furyl > 2-thienyl > 4-piperidyl.

Highly active derivatives, for example, phenothiazine- and coumarin-carboxylates are very toxic: they irritate the mucous membrane and depress the central nervous system. The best acid analogues of procaine are therefore the alkamino-esters of acids containing the benzene or naphthalene nucleus, either linked directly to the carboxyl group or separated from it by ethylene or methylene groups.

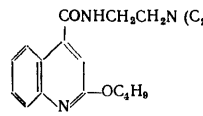
2. The Alkyl Component

In studies on the alkyl component, most attention has been paid to the bond between the carbonyl group and the methylene chain. Replacement of the ester by an amide group in several benzoic acids leads to a reduction in anaesthetic activity: the diethylaminoethylbenzamides are less active than the corresponding esters[116-121]. The highly active *N*-(dialkylaminoethyl)-*p*-dialkylaminobenzamides with radicals of high molecular weight at the nitrogen atom[122], and also the cyanamides[123] alkylated at the amide nitrogen, are the only exceptions to this rule. In contrast, several amides in the aliphatic series are far superior to the esters. Thus, the γ-dialkylamino-$\beta\beta$-diphenylpropylamides of acetic, propionic, and butyric acids (VI)[124] (with n = 0, 1, 2), and also the dialkylaminosuccinimides[125] are powerful local anaesthetics, but the esters of these acids are inactive.



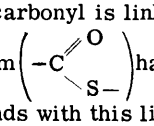
(VI)

However, the amides with the most pronounced physiological properties are those of heterocyclic acids, particularly of the quinolinecarboxylic acids; these include cinchocaine (sovcaine, dibucaine, nupercaine) (VII), now one of the most widely used anaesthetics,

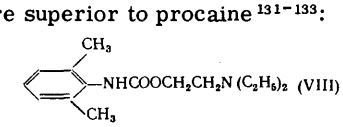


(VII)

which is about 25 times as powerful as procaine. Some of the analogues are also equally active; as usual, the effectiveness of the preparation increases with the size of the radical in the alkoxy-group[126,127]. However, all these compounds, including cinchocaine, are very toxic.

A variant in which the carbonyl is linked to the methylene chain by a sulphur atom  has also been examined. Some compounds with this link are highly active therapeutically[128,129]; for example, the 4-amino-2--hexyloxythiolbenzoate of diethylaminoethanol is 500 times as active as cocaine and only 60 times as toxic, with relatively little irritancy[60].

Carbamylation of procaine and procaine amide, that is, introduction of an NH-group between the carbonyl carbon and the acid nucleus, greatly increases the activity. These derivatives combine high anaesthetic activity with insignificant side effects[130]. *o*-Substitution in the nucleus of phenylcarbamic acid also increases the activity; compounds of type VII are superior to procaine[131-133]:



(VIII)

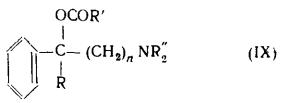
This may be related to stabilisation of the carbamate bond on *o*-substitution. The activity of several substituted phenylcarbamates, especially alkoxy-derivatives, changes in parallel with their capacity for coagulating colloids[134].

The relations between the structure of the carbamates and their properties are similar to those in the ester series. For example, the presence of an aromatic or heterocyclic radical is essential for activity in both series: aliphatic and alicyclic derivatives are inactive[135], and in both series

the diethylamino- and dibutylamino-groups confer optimum activity [136-138]. Of the carbamates, the *NN*-diarylcarbamates are the most powerful: diethylaminoethyl *N*-*p*-butoxyphenyl-*N*-phenylcarbamate is 76 times as active as cocaine in surface anaesthesia and 40 times as active as procaine in infiltration anaesthesia [139].

Elucidation of the part played by the length of the hydrocarbon chain between the carbonyl group and the nitrogen atom and the effect of branching of this chain have also been the subject of studies on the alkyl component. The many experimental results that have now accumulated suggest that the trimethylene chain, characteristic of cocaine (see Table 1), usually confers optimum activity. However, it is still impossible to make generalisations of any kind; for example, some of the diethylaminopropyl 2-alkoxy-4--aminobenzoates are more active and more toxic than the corresponding diethylaminoethyl esters [140], and the esters of chlorocinnamic and chlorobenzoic acids become less effective therapeutically because of increased toxicity as the chain is lengthened [141].

With regard to branching of the main chain, the work of Nazarov, Cherkasova, Erkolmaishvili, and others [94-96,142] on the local anaesthetic properties of the esters of tertiary aliphatic-aromatic amino-alcohols (IX):

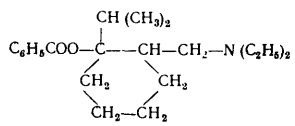


(IX)

(where R = H, CH_3, or C_2H_5, and n = 1, 2, or 3) may be mentioned. In this series, the esters of the 1-alkyl-3--dialkylamino-1-phenylpropanols (IX, n = 2) have been investigated in greatest detail; these may be regarded as acyl derivatives of the 4-phenyl-4-piperidols cleaved through the piperidine ring. Some of the uncleaved derivatives had previously been found to be powerful analgesics (for example, promedol), and cleavage of the ring was found to change the compounds from analgesics to local anaesthetics, the most potent anaesthetics being the esters of tertiary alcohols, which had hardly been investigated up to then. The esters of secondary alcohols have almost no anaesthetic activity. The nature of the acyl radical is very important: the esters of aliphatic acids are inactive, and the highest activity is shown by the phenoxyacetates and cinnamates of certain alcohols; for example, 3-dimethylamino-1-ethyl-2,2-dimethyl-1-phenylpropyl phenoxyacetate is as powerful as amethocaine but much less toxic. Several further conclusions on the relation between structure and physiological activity can be drawn from these investigations. The significance of the phenyl residue in the alcohol part of the molecule has also been confirmed by several workers outside the Soviet Union [73,87,143], but they find that some secondary alcohols are active [73], which is not in agreement with the results of the Soviet workers.

The introduction of ester-linked oxygen, sulphur, or an NH-group into the alkyl chain does not improve the pharmacological properties [144-147].

In recent years, there has been an increase in the number of papers on compounds in which the alkyl chain between the nitrogen and the oxygen is replaced by a cyclic grouping [148-150]; 2-diethylaminomethyl-1-isopropylcyclohexyl benzoate (X) is highly active; the *cis*- and *trans*--isomers differ in activity.



(X)

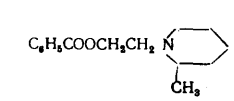
The first papers on compounds in which the alkyl chain is replaced by a heterocyclic residue showed that the 4-piperidyl benzoates [151,152] were highly toxic. Soviet workers later found that the introduction of substituents into the piperidine ring increased the therapeutic effect; this enabled highly active compounds of low toxicity to be prepared, especially by replacing the hydrogen on the ring--nitrogen atom by unsaturated residues [153-158]. Similar derivatives with the pyrrolidine residue, some of them as active as cinchocaine, were described [159-161] in 1960.

TABLE 1.

R	n	p-ROC$_6$H$_4$COO(CH$_2$)$_n$NR$'_2$			
		NR$'_2$	activity		LD_{50}, mm/kg
			surface	infiltration	
CH_3	2	$N(C_2H_5)_2$	0	0	575
C_2H_5	2	$N(C_2H_5)_2$	1.3	2.2	300
C_3H_7	2	$N(C_2H_5)_2$	1.7	1.6	254
C_3H_7	2	$N(CH_3)_2$	2.3	1.6	242
C_3H_7	2	NC_4H_8	2.4	1.8	208
C_3H_7	3	$N(C_2H_5)_2$	3.3	2.4	142
C_3H_7	3	NC_4H_8	3.6	2.8	73
C_4H_9	2	$N(C_2H_5)_2$	2.7	1.9	192
C_4H_9	2	$N(CH_3)_2$	2.6	1.5	258
C_4H_9	2	NC_4H_8	2.0	1.8	242
C_4H_9	3	$N(C_2H_5)_2$	3.6	2.6	192
iso-C_3H_9	2	$N(C_2H_5)_2$	3.9	2.8	158
s-C_4H_9	2	$N(C_2H_5)_2$	4.0	2.1	442
C_6H_{11}	2	$N(C_2H_5)_2$	3.6	2.5	291
C_8H_{13}	2	$N(C_2H_5)_2$	6.3	3.7	258
C_8H_{17}	2	$N(C_2H_5)_2$	0	0.6	175
$C_{16}H_{33}$	2	$N(C_2H_5)_2$	0	0	—
Procaine			—	1	202
Cocaine			1	1.8	62

3. The Amine Component

The amine component of the procaine molecule has been varied in three main ways: (*a*) the diethylamino-group is replaced by another dialkylamino-group or by a heterocyclic residue; (*b*) the tertiary amino-group is replaced by a secondary or primary group; (*c*) the tertiary amino--group is converted into a quaternary salt by coupling with an alkyl halide. Tests on the first modification showed that an increase in the molecular weight of the radicals at the nitrogen atom increases the activity and, to a lesser degree, the toxicity, the net results being an increase in the overall therapeutic effect of the compound. However, work done during the past ten years [69,73,97,162,163] suggests that the diethylamino-group gives the optimum effect (see Table 1); this may be related to the physiological specificity of the ethyl group, which was already emphasised by Ehrlich [164]. Of the other dialkylamino-groups, the dibutylamino- and the diallylamino-groups [165] may be of interest. Of the heterocyclic derivatives [166,167], the only compounds with high activity are some benzoates of piperidinoethanols, for example metycaine (XI); most of the



(XI)

compounds containing heterocyclic residues are either much more toxic than the diethylamino-analogues, or less effective. The monoalkylaminoalkyl esters are of interest here.

Because of their relatively low molecular weight (an increase in which usually increases the toxicity), these compounds would be expected to have a good therapeutic effect. In fact, many of the esters of the monoalkylamino-alcohols are not inferior in activity to the analogues with a tertiary amino-group, and they are therapeutically more effective than procaine or cocaine; examples include hexylcaine [168], monocaine, amylcaine, amylaminoethyl 3-amino-5-heptyloxybenzoate, which is more than 200 times as active as cocaine [79], and many others [169-172]. It is important to note that in the monoalkylamino-derivatives the effect of the structure of the alkyl chain on pharmacological properties was found to be opposite to that in the dialkylaminoalkyl ester series. Thus, compounds with the dimethylene chain are the most active, while esters of the monoalkylaminopropanols are very toxic [173]; α-branching of the chain enhances the activity, but β-branching diminishes it. Some compounds containing an alicyclic [174,175] or a heterocyclic [176,177] radical instead of the usual aliphatic alkyl (aliphatic alkyls with 5-7 carbon atoms confer optimum activity) are irritant, and they are inferior to procaine.

On the whole, investigation of the monoalkylaminoalkyl esters appears to be one of the most promising directions for research, especially as some compounds in this series have been found to have vasopressor action; this opens the possibility of preparing compounds that combine anaesthetic with vasoconstricting action.

The work of Ullyot [178] on the *p*-aminobenzoates of the aminoethanols describes one of the few attempts to discover local anaesthetics among the esters of amino-alkanols unsubstituted at the nitrogen atom. There are practically no pharmacological data in this field. The quaternary salts have been examined in detail, but the results obtained are fairly contradictory. French workers [179,180] have shown that in a series of well-known anaesthetics the methiodides are more toxic than the hydrochlorides, and they have a greater hypotensive effect and curare-like action, but lower anaesthetic activity; the anaesthetic properties are lost entirely when the amino-oxides are formed [31]. Barlow [1] states, "The quaternary salts cannot be local anaesthetics because they are always ionised". However, it was soon found that the benzyl bromides have high local anaesthetic activity and they are more long-acting because of slower absorption [181]. The quaternary salts of some anaesthetics with esters of the α-bromocarboxylic acids show a still greater increase in activity [73,182].

4. Brief Summary

The experimental material analysed here shows that general rules about the effect on pharmacological properties of structural changes in the acid, alkyl, and amine components of the procaine molecule can only be applied to a narrow range of its most closely related analogues. Outside this range the rules are modified and sometimes they are even contradictory. No definite generalisations on the relation between structure and local anaesthetic activity can therefore be made from the properties of procaine analogues.

III. COMPOUNDS NOT CONTAINING THE ANAESTHESIOPHORE GROUPING

These include many esters and amides, amino-ketones, amino-alcohols, amines, compounds containing no nitrogen, and some others grouped here according to some common structural feature.

1. Amino-Acid Derivatives

Benzocaine (anaesthesin, ethyl *p*-aminobenzoate) (XII) is one of the oldest anaesthetics, having been introduced into medical practice in 1902:

$$p\text{-}NH_2C_6H_4COOC_2H_5 \qquad \text{(XII)}$$

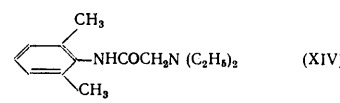
Benzocaine does not contain the anaesthesiophore grouping. Investigation of the alkyl esters of amino-acids has shown that the action of the 2-alkoxy-4-alkylaminobenzoates and the 4-amino-2,6-dimethylbenzoates of butyl and pentyl alcohols is much more prolonged than that of benzocaine [183-185]. Esters of alicyclic [186], heterocyclic [187,188], aliphatic-aromatic [189,190], and even aliphatic acids have also been found to be active. It has been shown [191,192] that the alkyl esters of dialkylamino-acids (XIII) are about as active as the alkyl esters of acids, but they are less toxic.

$$R'_2NCH_2COOCH_2R \qquad \text{(XIII)}$$

This work confirms that local anaesthetic action is associated with the structure and properties of the molecule as a whole and is not the sum of the activities of the component parts (for example, *p*-aminobenzoic acid and diethylaminoethanol), as some workers have asserted [193].

The alkyl esters of *p*-alkoxy- and *p*-aminoalkoxy--phenylcarbamic acids have also been found to be highly active, the most active being the heptyl and cycloheptyl esters [194-196]; for example, heptyl *p*-(2-morpholinoethoxy)-phenylcarbamate is 40 times as active as cocaine and twice as active as cinchocaine, with a lower toxicity [197].

In recent years much work has been devoted to investigation of amino-acids amides, primarily the diethylaminoacetanilides. One of these, lignocaine (xylocaine, maricaine, lidocaine) (XIV) proved to be a highly potent anaesthetic:



(XIV)

Its action is more rapid and more prolonged than that of procaine, and it is widely used in clinical practice. This led to the development of a number of analogues and homologues differing in the substituents on the nucleus and at the amino-acid nitrogen; as with the procaine analogues, it was found that an increase in lyophilic properties by the introduction of additional alkyl or alkoxy-groups into the nucleus prolongs the anaesthesia [198-208]. In contrast, reduction in the lyophilic properties and increased polarity due to the introduction of NO_2 and NH_2 substituents reduces the activity and increases the irritancy [199,209-212]. Thus a change in the electron-affinity greatly affects the properties of the compounds (see Table 2). However, the analogues of lignocaine do not show the direct relation between activity and basicity [199] that is found in the diethylaminoacetates of various alcohols and the dialkylaminoalkyl esters of some acids. Examination of other substituted anilides [213-223] has confirmed the relationships mentioned above.

With regard to substituents at the amino-acid nitrogen, it was found that the same relationships are observed here

TABLE 2.

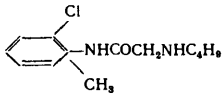
R	NR'_2	Change in pharmacological properties in comparison with lignocaine(xylocaine)	References
2,4,6-$(CH_3)_3$	$N(C_2H_5)_2$	increase in duration of action, decrease in toxicity and irritancy	198—200, 204, 203, 205—206
2-CH_3-6-t-C_4H_9	$N(C_2H_5)_2$		
2,6-$(CH_3)_2$-4-C_6H_5O	$N(C_2H_5)_2$		
2,6-Cl_2-4-R"O*	$N(C_2H_5)_2$		
2,6-Cl_2-4-R"S*	$N(C_2H_5)_2$		205—206
2-CH_3-	$N(C_4H_9)_2$	decrease in activity and increase in irritancy	210
2,4-$(CH_3)_2$-	$N(C_2H_5)_2$		211
2-CH_3-6-CH_3O	$N(C_2H_5)_2$		
2,6-$(CH_3)_2$-4-NO_2	$N(C_2H_5)_2$	ditto	199, 209
2,6-$(CH_3)_2$-4-NH_2	$N(C_2H_5)_2$	»	199 209
2,6-$(CH_3)_2$	$N(C_4H_9)_2$	increase in activity and toxicity	210, 224, 279
2,6-$(CH_3)_2$	NC_5H_{10}	increase in irritancy with retention of anaesthetic activity	198
2,6-$(CH_3)_2$	NC_4H_8	increase in activity and therapeutic index	226—227
2,4,6-$(CH_3)_3$	2,4,6-$(CH_3)_3$—C_6H_7N	increase in therapeutic index (23 times as large as that of cocaine)	225
2,4,6-$(CH_3)_3$	NHC_6H_{13}	increase in activity and therapeutic index	229—232
2-Cl-6-CH_3	NHC_4H_9	ditto	230

* R"=CH_3, C_2H_5, C_6H_7, C_6H_5.

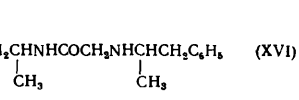
TABLE 3.

$NR'R''$ (2,4,6-$(CH_3)_3C_6H_2NHCOCH_2NR'R''$)	relative therapeutic effect: surface	relative therapeutic effect: infiltration	$NR'R''$ (2,4,6-$(CH_3)_3C_6H_2NHCOCH_2NR'R''$)	relative therapeutic effect: surface	relative therapeutic effect: infiltration
$N(C_2H_5)_2$	2.2	1.3	β-Pipecolyl	11.1	8.8
NHC_4H_9	1.1	1.2	γ-Pipecolyl	4.8	3.2
NHC_6H_{13}	10.0	10.6	2,6-Copelidyl	12.00	3.0
NHC_6H_{11}	2.9	2.2	2,4,6-Lupetidyl	23.0	8.7
NHC_6H_5	—	—	Morpholyl	1.0	3.6
Pyrrolidyl	1.6	1.9	N-carbethoxypiperazyl	0.4	1.5
Piperidyl	1.0	0.8	Cocaine	1.0	—
α-Pipecolyl	1.0	1.9	Procaine	—	1.0

as in the procaine-analogue series; thus, the $(C_2H_5)_2N$- -group[210,224] gives the optimum effect, with the $(C_4H_9)_2N$- -group[225] forming an exception. Pyrrolidine derivatives[226,227], and also compounds containing the piperidine ring with several substituent methyl groups[225], were found to be the best of the compounds containing a heterocyclic residue. "Quaternisation" of the amine nitrogen usually leads to shallower and more limited anaesthesia with increased toxicity[198,228]. In the amide series, the derivatives of monoalkylaminoacetic acids are very promising[228-232] (Table 3); these include hostacaine (XV), which is four times as active as procaine on the sciatic nerve of the frog[230].



(XV)



(XVI)

Of the amides, compounds of the type of N-(α-methylphenethyl)-α-methylphenethylacetamide (XVI) are of particular interest, as they have a pressor in addition to significant local anaesthetic activity[233,234].

Koelzer and Wehr[224,235,236] compared the homologues and analogues of lignocaine with well-known anaesthetics (procaine, amethocaine, cinchocaine) and they proposed a formula to represent the "overall suitability of a preparation":

$$Z = \frac{(a \ln d_m + b)(a \ln p_m + b)}{2a}$$

where d_m is the mean stimulating dose, p_m is the mean lethal dose, and a and b are constants. According to Koelzer and Wehr, this formula may be used to evaluate the quality of a preparation. In fact, application of the formula to the anilides of diethylaminoacetic acid (Table 4) gave results close to those obtained by application of the usual criteria, but it does not follow that this empirical formula, introduced for a narrow range of analogues, can be extended to other compounds.

The more remote analogues of lignocaine include compounds in which the benzene nucleus at the amide nitrogen is replaced by a naphthalene[237-239], anthracene, or fluorene[240-242] nucleus, by a β-aryloxyethyl residue[224,235], or even by an aliphatic radical with 7–9 carbon atoms, for example, N-(2-methyl-2-octyl)-piperidinoacetamide [probably N-(1,1-dimethylnonyl)piperidinoacetamide Ed. of Translation], which is 20 to 30 times as active as lignocaine[243]. Amides of longer-chain acids are also of interest. Koelzer and Wehr[244] found that, in contrast to the α-amino-acid anilides, in which chain lengthening reduces the pharmacological properties, the anilides of the ω-amino-acids become more active when the chain is lengthened. Good pharmacological qualities have been noted in the anilides of β-dialkylaminopropionic acid[245,246], the anilides of type (XVII)[235,247]:

$$ArNHCO(CH_2)_nX(CH_2)_mNR_2 \qquad (XVII)$$

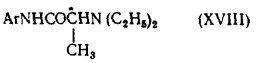
(where X = O or S), and especially in the aminobutyranilides[248-251]. The introduction of 2,6-dimethyl-, p-methyl-, or p-chloro-substituents into the aromatic nucleus of the aminobutyranilides greatly increases the toxicity without changing the activity; this contrasts with the behaviour of the acetanilides. On the other hand, carbalkoxylation of the nucleus produces an increase in activity and a decrease in toxicity.

Recent papers[252,253] by Soviet workers on the relation between local anaesthetic activity and optical isomerism are of great interest. Having confirmed the general principle mentioned above that α-branching of the acetamides greatly increases irritancy with a slight increase in activity, they turned their attention to the relation between

TABLE 4.

$R'R''C_6H_2NHCOCH_2NR_2$: R'	R"	NR_2	Z	$R'R''C_6H_2NHCOCH_2NR_2$: R'	R"	NR_2	Z
H	H	$N(C_2H_5)_2$	83	2-CH_3	4-Cl	$N(C_2H_5)_2$	0
2-CH_3	H	$N(C_2H_5)_2$	103	2-CH_3	6-Cl	$N(C_2H_5)_2$	125.8
2-C_6H_5O	H	$N(C_2H_5)_2$	0	2-Cl	6-Cl	$N(C_2H_5)_2$	78.2
2-C_4H_9O	H	$N(C_2H_5)_2$	0	2-CH_3	H	NC_5H_{10}	110
4-C_2H_5O	H	$N(C_2H_5)_2$	40.5	2-Cl	H	NC_5H_{10}	92
2-CH_3COO	H	$N(C_2H_5)_2$	0	4-C_6H_5O	H	NC_4H_8	0
2-CH_3	6-CH_3	$N(C_2H_5)_2$	114	2-CH_3	6-CH_3	NC_4H_8	154
3-CH_3	4-CH_3	$N(C_2H_5)_2$	9.7	4-Cl	H	NC_4H_9	8.36
2-Cl	H	$N(C_2H_5)_2$	0	2-CH_3	6-Cl	NC_4H_8	269
4-Cl	H	$N(C_2H_5)_2$	0	2-Cl	6-Cl	NC_4H_9	138
2-CH_3	3-Cl	$N(C_2H_5)_2$	0	4-Cl	5-CF_3	NC_4H_8	0

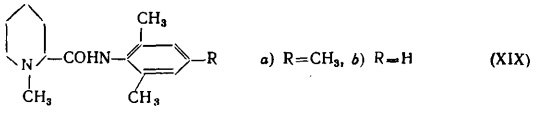
optical activity and stereoisomerism. They found that (-)-isomers of the α-diethylamino-α-methylacetanilides (XVIII):



(XVIII)

are generally more potent than the racemates, and the (+)-isomers are less potent; a definite correlation was observed between the magnitude of the specific rotation and the difference in activity between the (+)- and the (-)-isomers. Although these are preliminary results, in our view they are of fundamental importance for establishing the mechanism by which local anaesthetics act.

To conclude this section, we should mention the high activity of the amides of *N*-alkylpipecolinic, *N*-alkylnipecotinic and *N*-alkylisonipecotinic acids[254-256]; in this series the activity decreases in the ratio 7 : 2 : 1 and the toxicity in the ratio 2.7 : 1 : 1, that is, the *N*-alkylpipecolylanilides have the best therapeutic effect; these include such useful anaesthetics as carbocaine (XIX*a*)[255] and mepivacaine (XIX*b*)[256]:

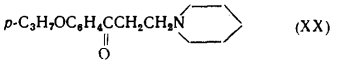


a) R=CH$_3$, *b*) R=H (XIX)

The amino-acid amides therefore include many compounds having very high local anaesthetic activity, although they do not contain the anaesthesiophore grouping.

2. Amino-Ketones

Because the –O–, –S–, –NH–, and –CH$_2$-groups are isosteric, the hetero-atom X between the carbonyl group and the alkyl chain may be replaced by a methylene group without loss of local anaesthetic properties. The well-known amino-ketone anaesthetic falicaine (XX) is 10 times as active as cocaine or procaine[257]:



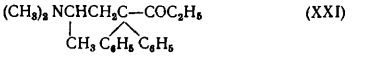
(XX)

Between 1950 and 1960, a large number of falicaine homologues and analogues were prepared[258-271]. It was found that, in contrast to other types of compounds (see above), piperidine was the most active nitrogen residue in this series of compounds, and alkylation of the piperidine in position 4 (with an ethyl or particularly with a butyl radical) increased the strength and duration of the anaesthetic activity[258,259]; moreover, the activity decreased in the order: pyrrolidine > morpholine > diethylamine > dimethylamine[260]. However, some morpholine, dipropyl and dibutylamino-analogues deserve attention, because they are less toxic and therefore therapeutically more effective than falicaine[261-264]; for example, *p*-butoxy-β-dibutylaminopropiophenone with a toxicity one-seventh that of falicaine is 10 times as active as cocaine and 17 times as active as procaine[264]. As a nuclear substituent, the C$_5$H$_{11}$O-group[260,265] gives the optimum effect in the β-piperidinopropiophenones, and the heptyloxy-group[261] in the morpholine analogues.

Further lengthening of the chain in both these groups reduces the activity. It is surprising that the butyl and isopentyl homologues of falicaine are not only more active, but also less toxic[266], although the toxicity usually increases with the size of R. When a normal alkyl is replaced by a branched or cyclic alkyl, the therapeutic effect is enhanced because of a decrease in toxicity; in contrast, the presence of unsaturated residues in the alkoxy-group impairs the pharmacological properties. Other modifications of falicaine have been examined, but, notwithstanding extensive research, falicaine is still superior[266,270,271] in its combined physiological properties (activity, toxicity, and lack of irritancy) to all closely related analogues.

The amino-ketones containing a diphenyl, diphenylmethane or benzidine residue instead of the phenyl nucleus, which were described by Profft[272] in 1960, form a characteristic group of falicaine analogues. These compounds have a high surface anaesthetic activity, the diphenylmethane derivative being equal to falicaine. Surprisingly, it was found that the introduction of an alkoxy-group reduces the activity. The phenyl nucleus linked to the carbonyl group may be replaced by a heterocyclic residue such as that of piperidine[273], phenothiazine[274], or hexamethylamine[275]; some of these compounds have a prolonged and powerful action.

Of other active amino-ketones, some analogues of amidone (XXI)[276-279] deserve mention:



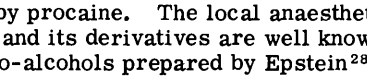
(XXI)

and also the series of 1-alkyl-2-dialkylaminoethyls aryl ketones (XXII), where the aryl radical may be anthracene, fluorene, thiophene, or other residue[279-284]:

(XXII)

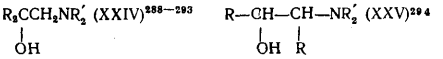
3. Amino-Alcohols

A hetero-atom linked to the carbonyl group is not an essential part of the anaesthetic molecule, and neither is the carbonyl group itself. Many amino-alcohols are effective anaesthetics. Conrad[285] noted the anaesthetic properties of ephedrine and Kupchik[286] showed that a 1% solution of ephedrine produces anaesthesia only slightly inferior to that produced by procaine. The local anaesthetic properties of quinine and its derivatives are well known. The synthetic amino-alcohols prepared by Epstein[287] (XXIII):



(XXIII)

are highly effective anaesthetics when R contains 4 to 6 atoms of carbon on the *o*- or *m*-positions. Compounds containing two phenyl, naphthyl, cyclohexyl, phenothiazine, or thiophene residues R (XXIV – XXV) have anaesthetic properties:



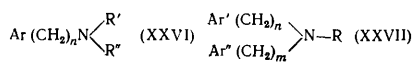
(XXIV)[288-293] (XXV)[294]

But on the whole the amino-alcohols as anaesthetics have been comparatively little studied; until recently attention has been mainly devoted to their action on peripheral nerve endings, in particular to their spasmolytic, vasodilating, and antihistaminic properties.

4. Amines

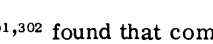
Compounds that have no ester, amide, or carbonyl group may have local anaesthetic properties. Some simple amines, in fact, are highly active. Unfortunately, in most

reports on these, quantitative pharmacological characteristics are not given, which makes comparisons difficult. However, it has been firmly established that *NN*-dialkylaralkylamines (XXVI) and *NN*-diaralkylalkylamines (XXVII):



(XXVI) (XXVII)

have anaesthetic properties. Compounds of type (XXVI) combine analeptic, spasmolytic, and antinarcotic properties[295-298] with anaesthetic activity. Some of these — for example, compounds with a diphenylmethane structure (XXVIII) — are much superior to procaine[299,300] in the rapidity and duration of their action:



(XXVIII)

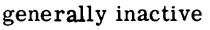
Heinzelmann[301,302] found that compounds of type (XXVII) containing alkoxy-groups in the nucleus with branched alkyl chains — for example, *N*-benzyl-*N*-(2-*o*-methoxyphenylisopropyl)alkylamines — had good pharmacological properties. The presence of a double bond in the chain between the aromatic residue and the nitrogen, or replacement of the aromatic by a heterocyclic residue, confers analgesic activity on the molecule, and in some compounds the local anaesthetic activity is completely suppressed[303-307].

Of the secondary amines, the *NN*-diaralkylamines have attracted most attention. Even *NN*-di-(2-phenylethyl)amine has some activity, and introduction of alkoxy-groups or the *p*-$(C_2H_5)_2N$-group into the aromatic nucleus leads to such effective preparations as *NN*-di-(2-*o*-methoxyphenylisopropyl)amine, which is 200 times as active as cocaine in surface anaesthesia, and 2 to 4 times as active as amethocaine in infiltration anaesthesia, with lower toxicity[308].

Although esters of the amino-alcohols with a primary amino-group are generally inactive (see above), some primary amines are active anaesthetics. As Niinobe[309,310] has shown, the physiological action of the primary amines depends more on molecular weight than on structure. Thus the alkyl and phenylalkylamines first show anaesthetic activity when the total number of carbon atoms in the molecule reaches 11, and the activity increases with the molecular weight; but the diphenylalkylamines (which have more than 11 carbon atoms) are all pharmacologically active. The molecular weight of the aromatic amines is also significant; the anaesthetic activity of the 2-alkoxy-4-nitroanilines increases markedly with the size of the alkyl group[311-313]. Unfortunately, most of the primary amines are strong irritants, which diminishes their value as anaesthetics. The *m*- and *p*-benzhydrylamines are the only exceptions here; these are sufficiently active but non-irritant to tissue.

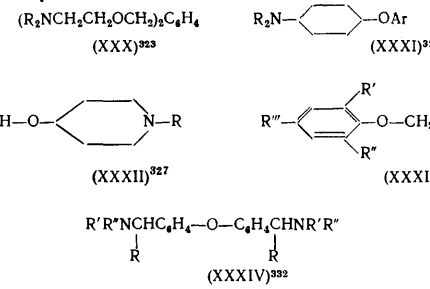
In contrast to procaine derivatives, in which quaternisation of the nitrogen generally eliminates the activity, the aralkyltrimethyl- and aralkyltriethylammonium bromides are powerful and long-acting anaesthetics[314].

Many papers have been published on amino-ethers; as in the esters of amino-alcohols, the introduction of an aromatic residue R' into the molecule (XXIX) confers local anaesthetic properties[315], whereas an aliphatic or an



(XXIX)

alicyclic residue does not[316]. A special feature of compounds of this type is the enhancement of anaesthetic activity on the introduction of halogen, CN-, COOR-, or other groups[317-321,329] into the phenyl nucleus. A great variety of amino-ethers [(XXX) – (XXXIV) and others] have been prepared by different workers; some of these are superior to cocaine and procaine in activity and they have few side-effects[322-336]:



(XXX)[323] (XXXI)[324] (XXXII)[327] (XXXIII)[326-331]

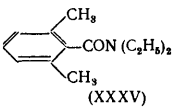
(XXXIV)[332]

The best anaesthetics of this type are the ethers of substituted isoquinoline[337,338]. Thus, some 3-alkyl-1-(2-diethylaminoethoxy)isoquinolines are active at concentrations lower than 0.001%, while the 3-butyl homologue (cuotan) is 1000 times as active as cocaine and 10 times as active as cinchocaine, with only half the toxicity of cinchocaine[338]. Compounds containing other heterocyclic rings, for example, phthalazine[339] or 4,5-diphenylthiazole[340], are active, but some of them are toxic. Replacement of oxygen by sulphur does not improve the properties of the compounds: the thio-derivatives are not superior to procaine, but they have antihistaminic properties[322,341].

To conclude this section, we shall mention the anaesthetic activity of heterocyclic compounds in which nitrogen enters into the ring, usually six-membered[342-365]. Derivatives of dihydroisoquinoline are the most valuable of these, especially 6-benzyloxy-7-methoxy-1-methyldihydroisoquinoline, a 0.15% solution of which produces more prolonged anaesthesia than a 1% solution of procaine[342,343]. Thus, a great variety of amines have local anaesthetic activity.

5. Simple Amides and Amidines

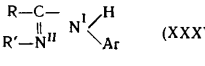
As mentioned above, some amides containing another NH_2-group are highly active pharmacologically, for example, cinchocaine and lignocaine. However, simple substituted amides, such as lidocaine (XXXV)¶:



(XXXV)

have powerful anaesthetic properties; 4-hydroxylidocaine is less active but also less toxic than lidocaine[366], and many other amides of aromatic and aliphatic–aromatic acids[367-371] are also active.

Many of the amidines (XXXVI) (compounds in which the >CO-group of the amides is replaced by the >C=N–R'-group) are more, rather than less, effective than the amides[372].



(XXXVI)

Like the amides, the amidines in which R is an aromatic or heterocyclic radical[372-378] are generally active. The only known exceptions are some acetamidines that have aromatic radicals attached to the N^I or N^{II} atoms[379] and act as

¶ The term "lidocaine" is used in some papers as a synonym for lignocaine (xylocaine).

local anaesthetics. Only fragmentary work has been done on the effect of other structural details on the activity of the amidines. For example, it has been found that the activity and toxicity increase[375-378,380] with the size of the alkyl radicals at N^I and N^{II}. The most active compounds have N^I and N^{II} dibutyl or diisobutyl, or N^I-monoaryl (especially with Ar-*p*-$CH_3C_6H_4$)[377] substituents. It has also been established that the introduction of a *p*-alkylthio-group into the benzamidine nucleus enhances the infiltration activity[375], but *p*-carboxylation diminishes it[381].

Finally, local anaesthetic activity, sometimes fairly high, has been found in a number of derivatives of guanidine, urea, hydantoin, carbonic acid[382-385], and also in some barbiturates and thiobarbiturates[386-389].

6. Compounds Not Containing Nitrogen

The work reviewed above is concerned with nitrogen-containing compounds. This is the only element common to these compounds that can be considered essential for anaesthetic activity. It is true that the anaesthetic properties of several alcohols, for example, octanol, salicyl alcohol, benzoylmethanol, etc. have been known for over 50 years, but as they have only surface anaesthetic activity and this is weak, they were regarded as forming an exception that did not violate the essential nitrogen concept. However, in 1950–1955, the preparation was described[390-392] of polyethyleneoxyethers (XXXVII) having considerable surface and infiltration activity, which reaches a maximum when R = $C_{12}H_{25}$ and n = 9.

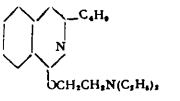
$$RO(CH_2CH_2O)_nCH_2CH_2OH \qquad \text{(XXXVII)}$$

During the same period, Kuhn and Dury[393] discovered the very powerful anaesthetic effect of diethyl-α,δ-dihydroxyadipate monobenzoate (XXXVIII):

$$C_2H_5OOCCH(OCOC_6H_5)-CH_2CH_2CH(OH)COOC_2H_5 \qquad \text{(XXXVIII)}$$

and of the bisalicyl esters of furandicarboxylic acid, which approach cocaine in physiological activity[394]. Recently, local anaesthetic activity was reported in polyglycol esters of benzoic and cinnamic acids[395-397], and in the alkyl esters of 3,5-dipropyl-4-allylhydroxybenzoic acid, which also have analgesic and narcotic properties[398]. Although these facts are still comparatively few, they show conclusively that organic compounds of the most diverse kind can act as local anaesthetics†.

TABLE 5. The most effective local anaesthetics.

Name	Formula	Pharmacological properties	References
Diethylaminoethyl *p*-ethylthiocinnamate	*p*-$C_2H_5SC_6H_4CH$= =$CHCOOCH_2CH_2N(C_2H_5)_2$	5 times as powerful as procaine by intravenous injection, and 20 times the surface action	83
Diethylaminoethyl 4-amino-2-hexyloxy-thiolbenzoate	4-NH_2-2-$C_6H_{13}OC_6H_3$— —$COSCH_2CH_2N(C_2H_5)_2$	500 times as active as cocaine and 60 times as toxic with slight irritancy	80
Diethylaminoethyl *N*-*p*-butoxyphenyl-*N*-phenylcarbamate	*p*-$H_9C_4OC_6H_4N$(COOCH$_2$CH$_2$N(C$_2$H$_5$)$_2$)(C$_6$H$_5$)	76 times as powerful as cocaine in surface anaesthesia and 40 times as powerful as procaine in infiltration anaesthesia	139
1-Ethyl-2,2-dimethyl-3-dimethylamino-1-phenylpropan-1-ol-phenoxyacetate	C_6H_5, $OCOCH_2OC_6H_5$ C_6H_5—C—C—CH_2—$N(CH_3)_2$ CH_3, CH_3	equal to amethocaine with much lower toxicity	84
Amylaminoethyl 3-amino-5-heptyloxybenzoate	3-NH_2-5-$C_7H_{15}OC_6H_3$— —$COOCH_2CH_2$—N(H)(C_5H_{11})	200 times as active as cocaine	70
Heptyl *p*-(2-morpholinoethoxy)-phenylcarbamate	*p*-$OH_2C_4NCH_2CH_2OC_6H_4$— —$NHCOOC_7H_{15}$	40 times as active as cocaine and twice as active as cinchocaine with lower toxicity	197
N-(2-methyl-2-octyl) piperidinoacetamide	$C_5H_{10}NCH_2CON$—C(CH$_3$)$_2$—CH_2—CH_3 CH_3	20 to 30 times as active as lignocaine(xylocaine)	243
p-Butoxy-β-dibutylaminopropiophenone	*p*-$C_4H_9OC_6H_4COCH_2CH_2N(C_4H_9)_2$	10 times as active as cocaine and 17 times as active as procaine with toxicity one-seventh that of falicaine	244
NN-di-(2-*o*-methoxyphenylisopropyl)-amine	[*m*-$CH_3OC_6H_4C(CH_3)_2$]$_2$NH	200 times as active as cocaine in surface anaesthesia; 2 to 4 times as active as amethocaine in infiltration anaesthesia	399
3-Butyl-1-(2-diethylaminoethoxy)-isoquinoline		1000 times as active as cocaine and 10 times as active as cinchocaine, with half the toxicity of cinchocaine	399

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† To assist the reader, we have selected the most effective (based on the evidence of the authors of the papers in which they are described) local anaesthetics and tabulated them in Table 5.

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USE OF *N*-BENZOYL-*N*-PHENYLHYDROXYLAMINE IN ANALYTICAL CHEMISTRY

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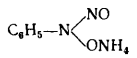
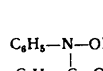
I. INTRODUCTION

Among the nitrogen-containing organic reagents which are greatly used in modern methods of analysis are not only 8-hydroxyquinoline but also the ammonium salt of *N*-nitroso-*N*-phenylhydroxylamine, cupferron[1-3]



the use of which as an analytical reagent was suggested by Baudisch in 1909.[4] However, cupferron has several disadvantages for this purpose. It is unstable to light and heat, and is readily oxidised in the air; the precipitation of cupferron derivatives from hot solutions is accompanied by decomposition and hydrolysis of the reagent. Cupferron derivatives of elements cannot be weighed for gravimetric determinations, but must be ignited to the oxides.

New reagents have therefore been sought which are similar to cupferron in their analytical behaviour but differ from it in not possessing these defects. In 1950 Shome[5] suggested using an analogue of cupferron, *N*-benzoyl-*N*-phenylhydroxylamine (BPHA) for the determination and separation of several elements for which the use of the former is not very convenient. In this compound the nitroso-group has been replaced by benzoyl



BPHA, while closely resembling cupferron in its analytical properties, differs considerably from the latter in other respects, especially in its stability towards light and heat. Several metals form with it crystalline precipitates of definite and constant composition, which may be weighed for gravimetric purposes. The compounds formed by BPHA with metals can in several cases be extracted with organic solvents.

During the past 5–6 years BPHA has attracted the attention of many analysts. The present review, covering the literature up to 1961 (and also the early papers in 1961), discusses the characteristics and the principal analytical applications of BPHA.

II. PREPARATION AND SOME PROPERTIES OF *N*-BENZOYL-*N*-PHENYLHYDROXYLAMINE

BPHA was first obtained by Bamberger[6], and Shome[5] only slightly modified the method to prepare the compound for analytical purposes. Phenylhydroxylamine (30 g) is dissolved in 1200 ml warm water, and the solution is filtered; after cooling, a little sodium hydrogen carbonate is added to the filtrate, and 45 g benzoyl chloride is run in with vigorous stirring, about 30 g sodium hydrogen carbonate are added in small portions periodically during this process in order to keep the solution alkaline. After stirring for 90 min, the solid (consisting of a mixture of mono- and di-benzoylphenylhydroxylamine) is filtered off, washed with water, ground in a porcelain mortar with 10% sodium hydrogen carbonate solution, filtered off, and washed with water. This treatment removes occluded benzoyl chloride. Monobenzoylphenylhydroxylamine is separated from dibenzoylphenylhydroxylamine by treatment with aqueous ammonia (sp. gr. 0.88), in which only the monobenzoyl derivative dissolves.

The solution is filtered, and a slight excess of dilute sulphuric acid, cooled in a mixture of ice and salt, is added. The resulting precipitate of monobenzoylphenylhydroxylamine is filtered off, and purified by recrystallisation from alcohol. The final product may also be recrystallised from hot water[7], benzene[8], or concentrated acetic acid (by dilution with water)[9].

Ryan and Lutwick[7] suggested using 3 *N* HCl instead of dilute sulphuric acid to neutralise the ammonia: this avoids the possibility of contamination by the brown oil formed by the oxidation of organic substances when sulphuric acid is used.

Pure BPHA consists of colourless needle-shaped crystals melting at 121°–122°. It is almost insoluble in cold water, but dissolves in hot water, ethyl alcohol, acetone, isopentyl alcohol, chloroform, benzene, cyclohexanone, and many other organic solvents. According to Dyrssen[8] the solubility of BPHA in water at 25° ± 0.3° is 0.00195 M, in good agreement with the earlier value[7,10] of 0.40 g litre^{-1} (0.0019 M). Its solubility in hot water[7] is ~0.5 g in 100 ml. Tables 1 and 2 give the solubility of BPHA in aqueous alcoholic mixtures and in various organic solvents.

Tsê Yün-hsiang[12] worked out a new extraction and spectrophotometric method for determining BPHA in water or in organic solvents, based on its reaction with quinquevalent vanadium. The solubility of BPHA in water at room temperature (~20°), determined by this method, was 0.34 g litre^{-1} (0.0026 M).

BPHA is stable towards air, light, and heat: no decomposition was observed when it was stored dry in an ordinary jar even for three years[12]. It is stable for a long time in

TABLE 1. Solubility of BPHA in aqueous alcohol mixtures at 22° ± 1°.[11]

Ethanol, vol. %	10	20	30	40	50	60	70	80	90	96
Solubility of BPHA, g litre^{-1}	0.610	0.920	1.394	2.732	6.430	11.320	16.625	33.90	87.865	109

TABLE 2. Solubility of BPHA in organic solvents at 22° ± 1°.[11]

Solvent	Solubility of BPHA, M	Solvent	Solubility of BPHA, M
CCl_4	0.026	Benzene	0.150
Xylene	0.034	Ethyl acetate	0.480
Toluene	0.061	Dichloroethane	0.280
Diethyl ether	0.135	Chloroform	0.580

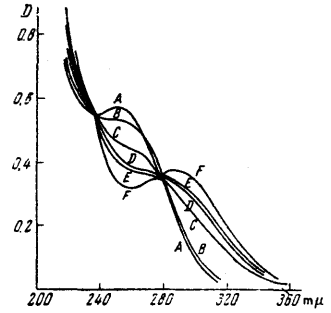


Fig. 1. Absorption spectra of aqueous solutions of BPHA at various pH values: *A*) 0.72–6.43; *B*) 6.8; *C*) 8.37; *D*) 7.85; *E*) 8.06; *F*) 11.20–11.50.

dilute sulphuric and hydrochloric acids (~8 *N*), but it gradually decomposes in dilute nitric acid (>5 *N*); comparatively rapid decomposition is observed also in alkaline and ammoniacal media[9].

BPHA is oxidised by potassium permanganate and potassium dichromate in acid medium, but it is quite stable towards hydrogen peroxide[9]. The process of oxidation is very complicated, the reaction is not stoichiometric, and it cannot be employed for quantitative purposes[12].

BPHA is an extremely weak acid, and does not form an ammonium salt when gaseous ammonia is passed through it in ethereal solution[5]. Tsê Yün-hsiang[12] found, by the isosbestic point method and the partition method, that the pK_a for the acid dissociation of BPHA is 7.97 ± 0.11 (at an ionic strength of 1.0); by a two-phase titration method Dyrssen[8] obtained a value of 8.15 ± 0.01 (at an ionic strength of 0.1). The corresponding constant for cupferron is 4.08 ± 0.02 [12] or 4.163 ± 0.007.[8]

The absorption spectrum of BPHA in water has a maximum at 253 mμ with a molar extinction coefficient of 7650.[8] At the isosbestic points (240 and 280 mμ) (Fig. 1) aqueous solutions of BPHA, like those of cupferron (at 235 and 266 mμ), obey the laws of light absorption[12]. According to Dyrssen[8] the partition coefficient of BPHA between chloroform and water is $10^{2.33\pm0.01}$. The value obtained by Tsê Yün-hsiang[12] (216.6 ± 5.0) is 4.5 times his value for the benzene–water system (45.54 ± 0.23). At pH 6 the extractibility of BPHA by chloroform is diminished, owing to dissociation of the BPHA [12] (cupferron starts to dissociate at pH > 3, which also results in a diminution in its extractibility by chloroform); the extractibility of BPHA decreases also in strongly acid medium (>4 *N* with respect to hydrochloric acid)[12].

BPHA reacts with many metal ions to form water-insoluble inner complexes; complex formation takes place by replacement of the hydroxylamino hydrogen by the metal ion with coordination of the carbonyl oxygen

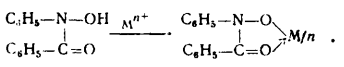


TABLE 3. Qualitative reactions of BPHA with metal ions[12].

Element	Degree of oxidation	Acidity of soln. for pptn.	Colour of ppt.	Colour of chloroform extract
Aluminium	3	pH ~ 3	white	colourless
Antimony	3	pH ~ 1	white	colourless
Antimony	5	~ 3*N*	white	colourless
Beryllium	2	pH ~ 5	white	colourless (floats)
Bismuth	3	pH ~ 3	white	colourless
Cadmium	2	pH ~ 4	white	colourless (floats)
Cerium	3	~ 6	white	colourless
Cerium	4	pH ~ 3*N*	orange	orange
Chromium	3	pH ~ 4	dirty yellow	yellow
Cobalt	2	pH ~ 5	pink	pink
Copper	2	pH ~ 3	yellow – green	yellow – green
Gallium	3	pH ~ 3	white	colourless
Germanium	4	pH ~ 3	white	colourless
Hafnium	4	pH ~ 3*N*	white	colourless
Indium	3	pH ~ 3.5	white	colourless
Iron	2	pH ~ 5	red	red
Iron	3	pH ~ 3	violet	violet
Lanthanum	3	pH ~ 6	white	colourless
Lead	2	pH ~ 4	white	colourless
Manganese	2	pH ~ 6	yellowish	yellowish (floats)
Mercury	1	~ 4	yellow	yellow – green (floats)
Mercury	2	~ 2	yellow	yellow – green (floats)
Molybdenum	6	~ 3	yellowish	yellowish
Neodymium	3	pH > 6	white	colourless
Nickel	2	pH ~ 5	greenish	greenish
Niobium	5	pH ~ 3*N*	white	colourless
Palladium	2	pH ~ 3	orange	pink
Praseodymium	3	pH ~ 6	white	colourless
Samarium	3	pH ~ 7	white	colourless
Scandium	3	pH ~ 3	white	colourless
Tantalum	5	pH ~ 3*N*	white	colourless
Thallium	3	~ 4	white	colourless
Thorium	4	pH ~ 3	white	colourless
Tin	2	~ 3*N*	white	colourless
Tin	4	~ 3*N*	white	colourless
Titanium	4	pH ~ 3*N*	yellow	yellow
Tungsten	6	pH ~ 3	yellowish	yellowish
Uranium	4	pH > 5	orange	yellow
Uranium	6	pH ~ 5	greenish yellow	yellow
Vanadium	5	pH ~ 3*N*	violet – red	violet
Yttrium	3	~ 6	white	colourless
Zinc	2	pH ~ 4	white	colourless (floats)
Zirconium	4	~ 3*N*	white	colourless

Complex formation is greatly dependent on the acidity of the medium. In strongly acid medium (~3 *N* with respect to hydrochloric acid) BPHA precipitates titanium, zirconium, hafnium, vanadium, niobium, tantalum, tin, and antimony; in weakly acid medium (pH 3–6) thorium, scandium, iron, zinc, chromium, aluminium, mercury, rare-earth metals, uranium, cadmium, nickel, copper, gallium, indium, thallium, etc. are precipitated[12].

Benzoylphenylhydroxylamine derivatives of all the elements mentioned, other than antimony, mercury, zinc, and cadmium, are readily extracted by organic solvents (chloroform, isopentyl alcohol). Several elements, for example titanium, vanadium, niobium, quadrivalent cerium, uranium, molybdenum, cobalt, nickel, iron, and copper, form coloured precipitates with BPHA, which dissolve to give correspondingly coloured solutions in organic solvents. Table 3 gives the qualitative reactions of BPHA with various metal ions [12].

The interaction of BPHA with metal ions becomes more selective in the presence of Complexone III†. In its presence at pH 5–6, for example, BPHA precipitates only titanium, vanadium, niobium, molybdenum, tin, uranium, beryllium, aluminium, and iron, other elements remaining in solution [12].

III. USE OF *N*-BENZOYL-*N*-PHENYLHYDROXYLAMINE FOR THE QUANTITATIVE DETERMINATION OF ELEMENTS

BPHA is used to determine several elements: aluminium [5], beryllium [13], vanadium [12,14-18], iron [5,12,19], cobalt [20], copper [5], molybdenum [21,22], nickel [20], niobium [23-26], tin [7,10,27], scandium [12,28], tantalum [23,24,26,29], titanium [5,12,26], thorium [30,31], cerium [30], and zirconium [12,32,33]. The methods for determining these elements with BPHA can be divided into three groups — gravimetric, absorptiometric, and titrimetric — among which gravimetric methods are at present outstanding in number and importance.

1. Gravimetric Methods

Aluminium, iron, and copper [5]. Addition of a slight excess of an ethanol solution of BPHA to hot solutions of salts of aluminium, iron, and copper, precipitates these elements as white, red, and yellow-green compounds respectively. The optimum pH ranges for the precipitation of aluminium, iron, and copper are 3.6–6.4, 3.0–5.5, and 3.6–6.0 respectively: at lower pH precipitation is incomplete, while at higher pH somewhat low results are obtained. The resulting precipitates are washed well with hot water, are dried briefly at 110°, and are then suitable for weighing in the gravimetric determination of the three metals. The analyses of the precipitates correspond to the formulae $Al(C_{13}H_{10}O_2N)_3$, $Fe(C_{13}H_{10}O_2N)_3$, and $Cu(C_{13}H_{10}O_2N)_2$. These benzoylphenylhydroxylamine derivatives melt at 238°–239°, 187°–188°, and 198°–199° respectively, are decomposed by mineral acids of moderate concentration, and are readily soluble in organic solvents. In the precipitation of aluminium the concentration of ethanol in the final solution should not exceed 5%, since the aluminium complex, in contrast to the iron and copper derivatives, is quite soluble in aqueous ethanol. Cobalt, cadmium, lead, mercury, manganese, nickel, uranium, zinc, and tartrate, do not interfere with the determination of aluminium, iron, and copper under the above pH conditions; tin, titanium, zirconium, vanadate, molybdate, and tungstate do interfere. The determination of aluminium and iron is impossible also in the presence of phosphate.

† Disodium ethylenediaminetetraacetate dihydrate (Ed. of Translation).

Beryllium [13]. With BPHA beryllium forms a coarse-grained white precipitate having the composition $Be(C_{13}H_{10}O_2N)_2$, which is insoluble in water (up to 70°), relatively insoluble in carbon tetrachloride, acetone, and 50% ethanol, but readily soluble in chloroform. This beryllium complex is decomposed by mineral acids, and melts with decomposition at 220°. Beryllium is quantitatively precipitated by BPHA from hot solutions (50°–60°) at pH 5.0–8.0 and a BPHA concentration of 0.1% (at pH 6.0). The beryllium can be determined either by direct weighing of the precipitate after it has been washed with warm water and dried at 110°, or by weighing beryllium oxide after ignition of the precipitated complex.

Vanadium. With BPHA in strongly acid medium vanadium forms a dark violet compound which is insoluble in water, but which is unsuitable for the gravimetric determination of the metal, since the precipitate is colloidal in character and readily passes through the filter [14]. However, this violet compound can be utilised for the absorptiometric determination of vanadium (see below).

Cobalt and nickel [20]. At pH 5.5–6.5 (in the presence of sodium acetate) BPHA precipitates these metals in the form of a pink and a yellow-green compound respectively. At pH values below the limit mentioned precipitation is incomplete, while lumpy precipitates are obtained at higher pH. The cobalt and nickel complexes can be weighed after being dried at 110°. In the precipitation of cobalt, hydroxylammonium chloride is first added to the solution to be analysed in order to avoid the formation of the tervalent cobalt complex. BPHA is inferior to dimethylglyoxime as a precipitant for nickel, but with cobalt it has the advantage over 1-nitroso-2-naphthol that the benzoylphenylhydroxylamine complex has a perfectly definite composition, and does not require to be subsequently ignited to the oxide or converted into cobalt sulphate.

Molybdenum [21,22]. In the sexivalent state, molybdenum forms with BPHA a yellowish white precipitate of $MoO_2(C_{13}H_{10}O_2N)_2$, which is slightly soluble in hot water (above 80°), in concentrated acids (at lower temperatures), and also in alcohol; the molybdenyl complex decomposes at 165°–166°. Molybdenum is precipitated quantitatively by BPHA from hot solutions (~70°) of acidity 0.01–2.5 *N* (with respect to hydrochloric acid) with a BPHA concentration of 0.03% (below 70°). Molybdenum can be determined either by direct weighing of the precipitate after being dried at 110°–115°, or by weighing molybdenum trioxide after igniting the precipitated complex at 500°–525°. In the presence of cobalt, nickel, or copper the precipitated molybdenyl complex is first washed with 0.2 *N* HCl (as also in the absence of these elements), and then with a 0.02 *N* solution of this acid (instead of water, which is used in the absence of interfering elements); iron(III) and vanadium(V) are masked with Complexone III. BPHA is oxidised by chromium(VI), which therefore interferes with the determination of molybdenum by the first method; tungsten(VI) in acid medium forms a precipitate with BPHA, and strongly interferes with the determination of molybdenum.

Niobium and tantalum. In acid medium BPHA precipitates these metals as white compounds: niobium comes down quantitatively from tartrate solutions starting from an acidity of 2 *N* (with respect to hydrochloric acid) up to pH 6.5; tantalum is completely precipitated only up to pH 1.5. [23,24] Niobium is quantitatively separated from

tantalum at pH 3.5–6.5; while in the presence of Complexone III and tartaric acid, niobium can be determined in the presence of iron, uranium, beryllium, thorium, chromium, aluminium, cerium, copper, cadmium, bismuth, lead, mercury, arsenic, antimony, tin, zinc, manganese, nickel, cobalt, calcium, strontium, barium, magnesium, rare-earth metals, phosphate, chromate, and tungstate; only titanium, zirconium, vanadium, and molybdate interfere. In the gravimetric determination of niobium, the complex is usually ignited to niobium pentoxide [23,24], but it can also be weighed directly (after being dried at 110°) [25], since it has a definite composition $NbO(C_{13}H_{10}O_2N)_3$ and is stable up to 229°. The tantalum precipitate is of indefinite composition, losing weight with rise in temperature, and is unsuitable for direct weighing. Tantalum can be determined in the presence of niobium, titanium, and zirconium by precipitation with BPHA from fluoride-containing solutions acidified with sulphuric acid to pH 1.0 ± 0.1; [29] the optimum temperature for the quantitative precipitation of tantalum lies within the range 5°–27° (it is advisable to keep the solution with the precipitate in cold water for $2\frac{1}{2}$ h before filtering). Good results have been obtained using BPHA for the gravimetric determination of niobium and tantalum in minerals containing titanium, uranium, thorium, and rare-earth metals [26].

Tin. BPHA precipitates tin quantitatively from solutions containing 1–8% conc. HCl. [7] The precipitates isolated from solutions of stannous and stannic salts are white in colour and have the same composition with a melting point of 171°. [7,10] The mechanism of formation and the structure of the tin derivative of BPHA are not known precisely. The compound is stable and is suitable for weighing after being dried at 110°. By means of BPHA tin can be determined gravimetrically in bronzes: copper, lead, and zinc do not interfere [7]. In acid medium (>1% HCl) only tin, vanadium, zirconium, and titanium are precipitated, and therefore BPHA is a selective and the best reagent for tin [10]. It has been recommended as a sensitive reagent for the detection of tin in qualitative semimicro-analysis [27]: in a solution of optimum acidity (0.6 *N* with respect to hydrochloric acid) 0.03 mg tin is easily detected in 1 ml of the final solution by the formation of a readily visible white precipitate.

Scandium [28]. With BPHA, scandium gives a white compound $Sc(C_{13}H_{10}O_2N)_3$, insoluble in water, which separates quantitatively at pH > 5.2 in the presence of a slight excess of the reagent. Thermogravimetric analysis of the scandium precipitate (Fig. 2) showed it to be stable up to 220°; in order to obtain a form of scandium oxide suitable for weighing it is sufficient to heat the precipitate to 600°.

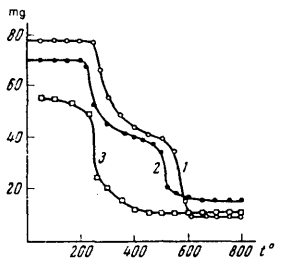


Fig. 2. Thermal decomposition curves for the benzoylphenylhydroxylamine complexes of: 1) scandium; 2) thorium; 3) zirconium.

Titanium. BPHA precipitates titanium as a yellow compound from solutions containing 0.1–0.4 *N* HCl (low results are obtained at higher acidities); it is advisable to carry out precipitation below 25°, since a sticky precipitate is formed at higher temperatures [5]. Langmyhr and Hongslo [26] suggest precipitating titanium from 5% sulphuric acid at 90°, and then cooling the solution and precipitate to 5° in order to precipitate the titanium completely. These workers obtained satisfactory results in the determination of titanium in minerals containing niobium, tantalum, uranium, thorium, and rare-earth metals. The use of BPHA yields good results also in the determination of titanium in ferrotitanium [12] (precipitation being carried out in 1 *N* HCl in the presence of ascorbic acid). The determination is complete by weighing as titanium dioxide, since the precipitate is of indefinite composition.

Thorium. At pH 4.5–5.5 thorium is quantitatively precipitated by BPHA as a white compound, which can be ignited to thorium dioxide [30]. According to Alimarin and Tsê Yün-hsiang [31], the quantitative precipitation of thorium has already begun at pH > 2; the flocculent white precipitate formed initially becomes crystalline after being heated on a water-bath for 5–10 min. The composition of the precipitate deposited from weakly acid solution and dried at 105°–120° is represented by the formula $Th(C_{13}H_{10}O_2N)_4$. Thermogravimetric analysis of the thorium complex (Fig. 2) indicates that it is stable up to 220°; in order to obtain a form of thorium dioxide suitable for weighing, it is sufficient to ignite the precipitate at 650°.

Cerium [30]. Cerium(III) is precipitated quantitatively by BPHA at pH 6.5–7.5 as a white compound; at pH > 7.5 the reagent solution gradually turns red, while at pH < 6.5 the precipitation of cerium is incomplete. Cerium(IV) is precipitated by BPHA at pH 5.0, but the resulting precipitate is gelatinous and is difficult to filter. Cerium(IV) must therefore first be reduced to the cerium(III) with hydroxylammonium chloride. The estimation of cerium is completed by weighing as cerium dioxide after igniting the cerium(III) complex.

Zirconium. According to Alimarin and Tsê Yün-hsiang [32], zirconium is precipitated from hot sulphate or chloride solutions at acidities up to ~3 *N* in the presence of a slight excess of the reagent, as a white compound of composition $Zr(C_{13}H_{10}O_2N)_4$, which is suitable for weighing. Thermogravimetric examination of the precipitate formed under these conditions (Fig. 2) indicates that it is stable up to 240°; in order to obtain a form of zirconium dioxide suitable for weighing, it is sufficient to ignite the precipitate at 500°. According to Ryan [33] the precipitate obtained from chloride solutions, although stable, is not constant in composition (probably owing to the simultaneous precipitation of variable amounts of basic salts, which is prevented in the case of sulphate solutions by the formation of sulphate complexes of zirconium in solution); in this case the precipitate should, in Ryan's opinion, be ignited to zirconium dioxide. The zirconium complex is precipitated quantitatively from sulphate solutions, according to Ryan, only at acidities below 0.5 *N*. The precipitate formed under these conditions has the constant composition $Zr(C_{13}H_{10}O_2N)_4$, is

stable on being heated at 130° for several hours, and is suitable for weighing. The following metals are not precipitated under the conditions of the estimation of zirconium with BPHA: iron, copper, aluminium, bismuth, cadmium, chromium, lead, magnesium, manganese, nickel, zinc, uranium, thorium, yttrium, and rare-earth metals [33]; interference by titanium, cerium(IV), niobium, tantalum, and vanadium [32] is eliminated by masking them with hydrogen peroxide.

2. Absorptiometric Methods

Vanadium. Practically the only element for which a photometric method of estimation using BPHA has been worked out is vanadium. Shome [14] found that, in aqueous ethanol medium at pH 1.9–2.8, BPHA gives with vanadium(V) an orange–red coloration which is suitable for photometric measurement (maximum absorption at 480 mμ). The colour is most stable at pH 2.6, and remains unchanged for 5 h. The sensitivity of the colour reaction is 0.33 mg of vanadium per litre. Many elements (iron, aluminium, titanium, manganese, tungsten, chromium) interfere with the determination of vanadium. Zharovskii and Pilipenko [15] showed that interference by iron and titanium can be avoided by estimating the complex after extracting it with chloroform at pH 5.1–6.0 in the presence of sodium fluoride and phosphoric acid. The chloroform solution of the vanadium complex $V_2O_3(C_{13}H_{10}O_2N)_4$ shows maximum light absorption at 445 mμ (Fig. 3), the molar extinction coefficient being 3600. Satisfactory results in the determination of 0.01–0.3% of vanadium in titanium tetrachloride were obtained, the determination taking 10–15 min. Tsê Yün-hsiang [12] determined vanadium after extracting its complex with a mixture of equal volumes of chloroform and isopentyl alcohol from 0.1–1.5 *N* HCl solutions, and showed that the light absorption of the extracts remains constant for 10 h (maximum absorption at 445 mμ). Ryan [16] showed that it is possible to extract the vanadium complex from more acid media: extraction from 5–9 *N* HCl solutions of vanadate using a chloroform solution of BPHA yields a purple extract having an absorption maximum at 530 mμ (Fig. 4) and a molar extinction coefficient of 4490. The orange extracts obtained from dilute sulphuric-acid solutions of a vanadate also become purple on further acidification with hydrochloric acid. Extraction from strongly acid medium ensures that the photometric determination of vanadium is highly specific: the elements which normally accompany vanadium do not then interfere. Extremely good results have been obtained in the determination of small amounts of vanadium in steels and in chromium ores. Priyadarshini and Tandon [17,18] concluded, from a detailed study of complex formation between vanadium(V) and BPHA, that two complexes are formed in acid medium: a violet complex in strongly acid solutions (>2 M), and an orange–red complex in weakly acid solutions (<0.1 M); the amethyst colour observed at an acidity of 0.1–2.0 M (with respect to hydrochloric acid) results, in their opinion, from the mixing of the colours of the above two complexes (Fig. 5). The violet vanadium complex is readily extracted by chloroform, carbon tetrachloride, ethyl acetate, diethyl ether, benzene, and other organic solvents; all the extracts have an absorption maximum at ~510 mμ. The most suitable extractant is chloroform. At an acidity of 2–10 M (with respect to hydrochloric acid) the position of maximum absorption by the chloroform solution of the complex remains unchanged, but the intensity of absorption remains constant only at 2.8–4.3 M. Beer's law is obeyed (at 510 mμ) at vanadium concentrations of 0.7–12 p.p.m. Even large quantities of aluminium, cobalt, chromium, copper, iron, manganese, nickel, thorium, uranium, zinc, nitrate, and sulphate do not interfere with the determination of vanadium. In the opinion of the above authors, the method is extremely valuable for the direct determination of small quantities of vanadium in ores, alloys, petroleum products, and biological materials.

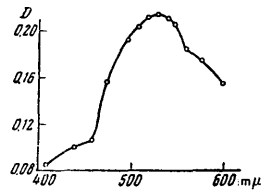


Fig. 4. Absorption spectrum of a chloroform solution of the benzoylphenylhydroxylamine complex of vanadium.

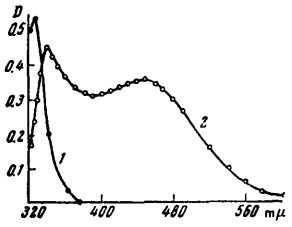


Fig. 3. Absorption spectra of chloroform solutions of: 1) BPHA; 2) BPHA complex of vanadium.

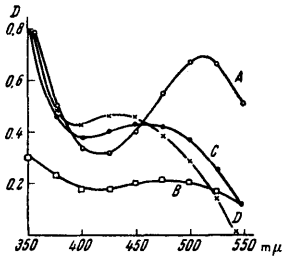


Fig. 5. Absorption spectrum of BPHA–vanadium system in chloroform with various molar concentrations of hydrochloric acid in aqueous phase: *A*) 3.6; *B*) 1.8; *C*) 1.0; *D*) 0.01.

Iron [12]. In aqueous acetone medium (50% acetone) at pH 4–7, iron forms with BPHA a soluble complex which remains stable for a long time and is suitable for the photometric determination of the metal. Beer's law is obeyed for iron concentrations of 0.5–10 μg ml^{-1}; the sensitivity of the reaction is close to that for the sulphosalicylate complex of iron.

3. Titrimetric Methods

This group comprises a small number of methods for determining elements based on the use of BPHA as a complexometric indicator.

Iron. Tervalent iron reacts stoichiometrically with Complexone III at pH 1.0–1.5 and 50°–60°, and can be readily titrated complexometrically at 50° in the presence of 1 ml of a 0.5% acetone solution of BPHA (change in colour from red-violet to lemon yellow or colourless) [19]. The end-point of the titration can be determined either visually or spectrophotometrically (at 500 mμ). Small amounts of cobalt, nickel, copper, aluminium, uranium, and rare-earth metals do not interfere with the titration of iron; but titanium, zirconium, and thorium do interfere. Good results have been obtained in the complexometric determination of iron in iron ores and in magnesite bricks.

Scandium and zirconium. These elements are determined by back-titration of the excess of Complexone III with a ferric solution using BPHA as indicator under the above conditions [12]. The presence of aluminium, beryllium, uranium, and rare-earth metals does not interfere.

IV. USE OF *N*-BENZOYL-*N*-PHENYLHYDROXYLAMINE FOR THE ANALYTICAL SEPARATION OF ELEMENTS

The benzoylphenylhydroxylamine complexes of different elements are quantitatively precipitated from solutions of different acidities, and this makes it possible to use BPHA to separate several elements by precipitation. The selective extraction of the complexes by organic solvents is also used for the separation of elements. In both cases the selectivity of the separation is considerably increased by the presence of masking agents.

1. Separation of Elements by Precipitation

Sinha and Shome [30] found that thorium and cerium(III) are quantitatively precipitated by BPHA at pH 4.5–5.5 and 6.5–7.5 respectively. On this basis they worked out a method for separating thorium and cerium: from a solution containing thorium and cerium(IV), the thorium is first precipitated at pH ~5 by means of BPHA in the presence of hydroxylammonium chloride (to keep the cerium in the tervalent condition); the pH of the solution is then raised with ammonia to ~7, and the cerium is precipitated with the same reagent. Determination of the separated metals is completed gravimetrically by igniting the resulting precipitates to the oxides.

The same workers [20] demonstrated the possibility of separating cobalt or nickel from copper: from a solution containing copper and cobalt, or copper and nickel, the copper is first precipitated with BPHA at pH ~4 (sulphuric acid + sodium acetate), and the the cobalt or nickel at pH 5.5–6.5 (sodium acetate); in the precipitation of cobalt, formation of the cobalt(III) complex is avoided by first adding hydroxylammonium chloride. Determination of the separated metals is effected gravimetrically by the direct weighing of the precipitates.

Majumdar and Mukherjee [23,24] used BPHA in the separation of niobium and tantalum. Their method is based on the precipitation of niobium with BPHA in tartrate medium at pH 3.5–6.5 (ammonium acetate), subsequent lowering of the solution pH to ~1 with sulphuric acid, and precipitation of tantalum at this pH with the same reagent; the separated metals are weighed as their oxides. In the opinion of these workers, a single precipitation is sufficient to separate by this method niobium and tantalum when they are present in proportions varying from 1 : 16 to 100 : 1; when their ratio is 1 : 100, a double precipitation is required. The time necessary for the analysis is considerably less than with other methods.

A slightly modified form of this method [24] was used by Langmyhr and Hongslo [26] in the analysis of mixtures of titanium, niobium, and tantalum. Niobium and tantalum are precipitated together from the test solution by means of BPHA in 1 *N* sulphuric acid, the titanium being kept in solution with Complexone III and hydrogen peroxide. The precipitate is ignited to the oxides and fused with potassium pyrosulphate, for the separation of niobium and tantalum with BPHA; the filtrate is evaporated to decompose the organic compound, and then titanium is precipitated in 5% sulphuric acid medium by means of the same reagent. These workers obtained satisfactory results in the analysis of two complicated minerals, blomstrandine and euxenite, using hydrofluoric acid to decompose the specimens; a single precipitation of titanium, niobium, and tantalum with BPHA in the presence of Complexone III and tartaric acid is sufficient for a preliminary overall separation of these metals from other components of the minerals.

Alimarin and Tsê Yün-hsiang examined the use of BPHA to separate a series of rare elements, and obtained satisfactory results for the separation of scandium from the rare-earth metals and zirconium [28]; thorium from rare-earth metals and uranium(VI); [30] and zirconium from iron, titanium, niobium, and tantalum [32]. In the separation of scandium from rare-earth metals (in proportions from 1 : 5 to 1 : 40) the scandium is first precipitated with BPHA in an acetate buffer at pH 5.2–5.4, and then ammonia is added to the filtrate to precipitate the rare-earth metals as their hydroxides. The separation of scandium from zirconium (in proportions of 1 : 20) is based on the ability of the latter to be precipitated by BPHA in strongly acid medium (2–3 *N* with respect to hydrochloric acid); under these conditions scandium is not precipitated. Thorium is separated from rare-earth metals (in proportions varying from 1 : 10 to 1 : 100) by precipitating it with BPHA in an acetate buffer at pH ~4.5, and from uranium (in proportions between 1 : 4 and 1 : 2000) by precipitation in ammonium carbonate medium at pH 7.0–8.5. Zirconium can be separated from titanium, niobium, and tantalum by precipitating it with BPHA in ~2.5 *N* HCl medium in the presence of hydrogen peroxide, and from iron by precipitation in the presence of ascorbic acid.

BPHA can also be used to separate beryllium from iron, aluminium, and titanium [13]. In this case iron and alumnium (at pH ~4) or titanium (at pH ~1) are first precipitated with BPHA, and then beryllium is brought down from the filtrate (at pH 5.5–6.5) with the same reagent; the precipitate of the beryllium complex is weighed directly after being dried at 110°.

The precipitation of molybdenum(VI) from strongly acid medium (~10 *N* with respect to hydrochloric acid) is used for its separation from cobalt, nickel, and copper, and also from iron(III) and vanadium(V) (in the presence of Complexone III)[22].

2. Separation of Elements by Extraction

The separation of elements by extracting their benzoylphenylhydroxylamine complexes with organic solvents has been little studied. However, preliminary results indicate good prospects for using BPHA as a complexing agent in the extractive separation of elements.

Dyrssen[8] was the first to study the extraction characteristics of BPHA, and he showed that tantalum can be easily separated from uranium and thorium by a single extraction of it, from perchlorate solutions at pH 4.5, with a 0.1 M chloroform solution of BPHA; good separation of uranium and thorium is achieved with a rather greater degree of fractionation. The extraction of lanthanum and uranium is much better with BPHA than with cupferron, which in Dyrssen's opinion is due to the greater stability of the BPHA.

Zharovskii[9] studied the conditions of formation and extraction of the compounds formed by BPHA with cations of Groups III and IV of the analytical tables, and separated several elements (iron, titanium, and vanadium from aluminium; iron from manganese; cadmium from copper; mercury from lead; etc.) by extraction. He worked out a technique for extracting iron and titanium from acid solution (0.5 *N*) with chloroform, and used it to separate these elements from aluminium in the analysis of artificial mixtures and standard specimens of iron ores.

Alimarin and others[12,28,30,34] investigated the effect of the acidity of the solution and the presence of masking agents on the extraction of several metal benzoylphenylhydroxylamine complexes by organic solvents (isopentyl alcohol, chloroform, benzene). The experimental results[12,28] showed that the complexes of titanium, zirconium, hafnium, niobium, and tantalum are extracted in amounts exceeding 90% (single extraction) from a hydrochloric-acid medium (>2 *N*) in the presence of excess of BPHA; the vanadium complex is extracted quantitatively (double extraction) at acidities of 0.1–1.5 *N* (with respect to hydrochloric acid). Other elements, apart from cerium(IV) and tin(II) and (IV), are not extracted in strongly acid media. This makes it possible to separate titanium, zirconium, hafnium, niobium, tantalum, and vanadium from many other elements, for example titanium from iron (in proportions from 1 : 1 to 1 : 3), zirconium from iron (1 : 1 to 1 : 7), zirconium from scandium (200 : 1), vanadium from uranium (1 : 30 to 1 : 20), and niobium from tungsten (1 : 7 to 1 : 70). The ferric, scandium, and thorium complexes are extracted quantitatively by isopentyl alcohol at pH values exceeding 2.5, 4, and 3.5 respectively, whereas the rare-earth metal complexes are not extracted by this solvent at pH 5.8; this forms the basis of extraction techniques for separating scandium and thorium from rare-earth metals (in proportions of 1 : 600 and 1 : 10 respectively)[28,30]. Experiments with radioactive isotopes (niobium-95 and tantalum-182) have shown[34] that, in the presence of tartaric acid at pH 4–6, a single extraction with chloroform removes 98–100% of niobium as its benzoylphenylhydroxylamine complex; tantalum is not extracted at all under these conditions (Fig. 6). Thus rapid separation of niobium and tantalum becomes possible when they are present in proportions ranging from 100 : 1 to 1 : 100. The possibility of separating niobium and tantalum by extraction from fluoride-containing solutions at pH 1 has been mentioned[35].

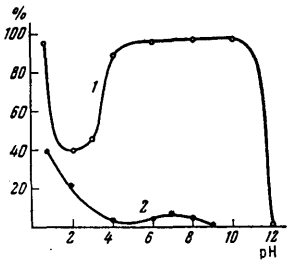


Fig. 6. Effect of pH of aqueous phase on extraction of benzoylphenylhydroxylamine complexes of: 1) niobium; 2) tantalum.

V. DERIVATIVES AND ANALOGUES OF CUPFERRON AS ANALYTICAL REAGENTS

Besides BPHA, several derivatives and analogues of cupferron, all derivatives of hydroxylamine, have been studied for possible analytical applications.

Lutwick and Ryan[10] and also Armour and Ryan[36] prepared and studied a large number of aromatic and acyl derivatives of phenylhydroxylamine and also *N*-benzoyl-*N*-naphthylhydroxylamine and *N*-acetylhydroxylamine. Table 4 gives some physical properties of the compounds investigated. All these compounds are solid crystalline substances which are white in colour — with the exception of *N*-(3,5-dinitrobenzoyl)-*N*-phenylhydroxylamine, which is yellow — and are more or less soluble in water. Many of them melt with decomposition, becoming red or black. Their stability is appreciably greater than that of cupferron: they can be kept for two or more years without appreciable decomposition. All the compounds studied possess in general similar chemical properties, although definite differences exist between them in their ability to react with metal ions in aqueous solutions. In the aromatic phenylhydroxylamines their selectivity towards metal ions increases with increase in acidity of the oxime group of the reagent: in acid solutions (≥1% of acid) only vanadium, tin, titanium, and zirconium are precipitated[10]. With copper as example it has been shown that decrease in the acidity of the reagent is accompanied by an increase in the lower pH limit necessary for complete precipitation of the metal (Table 4). However, a strengthening of the acidic character of the reagent by introducing appropriate substituents results in a decrease in stability of the complexes formed by the reagent. This last statement is true also of acylphenylhydroxylamines[36].

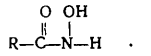
Among the compounds examined only *N*-furoyl-*N*-phenylhydroxylamine, which is able to form an ammonium salt[10], is of some analytical interest. In general, none of the reagents studied possesses any advantages over cupferron or BPHA. The same applies to some other newly investigated reagents: phenylacetylphenylhydroxylamine[37],

TABLE 4. Physical properties of various derivatives of hydroxylamine[10,36].

Substituted hydroxylamine	Colour	M.p., °C	Solubility in water, g per 100 ml	pH of 1% soln. of reagent in ethanol	Lowest pH for complete pptn. of Cu
N-Benzoyl-*N*-phenyl -	white	121	0.040	7.5	3.0
N-*o*-Ethoxybenzoyl-*N*-phenyl-	white	103	0.011	7.3	3.3
N-*o*-Iodobenzoyl-*N*-phenyl-	white	128	0.010	7.3	3.0
N-Naphthoyl-*N*-phenyl-	white	129	0.003	7.2	3.4
N-(3,5-Dinitrobenzoyl)--*N*-phenyl-	yellow	133	0.007	5.8	4.2
N-Furoyl-*N*-phenyl-	white	134	0.013	6.85	3.0
N-(2,4-Dichlorobenzoyl)--*N*-phenyl-	white	137	0.006	6.8	3.7
N-Benzoyl-*N*-naphthyl-	white	164	0.013	4.5	5.5
N-Thenoyl-*N*-phenyl-	white	97		6.85	3.0
N-Nicotinyl-*N*-phenyl-	white	134			
N-Cyclohexanoyl-*N*-phenyl-	white	124		7.25	4.5
N-Hexanoyl-*N*-phenyl-	white	67		7.30	4.5
N-Heptanoyl-*N*-phenyl-	white	60			
N-Acetyl-	white	30			

cinnamoylphenylhydroxylamine[37], phenylazophenylhydroxylamine [3-hydroxy-1,3-diphenyltriazen (Ed. of Translation)][38,39], 2-fluorenylcupferron[40], *p*-phenylcupferron[41-44], and *N*-nitroso-α-naphthylhydroxylamine (neocupferron)[41-44].

More promising compounds from the analytical point of view are the hydroxamic acids



An excellent survey of the literature on the analytical study and application of hydroxamic acids has recently been published by Brandt[45]. A brief survey of various derivatives and analogues of cupferron which are of analytical importance has been given by Macdonald[46,47].

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BPHA, while possessing favourable analytical properties, is stable and will certainly be used in analytical chemistry. The analytical techniques based on its use are simple in execution and effective in results. The possibilities of BPHA as an analytical reagent are far from being exhausted; many types of use are only beginning to be developed, and some of its analytical possibilities have not been studied at all. The analytical study of BPHA is being very vigorously pursued by many investigators.

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RECENT ADVANCES IN THE CHEMISTRY OF THE SESQUITERPENES

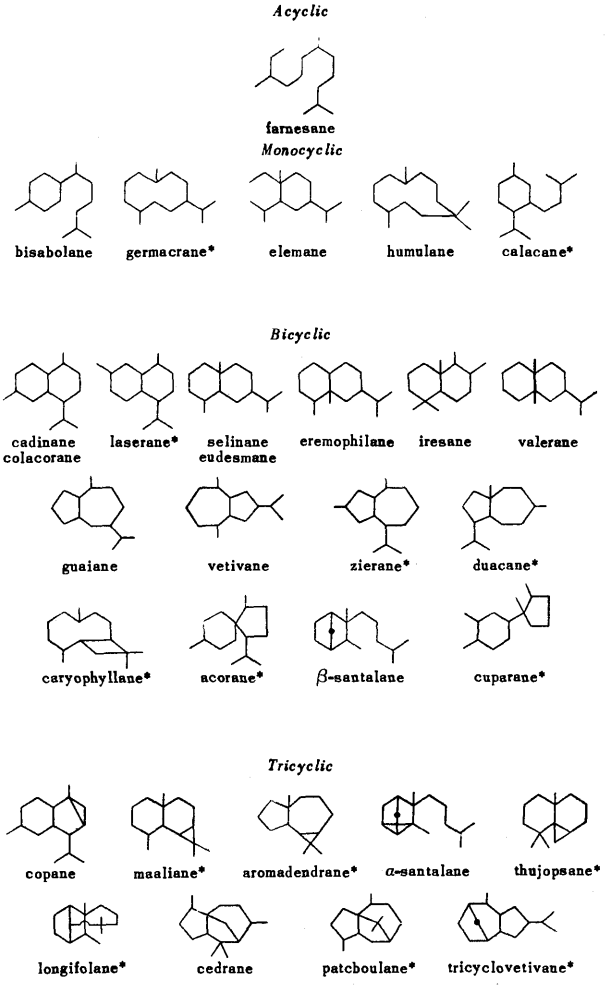
M. Suchý, V. Herout, and F. Šorm

The general study of living matter provides a constant source of information and is of great theoretical and practical value. The very origin of organic chemistry lay in the urge to investigate products of the metabolism of living organisms. Since that time the study of natural products has always formed an important part of organic chemistry. The study of substances contained in plants, which represent the major part (more than 99.9%) of living matter on the earth, has been of especial value in the development of our science. All the types of compound which make up the world of living organisms are produced in plant metabolism; this process is the source of characteristic groups of organic compounds, including especially terpenes, alkaloids, and glycosides. The thorough study of the chemical structure of numerous, genetically interrelated compounds of these groups was stimulated by their biological activity, and sometimes also by their practical importance. Their systematic study contributed to the creation of the best traditions in organic chemistry and to its present diversity.

The study of terpenes and steroids was undoubtedly of great value in the development of organic chemistry. Both groups are restricted by their simple composition, limited by containing only three principal elements, and by the individual structural regularities in each group. However, their great structural diversity and wide distribution was led to the study of terpenes and steroids becoming a subject of deep interest to many laboratories in the world. The principal methods for determining the structure of organic compounds, especially degradation, were discovered and tested in the investigation of compounds of both groups; this simultaneously stimulated the development of synthetic methods. The study of terpenes and steroids laid the foundations of stereochemistry, and constituted the starting points for modern concepts of the spatial structure of organic compounds. Chemistry was simultaneously enriched with very valuable methods for isolating pure organic substances from complex mixtures, and for their determination and identification by means of physical constants or the relations between chemical structure and physical, especially spectroscopic properties, without which modern organic chemistry cannot be imagined.

In our first review paper, published in this journal in 1953,[1] we surveyed the work carried out up to 1952 in the Institute of Organic Chemistry of the Czechoslovak Academy of Sciences. The present paper reviews some later results obtained in the Institute of Organic Chemistry and Biochemistry of the Czechoslovak Academy of Sciences in Prague, especially on terpenoid compounds of the sesquiterpene group which had been little studied previously.

Scheme 1
Survey of types of sesquiterpene hydrocarbons



These compounds, in the study of which great interest has been shown, are very varied. This can be seen from Scheme 1, on which are represented all the hydrocarbon skeletons which have now been established in this group. The asterisks indicate formulae corresponding to structures which have been discovered and proved beyond doubt during the past fifteen years; the remaining structures were investigated earlier. The names of the structural types derive from those of some important sesquiterpenoid hydrocarbons containing the given hydrocarbon skeleton.

The infra-red spectra of the sesquiterpenes and the spectra of their derivatives have been collected in a new volume, which has recently been published by the German Academy of Sciences in Berlin[2].

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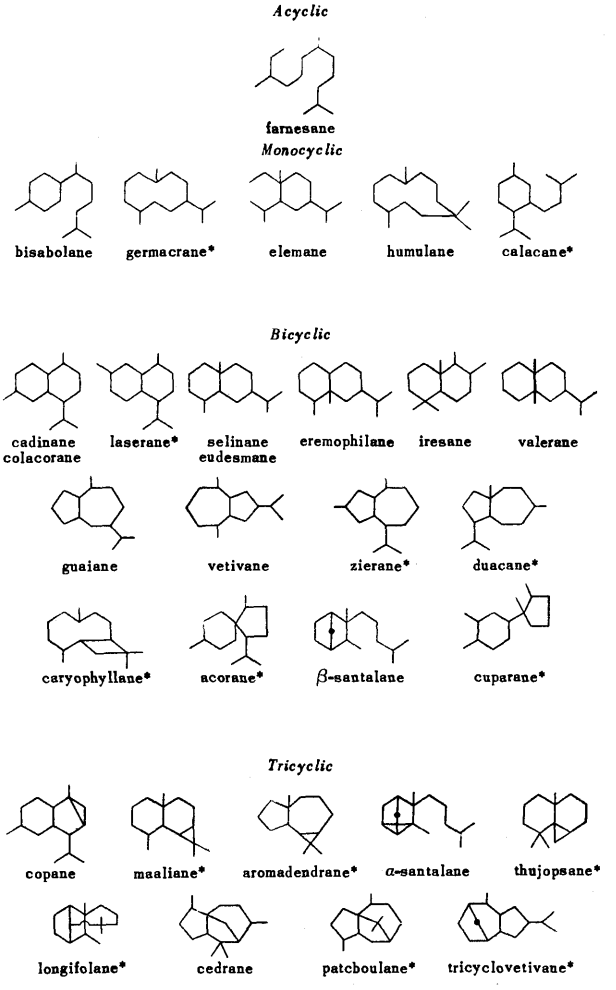

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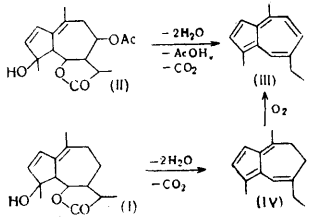
Those natural products which are sesquiterpene derivatives having a bicyclic five- or seven-membered carbon skeleton and containing a γ-lactone group are worthy of

more detailed study. A large group of these substances are structurally related to guaiane, since their fundamantal skeleton is the carbon skeleton of guaiane, and we therefore term them *guaianolides*. They are found in many plants of the *Compositae* family. The discovery of this group of substances is associated with the study of the chamazulenogenic substances in wormwood and camomile[3,4], and with the study of the structure of chamzulene[5-7]. During 1951-1952 the problem of the structure of chamazulene and of substances, present in both plants of the *Compositae* family, which form chamazulene on distribution in steam, was solved. Since azulene is absent from the plant extract, it can be assumed to have been formed only as a result of changes occurring on distillation of the vegetable material in steam. We therefore turned our attention to the isolation of these new substances, precursors of chamazulene.

Our first result was the isolation of two crystalline hydroxylactones from bitter wormwood and pharmaceutical camomile. We determined the chemical structure of both substances, and termed them *artabsin* (I)[8] (from wormwood) and *matricin* (II)[9] (from camomile) (see Scheme 2).

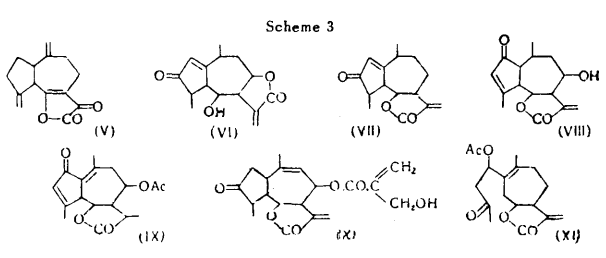
Scheme 2



These compounds are unstable: when heated in weakly acid solution they are converted into chamazulene (III) as a result of dehydration and decarboxylation. In the case of artabsin an unstable orange hydrocarbon of fulvene type is formed at first. This readily polymerisable substance had previously been obtained and identified by us in the essential oil of wormwood. It had then been named *chamazulenogen* (IV),[10] and its structure determined, being found to correspond to a dihydrochamazulene. This substance is converted into chamazulene by oxidation in the air. These reactions of artabsin, as also of matricin, which is an acetoxy-derivative of artabsin, led to the correct formula for chamazulene and at the same time enabled its composition to be established as $C_{14}H_{16}$, which is unusual for a sesquiterpenoid compound. We confirmed the structure of chamazulene by a complete synthesis.

The discovery of this new type of compound in nature stimulated further study of products extracted from plants of the *Compositae* family. This opened the way to the establishment of the structure of several similar compounds, some of which had already been known for a long time, although their structure had not been determined (Scheme 3).

Scheme 3



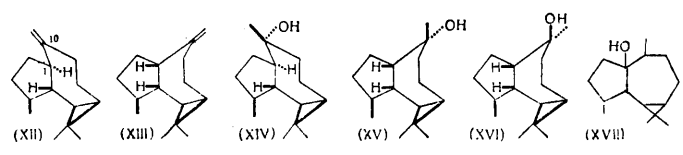
In this way structures were established for dehydrocostus lactone (V)[11,12] from the essential oil of the roots of *Saussurea lappa*, helenalin (VI)[13,14] from several species of *Helenium*, ambrosin (VII)[15,16] from *Ambrosia maritima* (a plant growing in the Nile Delta), lactucin (VIII)[17,18] from *Cichorium intybus* and several *Lactuca* species, matricarin (IX),[19] a lactone from *Matricaria chamomilla*, absinthin and anabsinthin from wormwood[20-22] cynaropicrin (X)[23,24] from *Cynara scolymus* and *Cynara cardunculus*, xanthinin (XI)[25,26] from *Xanthium pensylvanicum*, and globicin from *Matricaria globifera*[27].

All these compounds confer a bitter taste on plants containing them. Recently the structures of other guaianolides have been determined, for example arborescin[28] from *Artemisia arborescens*, carpesia lactone[29] from *Carpesium abrotanoides*, isohelenalin[30], tenulin, and isotenulin[31] from different *Helenium* species, and geigerin[32] from the South African plant *Geigeria aspera*.

We shall not give a complete catalogue of these substances: new papers are constantly appearing on the structure of new guaianolides. The number of derivatives studied so far shows that we are dealing with substances which occur very often in plants of the *Compositae* family.

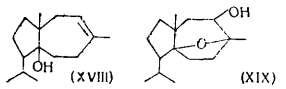
Another interesting group of compounds with a similar structure are those of the aromadendrane type, which are distinguished from the guaiane type by containing an additional three-membered carbon ring. We have discovered the hydrocarbon alloaromadendrene, which is an isomer of the already known aromadendrene. The two hydrocarbons differ in configuration at $C_{(1)}$. We established the precise structure of aromadendrene, *i.e.* the position of the three-membered ring[33], by degradation. Spatial structures were determined for both hydrocarbons, and are represented by the formulae (XII) for aromadendrene and (XIII) for alloaromadendrene[34]. Globulol (XIV), which contains the same skeleton, had been known previously. This group was extended to the following sesquiterpenoid alcohols: ledol (XV), viridiflorol (XVI), and palustrol (XVII). All these sesquiterpenoid alcohols yield the same diol on dehydration followed by hydroxylation[35-37], so that they differ only in the position of the hydroxyl group or in their spatial structure. However, the differences between them extend only to the carbon atoms $C_{(1)}$ and $C_{(10)}$. We have found that ledol corresponds to the spatial formula (XV), viridiflorol to (XVI), and globulol to (XIV). Palustrol was established as a position isomer with the hydroxyl group attached to $C_{(1)}$, as can be seen from the formula (XVII) (Scheme 4). Büchi *et al.*[38] reached the same conclusions, independently of us, in a study of the structure of aromadendrene, ledol, viridiflorol, and globulol.

Scheme 4



The azulane skeleton is also present in two sesquiterpenoid alcohols, carotol (XVIII) and daucol (XIX), which are found in the carrot, *Daucus carrota* L. In contrast to other

workers, we have suggested the formulae (XVIII) and (XIX),[39] based on identification of the oxidation products. They are confirmed by the work of Shoolery *et al.*[40] using nuclear magnetic resonance data. We obtained further interesting results in a study of a group of substances containing medium carbon rings (by this we imply rings containing 8–11 carbon atoms).

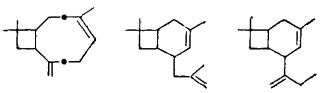


(XVIII) (XIX)

Compounds containing nine-, ten-, or eleven-membered rings have been found among natural products. The discovery of these compounds in plants was somewhat unexpected, since it was only recently that the existence of large rings in nature was rigorously proved in macrocyclic aromatic ketones which were also products of animal metabolism. The difficulties involved in the synthesis of medium-ring alicyclic compounds, which were surmounted only a few years ago by means of the acyloin condensation, together with certain theoretical aspects of their conformation, supported the previously accepted view that substances of this type were unknown in nature.

The existence in nature of a medium-sized alicyclic ring was first demonstrated by us in an investigation of the structure of caryophyllene[41]. Much work had been done on this hydrocarbon, and the two alternative structural formulae (XXa) and (XXb) were regarded as the most probable. Perhaps the major proportion of the work in the field of sesquiterpenoid compounds in general has been devoted to elucidating the structure of this hydrocarbon. It was known long ago that caryophyllene (XXI) is a bicyclic hydrocarbon containing two double bonds and a characteristic four-membered ring with two geminal methyl groups. At first we wanted to know which of the two possible formulae then proposed[42-45], (XXa) (Ruzicka) or (XXb) (Treibs), corresponded to this substance (Scheme 5).

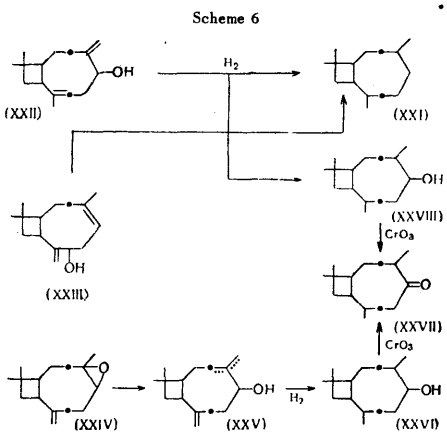
Scheme 5


(XXI) (XXa) (XXb)

However, the cleavage reactions which we carried out[48] permitted four new formulae to be ascribed to caryophyllene, according to which the molecule contains a nine-membered carbon ring. Two of them were then excluded on the basis of the structure of homocaryophyllenic acid (one of the oxidation products of caryophyllene) determined by Dawson and Ramage[46]. Simultaneously, Barton *et al.*[47] proved one of the two remaining formulae to be correct, and determined the absolute configuration of caryophyllene. The structure of the main skeleton of caryophyllene (XXI) was later confirmed by us by the partial synthesis of tetrahydrocaryophyllenic acid.

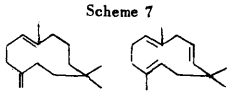
We subsequently demonstrated the presence of a caryophyllene skeleton in two sesquiterpenoid alcohols, the so-called α-betulenol (XXII) and β-betulenol (XXIII),[49] which are found in the essential oil of birch buds. Both are secondary alcohols. Scheme 6 shows the correlation of these two substances with a caryophyllene derivative, and monoepoxide (XXIV).

Scheme 6



The hydrocarbon humulene was the next compound in which it was possible to demonstrate the presence of a medium-sized, in this case an eleven-membered, ring. This hydrocarbon is supposed to be closely related genetically to caryophyllene, as is indicated by its structure and by the fact that it is often found in essential oils, for example, oil of cloves and oil of hops. Humulene[50,51] is a monocyclic compound containing three double bonds. We suggested a structure for it, which was soon confirmed by Clemo[52] on the basis that oxidative cleavage of the hydrocarbon yields only formaldehyde and acetic acid apart from 2,3-dimethylsuccinic acid: no higher monofunctional cleavage products are formed. Only the complete synthesis of hexahydrohumulene (humulane)[53] finally confirmed the humulene skeleton. The synthetic hydrocarbon which we obtained was identical with the product of complete hydrogenation of natural humulene (as established by an examination of the infra-red spectra). The question of the position of the double bonds was completely solved only recently, when we discovered that two humulenes, α (XXIX) and β (XXX),[54] occur in nature. In the first of these compounds one double bond is exocyclic and methylenic; in the other compound it is located in a carbocyclic ring (Scheme 7).

Scheme 7

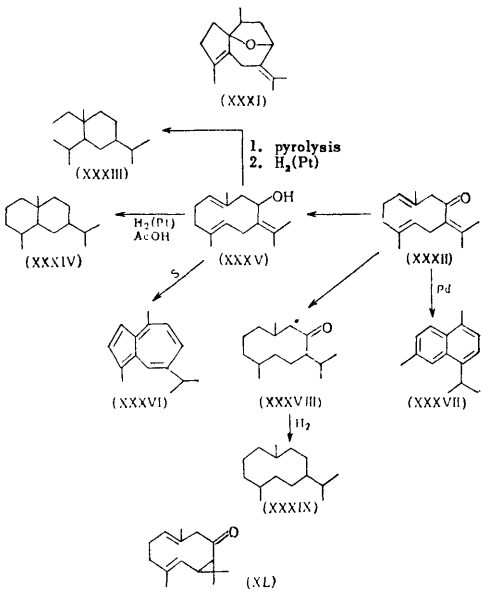

(XXIX) (XXX)

Recently Dev[55] discovered, from a comparison of the infra-red spectra of a saturated hydrocarbon obtained from the sesquiterpenoid ketone zerumbone and of humulane, that zerumbone possesses a humulane skeleton. It is probable that humulene and caryophyllene are interrelated genetically in the sense that the latter is a product of the cyclisation of the former. However, it has not yet proved possible to effect this cyclisation by chemical means because of the comparative instability of humulene.

The next constantly increasing group of sesquiterpenoid compounds comprise substances containing a ten-membered ring. These compounds, in the form of their oxygen derivatives, are probably frequent metabolic products, especially of plants of the *Compositae* family; they are of great importance in the biogenesis of several other bicyclic sesquiterpenoid compounds, as will be shown later.

The first natural product in which the presence of a ten-membered ring was suggested was the lactone pyrethrosin, studied by Barton[56,57]; the first compound in which the presence of this ring was precisely demonstrated was the ketone germacrone[58], the main constituent of "health" oil. It is interesting to recall the history of the investigation of this substance, which had already been known earlier under the name "germacrol" and investigated in detail by Treibs, who suggested the formula (XXXI) for it (Scheme 8).

Scheme 8

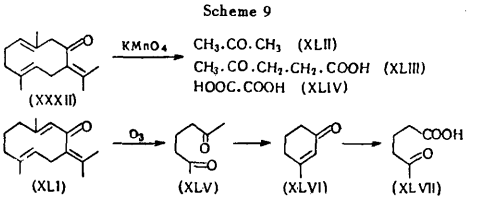


According to Treibs, germacrol was an internal ether having a guaiane skeleton. In collaboration with Bulgarian colleagues, we initiated work to check the structure of this compound, and found from the infra-red spectrum of germacrol that it is not an ether but an unsaturated ketone (absorption band for the carbonyl group at 1675 cm^{-1}).[58] When we tried to obtain hydrogenation and dehydrogenation products of germacrone (XXXII) (as we renamed the substance in conformity with the nature of the oxygen function), we obtained surprising and contradictory results. After hydrogenation in acetic acid in the presence of a platinum catalyst, we isolated two pure hydrocarbons. One of them had the composition $C_{15}H_{30}$, and according to its infra-red spectrum was elemane (XXXIII). The other, $C_{15}H_{28}$, was identical with selinane (XXXIV). Reduction of germacrone with aluminium isopropoxide yielded an alcohol (XXXV), which could be reconverted into crystalline germacrone by oxidation. Dehydration yielded a mixture of hydrocarbons, dehydrogenation of which gave a considerable quantity of guaiazulene (XXXVI). It was known that the dehydrogenation of germacrone under severe conditions will lead to the production of cadalene (XXXVII).

Thus from germacrome and its derivatives it is possible to obtain, under mild or severe conditions, derivatives of four different types of sesquiterpenes, of which only the elemane type (XXXIII) corresponds to the suggested monocyclic character of germacrone. Since it was difficult to assume the formation of other bicyclic sesquiterpenoid compounds from those of the elemane type, we concluded that germacrone is not a derivative of known types of sesquiterpenes. This was demonstrated by hydrogenation, which yielded a saturated ketone, hexahydrogermacrone $C_{15}H_{28}O$ (XXXVIII) and a hydrocarbon $C_{15}H_{30}$ (XXXIX). The infra-red spectrum of the latter showed it to represent a then unknown type of sesquiterpene, which we termed the germacrane type. All the reactions described so far can be explained if it is assumed that a ten-membered ring is present in germacrone and in germacrane (XXXIX). This is indicated also by the physical properties of hexahydrogermacrone (XXXVIII), whose infra-red spectrum showed a ketone peak (1704 cm^{-1}) characteristic of medium rings. The final proof of this was our synthesis of one of the cleavage products of germacrone[59], and especially the complete synthesis of germacrane (XXXIX). The synthetic hydrocarbon[60] was completely identical with the substance obtained from germacrone. It was extremely difficult to prove the location of the double bonds in germacrone, especially in view of the anomalous character of the infra-red and ultra-violet spectra of this compound[61]. New formulae were therefore proposed for germacrone, one of which was, for example, the formula of the maaliol type (XL) suggested by Ohloff *et al.*[62]

It has recently proved possible[63] to demonstrate the location of the double bonds from a study of the products of the alkaline oxidation of germacrone (XXXII) and its isomer, the so-called isogermacrone (XLI). On ozonolysis or oxidation with alkaline potassium permanganate, germacrone yields, apart from 1.5 moles of acetone, laevulinic acid (XLIII) and oxalic acid (Scheme 9).

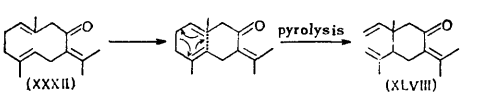
Scheme 9



Only 0.6 mole of acetone is formed by the ozonolysis of isogermacrone under similar conditions. When the heptane-2,6-dione (XLV) obtained at first was oxidised under analogous conditions, 3-methylcyclohex-2-enone (XLVI) was isolated, and this oxidised to homolaevulinic acid (XLVII). In view of this, we suggest that germacrone has the formula (XXXII), while isogermacrone is (XLI). It follows that (XLI) arises from germacrone by the displacement of one double bond; the nature of its ultra-violet spectrum also changes in conformity with this.

Our proposed formulae for germacrone are consistent also with reactions leading to other types of sesquiterpenes. The transition to the elemane group is especially interesting. Simply heating germacrone yields β-elemenone (XLVIII), involving the formation and rupture of carbon–carbon bonds. This particular reaction is favoured by the arrangement of double bonds in germacrone (Scheme 10).

Scheme 10



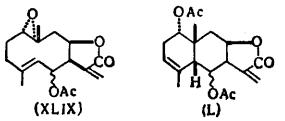
Owing to the change in position of the double bonds involved in the reaction under such conditions, isogermacrone does not pass into β-elemenone. In contrast to natural elemane derivatives, β-elemenone obtained from germacrone is optically inactive. If the natural elemane derivatives which do not possess a regular isoprene structure are formed by the above mechanism, it must be supposed that this process involves the participation of specific biocatalysts.

The transformation of germacrone into other sesquiterpenoid types on hydrogenation or dehydrogenation, and especially its conversion into compounds of the selinane type (XXXIV), can be explained by transannular cyclisations, which have been observed also in other cases[64-66].

Many compounds having a ten-membered ring have been found in a detailed study of sesquiterpenoid lactones obtained from plants of the *Compositae* family. The investigation was made after the discovery of the guaianolides, a huge new group of sesquiterpenoid compounds having a guaiane skeleton, which are closely related to the santonin group.

At the beginning of 1957 Barton published his first paper on pyrethrosin, a sesquiterpenoid lactone from *Chrysanthemum cinerariaefolium*[56] having the composition $C_{17}H_{22}O_3$ (Scheme 11).

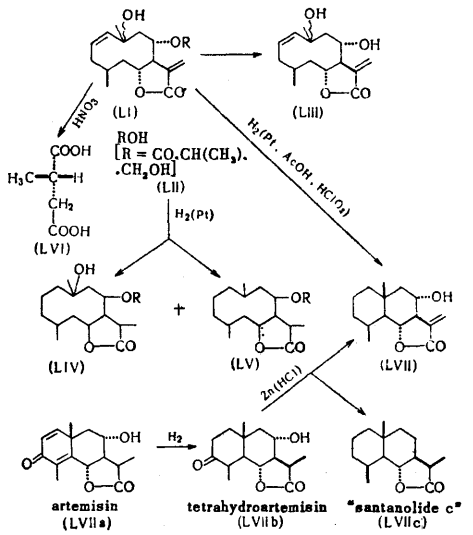
Scheme 11



On the basis of a detailed study of the reactions of cyclopyrethrosin and of the physical properties of the derivatives obtained, Barton[57] has recently proposed a final structure for pyrethrosin (XLIX) and its cyclisation product (L), and at the same time has almost completely established its configuration.

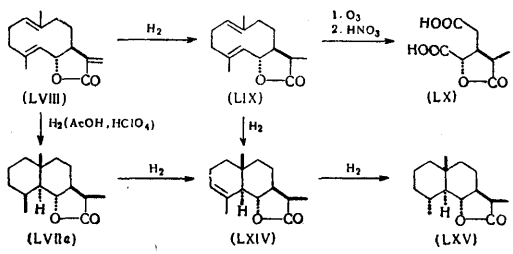
At the same time we discovered, in a study of arctiopicrin (LI),[67,68] the lactonic bitter principle of the plant *Arctium minus*, that the formula previously assigned to it was incorrect, it being actually an ester of 3-hydroxy-2-methylpropionic acid (LII) and a sesquiterpenoid lactone, which we called *arctiolide* (LIII). Since the empirical formula of (LIII) was $C_{15}H_{22}O_4$ and it contained two double bonds, its main carbon skeleton was clearly monocyclic. Further study of arctiolide by the hydrogenation of arctiopicrin proved that it was a secondary hydroxyl group which had been esterified. Reduction also involved hydrogenation of a tertiary hydroxyl, and so the ester-lactone (LV) was isolated in addition to the hydroxy-ester-lactone (LIV). The position of the double bond in the ring was then confirmed by oxidising arctiopicrin with nitric acid, the ensuing isolation of *L*(-)-methylsuccinic acid indicating the absolute configuration of the tertiary methyl group. The main proof of the structure of arctiopicrin was the direct correlation with compounds of the santonin group[64]. Here, the first observation was made of a stereospecific conversion from the germacrone group by transannular cyclisation into the selinane group. Hydrogenation of arctiopicrin in glacial acetic acid in the presence of a small amount of perchloric acid yielded a bicyclic product which after hydrolysis proved to be identical with deoxytetrahydroartemisin (LVII); this last compound was also prepared synthetically by Clemmensen reduction from artemisin (LVIIa). "Santanolide c" (LVIIc) and tetrahydroartemisin (LVIIb) were obtained as byproducts (Scheme 12).

Scheme 12



Recently the Indian workers Somasekar Rao *et al.*[69] have studied a monocyclic sesquiterpenoid lactone from the Himalayan plant *Saussurea lappa*, which they termed *costunolide* (LVIII) and showed it to contain also a germacrane cyclodecane skeleton. At the same time we were studying substances present in the Asian species of wormwood *Artemisia balchanorum*, and isolated a lactone identical with costunolide, as the main constituent of this plant. We were able[70] to prove that it corresponds to the formula (LVIII) suggested by the Indian workers (Scheme 13).

Scheme 13

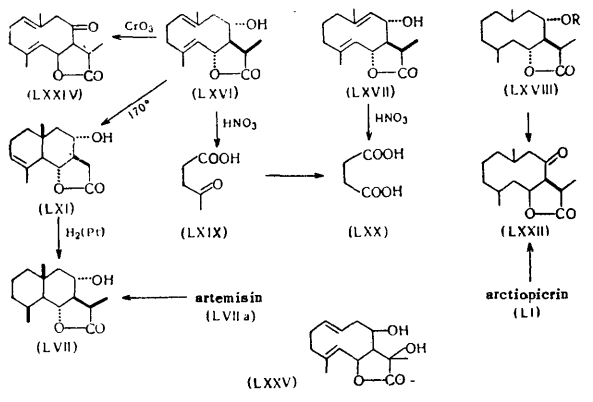


In this proof, we were assisted by the fact that among the products of the ozonolysis and further oxidation of dihydrocostunolide (LIX) was a lactone-dicarboxylic acid $C_8H_{10}O_6$ (LX) which we had already isolated earlier and identified as an oxidation product of santonin, artabsin, and absinthin[20-22]. We were also able to demonstrate rigorously the absolute configuration of costunolide. In this we were again helped by transannular cyclisations, which could now be carried out in several ways. Thus the product of the hydrogenation of costunolide in acid medium was identical with santanolide c (LVIIc), one of the reduction products of santonin (LXII). By being boiled with a mixture of acetic acid and acetic anhydride, dihydrocostunolide (LIX) could be converted into an unsaturated bicyclic lactone, which was identified as 3-santenolide (LXIV), described by Cocker and McMurry[71]. Further hydrogenation of this

initial product of cyclisation yielded a mixture of santanolide a (LXV) and santanolide c (LVIIc), already described earlier[72]. In conformity with the known configuration of santonin (LXII) all these reactions show that costunolide possesses the configuration indicated in Scheme 13. The configuration which we proposed for costunolide (LVIII) was later confirmed also by the Bhattacharyya school[73].

Costunolide is not the only lactone from *Artemisia balchanorum*. Paper chromatography of the plant extracts showed the presence of at least four lactones, three of which we were able to isolate in crystalline form. They all contain a cyclodecane ring[66]. Two of the lactones have the composition $C_{15}H_{22}O_3$, and they both contain two double bonds and one hydroxyl group. We named them *balchanolide* (LXVI) and *isobalchanolide* (LXVII). The two compounds differ only in the position of the double bonds, since hydrogenation and acetylation yield the acetyltetrahydrolactone (LXVIII) (Scheme 14). The location of the double bonds in the two lactones was determined by oxidative cleavage, which in the case of balchanolide (LXVI) yielded laevulinic acid (LXIX) and succinic acid (LXX). After cyclisation of balchanolide by the usual method in acid medium or by heating at 170° and hydrogenation of the cyclisation product (LXI), deoxytetrahydroartemisin (LVII) was obtained, a compound which we had already obtained in our work with arctiopicrin (LI). Thus the structure and the absolute configuration of both lactones were determined, and were then confirmed by correlation with derivatives prepared from arctiopicrin (LI). After oxidation of the hydroxyl group in tetrahydroisobalchanolide (LXVIII: R = H) the ketolactone (LXXII) was isolated and found to be identical with a known compound obtained from arctiopicrin (LI) and cnicin (LXXIII). The proposed structure (LXVI) is also confirmed by the fact that oxidation yields an unsaturated ketolactone (LXXIV) with a non-conjugated keto-group (Scheme 14).

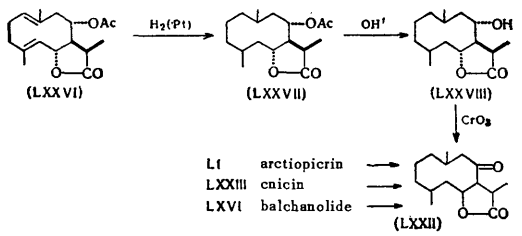
Scheme 14



The third of the substances which we isolated from *Artemisia balchanorum* had the composition $C_{15}H_{22}O_4$ (LXXV). We were able to demonstrate, by a series of reactions, that the position of the double bonds in this compound is the same as in balchanolide, and to determine the position of the tertiary hydroxyl group.

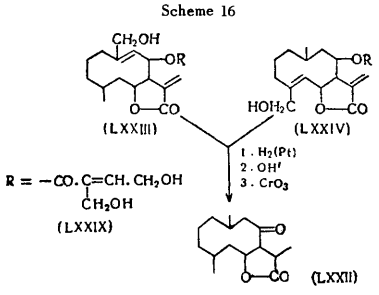
We have recently discovered[74] that one of the lactones isolated from yarrow, *Achillea millefolium*, is very closely related to balchanolide (LXVI). Chamazulene can be isolated from this plant, as also from camomile, by distillation in steam. This implies that *Achillea millefolium* contains its lactone precursors of the guaianolide group. It has not yet proved possible to isolate the original lactone in a pure form because of its instability. From yarrow itself, however, we have isolated three other crystalline lactones. One of them, having the empirical formula $C_{17}H_{24}O_4$ (LXXVI), gave acetic acid on hydrolysis. The lactone contained two double bonds in the molecule, and hydrogenation yielded a tetrahydro-derivative (LXXVII), which on hydrolysis gave a hydroxylactone (LXXVIII) (Scheme 15).

Scheme 15



When it was oxidised with chromium trioxide, we obtained a ketolactone (LXXII), which was identical with the known ketolactone prepared from arctiopicrin (LI) and cnicin (LXXIII). These facts give grounds for assuming that the new lactone from yarrow might be acetylbalchanolide (LXXVI), as was confirmed by the mixed melting-point method with acetylated balchanolide and from a comparison of the infra-red spectra.

Scheme 16

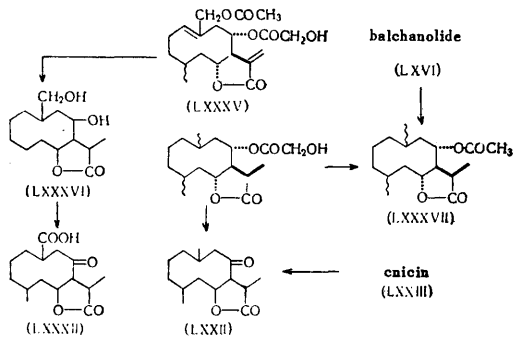


The germacrane group includes the bitter principle of *Cnicus benedictus*, which has been known for a century. This compound was assigned an incorrect formula[75], and only recently[76,77] has it been demonstrated that cnicin (LXXIII) is an unsaturated monocyclic sesquiterpenoid lactone esterified with the unusual 2,3-di(hydroxymethyl)acrylic acid (LXXIX). The free lactone has the composition $C_{15}H_{22}O_4$ and contains two hydroxyl groups and two double bonds (Scheme 16), one of the latter being conjugated with the carbonyl group of the lactone. The properties of the hydrogenation products of cnicin indicate that the esterified hydroxyl group is secondary, whereas the other hydroxyl is primary, since oxidation of the diol (LXXXI), obtained by saponification of the completely hydrogenated cnicin, yielded a ketolactonecarboxylic acid (LXXXII). The position of the esterified hydroxyl was determined from the fact that hydrogenolysis and saponification of cnicin gave a product which after oxidation with chromium trioxide yielded a ketolactone (LXXII) identical with a known compound obtained from arctiopicrin (LI). This indicates that a double bond must be located near the primary hydroxyl group (hydrogenolysis occurring readily). Hydrogenation of cnicin results in partial elimination of 2-methylbutyric acid, *i.e.* to further hydrogenolysis, indicating that cnicin

probably has the structure (LXXIII). However, the structure (LXXIV), although less probable, is not excluded. The proposed formulae are supported also by the oxidation products of hydrogenated cnicin, from which were isolated succinic, methylsuccinic, α-methylglutaric, and α-methyladipic acids. The configuration of the lactone group follows from the correlation with scabiolide (LXXXV), the configuration of the esterified hydroxyl group probably being analogous to that of the corresponding hydroxyl in scabiolide.

Cnicin, which we have recently found also in the plant *Centaurea rhenana*, is very closely related to another germacranolide, scabiolide (LXXXV), the main constituent of the oil of the cornflower species *Centaurea scabiosa*[78]. This crystalline substance is a diester of a sesquiterpenoid lactone, the esterifying acids being acetic and glycollic. The pure lactone contains two double bonds, one of which is as usual conjugated with the lactone carbonyl. One of the hydroxyl groups in scabiolide is primary, as in cnicin, the other is secondary. It has also proved possible to elucidate the relation between scabiolide (LXXXV) and cnicin (LXXIII). For this purpose the products of the complete hydrogenation of scabiolide and cnicin were saponified, and the resulting tetrahydro-derivative of the free dihydroxygermacranolide (LXXXVI) was oxidised with chromium trioxide. The same ketolactonecarboxylic acid (LXXXII) was obtained in this way. Hydrogenation of scabiolide yielded a monoester of glycollic acid (involving the carboxyl group) with the deoxytetrahydrolactone (LXXXVII), which after hydrolysis and oxidation yielded the already known ketogermacranolide (LXXII). In this way the germacrane skeleton of scabiolide was again confirmed, and the structure of its lactone ring proved (Scheme 17).

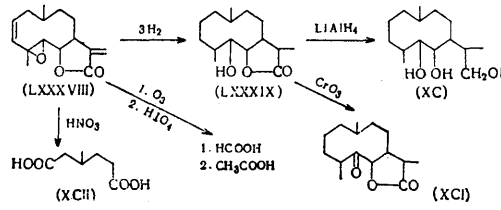
Scheme 17



The configuration of most of the centres of asymmetry in the scabiolide molecule, like that of most of the other germacranolides, was determined[79] by preparing acetyltetrahydrobalchanolide (LXXVII) from the deoxytetrahydrolactone after selective hydrolysis and acetylation with acetic anhydride.

Parthenolide[80], which we have isolated from the plant *Chrysanthemum parthenium*, is also a monocyclic lactone of the germacrane type having the composition $C_{15}H_{20}O_3$ (Scheme 18). It contains two double bonds, one of which is conjugated with the lactone carbonyl. The third oxygen atom forms an ether group, as follows from the chemical reactions and the physical constants of parthenolide. The position of one double bond was determined by ozonolysis: formic acid was produced, whereas acetic acid was obtained from the volatile residues after oxidation with periodic acid. The course of oxidation is shown in Scheme 18.

Scheme 18

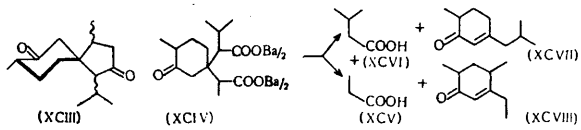


Parthenolide (LXXXVIII) is converted on catalytic hydrogenation into a hydroxylactone (LXXXIX), and on further reduction with lithium tetrahydroaluminate into a triol (XC) in which two secondary hydroxyl groups are linked to neighbouring carbon atoms. After oxidation of the hydroxylactone (LXXXIX) with chromium trioxide, a ketolactone (XCI) was isolated. The isolation of β-methyladipic acid (XCII) after oxidation of parthenolide with nitric acid enabled the position of the cyclic double bond to be determined.

The ease with which transannular cyclisations occur in sesquiterpenoids of the germacrane type, especially those resulting in compounds of the selinane type, *i.e.* in lactones of the santonin group, indicates that these reactions may be of great significance in biogenesis. It may be supposed that in nature lactones containing a cyclodecane ring are formed initially, and that substances of the santonin or guaianolide group are only formed from them by secondary reactions, analogous to the stereospecific transannular reactions which have been described. This possibility is suggested not only by the smoothness of the transannular reactions but also by the very wide distribution of the germacrane type of lactones in plants of the *Compositae* family, which contain also substances of the santonin group. Eleven very closely related lactones of the germacrane type, whose structures have been completely proved, have already been isolated within a short period. However, there is as yet no direct proof of the occurrence of such cyclisations in nature.

Many other interesting sesquiterpenoid derivatives are found in nature. An unusual structure predicted theoretically by Ružicka[81] in his paper on the biosynthesis of terpenes is shown by the diketone acorone (XCIII). This crystalline substance, obtained from *Acorus calamus*, was identified on further investigation[82-84] as a spiro-diketone having one six-membered and one five-membered ring (Scheme 19).

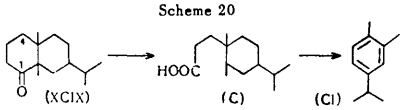
Scheme 19



The main evidence for the structure of acorone was provided by pyrolysis of the barium salt of the dicarboxylic acid (XCIV).[82] In this way propionic acid (XCV) and isovaleric acid (XCVI) were obtained together with two unsaturated ketones, isopropylmethylcyclohexenone (XCVII) and ethylmethylcyclohexenone (XCVIII). The proportions of the individual diketones were determined from the difference in optical rotation and the rotatory dispersion curves, and conclusions concerning their relative configurations were published[85].

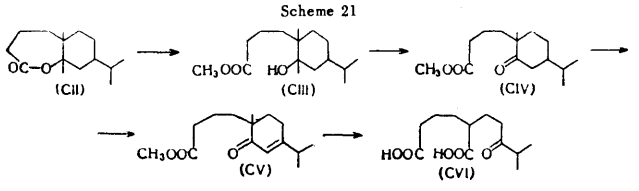
The saturated bicyclic sesquiterpenoid ketone valeranone (XCIX), which was found in *Valeriana officinalis*[86], gave rise to great difficulties in the determination of its structure. The latter was proved by the following series of reactions[87]. On photolytic cleavage valeranone gives a monocyclic acid (C), which on undergoing Barbier–Wieland degradation three times with subsequent dehydrogenation forms 1-isopropyl-3,4-dimethylbenzene (CI)(Scheme 20).

Scheme 20



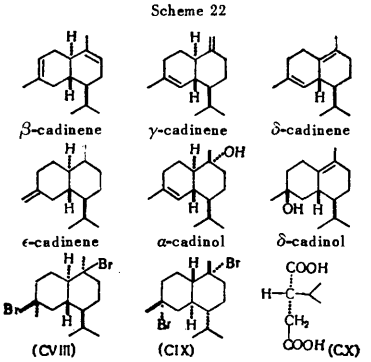
It has thus been proved that valeranone has a 7-isopropyl-9,10-dimethyldecalin hydrocarbon skeleton in which an oxo-group occupies position 1 or 4. The following series of reactions enables us to select[88] 7-isopropyl-9,10--dimethyldecalone from the two alternative formulae. Valeranone (XCIX) was oxidised with perbenzoic acid, yielding a lactone (CII). The methyl ester (CIII) obtained from it after hydrolysis was then dehydrated and ozonised. The keto-ester (CIV) after successive bromination and dehydrobromination gave an $\alpha\beta$-unsaturated keto-ester (CV), oxidative cleavage of which yielded a keto-dicarboxylic acid (CVI). From this it can be concluded that the oxo--group in valeranone is in position 1, since if it were in position 4, a tricarboxylic acid should be formed by the above reactions. This work corrected the erroneous conclusions of Indian workers[89,90], who call this substance "jatamansone".

Scheme 21



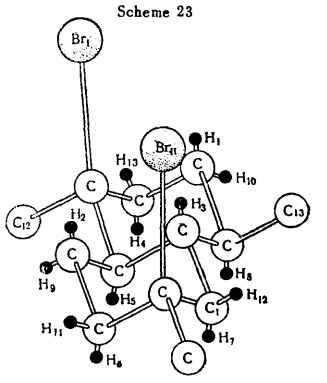
In conclusion we must mention the solution of a complicated problem, the establishment of the absolute configuration of compounds of the cadinane type. Physical methods have been of particular value in solving the structure of these natural products.

Scheme 22



We had investigated cadinane derivatives previously[91–93] as their presence had been discovered in natural materials. The structures suggested by ourselves and other investigators are indicated in Scheme 22. A common derivative of all these compounds is cadinene dihydrochloride (CVII) or even cadinene dihydrobromide (CVIII). Both derivatives contain the relatively heavy halogen atom in the molecule, and therefore are particularly easy to analyse by means of X-ray diffraction. From measurements on the X-ray patterns and calculations made by Hanic[94] it was clear that cadinene dihydrobromide (CVII) corresponds to the configuration represented diagrammatically in Scheme 23, which is equivalent to the formula (CVIII) or its mirror image (CIX).

Scheme 23



The configuration of the centres 1, 6, and 7, which are unaffected in the preparation of the halogeno-derivatives, should be identical in all these compounds. In order to determine the absolute configuration of the molecule, it was sufficient to determine the absolute configuration merely of one of these centres. On oxidative degradation of β-cadinene we obtained $D(+)$-isopropylsuccinic acid (CX), a compound whose absolute configuration has long been known. Hence the formula (CVIII) represents the absolute configuration of cadinene dihydrobromide, and consequently of other cadinene derivatives as well.

Note. Some of the formulae designated by Roman numerals are not given in the Russian original.(Ed. of Translation).

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GRAFT POLYMERS

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I. INTRODUCTION

The properties of high-molecular-weight compounds can be modified by grafting side chains on the polymer backbone, the nature of the side chains being either similar to the backbone or entirely different. Whereas some properties of graft copolymers are determined by those of the constituent backbone and side chains, others are not shown by any of the constituent polymers. An example of this is the graft copolymers which contain hydrophilic and hydrophobic chains (*e.g.* polystyrene on starch). Graft copolymers can also emulsify "oil–water" systems when none of the constituent polymers is an emulsifying agent.

The number of publications dealing with the preparation and properties of graft polymers is growing yearly and there is now a need both for a systematic treatment of the literature and for classification of graft polymers. Several surveys have been published[1-27] in which the material is arranged according to the methods of synthesis. We suggest that classification of graft polymers be considered from two viewpoints: first, from the position of all graft polymers within the series of other high-molecular-weight compounds and second, from the inter-relations of the individual members of the graft polymer series. This can be achieved by various means but the most rational one, in our view, is that adopted by Korshak whose classification is based on chemical structure[28]. We used the same principle for suggesting[29] the division of graft polymers into four types:

I. Homo-chain polymer backbone with grafted homo-chain branches (homo-chain graft polymers).

II. Homo-chain polymer backbone with grafted hetero-chain branches (homohetero-chain graft polymers).

III. Hetero-chain polymer backbone with grafted hetero--chain branches (hetero-chain graft polymers).

IV. Hetero-chain polymer backbone with grafted homo--chain branches (heterohomo-chain graft polymers).

The constituent polymer fragments in a graft copolymer can form either regular or random structures depending on the conditions of synthesis. The same polymer chains can be more or less regular or completely random in structure depending on the conditions of preparation. If the former are referred to as "crystalline" and the latter as "amorphous" the graft polymers of each of the above four types can be divided into four groups: (*a*) amorphous backbone and side chains (amorphous graft copolymers); (*b*) amorphous backbone, crystalline side chains (amorphous–crystalline graft copopolymers); (*c*) crystalline backbone and

side chains (crystalline graft copolymers); and (*d*) crystalline backbone, amorphous side chains (crystalline–amorphous graft copolymers).

The above division into types and groups makes it possible to include the structural and chemico-structural properties in the nomenclature of graft copolymers. This classification can embrace both organic and inorganic copolymers; we believe that it can not only group systematically the already known graft polymers but also reveal new groups of these substances.

The methods of preparation of graft copolymers include mechanical–chemical, irradiation–chemical, and various chemical ones. This review will be limited to the chemical methods of synthesis. Only polymers having carbon chains for the backbone and side chains have been considered as an example of homo-chain polymer constituents. The review does not include the formation of graft copolymers from naturally-occurring polymers. The literature references to graft polymers are arranged according to the chemical–structural principle mentioned above.

II. CARBON-CHAIN GRAFT POLYMERS (CARBON-CHAIN POLYMER BACKBONE WITH GRAFTED CARBON-CHAIN BRANCHES)

Much has been published on the synthesis of this type of graft polymers. The methods vary with respect both to the nature of the starting materials and the mechanism of the grafting reaction. The most widely used synthesis is based on free radical polymerisation; it is the most important method of preparation and gives graft polymers of different composition with diverse properties, but the spacing of the grafts and the length of the side chains are not easy to control. Another method of preparation is ionic polymerisation.

1. GRAFTING BY RADICAL POLYMERISATION

Despite the general nature of such polymerisation, various paths have to be followed for the formation of the radicals required for grafting. These include chain transfer during polymerisation of monomers in the presence of polymers, copolymerisation of monomers with polymers containing double bonds and the so-called "two-step method" based on the introduction into the polymer of groups able to break down under the polymerisation conditions to form active centres at which side chain grafting occurs.

A. Chain Transfer Reaction

This widely used method is based on chain transfer which occurs on polymerisation of monomer B in the presence of an initiator and previously introduced carbon-chain polymer AAAAA, which is either in solution or in a swollen state[30–32]. The reaction can be carried out in the block† in solution, in emulsion, and in latex. Growing chains begin to form from monomer B as the initiator breaks down. The growing polymer radicals react with molecules of the previously introduced AAAAA polymer and detach from it hydrogen or other labile atoms with consequent formation of free radicals on the polymer chains. These newly formed radicals initiate polymerisation of monomer B and side chains BBBBB are formed which are chemically bound to the polymer backbone. The number of grafted side chains depends both on the nature and molecular weight of polymer AAAAA and on the nature of the attacking radicals.

Omitting the stage of formation of the growing polymer radical, the process can be represented as follows:

$$\dot{R} + \cdots CH_2CHXCH_2CHX\cdots \rightarrow RH + \cdots CH_2\dot{C}XCH_2CHX\cdots \quad (1)$$

$$\cdots\!-\!(CH_2CHY)_nCH_2\dot{C}HY + \cdots CH_2CHXCH_2CHX\cdots \rightarrow$$

$$\rightarrow \cdots(CH_2CHY)_nCH_2CH_2Y + \cdots CH_2\dot{C}XCH_2CHX\cdots \quad (2)$$

$$\cdots\!-\!CH_2\dot{C}XCH_2CHX\cdots + mCH_2{=}CHY \rightarrow \cdots CH_2CXCH_2CHX\cdots$$

$$\cdots YCHCH_2CHYCH_2CHYH_2\dot{C} \quad (3)$$

$$\cdots CH_2\dot{C}XCH_2CHX\!-\!\cdots + \dot{C}HYCH_2(CHYCH_2)_n\!-\!\cdots \rightarrow$$

$$\rightarrow \cdots\!-\!CH_2CXCH_2CHX\!-\!\cdots$$

$$\quad\quad\quad

stem[35]. Benzoyl peroxide is an effective graft initiator for rubber, whereas azoisobutyric acid dinitrile fails to give a graft copolymer[36-38].

Schulz *et al.*[39] determined the chain transfer constants‡ during the formation of graft copolymers by polymerisation of monomers in the presence of low-molecular-weight polymers. This is the first and therefore a very interesting attempt to investigate the mechanism of graft polymer synthesis by the chain transfer method.

The role of the chain transfer through the polymer is enhanced by a rise in temperature since the energy of activation of the chain transfer reaction is greater than that of the growth reaction. The rate of chain transfer also depends on the polymer : monomer ratio, the lability of the atom being detached and the reactivity of the polymer radical[8,9]. As expected, graft polymers are usually obtained more readily by increasing the polymer : monomer ratio[40]. But when the polymer concentration is very high the grafting may be complicated by the increasing viscosity of the system which may alter the chain transfer constant and by the graft polymer forming a new phase which would lower the graft polymer yield and reduce the number and length of grafted side chains. Hayes[41] and Berlin *et al.*[42] also observed that the yield of graft polymers declined with increasing concentration of polymer in the system.

When the polymer contains highly reactive centres (bromoethyl[43], bromophenyl[44-47], or thiol groups[48-49]) the high rate constants for chain transfer by these groups ensure the formation of side chains. Thus when thioglycollic acid or hydrogen sulphide acts on the copolymer of methyl methacrylate with glycidyl methacrylate the number of SH-groups formed in the copolymer depends on the number of glycidyl methacrylate residues in the copolymer. Side chains can be grafted at the sites of the SH groups[48,49]. Fox, Gluckman, and others[48,49] have devised an equation, based on the kinetic reaction scheme, for determining the effectiveness of grafting§ in a system where the grafting is achieved by chain transfer by the SH-groups joined to the backbone. They postulated that the molecular weight of the side chains was independent of the degree of grafting and that all the free radicals, including the sulphur ones, react at the same rate. Their equation is given below:

$$E \cong \left[\frac{(1-\Phi)}{1-\Phi-y_0 \ln \Phi}\right]\left[1+\frac{(1+r)y_0^2}{(\Phi+y_0)(1+y_0)}\right],$$

where Φ is the unreacted fraction of the chain transfer centres, *i.e.* $[SH]_{final}/[SH]_{initial}$, y_0 is the initial ratio of the number of chain terminations effected by radicals to the number of chain terminations effected by chain transfer by the polymercaptan, *i.e.*

$$y_0 = \frac{\left(\frac{k_{term}}{k^2_{growth}}\right) \times \text{initial rate of polymerisation}}{C_s [SH]_0},$$

C_S being the chain transfer constant and r the fraction of chain terminations occurring by disproportionation, *i.e.*

$$r = \frac{k_{term\ disproport}}{k_{total\ term}}.$$

In one instance the observed value of E was 0.79 and that calculated from the equation was 0.86.

‡ The chain transfer constant is the ratio of the rate constant of chain transfer to the rate constant of chain growth.

§ The effectiveness of grafting is the fraction by weight of the polymer grafted on the backbone relative to the total weight of the newly formed polymer (grafted branches + new homopolymer).

Some functional groups in a chain are sometimes characterised by an enhanced rate constant for chain transfer, *e.g.* the methyl and phenyl groups in poly(vinyl acetate) and poly(vinyl benzoate)[50-52]. Polymer chains containing labile atoms can be obtained by copolymerisation with either a monomer containing labile atoms or one capable of acquiring such atoms by additional chemical treatment when already in the copolymer. Thus saponification of the styrene–allylydene diacetate copolymer yields a copolymer which contains CHO groups whose hydrogen atoms participate readily in chain transfer. Polymerisation of any vinyl monomer in the presence of a saponified copolymer gives graft copolymers[53].

Chain transfer reactions are important in the synthesis of graft polymers in the case of rubber and synthetic polydienes and occur simultaneously with direct addition across double bonds[54-57]. In these cases the dinitrile of azoisobutyric acid is, unlike benzoyl peroxide[58-60], practically unable to initiate grafting. When poly(methyl methacrylate) and polystyrene are grafted on rubber the side chains are short and small amounts of homopolymers are formed, *i.e.* the grafted monomer is used up almost entirely in forming the graft copolymer[38,62-65].

Other factors, besides the conditions of the chain transfer reaction, which are extremely important in the synthesis of graft copolymers by radical polymerisation of the monomer in the presence of a polymer are steric hindrances and the chemical nature of the polymer and the monomer, which determines their polarity and reactivity. The monomers and polymers can be graded as follows according to ease of graft copolymer formation: vinyl chloride > > vinyl acetate > styrene and poly(vinyl chloride) > polyacrylonitrile > poly(vinyl acetate) > polystyrene[41].

Chain transfer has often been used for the preparation of graft polymers[40,50,66-102]. Thus Roland and Richards[50] polymerised ethylene under pressure in the presence of poly(vinyl acetate) and ethyl peroxide and they obtained a graft polymer which contained polyethylene side chains and polyethylene fragments in the backbone.

Miller[98] grafted polyacrylonitrile on polyacrylamide and found that all the initial polyacrylamide participated in the formation of the graft polymer. The softening point of graft polymers drops with increasing number of grafted side chains and approaches, within limits, the softening point of the random copolymer containing an equal number of acrylamide and acrylonitrile residues.

Polyampholytes have been obtained by polymerisation of 2-vinyl pyridine in the presence of poly(ethyl acrylate) (initiator: dinitrile of azoisobutyric acid) with subsequent acid hydrolysis[86]. The following grafts have also been effected: poly(vinyl acetate), poly(vinyl chloride), poly(vinyl formate), and polystyrene on polyethylene[40]; acrylic acid on polyacrylamide[101]; poly(vinyl chloride) on the copolymer of butyl methacrylate and methacrylic acid[42,102]; poly(vinyl acetate) on poly(ethyl α-chloroacrylate)[35]; poly(vinyl acetate) on poly(vinyl chloride)[41]; and poly(vinyl acetate) and poly(methyl methacrylate) on poly(vinyl benzoate)[51].

Pure copolymers cannot be obtained by the chain transfer reaction but it has the advantage of simplicity, and hence is widely used industrially. Rubber-like graft copolymers are prepared by polymerisation of monomers (styrene, methyl methacrylate, acrylonitrile) in the latex of natural or synthetic rubber in the presence of water-soluble initiators or by polymerisation of monomers in

the presence of rubber which has been dissolved or allowed to swell in them [93,103]; when vulcanised these rubbers show enhanced durability, resistance to atmospheric effects and to friction and are suitable for the preparation of gas-filled elastomers.

Graft polymers suitable for the production of plastics can be synthesised from the appropriate monomer and rubber, the amount of the latter usually constituting no more than 10% of the former, but the yield is, as a rule, low. The graft polymer obtained by polymerisation of styrene in the presence of 30% rubber shows good impact strength but reduced hardness and marked residual deformation (compared to polystyrene) following compression and stretching [102]. Berlin and Khanukaeva [104] found that the graft polymers prepared by polymerisation of styrene in the presence of 5–10% rubber are hard, elastic, and able to withstand impacts 3–5 times greater than those withstood by polystyrene or styrene–acrylonitrile copolymers.

The graft polymers prepared by polymerisation of vinyl chloride in the latex of butyl methacrylate and acrylic acid copolymer and by polymerisation of a mixture of butyl methacrylate and acrylic acid in a poly(vinyl chloride) latex show good adhesive properties, photostability as well as resistance to abrasion and to the effect of water, solvents, and many chemical compounds [42,102].

B. Methods Based on the Presence in the Polymer of Groups Capable of Breaking Down to Form Active Centres which Initiate Monomer Polymerisation

Introduction of groups into polymer macromolecules which readily form active polymerisation centres (polymer initiators) is another important method of preparation of graft polymers. These include peroxide and hydroperoxide [105–114], diazo- [115], diazoimino- [116], and dithiocarbonic [117] groups.

The peroxide and hydroperoxide groups are used most frequently. They are usually formed in the polymers by oxidation [75,118,199], ozonation [58,120–127], action of peroxide compounds (*e.g.* on the acid chloride of poly(acrylic acid) [118,128–130] and on polyaldehydes [131]), irradiation by X-rays or γ-rays in the presence of air [24,25,132], electrolysis of aqueous solutions of poly(acrylic acid) or other polymers containing the carboxyl group [133,134] and other methods used in the synthesis of low-molecular-weight peroxides and hydroperoxides.

Homolytic breakdown of peroxide and hydroperoxide groups leads to a simultaneous formation of macro- and micro-radicals which initiate polymerisation of the monomer present to give a graft copolymer and homopolymer respectively. These can be separated by fractionation of the graft reaction products and the relative reactivities of the radicals can be compared. Smets *et al.* [134] fractionated the product of polymerisation of styrene in dioxan in the presence of a copolymer of methyl acrylate and t-butyl peracrylate and found that the ratio of graft polystyrene and homopolystyrene depended largely on the viscosity of the solution and increased with increase in viscosity. This ratio is a function of monomer concentration and is inversely related to it. Riess and Banderet [135] confirmed these results.

The difference in lability of micro- and macro-radicals is also important in the synthesis of graft polymers. Microradicals and the chains formed from them are much more labile than macro-radicals and the chains which they enter. The rate of termination of the more labile chains is considerably higher than that of the less labile ones so that less homopolymer is formed.

The ability to form polymer peroxides depends on the structure of the macromolecules. Mark [136,137] had suggested that polystyrene would readily give a hydroperoxide since its chains contained tertiary carbon atoms similar to those of the cumene side chain. However, this only occurs extremely slowly and with great difficulty [75,110,118,138–141]. Metz and Mesrobian [75,110,140] and others [47,109,118] have suggested that polystyrene be converted to poly-*p*-isopropylstyrene in which the isopropyl group is easily oxidised to give a hydroperoxide.

Poly-α-olefines and α-olefine copolymers which contain tertiary carbon atoms form hydroperoxide groups on atmospheric oxidation under relatively mild conditions ($\sim 70^\circ$ and 3 atm pressure) [119]. Isotactic polymers react only on the surface or in the amorphous regions close to the surface; with atactic polymers the hydroperoxide groups are formed within the whole bulk of the polymer although here, too, the surface area subjected to the action of ozone is very important, the rate of peroxide formation dropping with diminution of the "surface : volume" ratio [142,143]. Grafting of poly(methyl methacrylate) on polypropylene reduces the tensile strength somewhat but enhances the elongation. Polystyrene grafted on polypropylene and on polybutene gives copolymers of great impact strength unaffected by aging [119]. Ozonisation of polypropylene and polyethylene and subsequent polymerisation of vinyl monomers in their presence have been used to obtain graft copolymers by other authors as well [144–150]. The gas permeability of polyethylene can be markedly reduced and its photostability increased by grafting polyacrylonitrile on crystalline polyethylene [144]; grafting of 15% acrylic acid on polyethylene fibres and films gives strong, hydrophilic materials which can be dyed by basic dyes [145,146].

Grafting of poly(vinyl chloride) on polypropylene and polybutene enhances elasticity [119]. The plasticising effect of the hydrocarbon component of such graft copolymers differs from that of the normal plasticisers used for poly(vinyl chloride); these contain polar groups which associate with the polar groups of the polymer and act as solvents. Poly-α-olefines do not combine with poly(vinyl chloride) and the macromolecules of the latter cannot associate with one another; consequently the temperature of the second order transformation does not drop as occurs when ordinary plasticisers are used.

A graft copolymer which showed highly-elastic deformation between 85° and 235° was obtained by polymerising polystyrene in the presence of ozonised isotactic polystyrene. This graft copolymer shows transformation points characteristic for each individual copolymer [124,151,152]. Graft copolymers of different degrees of crystallinity can be obtained by varying the ratio of the initial substances and the degree of ozonisation. Such graft copolymers are formed by polymeric chains consisting of chemically homogeneous links of different spatial configuration. Ozonisation followed by decomposition of the peroxide groups gives graft copolymers from polyvinyl chloride and various monomers (ethyl acrylate, vinylidene chloride, methyl methacrylate, acrylonitrile, styrene and vinyl acetate) [153], from polystyrene and poly(acrylic acid) [127], and from other substances [154].

The random copolymer of methyl methacrylate and isopropenyl acetate gives on hydrolysis a copolymer which contains tertiary OH groups oxidised by hydrogen peroxide to hydroperoxide groups. Methyl methacrylate polymerised (thermally or by oxidation–reduction) in the presence of such a macrohydroperoxide yields graft copolymers [130]. The rate of the grafting reaction is proportional to the square root of the concentration of the macrohydroperoxide.

Electrolysis of partially neutralised polymeric carboxylic acids gives free radicals at the anode which are simultaneously oxidised by the oxygen formed to hydroperoxides with a yield of 1%. Such hydroperoxides have been used by Smets for initiation of acrylamide polymerisation in an aqueous solution [134].

Formation of homopolymers is an undesirable side reaction in grafting by monomer polymerisation in the presence of macroperoxides. This can be practically completely suppressed by ferrous ions [111,155–158]. The ·OH radicals formed by the decomposing macrohydroperoxides are converted into OH^- anions and no homopolymers are formed. The reaction must be carried out in emulsion and has yielded graft polymers from styrene and polystyrene or the copolymer of styrene and 4-vinyl cyclohex-1-ene [111]. A very promising but little investigated synthesis of graft copolymers is based on an oxidation–reduction reaction between certain cerium salts (such as cerium ammonium nitrate) and compounds containing the OH, SH, CHO, or NH_2 groups [159]. Polyacrylonitrile, poly(methyl acrylate) and polyacrylamide have been successfully grafted on poly(vinyl alcohol) [16,159,160] by this method.

$$Ce^{4+} + \sim\sim CH_2CH(OH) \sim\sim \rightarrow [\text{complex}] \rightarrow$$
$$\rightarrow Ce^{3+} + H^+ + \sim\sim CH_2C(OH)\sim\sim \text{ (or } \sim\sim CH_2\overset{\cdot}{C}H\sim\sim\text{)}.$$
$$\quad\quad\quad

2. GRAFTING BY IONIC POLYMERISATION

A. Cationic Polymerisation

Descriptions of ionic polymerisation often employ the terminology used for radical polymerisation (initiation, chain growth, chain termination, chain transfer) although the mechanisms of the two types of polymerisation are entirely different. The synthesis of graft polymers by copolymerisation of styrene in carbon tetrachloride or other solvents, in which poly-*p*-methoxystyrene is dissolved, in the presence of BF_3 or $SnCl_4$ at $0°-20°$ can be regarded as based on a chain transfer reaction although the mechanism of this reaction has not yet been finally elucidated. The rate of styrene polymerisation is independent of, and the composition of the graft copolymer almost independent of the concentration of poly-*p*-methoxystyrene [169]. Styrene does not polymerise when the molar ratio styrene : poly-*p*-methoxystyrene is less than 1.65 : : 0.377. Attempts to prepare graft polymers from poly-*p*-methoxystyrene and n-butyl vinyl ether, ethyl vinyl ether, pinene, isobutene, or *N*-vinylpyrrolidone failed. The authors [169] concluded that the number of polymer–monomer combinations was limited because: (1) the polymer must react with the attacking carbonium ions, (2) the polymer must be soluble in a solvent suitable for cationic polymerisation, and (3) the difference in solubility must be sufficient for separation of homopolymers from graft copolymers.

Graft copolymers have been obtained [170] by polymerisation of styrene in the presence of aluminium chloride and poly(vinyl chloride), polystyrene forming the side chains; homopolymerisation of styrene and destruction of poly(vinyl chloride) also occur in this reaction. Styrene and indene branches are easily grafted on poly(vinyl chloride) and the copolymer of vinyl chloride with vinylidene chloride; this also applies to *trans*-stilbene and indole. Destruction of graft copolymers is considerably reduced at lower polymerisation temperatures when titanium tetrachloride is used instead of aluminium chloride. The same method has been used to obtain a graft copolymer from poly(chloromethyl) styrene and isobutene in the presence of aluminium bromide [171].

B. Anionic Polymerisation

Polybutadiene and its copolymers containing double bonds react with styrene, acrylonitrile, and α-methacrylonitrile in the presence of sodium or sodium hydride to form graft copolymers with branches starting from the backbone at the sites of unsaturation. It is desirable to use no solvent since a high concentration of monomer favours the formation of graft copolymers [172].

Recently [173] graft copolymers have been obtained in which poly(methyl methacrylate) forms the main chain and polystyrene the side ones. Their synthesis is based on the reaction between the polystyrene carbanions and the ester groups of poly(methyl methacrylate). Benzylsodium and phenylisopropylpotassium were used as catalysts; they are ionised in tetrahydrofuran to form reddish violet solutions. The colour changes to reddish orange after the addition of the first few drops of styrene, which indicates the formation of styrene anion and its polymerisation. When concentrated poly(methyl methacrylate) in tetrahydrofuran is added at a low temperature the colour begins to change as the polystyrene monocarbanion disappears by reacting with the ester groups to form side chains.

3. GRAFTING BY CHEMICAL REACTION

Graft copolymers in which the carbon-chain backbone and the carbon-chain branches are linked by non-carbon-to-carbon bonds can, provisionally, be regarded as carbon-chain graft polymers. The relative proportion of such hetero-chain links can be extremely small and their presence will then have no effect on the properties of the graft polymers. The latter are obtained by interaction of polystyrene with an end amino-group (such polystyrene is formed by polymerising styrene in the presence of sodium in liquid ammonia) with copolymers containing small amounts of β-isocyanatoethyl methacrylate [174]; in these graft polymers the side chains and the backbone are joined by urea-groups. The initial copolymers were those of β-isocyanatoethyl methacrylate with methyl methacrylate, butyl methacrylate, lauryl methacrylate, butyl acrylate, acrylonitrile, styrene, and vinyltoluene. The grafting reaction could be followed by the disappearance of titratable amino-groups in time. The most studied system was the graft of styrene on the copolymer of methyl methacrylate and β-isocyanatoethyl methacrylate.

III. CARBON-HETERO-CHAIN GRAFT COPOLYMERS (HETERO-CHAIN BRANCHES GRAFTED ON CARBON-CHAIN POLYMER BACKBONE)

These graft copolymers are most frequently prepared from carbon-chain polymers containing reactive side atoms and groups (NH_2, OH, SH, Cl, COOH, COCl, COOR, $CONH_2$, SOCl, CHO, and others [11,26,136,175-199]). They can also be prepared by copolymerisation of vinyl monomers with hetero-chain polymers with an unsaturated end group [196,197,200,201]. Another method involves the simultaneous polymerisation and polycondensation which occur when mixtures of a vinyl monomer containing an ester or carboxyl group and an ω-hydroxycarboxylic acid or its polyester are heated [196,197,202-204]. The polyester of an ω-hydroxycarboxylic acid can be replaced by polyesters of dicarboxylic acids and glycols, but the reaction is complicated by the formation of three-dimensional structures [203].

Recently [205] graft carbon-hetero-chain copolymers have been prepared by interaction of phenol–formaldehyde resins with the acid chlorides of dicarboxylic acids and bis-phenols at their interface. This method yields products whose properties vary depending on the nature and ratio of the starting materials.

Several works are devoted to grafting polyoxyethylene on various polymers and copolymers by reacting the latter with ethylene oxide. Polyoxyethylene grafted on poly(vinyl alcohol) reduces the rigidity and hardness of poly(vinyl alcohol) films and enhances their thermoplastic and adhesive properties. The graft copolymers so obtained remain readily soluble in water and can be used in various reactions since they contain primary OH groups in the side chains and secondary OH groups in the backbone [178]. Polyoxyethylene side chains can be grafted on copolymers of styrene and vinyl alcohol obtained by saponification of styrene copolymers with small amounts of vinyl acetate. The resultant graft copolymers contain hydrophobic backbones and hydrophilic side chains [136]. Copolymers of styrene and acrylic acid also react with ethylene oxide, forming graft copolymers with polyoxyethylene side chains [179]. These adhere well to glass and can be used to prevent the accumulation of static electric charge on polymeric materials. Three-dimensional elastic products

result from the action of 2:4 diisocyanatotoluene on such graft copolymers. The ester groups in the copolymer of styrene and dimethyl moleate were converted into β-hydroxyethylamide groups and graft copolymers with polyoxyethylene side chains were obtained on reaction with ethylene oxide[175]. When the copolymer of styrene with allyl acetate was hydrolysed to the corresponding allyl alcohol copolymer the latter reacted with ethylene oxide, the side chains grafting on at the sites of the OH groups[175]. Ethylene oxide reacts with polyacrylamide to give graft copolymers with a low coefficient of side chain polymerisation[180] and simultaneous formation of cross-linked polymers. Condensation of polyacrylamide or copolymers of acrylamide with polyethylenechlorohydrin also forms graft copolymers[181].

Carbon-hetero-chain graft copolymers with polyester side chains can be prepared both by trans-esterification of polyesters with polymers containing ester or carboxyl groups and by copolymerisation of vinyl monomers with polyesters of ω-hydroxycarboxylic acids with an unsaturated end group; they are also formed by simultaneous polymerisation and polycondensation of vinyl monomers with the ester groups of ω-hydroxycarboxylic acids or their esters[189,204]. When hetero-chain polyesters able to form ordered structures are grafted on poly(methyl methacrylate) the graft copolymers formed also have such an ordered structure[175,189-193,195-197,199,203,204] that spherulites could be seen by polarised light[197,198,200,203,204].

Studies of trans-esterification between poly(methyl methacrylate) and various hetero-chain polyesters showed that grafting of side chains from polyesters able to form ordered structures led to: (1) folding of the macromolecules in solution into more symmetrical globules, reflected in lowered intrinsic viscosity and simultaneous increase of the Huggins constant; (2) change in physical properties, in particular a reduction in the tensile strength and a considerable increase in the elongation at rupture (up to 200–240%); (3) rise of softening point for a definite optimal ratio between the side chains and the backbone. The structure and properties of graft copolymers given by trans-esterification depend not only on the ratio of the initial substances and their nature but also on the duration of the trans-esterification reaction[195]. If the optimal time is exceeded esterolysis of the polyester side chains by the ester groups of poly(methyl methacrylate) occurs, with loss of structural order and change in the physical properties, which then approach those of poly(methyl methacrylate).

One of the present authors and Gurgenidze had shown that graft copolymers of ordered structure could also be formed by the reaction of isotactic poly(methyl methacrylate) with poly(ethylene azelate)[192].

Graft copolymers containing side chains of polyesters of ω-hydroxycarboxylic acids have been obtained from ω-hydroxypelargonic acid and a copolymer of styrene with maleic anhydride, under conditions ensuring polycondensation of the hydroxycarboxylic acid, and from styrene–maleic anhydride copolymer and polyesters of ω-hydroxyenanthic, ω-hydroxypelargonic, and ω-hydroxyundecanoic acids[197,198]. In this case also ordered graft copolymers able to form spherulites can be obtained. The thermomechanical properties of the graft copolymers are intermediate between those of the polyesters and the styrene–maleic anhydride copolymer. Grafting of polyesters to the latter gives products which are highly elastic at high temperatures, similar to graft polymers of polyacrylic acid and polystyrene[127]. The infra-red spectra of the graft copolymers given by the styrene–maleic anhydride copolymer and polyesters differ from that of the initial copolymer in having absorption bands at 1700–1750 and 1200 cm^{-1} characteristic of ester groups and an absorption band at 3000 cm^{-1} characteristic of the COOH group[198].

Graft copolymers of ordered structure have also been obtained by copolymerisation of methyl methacrylate and acrylonitrile with polyesters of ω-hydroxypelargonic and ω-hydroxyenanthic acids; the polyesters contained a terminal methacrylic group which was introduced by treating the polyesters with the acid chloride of methacrylic acid[175,197,200]. Copolymerisation with methyl methacrylate was carried out in the bulk phase[175,197] and with acrylonitrile in the bulk phase and in an emulsion[200].

Graft copolymers with hydrophobic and hydrophilic properties were obtained by simultaneous polymerisation and polycondensation of methacrylic and ω-hydroxypelargonic acids, the former constituting the backbone and the polyester of the latter the side chains. These graft polymers are, unlike polymethacrylic acid, elastic at high temperatures and have an ordered structure when the ω-hydroxypelargonic acid content of the initial mixture is 50 wt. % and over. Spherulites were formed in this case also[203]. The same method was used to prepare graft copolymers from methyl methacrylate and ω-hydroxypelargonic acid and from methyl methacrylate and ω-hydroxyenanthic acid.

Several publications are devoted to the grafting of polyamide side chains to carbon-chain polymers[182-188,197,205]. Graft copolymers can be obtained from ε-caprolactam with (i) polyacrylic acid, (ii) poly(methyl acrylate)[182], or (iii) copolymers of styrene with acrylic acid, methyl acrylate, and maleic anhydride[183,188]. The reaction is limited by a number of factors: loss of amino-groups, cross-linking, heterogeneity of the molten reaction mixture, etc. An important factor is the compatibility of the starting materials. Wichterle and Gregor[184] attempted to react ε-caprolactam and styrene–*N*-methacrylcaproamide copolymer in the presence of Na-caprolactam but, despite the low temperature (70°–80°), the reaction mixture began to gel at the outset because cross-linking occurred by the Claisen reaction between the diacyl imide groups belonging to different polymer chains. Dogadkin and his coworkers found that when butadienestyrene rubbers containing carboxylic groups were heated at 200°–220° with ε-caprolactam the latter slowly added on to the rubber. The reaction was accelerated by using sodium and boron trifluoride–diethyl ether[185,186]. Valentine[187] obtained graft copolymers from poly(methyl methacrylate) and caprolactam.

We have prepared graft copolymers with polyenanthamide side chains by polycondensation of aminoenanthic acid in the presence of styrene–maleic anhydride copolymer or in the presence of polyacrylic acid when hydrophobic–hydrophilic products were obtained[197,206]. The solid-phase reaction at 185° gives either amorphous or ordered graft copolymers depending on the ratio of the initial substances.

IV. HETERO-CHAIN GRAFT COPOLYMERS (HETERO-CHAIN BRANCHES GRAFTED ON HETERO-CHAIN POLYMER BACKBONE)

Hetero-chain polymers with reactive groups (CONH, SO_2NH, NHCONH, NHCOO, etc.) in the chain can be con-

verted into hetero-chain graft copolymers either by reaction with substances which can yield hetero-chain polymers (*e.g.* alkylene oxides) or with already formed polymers[207].

The application of polyamide synthetic fibres used in modern textiles is limited by their poor hydrophilic properties. Grafting of polyoxyethylene side chains on the polyamides (at the nitrogen atom) has given the most promising results in attempts to synthesise high-melting hydrophilic polyamides.

Haas *et al.*[208] investigated polyoxyalkylation of a number of polyamides (polycaprolactam, polyhexamethyleneadipamide, mixed polyamides, methoxymethylated polyamides, polyamides containing sulphamide groups in the chain, polyurea synthesised from 2,4-diisocyanotololuene and hexamethylenediamine). Ethylene oxide, propylene oxide, ethylene carbonate, and epichlorohydrin have been tried as oxyalkylating agents, but satisfactory results were obtained only with ethylene oxide. The synthesised graft copolymers with polyoxyethylene side chains had almost the same melting points, crystallinity, and solubility as the original polyamides; thus, grafting of ~60% polyoxyethylene on polyhexamethyleneadipamide lowers the m.p. to ~220°. Since polyoxyethylene branches act as internal plasticisers the graft copolymers are more elastic than the original polyamides; they are not, however, as strong. Introduction of polyoxyethylene side chains affects markedly the vapour permeability of the polyamides: the figure for polyhexamethyleneadipamide is 3.13 g m^{-2} h^{-1} but when 50% polyoxyethylene is grafted on it, rises to 52.8 g m^{-2} h^{-1}.

Sonnerskog[209] has also described the preparation of graft copolymers with polyoxyethylene branches by the action of ethylene carbonate on polyamides.

The grafting of polyoxyethylene on caprone powders, films, and fibres[180,210,211], and on films of polyhexamethylenethiodivaleramide and of mixed polyamide anid G-669[180,210] have also been investigated and the reaction was found to occur not only at the surface but also within the substance of the films, fibres, and powders. The products were a polyoxyethylated polycaprolactam, which was readily soluble in alcohol, and polyoxyethylated anid G-669, which was water-soluble. Graft polymers in which polyacrylic acid branches were grafted on the polyamide backbone have also been prepared[212].

Coleman[213] prepared graft copolymers of polyethyleneterephthalate which were high melting, possessed good physical properties, and gave fibres which could be more readily dyed; his starting materials were the sodium derivative of the dimethyl ester of hydroxyterephthalic acid and polyoxyethylene whose terminal OH group was replaced by chlorine atoms followed by trans-esterification with ethylene glycol.

Amino-acid graft polymers have been prepared by polymerisation of *N*-carboxy-α-amino-acid anhydrides in the presence of polylysine or polyornithine used as macroinitiators[214]. A water-soluble graft copolymer has been prepared from trypsin and *N*-carboxytyrosine anhydride. Enzymes modified in this way with 5 to 10% grafted tyrosine fully retain their proteolytic activity[215]. It has been suggested that linear side chains could be grafted on the biologically least important functional groups in enzymes, antibodies, and antigens to give modified biologically active proteins; these could then be linked by covalent bonds to water-insoluble polymers.

V. HETERO–CARBON-CHAIN GRAFT COPOLYMERS (CARBON-CHAIN BRANCHES GRAFTED ON HETERO--CHAIN POLYMER BACKBONE)

These are prepared by polymerisation of vinyl monomers in the presence of hetero-chain polymers making use of either peroxide groups or chain transfer reactions.

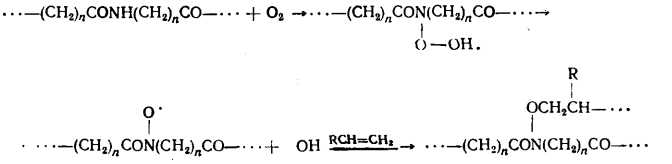
Hetero-chain polymer compounds containing peroxide groups are formed when such polymers are treated with ozone or atmospheric oxygen at high temperatures. They initiate polymerisation of vinyl monomers and so lead to the formation of hetero-carbon-chain graft copolymers. This method is being thoroughly investigated by Korshak and his coworkers[216-226]. They have succeeded[216-221] in grafting polystyrene, poly(methyl methacrylate), poly(vinyl acetate), poly(vinylidene chloride), and polyacrylonitrile on fibres and films of caprone, anid, enanth, mixed polyamide anid G-669, and poly(ethylene terephthalate) (Lavsen) by ozonising hetero-chain polymers and then polymerising the vinyl monomers. Styrene showed the greatest reactivity under the conditions adopted by them. The yield of graft copolymers is inversely related to the degree of orientation of the polyamide; under similar conditions of ozonisation and grafting, the increase in weight following grafting of styrene on anid G-669 is several times greater than that observed in the case of caprone[220]. If the optimum ozonisation period is exceeded, the mechanical strength of the graft copolymers diminishes but even after treatment for 6 h and subsequent grafting of polystyrene the caprone film strength amounted to 72% of that of the original film.

Poly(ethylene terephthalate) has demonstrated that hetero-chain polyesters can yield graft copolymers with carbon-chain branches when preliminary ozonisation is used to create polymerisation centres[221]. Of the monomers tried (styrene, vinylidene chloride, acrylonitrile, and vinyl acetate) styrene gives graft copolymers most readily; as in the case of the polyamides, the yields of graft copolymers drop with increasing orientation of the material (film, fibre) undergoing grafting.

Brief ozonisation and subsequent copolymerisation of poly(ethylene terephthalate) with styrene increases the elongation but this is accompanied by a decrease in tensile strength. The same method has been used for the preparation of graft copolymers from poly(ethylene terephthalate) and acrylic acid[154].

Korshak and his coworkers have suggested activating polyamides and polyesters by heating films and fibres made of these polymers in an atmosphere of air or nitrogen[222-226] instead of ozonisation. Such activated films and fibres form graft copolymers in their surface layers when they are heated with vinyl monomers.

The authors suppose that polyamide and polyester products (films, fibres, powders) contain some sorbed air, which reacts during storage with polyamides or polyesters to form peroxide centres. When such materials are heated even in the absence of oxygen the peroxide centres break down and free radicals are produced, which initiate copolymerisation with vinyl monomers. They suggest the following mechanism of initiation:



Such thermal treatment does not lower the strength of the original polymers and enhances that of the graft copolymers. Grafting of polystyrene on caprone fibre gives a polystyrene layer amounting to 23.6% of the fibre weight. When the fibre carrying the grafted polystyrene layer was treated with acid the polystyrene was stripped as a hollow tube; the molecular weight of grafted polystyrene can reach 60 000–80 000.[225] Grafting of acrylic acid on poly(ethylene terephthalate) films[226] increases the adhesion of photographic emulsions to the poly(ethylene terephthalate) base, which is of great practical interest since it makes it possible to reduce the weight of photographic and cinematographic films without impairing their mechanical properties (as compared to films based on cellulose triacetate).

The chain transfer reaction has been used to obtain graft copolymers of styrene and polyester synthesised from adipic acid and pentaerythrol dibromide [2,2-di(bromomethyl)propan-1,3-diol]. Polymerisation of styrene in the presence of this polyester and benzoyl peroxide gives a mixture of the original polyester, polystyrene, and graft copolymer[43] which is separated by selective solution: the polystyrene dissolves in cyclohexane and the polyester in acetone. The graft polystyrene branches are detached from the main polyester chain by esterolysis with ethyl acetate. The molecular weight of the isolated polystyrene was determined and it was found that the particular specimen of graft copolymer contained one polystyrene chain per 23 000 elementary ester units, with a degree of polymerisation of 600. The transfer reaction constant was 40.5×10^{-5} at 60°. Hurd and Roedel[227] copolymerised vinyl monomers (methyl methacrylate, styrene, dichlorostyrene, etc.) with polysiloxanes containing vinyl or allyl groups in the presence of peroxides (the vinyl-containing polysiloxanes are prepared by hydrolysis of methyl vinyl dichlorosilane and the allyl-containing ones are obtained similarly).

This literature survey indicates the extensive interest in the synthesis of graft polymers. Most of the chemical methods used, however, are based on either the chain transfer reaction or the presence (or introduction) of active groups in the main polymer which can initiate the growth of side chains. Other chemical methods have not been sufficiently investigated and we believe that extension of the methods of synthesis of graft polymers will be fruitful, both theoretically and practically in enlarging the range of new polymer materials with the desired properties.

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PRESENT STATE OF ION-EXCHANGE CATALYSIS

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1. CONCEPT OF ION-EXCHANGE CATALYSIS AND ITS TERMINOLOGY

Like the corresponding ions in homogeneous media, the counter-ions of the high-molecular-weight polyelectrolytes are capable of catalysing many organic reactions of varying character.

This new application of ion exchangers, which can be termed ion-exchange catalysis, is now being developed and our knowledge is still incomplete. Nevertheless, the results of both laboratory studies and industrial applications of ion exchangers as catalysts are encouraging for the future prospects of ion-exchange catalysis.

The catalytically active counter-ions of ion exchangers are in a solvated state, and in this respect are similar to the so-called free ions in ordinary electrolyte solutions. For that reason both the reactions catalysed in solution by ions and those catalysed by counter-ions of ion-exchange resins are able to proceed in accordance with the same mechanism, and are of the same kinetic order. The rate of a given reaction depends, however, on whether a given amount of catalytically active ions is present in the form of a soluble electrolyte, or in the form of an ion exchanger.

As suggested by Haskell and Hammett[1], the ratio of the reaction rate in a heterogeneous system to that in a homogeneous system, at equivalent concentrations of catalyst ions, is termed the efficiency of the ion exchanger. The efficiency of the ion exchanger q may be equal to, larger than, or smaller than unity, and depends on the properties of the catalyst itself, as well as on those of the solvent.

The essence of this concept may be exemplified by the irreversible first-order reaction of decomposition of AB into A and B, using Q_{AB} moles of the starting compound.

The rate of the reaction in a homogeneous system is $dQ_{AB}/dt = k_h.Q_{AB}$, where k_h is the velocity constant of a homogeneous reaction. For the corresponding heterogeneous reaction, carried out in the presence of an ion exchanger $dQ_{AB}/dt = k_{het}Q_{AB}$. The efficiency of the ion exchanger, *i.e.* the ratio between the velocity constants of the heterogeneous and homogeneous reaction is $q = k_{het}/k_h$. The relationship of the efficiencies of an ion exchanger for two compounds belonging to the same chemical class, is termed the specificity ratio[2]. If the reactants, *e.g.* esters, are simultaneously placed in contact with the catalyst, the value $r = q_1/q_2$ is a measure of the selectivity of the transformation of one component with respect to the other. This value is quantitatively related to the standard free energies of four intermediate states:

$$RT \ln q_1/q_2 = (F_{R_1} - F_{H_1}) - (F_{R_2} - F_{H_2}),$$

the subscript H corresponds to the reaction under homogeneous, and the subscript R to the same reaction under heterogeneous conditions of catalysis.

By changing the reaction conditions the efficiency of the ion exchanger with respect to different components in the mixture may be altered, and by changing the specificity ratio a more extensive conversion of one compound relative to another may be caused.

The efficiency of ion exchangers depends on the following factors: (*a*) the properties of the catalyst and the reactants, which determine the activation energy of the reaction; (*b*) the distribution constant of reactants between the solution and the catalyst; (*c*) the nature of the solvent.

The efficiency of ion exchangers may be less than unity if the distribution constant of the reactants between the resin and the liquid phase is less than unity. This includes the limiting case where, owing to their large molecular volume, the reactants diffuse slowly, or not at all, inside resin beads, so that the reaction is mainly limited to the interface.

The efficiency of ion exchangers is promoted by an increase in the distribution coefficient of the reactants and by changes in the system which cause a greater reduction of the entropy of formation of the active complex from the reacting molecules and the catalyst.

Riesz and Hammett[3] have shown that partial substitution of H^+ ions by quaternary ammonium cations results in an increased rate constant of the heterogeneous reaction of ester hydrolysis, in 1 N solutions. In all probability, the introduction into the resin of mobile ions similar to the reactant causes an increase in the distribution constant, and consequently, in the efficiency of the ion exchanger.

In certain cases the efficiency of the ion exchanger can be increased by introducing an organic solvent which would increase the solubility of the reactants. For example, the addition of ethanol considerably increases the rate of hydrolysis of fats in the presence of ion-exchange resins[4].

The addition of acetone has an adverse effect on the efficiency of sulphonated phenolformaldehyde cation exchangers in the saponification of acetates. In aqueous and aqueous acetone solutions containing $< 35\%$ acetone this resin is a more efficient catalyst than the equivalent amount of HCl. At high acetone concentrations the ratio of the velocity constants changes and the resin becomes a less efficient catalyst than HCl[5].

According to other authors[6,7] the efficiency of ion exchangers in the hydrolysis of a series of esters in aqueous solutions exceed unity, and increases with increasing molecular weight of the compound undergoing hydrolysis. If the same reaction is carried out in 70% aqueous acetone[8], the efficiency of the ion-exchange resin is less than unity, and decreases with increasing molecular weight of the compound hydrolysed.

The reaction rate in the above cases is affected by the distribution of the solvent between the ion exchanger and the liquid phase. The ion exchanger is undoubtedly enriched by the compound with the higher dielectric constant, namely water, while the concentration of acetone in the liquid phase rises. The ester concentration rises in the liquid phase enriched by organic solvent, and this is increasingly the case the longer their hydrophobic radical. This is why the rate of the heterogeneous reaction decreases with an increase in the ester molecular weight.

The rate of ion-exchange reactions is undoubtedly determined by the ratio of the reactant's molecular size to the size of "micropores" of the ion exchanger. It is therefore not surprising that the rate of sucrose inversion in the presence of a sulphonated phenolformaldehyde cation exchanger is smaller than in HCl solutions, and that it depends on the size of resin particles[9-11]. The efficiency of cation exchangers with compact structures as catalysts in the hydrolysis of esters is less than unity and decreases with increasing length of the molecule undergoing saponification. At a small degree of cross-linking the "micropores" of ion exchangers permit free passage of reacting molecules, and the process therefore proceeds faster under heterogeneous than under homogeneous conditions[12]. The efficiency of open-structure ion exchangers in the reaction of iodine with acetone also exceeds unity[13]. Finally, the rate of a reaction catalysed by ion exchangers depends on the concentration of the catalytically active counter-ions in the unit volume of catalyst.

This problem is considered in great detail, alongside the significance of diffusion in ion-exchange catalysis, in the work of Noller and Hässler[14,15] on the kinetics of the decomposition of aqueous diazoacetic ester into glycollic acid ester and elementary nitrogen. In this system six different specimens of sulphonic polystyrene cation exchangers were used as catalysts and their capacity for H^+ ions, varied by partial substitution with Na^+ ions, was 0.03, 0.31, 0.51, 1.06, 1.61, and 3.45 mg-equiv., respectively. The activity of the catalyst naturally depended on its content of H^+, since Na^+ ions do not accelerate the reaction.

Depending on the catalyst's activity, two limiting reaction mechansims are possible: (*a*) when the catalyst is not very active, and contains only a few protons in active sites per unit weight and the reaction molecules have to travel a long way inside the solid phase in order to react, the reaction proceeds slower than diffusion and therefore controls the kinetics; (*b*) when there are many protons per unit weight of the resin, the reaction proceeds faster than diffusion, and the cation exchanger's "pores" then contain the reaction products, the concentration of reacting molecules decreasing in the direction of the particle interior. Owing to the relatively small diffusion rate (which in this case governs the reaction kinetics) some of the cation-exchanger protons do not take part in its activity. For that reason, irrespective of the general increase of the reaction rate with increased concentration of H^+ ions, the velocity constant per 1 mg-equiv. of catalytically active ions must fall.

Experimental data show in fact that, for a constant quantity of ion exchanger (165 mg), the velocity constant of the decomposition of diazoacetic acid, referred to 1 mg-equiv. of catalytically active ions, increases as their concentration per unit weight of catalyst falls. Equal amounts of hydrogen ions accelerate the reaction in inverse proportion to their concentration per gramme of ion exchanger.

The general activity of sulphonic polystyrene cation exchangers in the decomposition of diazoacetic ester decreases with increasing concentration of H^+ ions in the catalyst, but the linear relationship between the velocity constant and the quantity of cation exchanger is not fulfilled. The above considerations emphasise the great effect of diffusion on the reaction rate of ion-exchange catalysis, which in this respect should be considered as a variant of the heterogeneous catalysis.

The experimentally established increase in the activation energy of diazoacetic ester[15] with increased concentration of H^+ ions in the catalyst, accords completely with the concept of diffusion as a factor governing the reaction kinetics. The actual activation energy, corrected for the energy of activation of diffusion, is independent of the amount of catalyst and practically equals its value for the reaction under homogeneous conditions. The identity of the intermediate compound in both cases becomes apparent here: irrespective of its phase composition, the catalyst (ion exchanger or a water-soluble acid) yields a proton to react with a molecule of the reactant and form a carbonium ion.

Further development of work on the reaction kinetics

underlying the ion-exchange catalysis is of great theoretical significance.

The important aim in the near future should be the construction of a general theory taking into account the effect of the various factors on the rate of reactions catalysed by ion exchangers. Such a theory should open new paths towards a systematic planning of chemical processes and establish favourable conditions for the further development and practical application of ion-exchange catalysis. Ion exchangers are already used in more than 20 types of different chemical reactions.

The extensive possibilities of the practical application of ion-exchange catalysis have aroused widespread interest in this new field of chemistry. Since 1946 an increasing number of publications have appeared dealing with ion-exchange catalysis, and since 1951 reviews have appeared in journals [16-23], ion-exchange symposia [24,25] and monographs [26,27] on the use of ion exchangers as catalysts in organic syntheses.

The present review, although not claiming to be exhaustive, covers the most important work on ion-exchange catalysis published prior to October 1961.

2 ION EXCHANGERS AS CATALYSTS IN HYDRATION

One of the most interesting and significant examples of the application of ion-exchange catalysis is perhaps the preparation of ethylene glycol by hydration of ethylene oxide.

The hydration of ethylene oxide is accelerated by all known sulphonic and phosphoric cation exchangers, and also, according to some data [28], by some strongly basic anion exchangers. According to some later results, however [29], neither the strongly basic anion exchanger AV-16† nor the medium basic anion exchanger EDE-10P‡ are efficient in catalysing the hydration of ethylene oxide. According to both the papers quoted above, the carboxyl cation exchanger, which is a polymerisation catalyst, does not accelerate this reaction, although other authors have indicated the possibility of hydrating ethylene oxide over the Amberlite IRC-50 resin [30]. The reaction rate in the presence of the carboxyl cation exchanger is one order of magnitude smaller than in the case of strongly acidic resin. Hydration can be carried out in a flask by stirring the mixture of ethylene oxide while adding large excesses of water and resin [31], or in a flow system [28,31] with an ion-exchange column as a reactor.

The scheme of one variant of the flow system is given in Fig. 1.

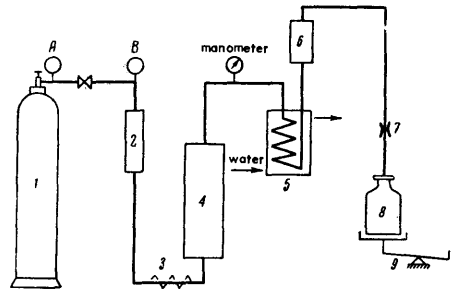


Fig. 1. Schematic diagram of the laboratory flow apparatus for ethylene oxide hydration.

About 20 litres of distilled water and the required quantity of ethylene oxide are introduced into the tank *2*. The reactor *4* is provided with a sieve (80 mesh), and packed with the sulphonic cation exchanger of type Amberlite IR-120. The reacting mixture is fed under pressure of nitrogen from cylinder *1* (nitrogen pressure is adjusted by regulator *B* and is indicated on pressure gauge *A*). The liquid flow is controlled by rotameter *6*, and the reactor temperature is determined by a thermocouple. The product is collected in receiver *8*, located on a balance.

One of the greatest advantages of the ion-exchange catalysis, the simplicity of the apparatus which is required, is quite obvious from this system.

This reaction shows another advantage of ion-exchange catalysts over soluble acids, namely greater selectivity. While the hydration to ethylene glycol in the presence of ion exchangers proceeds considerably faster than the side-reactions resulting in di- and tri-ethylene glycol, in the presence of sulphuric acid these transformations proceed at practically the same rate. As a result, under the conditions of homogeneous catalysis, the yield of side-products increases at the expense of that of ethylene glycol [29].

The indisputable advantages of the hydration of ethylene oxide over ion exchangers are: (*a*) the possibility of the continuous use of the catalyst, (*b*) the simplicity of its regeneration, and (*c*) the ease of separation of the product from the cation exchanger.

The only substantial disadvantage of the method of hydration described is the limited thermal stability of the ion exchanger. After a run of 5–6 h in a continuous plant at 50° the capacity of the cation exchanger KU-1§, and also KU-2¶, fell to 70–80%, and its sulphur content to 30–40%. In our view these losses can be reduced by removing the enormous heat of hydration of ethylene oxide with a special cooling system or by increasing the amount of water in the reaction mixture.

We have developed a method of hydration of tertiary pentenes, whereby the water used in the reaction is immobilised in the cation exchanger by preliminary swelling. Water is not introduced into the reactor as an independent liquid phase [32].

In its simplest terms, our method consists in placing tertiary pentenes, in contact with the hydrated KU-2 resin

† AV-16 is a polyfunctional, strongly basic anion-exchange resin prepared by the condensation of polyethylenepolyamines, pyridine, and epichlorohydrin. It contains secondary, tertiary, and quaternary (pyridinium) nitrogen groups (Ed. of Translation).

‡ EDE-10P is a polyfunctional weakly or strongly basic anion-exchange resin prepared by the condensation of polyethylenepolyamines with epichlorohydrin, and contains secondary, tertiary, and quaternary nitrogen groups (Ed. of Translation).

§ KU-1 is a difunctional, strongly acid cation-exchange resin with $-SO_3H$ and $-OH$ active groups, prepared by the condensation of *p*-phenolsulphonic acid with formaldehyde in acid (Ed. of Translation).

¶ KU-2 is a monofunctional, strongly acid cation-exchange resin with $-SO_3H$ active groups, prepared by treating a swollen styrene–divinylbenzene copolymer with chlorosulphonic acid, then saponifying the sulphonyl chloride (Ed. of Translation).

at room temperature, and subsequently decanting and fractionally distilling the catalysate [32]. The ion-exchange hydration of pentene differs from other methods of preparation of pentanol, *e.g.* the Grignard reaction or the hydrolysis of t-pentyl chloride, in being simple, economical, and safe [33].

Various sulphonic cation exchangers are suitable for the hydration of tertiary pentenes. The effect of different ion exchangers on the conversion of 2-methylbut-2-ene under non-equilibrium conditions is shown in Table 1. The main physicochemical properties of the resins are also given.

The data in Table 1 show that the catalytic activity of resins is determined not only by their exchange capacity, but by all their properties, which depend on the structure of the high-molecular-weight organic radical. The highest activity is displayed by the cation exchanger SBS, which is obtained by a two-stage sulphonation of rubber SKS-30†. The cation exchangers prepared by graft copolymerisation exhibit neither a high catalytic activity, nor a high exchange capacity, according to a recent report in the literature [34]. The cation exchanger SDV(VP), which exhibits very low exchange capacity with respect to sulpho-groups, is a very inefficient catalyst. The same holds for phosphoric acid cation exchangers of type KF-1‡ or VF.

As expected, the extent of the equilibrium conversion of tertiary pentenes to isopentyl alcohol is independent of the nature of the cation exchanger, but is inversely proportional to the concentration of hydrocarbons undergoing hydration in a mixture with other alkenes and alkanes.

The lower conversion of t-pentene due to dilution by inert solvents is incompatible with the classical laws of equilibrium.

The working hypothesis which accounts for the anomalous behaviour of this system is based on the assumption that the degree of association of isopentyl alcohol changes as a result of dilution with organic solvents. If it is supposed that at higher dilutions the degree of association of the t-pentyl alcohol is decreased, then the equilibrium of the reaction:

$$C_5H_{10}+H_2O \rightleftarrows C_5H_{11}OH\,,$$

should shift towards the left when the concentration of the hydration product is reduced. With a rise in concentration, the degree of association of the alcohol increases and the equilibrium is displaced towards the right.

The equilibrium of the system can be shifted in two ways, *i.e.* (1) by increasing the concentration of water in the system (or of its partial pressure in the case of the vapour-phase hydration), or (2) by removing the reaction product from the reaction zone. The use of the first method is limited in liquid-phase hydration by the small reciprocal solubility in the pentene–water system. For that reason the continuous removal of t-pentyl alcohol by excess water, or by another solvent immiscible with pentenes, leads to higher conversion.

The recent publication by Odioso and his coworkers [35] shows in fact that in a flow system, at 93.3°, in the presence of excess water, the conversion of the industrial pentane–pentene fraction over Amberlite IR-120 reaches 9.8%. In our view this method offers good prospects of being suitable for the selective extraction of tertiary pentenes, by whose dehydrogenation isoprene can be obtained simply and cheaply.

The hydration of pentenes and other alkenes proceeds according to a protonic mechanism *via* an intermediate formation of carbonium ions. Thus, the addition of the elements of water to isobutene in the presence of sulphonic cation exchanger ZSO_3H is preceded by the reaction:

$$(H_3C)_2C{=}CH_2+ZSO_3H \rightleftarrows (H_3C)_2C^+{-}CH_3+ZSO_3^-\,.$$

The carbonium ion formed in this way reacts vigorously with water to yield trimethylmethanol, while the catalyst is recovered:

$$(H_3C)_2C^+{-}CH_3+H_2O+ZSO_3^- \rightleftarrows (H_3C)_2COH{-}CH_3+ZSO_3H\,.$$

This reaction was recently carried out successfully over sulphonic cation exchangers by Menyailo *et al.* [36]. It has since been used as an industrial method for the preparation of trimethylmethanol, whose dehydration yields isobutene of high purity.

Attempts to hydrate propene over the weakly acidic cation exchanger KMG§ were unsuccessful, but this reaction proceeded very slowly over the phosphoric acid resin RF¶. [36] The strongly acidic cation exchangers were found to be very efficient catalysts of the hydration of propene [36]. Nonetheless, under the conditions employed (160°, 150 atm) these resins were not heat-resistant, and their activity rapidly deteriorated.

Like mercury salts, the Hg-form of sulphonic cation exchangers catalyses the addition of the elements of water to the acetylenic bond. In the presence of Hg-cation exchangers, acetylene [37], and phenylacetylene [38] form acetaldehyde and acetophenone, respectively.

TABLE 1. Effect of different cation exchangers on the conversion of 2-methylbut-2-ene at 50°.

Resin	Type of resin	Resin capacity for sulpho-groups, mg-equiv. per g		Coeff. of moisture capacity	Conversion of pentene, %	
		hydrated	anhydrous		1.5 h	4 h
SDV(VP)	vinylpyridine grafted on SDV-3 resin*	0.57	0.68	0.41	3.6	—
KU-2	sulphonated styrene – DVB copolymer	2.22	4.89	1.23	8.3	14.8
KU-1G	sulphonated phenol – formaldehyde resin	1.11	2.69	1.77	8.8	18.7
KU-1	ditto	1.14	2.13	0.83	10.3	19.5
SDV(VS)	vinylsulphonic acid grafted on the SDV-3 resin	2.24	4.05	0.93	10.9	19.7
SBS	sulphonated butadiene – styrene rubber	2.03	3.44	0.73	10.9	23.6

* SDV-3 is a strongly acidic cation–exchange resin with $-SO_3H$ groups. It is based on styrene (Ed. of Translation).

† Synthetic rubber made by polymerising butadiene + 30% styrene at 48°–50° (Ed. of Translation).

‡ KF-1 is a strongly acidic cation-exchange resin with $-PO_3H_2$ active groups. It is based on styrene, vinylnaphthalene, and acenaphthene (Ed. of Translation).

§ KMG is a weakly acidic cation-exchange resin with –COOH active groups (Ed. of Translation).

¶ RF is a strongly acidic cation-exchange resin with $-PO_3H_2$ active groups (Ed. of Translation).

3. ION EXCHANGERS AS CATALYSTS IN HYDROLYSIS

Inversion of sucrose in the presence of ion exchangers has an important place in investigations of this kind. One of the first studies[39] gave interesting results on the effect of the nature of the catalyst and of temperature on the inversion. These are collected in Table 2.

Table 2 shows that the rate of inversion increases sharply with a rise of temperature. A more detailed quantitative study of the kinetics of reaction carried out over sulphonated phenol–formaldehyde[40] or sulphonated benzaldehyde–phenol–formaldehyde cation exchangers[41] indicates a linear relationship between the logarithm of the velocity constant and the reciprocal of the absolute temperature. An increase in the amount of the catalyst, Amberlite IR-120 resin, also increases the velocity constant: according to Bodamer and Kunin[39] the 10^4k values at 50° and resin quantities of 5, 28, 40, and 80 g per 1 g sucrose are 4.8, 26.3, 34.4, and 71.6 min^{-1}, respectively. It follows from these results that the chemical reaction itself is the sole process controlling the rate of inversion of sucrose in the presence of cation exchangers.

The state of bonding of mobile hydrogen ions in active sites affects the catalytic activity of cation exchangers considerably. Thus, while all sulphonated cation exchangers with a limited degree of cross-linking are effective catalysts for inversion, the carboxylic resins either completely fail to accelerate this reaction[39,40], or, in the case of weakly cross-linked resins, fall far behind the strongly acidic cation exchangers in their activity. For this reason sulphonated cation exchangers are recommended for use in the industrial inversion of sucrose[42]. Processes such as the purification of sucrose, on the other hand, in which inversion is harmful, should be carried out in the presence of carboxylic cation exchangers[19].

Since the majority of reactions catalysed by ion exchangers are effected in the interior of the catalyst's beads, the reaction rate is greatly affected by the lattice structure, and above all, by the degree of cross-linking of the resin. The results in Table 3 show a linear relationship between minus the logarithm of the velocity constant and the degree of cross-linking of the cation exchanger. In the presence of the strongly cross-linked resin, at 50°, the inversion proceeds very slowly, while at room temperature it altogether stops. Consequently, the increased structural density of the resin, due to cross-linking, hinders internal diffusion, and may eventually lead to the localisation of the reaction at the surface of the ion-exchanger beads, or even to a complete standstill.

TABLE 2. Effect of the nature of the catalyst and temperature on the velocity constant of sucrose inversion.

Catalyst	10^4k at various temperatures		
	25°	50°	75°
Amberlite IRC-50	0.0	0.0	0.0
Amberlite IR-120	0.7	26.3	117.0
0.001 *N* HCl	—	0.5	12.0
0.18 *N* HCl	18.0	790.0	—

TABLE 3. Effect of the extent of cross-linking in Amberlite IR-120 resin on the velocity constant of sucrose inversion.

Divinylbenzene in the resin, %	10^4k at various temperatures		
	25°	50°	75°
1	7.6	199.2	—
10	0.7	26.3	117.0
20	—	0.7	23.2

Examples of the hydrolysis of other carbohydrates or esters show that the efficiency of ion-exchange catalysis is often determined by the size of their "micropores" and of the molecules undergoing transformation[43,44]. The data in Table 4 illustrate this conclusively.

It is obvious from Table 4 that ion-exchange catalysis offers great possibilities for the selective hydrolysis of the components of a mixture. Certain authors[43] indeed compare ion exchangers with enzymes in their capacity to catalyse reactions selectively.

If necessary, the ion exchanger can be activated for use as a catalyst of the hydrolysis of carbohydrates of large molecular weight[45]. Thus this can be achieved by the addition of acids which break down large molecules into smaller ones which can be transported into the beads of the ion exchanger. In most cases the total catalytic activity of the cation exchanger and the acid used simultaneously in the hydrolysis of starch exceeds the sum of the activities of the two components taken separately.

In certain reactions involving ion-exchange catalysis the specific interaction between the ion exchanger and the reactant improves the reaction kinetics. For example, owing to the capacity of proteins to form coordination bonds with the anions of the resin, Dowex-50 is a more efficient catalyst in their hydrolysis than are the water-soluble acids[46].

Sulphonated cation exchangers are used with advantage as catalysts in the hydrolysis of esters. The catalytic activity of the sulphonated phenol–formaldehyde cation exchanger Amberlite IR-100 is 11 times greater than that of a carboxylic cation exchanger of twice that capacity[6]. It is 1.8 times more active than the equivalent amount of HCl in the hydrolysis of methyl acetate, and this factor is increased to 2.3 in the hydrolysis of ethyl acetate, and to 20 in the hydrolysis of benzyl acetate. The very high

TABLE 4. The extent of hydrolysis of certain carbohydrates and esters[44].

Compound hydrolysed	Time, h	Temperature, °C	Extent of hydrolysis, %
Maltose	10	98	100
Glycogen	10	98	0
Ethyl acetate	10	65	100
Poly(vinyl acetate)	10	65	15.3
Methyl galacturonate	10	98	100
Poly(methyl galacturonate)	10	98	6.45

activity of cation exchangers can be explained by the positive sorption by the catalyst of molecules undergoing hydrolysis. The sorption increases with rising molecular weight of the ester. As mentioned above, the addition of large amounts of acetone lowers the efficiency of ion exchangers as catalysts for ester hydrolysis [1].

A thorough study of the kinetics of hydrolysis of a series of esters in 70% acetone was carried out by Haskell, Bernhard, and Hammett [1,8]. Their values for the velocity constant of hydrolysis in the presence of water-soluble acids (k_H) and the cation exchanger Amberlite IR-120 (k_R) are collected in Table 5.

As was expected, the rate of hydrolysis depends not only on the dimensions, but also on the structure of the ester molecule. The rate of hydrolysis of straight-chain esters decreases sharply with an increasing number of carbon atoms in the molecule. The effect of the chain length on the velocity constant is most pronounced in the case of an ion-exchange catalyst, since it also involves the slowing down of the internal diffusion. For that reason the efficiency of the ion exchanger q progressivley decreases from methyl acetate to ethyl n-octanoate. The increase of cross-linking in Amberlite IR-120 has the effect of further reducing the efficiency of the ion exchanger, which is more prominent in the hydrolysis of ethyl n-hexanoate than in that of methyl acetate. By changing the degree of cross-linking one can systematically alter the specificity ratio and thereby improve the selectivity of the hydrolysis of one of the components in a mixture of esters.

TABLE 5. Hydrolysis of esters in 70% acetone in the presence of 0.466 N HCl and Amberlite IR-120.

Ester	Temperature, °C	$10^6 k_H$, sec^{-1}	$10^6 k_H$, sec^{-1}	q	References
Methyl acetate	25.0	54.5	27.20	0.500	1
Ethyl acetate	25.0	46.4	15.00	0.330	1
Ethyl n-butyrate	25.0	19.2	2.56	0.134	1
Ethyl n-hexanoate	25.0	15.3	0.74	0.049	1
Methyl n-octanoate	25.0	16.8	0.95	0.056	8
Methyl phenylacetate	25.0	21.6	2.13	0.098	8
Methyl α-naphthylacetate	37.5	15.5	1.27	0.082	8
Methyl chloroacetate	25.0	38.0	11.00	0.29	8
Methyl benzoate	45.0	0.61	0.13	0.22	8
Methyl cyclopentanecarboxylate	25.0	24.0	3.47	0.14	8

The hydrolysis of esters can be carried out in plants of the continuous type, as described by Andreas [47] and Dierichs [48].

The hydrolysis of ethyl acetate solutions is catalysed by the addition of weakly or strongly alkaline ion exchangers, which are able to bind the acetic acid formed and thereby affect the reaction equilibrium [49]. It appears that the OH-form of Amberlite IRA-400 acts by the same mechanism. This resin was used for the hydrolysis of nicotinic nitrile into nicotinamide [50].

4. ION EXCHANGERS AS CATALYSTS IN ESTERIFICATION

Esterification is perhaps one of the main fields of the catalytic application of ion exchangers.

One important advantage of ion exchangers emerges from the study of esterification, namely the possibility of isolating compounds which cannot be isolated under the conditions of homogeneous acid hydrolysis. In this respect the esterification of polyhydroxyoxocarboxylic acids [51] and the preparation of the monoesters of lauric acid and diethylene glycol [52] are especially noteworthy. Homogeneous catalysis in the presence of acid yields only ethylene glycol diacetate with no more than trace amounts of monoester. Using sulphonated cation exchangers both mono- and di-esters are obtained, but the quantitative ratio of the reaction products depends on the reaction conditions. For instance, the reaction of equimolar amounts of lauric acid and diethylene glycol in the presence of toluene yields 24% monoester. By changing the ratio of acid to glycol to 1 : 4 and 1 : 6, and using sulphonated polystyrene resin as a catalyst, the yield is increased to 67 and 86%, respectively [52].

At an ethylene glycol : acetic acid ratio of 1 : 2, in the presence of 1% KU-2 resin the diester was obtained [29]. The efficiency of the ion exchanger in this synthesis is practically unity. The same resin sample showed no fall of activity when used nine times, but after that its activity decreased somewhat and disappeared almost completely after the eleventh run. It appears that in this case there is no irreversible resin change of the thermal desulphonation type [53,54], but rather a blocking of active sites by the large molecules of the reaction product, since the activity of the sample almost fully recovered after six days without use [29].

According to Losev and Trostyanskaya [55], who investigated the preparation of butyl butyrate, the sulphonated phenol–formaldehyde cation exchanger MSF† and the sulphonated styrene–butadiene copolymer (resin SBS) undergo an irreversible reduction of exchange capacity and catalytic activity during the esterification. Table 6 shows the change of the catalyst's acidity (which is a measure of the exchange capacity) after repeated use in the synthesis of butyl butyrate. As a result of the loss of catalyst's activity, the reaction time t increases with each run.

In view of their thermal instability, the authors [55] recommend that the resins should not be used as catalysts in esterification above 120°. Data in Table 6 show that the

TABLE 6. The change of activity of sulphonated cation exchangers during their repeated use as catalysts in esterification.

Resin	Initial acidity of resin (a), mg KOH per g resin	Run I		Run II		Run III		Run IV	
		t	a	t	a	t	a	t	a
SBS	140	60	124	203	100	300	90	320	87
MSF	174	37	101	44	77	71	64	—	—

† MSF is a strongly acidic cation with $-SO_3H$ and $-OH$ active groups. It is based on phenol (Ed. of Translation).

resin SBS is more heat-resistant than the cation exchanger MSF, although less catalytically active. The phosphoric acid cation exchanger FS is even less active, while the carboxylic resin KM‡ does not catalyse esterification at all.

Notwithstanding their low heat-resistance the sulphonated phenol–formaldehyde cation exchangers are widely used for the preparation of methyl and ethyl esters of chloroacetic, succinic, tartaric, maleic, and adipic acids[56], butyl esters of carboxylic acids[57], and diallyl phthalate[58], which is an important raw material in the manufacture of polyester resins. By replacing *p*-toluene sulphonic acid with a cation exchanger in the synthesis of diallyl phthalate the resinification of the reaction product can be avoided and its purification, which consists in the absorption of phthalic acid by an anion exchanger, can be greatly simplified. To increase the yield of the ester the reaction mixture C_6H_6 [58] or CCl_4 [56] is added to give an azeotropic system.

The esterification of n-butanol with oleic acid in the presence of a sulphonated phenol–formaldehyde cation exchanger[59] is characterised by a high velocity constant which is proportional to the catalyst surface per unit weight of the reacting mixture. It could be assumed that owing to large volume of the oleic acid molecule the esterification rate is governed by internal diffusion. An interesting feature of the reaction is the existence of a slow initial induction period, at the end of which the reaction proceeds according to second order kinetics.

The esterification of butanol with benzoic acid over Amberlite IR–120 and Dowex-50 is also characterised by an induction period. No induction period is observed when the cation exchanger has previously been treated with water or butanol[60].

Investigations of the kinetics of the vapour-phase esterification of acetic acid and butanol in the presence of KU-2 cation exchanger showed that the velocity constant of this reaction decreases with rising temperature. This unexpected fact, which is not observed in the liquid-phase reaction[61] is explained by the lower sorption of the reactants by the resin at higher temperatures.

Esterification in the liquid phase often proceeds at a lower rate in the presence of ion exchangers than under the conditions of homogeneous catalysis by acid solutions. Thus, after reaction of methanol and adipic acid for 3 h under various reaction conditions, the catalysate was found, under static conditions, to contain the following percentage of ester: without catalyst 48.5%, with cation exchanger 82.5%, and with H_2SO_4 91.9%. In the presence of the cation exchanger the reaction equilibrium is not established even after 3 h, while in the presence of sulphuric acid it is reached after 1 h.

To obtain esters on the preparative or industrial scale the esterification should preferably be carried out not under static conditions but by passing the reaction mixture through a column-type reactor.

Fig. 2 shows a simplified diagram of the column used in the preparation of methyl adipate[62]. Methanol–acid mixture is added to the top of the column packed with Wofatit resin, and heated by steam. A methanol vapour stream, introduced in the lower part of the column facilitates the elimination of water formed in the reaction through the top of the column. Owing to the shift towards equilibrium,

‡ KM is a weakly acidic cation-exchange resin with –COOH active groups (Ed. of Translation).

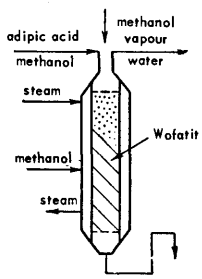


Fig. 2. Diagram of the column used for the preparation of methyl adipate.

pure ester is collected at the bottom. To secure continuous liquid flow, the column, 2 m long and 5 cm in diameter, has to be packed with cation exchanger (bead size 8–15 mm), obtained by cementing fine beads together with a Wofatit P gel[47]. At larger bead sizes of the cation exchanger the reaction proceeds slowly and yields a product containing large amounts of acid. Higher yield and purity of the end product can be achieved by using another column, packed by the finely ground ion exchanger, for preliminary esterification. The warm partly reacted mixture is then passed in through the top of the main column where the esterification proceeds to completion.

In an industrial plant producing 50 tons of ester monthly, the column for preliminary esterification is packed with 200 litres finely ground ion exchanger and the main column with 200 litres coarse resin.

The insufficient mechanical and thermal stability of cation exchangers tend to prevent the full utilisation of the plant. After two months' operation the mechanical losses of the resin are about 10%. Above 180° the thermal desulphonation of the cation exchanger and the loss of formaldehyde take place. In our opinion, under very harsh conditions both sulphonic polystyrene and sulphonic phenol–formaldehyde resins should be avoided.

In certain cases, as for instance in the synthesis of dibutyl phthalate, the cation exchanger partly dissolves in the reaction mass[63]. Such reactions should be carried out in the presence of soluble acids as catalysts.

When the thermal or chemical destruction of ion exchangers is excluded, the use of these catalysts in industrial esterification[47,57,64] can simplify the technology and lower the cost of production.

Esterification of carboxylic acids, like the hydration of alkenes, proceeds according to a protonic mechanism:

$$R'COOH+ZSO_3H \rightleftarrows R'C^+(OH)_2+ZSO_3^-,$$

$$R'C^+(OH)_2 \rightleftarrows R'C^+=O+H_2O,$$

$$R'C^+=O+ROH+ZSO_3^- \rightleftarrows R'COOR+ZSO_3H.$$

Besides the usual case of the reaction of carboxylic acids with alcohols, other reactions can also be used to obtain esters by ion-exchange catalysis. A few examples are considered below. Strongly acidic cation exchangers catalyse the liquid-phase esterification of alkenes by organic acids[18] with yields of the order of 50%. Esters derived

from diacetone alcohol can be prepared by reacting mesityl oxide[65] with alcohols in a column packed by the H-form of Dowex-50 resin.

Interesting liquid- and vapour-phase techniques have been suggested for the preparation of diethyl Cellosolve by reacting ethanol with ethylene oxide over sulphonic cation exchangers[66,67]. With KU-1 resin the consumption of ethylene oxide is considerably reduced as compared with the usual method of preparation under pressure. The yield of the principal product in the vapour-phase process is 95% at the start but is finally reduced to 80% owing to the formation of diethylene glycol monoethyl ether and the sorption of diethyl Cellosolve§ by the resin. Flushing of the cation exchanger by alcohol during the operation results in the removal of the sorbed diethyl Cellosolve and increases its yield.

Attempts to carry out the reaction at 140°–150° over KU-2 resin (which lowers the sorption of diethyl Cellosolve) were unsuccessful, since local overheating of the cation exchanger results in rapid charring and loss of activity[67].

In conclusion it may be added that the ion-exchange catalysis can be used to prepare esters by transesterification[15,68,69]. Interest in transesterification is continuously growing owing to the development of the chemistry of new synthetic materials. Transesterification of dimethyl terephthalate with ethylene glycol yields diethylol terephthalate, whose polymer is used in the manufacture of the of the best synthetic fibres — Lavsan. In industry the transesterification of dimethyl terephthalate is carried out in the presence of lithium oxide at 180°–200°, the reaction lasting 3–8 h. In the presence of the cation-exchange resin KU-2 this process, carried out at 140°–160°, is completed in 40–105 min with almost the quantitative yield of end-product[68].

Transesterification of methyl methacrylate with n-heptanol, n-octanol, or 2-ethylhexanol[68] is carried out at 130°–140°, and after 2–3 h gives the esters of these alcohols in 88, 32, and 89% yields, respectively. The lower yield of octyl methacrylate seems to be due to the larger size of both reacting molecules, which limits internal diffusion.

Transesterification can easily be carried out continuously. One such scheme is recommended for the transesterification of dimethyl adipate to dibutyl adipate. It should, however, be noted that under harsh reaction conditions (200°–210°) the life of the catalyst tends to be short.

5. ION EXCHANGERS AS CATALYSTS IN DEHYDRATION

As early as 1946 Sussman[4] demonstrated the possibility of dehydrating trimethylmethanol to isobutene using the sulphonated carbon Zeo-Karb H as a catalyst.

Quite resently Rozantsev *et al.*[33] carried out the dehydration of t-pentyl alcohol using the resin KU-2 in the hydrogen form.

In collaboration with the author of this review and Potudina, Markevich[70] made a thorough study of the kinetics of dehydration of t-pentyl alcohol over KU-2 resin and the phosphoric acid cation exchanger KF and found that the reaction product consisted of a mixture of tertiary pentenes, with 2-methylbut-2-ene predominating. The preparation of tertiary pentenes using ion-exchange resins differs from the standard method of dehydration by means of sulphuric acid in being simple, economical, and rapid. Another very important advantage of this method is the fact that the catalyst can be used several times without regeneration.

For selective dehydration of t-pentyl alcohol Odioso and his coworkers[35] used sulphonated polystyrene cation exchanger Amberlite IR-120. Heating a mixture of equimolar amounts of t-pentyl alcohol, pentan-1-ol, and pentan-2-ol to 200° yields a mixture containing 18.3% 2-methylbut-1-ene, 80.3% 2-methylbut-2-ene, 0.4% pent-1-ene, 0.3% *trans*-pent-2-ene, and 0.6% *cis*-4-pent-2-ene. Tertiary pentenes of sufficient purity are obtained from a mixture of pentanols by the same method.

Heated to 150°–170° in the presence of a sulphonic polystyrene resin, ethylene glycol undergoes dehydration to dioxan[25]. According to the author of a chapter on ion-exchange catalysis[25] the catalyst's activity remained unchanged in a continuous experiment lasting 40 h. Bearing in mind the limited heat-resistance of resins of sulphonated polystyrene type we doubt this statement and think that it requires further experimental confirmation.

The dehydration of another dihydric alcohol, butane-1,4-diol, resulting in the cyclic ether tetrahydrofuran, has been effected in the presence of cation exchangers[71]. Ethers are the main products of dehydration of primary aliphatic and aromatic alcohols, but they are usually somewhat contaminated with alkenes[72]. Yields of up to 80% are obtained.

Heating cyclohexanol to 145°–155° for 12 h in the presence of sulphonated phenolformaldehyde resin gave over 70% cyclohexene. Cyclohexane-1,2-diol undergoes dehydration at 185° forming a mixture of cyclohexa-1,3-diene and cyclohex-1-en-1-ol. Other cyclic alcohols behave similarly[73].

Terpenic alcohols also undergo dehydration in the presence of cation exchangers. According to Matsumoto[74], on distillation in the presence of the sulphonated phenolformaldehyde resin, terpinol hydrate yields terpineol. The author of this review and Kozlova found that under mild conditions (75°) the tertiary alcohol linaloöl undergoes dehydration in the presence of the hydrated H-form of the resin. Under the same conditions the primary alcohol geraniol withstands dehydration, but undergoes certain other chemical changes whose nature has not yet been definitely established. Investigations of the behaviour of terpenic alcohols in the presence of ion exchangers are very important for the chemistry of natural compounds. Work in this field should be further developed.

6. USE OF ION EXCHANGERS AS CATALYSTS IN ALKYLATION

Alkylation is in fact an addition of a paraffinic or aromatic compound to alkenes resulting in the formation of an alkane or an aromatic compound of higher molecular weight.

The application of ion exchangers as alkylation catalysts shows most promise in the alkylation of phenols, the reaction which is widely used for preparing the starting materials for the synthesis of surface-active agents, antioxidants, growth-promoting substances, weedkillers, perfumes, and many other valuable products[75–77].

§ Diethyl Cellosolve is ethylene glycol diethyl ether (Ed. of Translation).

According to current views the alkylation reaction proceeds *via* the formation of a carbonium ion[75] and is therefore accelerated by various acidic catalysts, including the strongly acidic sulphonic cation exchangers.

The replacement of liquid acid catalysts by solid ion exchangers was a big step forward in the technology of alkylphenols. The problem of the treatment of harmful phenol-containing waste waters was eliminated, the catalyst could be used repeatedly, and side-reactions were considerably reduced.

The school of Isagulyants[68,75,78-85] has carried out the most thorough and varied investigations of the application of ion exchangers to alkylation of phenols.

For better yields the cation exchangers used in alkylation should be free of water. Water is removed by heating *in vacuo* at 60°–90° to constant weight[79] or by boiling in benzene[82]. For heat-resistance, the sulphonated polystyrene resin KU-2 should be chosen in preference to the sulphonated phenol–formaldehyde cation exchanger KU-1, which is liable to undergo thermal desulphonation.

According to Isagulyants[79] the cation exchanger KU-2 gives good yields of alkylation products and can be used up to 12 times at 134°–135° without noticeable reduction of activity. Under the same conditions Vertlib and coworkers[82] used the cation exchanger KU-2 29 times, and then regenerated it by boiling with benzene and by subsequent treatment with 95% sulphuric acid for one hour. The static exchange capacity of the regenerated resin was, however, considerably lower (4.0 mg-equiv. g^{-1}) than that of the starting resin (5.4 mg-equiv. g^{-1}). It can be assumed that the lower exchange capacity is a result of the partial thermal desulphonation of the resin at the relatively high temperature required in alkylation. Alkylation can be effected under static conditions[79,82], in columns operating continuously[68,79], or by using the cation exchanger as a fluidised bed[85]. The general scheme of the most typical plants is given in Figs. 3–5.

The alkylating agents used are free alkenes (isobutene[68,84], diisobutene¶[68,79,86], isopentenes[68], cyclohexene[68], styrene[68], α-methylstyrene[68], octalin†, non-1-ene[86]), industrial mixtures of polymerised benzine type[79,82], and alcohols[78,79].

The alkylation of phenol by the diisobutene fraction boiling in the 95°–125° range gives a mixture of substituted phenols of molecular weight 200–210. Destructive alkylation, depolymerisation of diisobutene, and formation of substituted phenols of lower molecular weight, usually observed in systems using homogeneous acid catalysts, are absent in reactions catalysed by ion exchangers[79]. The absence of side-reactions is on the whole one of the greatest advantages of ion-exchange catalysis.

The most salient examples of the application of ion exchangers in alkylation reactions are collected in Table 7.

In most cases anhydrous resins had to be used, although the presence of moisture did not interfere with the course of the reaction[85].

Alkylation is carried out at 80°–165°, but cresols require milder conditions than phenols. The optimal amount of catalyst in the batch alkylation is 4–6.5% of the weight of reactants. Under dynamic conditions the yield of the final

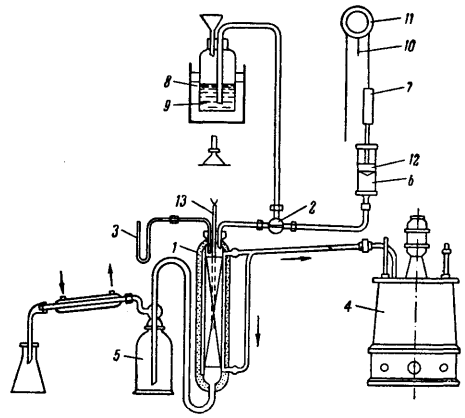


Fig. 3. Schematic diagram of the laboratory plant for the preparation of substituted phenols: 1) reactor; 2) three-way tap; 3) manometer; 4) thermostat; 5) receiver; 6) injection pump; 7) weight; 8) heating bath; 9) raw material container: 10) pendulum; 11) clock mechanism; 12) piston; 13) thermocouple.

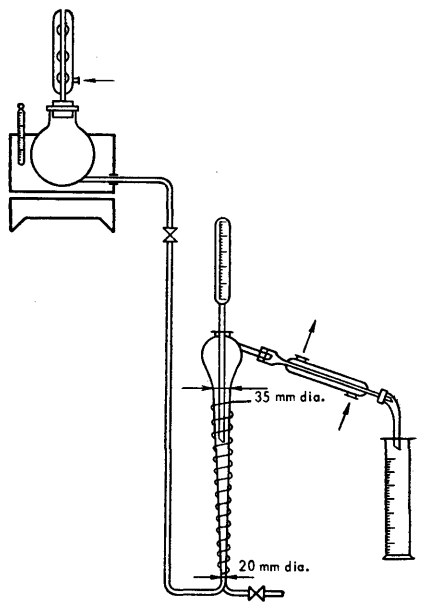


Fig. 4. Schematic diagram of the apparatus for the continuous alkylation of phenol in a fluidised bed of resin.

product is affected not only by the amount of catalyst and the temperature, but also by the rate of introduction of the reactants[79,85]. According to one of the most recent reports[85], for the alkylation of phenol by diisobutylene in a fluidised bed of KU-2 resin the reactants should be fed in at the rate of 3.5–4.4 ml per 1 g catalyst per hour. The reduction of the feeding rate to 0.5 ml only slightly increases the degree of conversion of phenol, while the increase to 5 ml per 1 g catalyst per hour interferes with the separation of the alkylate from the cation exchanger.

¶ 2,4,4-Trimethylpent-1-ene or 2,4,4-trimethylpent-2-ene (Ed. of Translation).

† Octahydronaphthalene (Ed. of Translation).

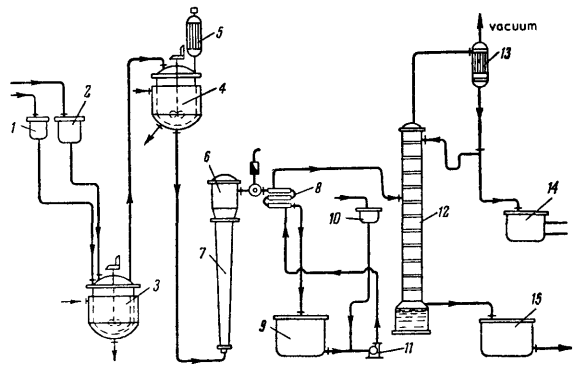


Fig. 5. Schematic diagram of an experimental plant for the continuous production of tertiary alkylphenol: 1) flowmeter for phenol; 2) flowmeter for isooctene; 3) mixing tank; 4) supply tank; 5) reflux condenser; 6) separator; 7) reacting column; 8) heat exchanger; 9) receiver for raw alkylphenol; 10) supply tank of alkali; 11) centrifugal pump; 12) fractionating column; 13) condenser; 14) florentine receiver; 15) receiver for dry alkylphenol.

TABLE 7. Most important uses of cation exchangers as catalysts in alkylation reactions.

Alkylating agent	Catalyst	Final product	References
Isobutene	KU-2 resin	t-butylphenol	68, 86
Diisobutene	KU-2 resin	t-octylphenol	68, 85
Polymer distillate	KU-2 resin	mixed alkylphenols	82
Cyclohexene	KU-2 resin	cyclohexylphenol	68
Styrene	KU-2 resin	methylbenzylphenol	68
α-Methylstyrene	KU-2 resin	dimethylbenzylphenol	68, 79
Octalin	KU-2 resin	α-decalylphenol	68, 79
Isobutyl alcohol	KU-2 resin	t-butylphenol	75, 78, 79
Isobutene	KU-1 and KU-2 resins	2,6-di-t-butyl-4-methylphenol	84
Isobutene	KU-2 resin	2-t-butyl-4-methylphenol	80
Isobutene	KU-1 resin	4,6-di-t-butyl-3-methylphenol	80
Pentenes	KU-1 and KU-2 resins	t-pentylphenol	83

It is noteworthy that the output of the plant operating with the fluidised bed of catalyst (Fig. 5) is 1.39 g alkylphenol per 1 ml reactant, which is 18 times higher than that obtained in plants with cyclic action when using the same catalyst, and 35 times higher than that obtained in the presence of benzene sulphonic acid. Moreover, alkylphenols obtained by ion-exchange catalysis form better quality detergents than the products of alkylation prepared in the presence of benzene sulphonic acid.

The industrial application of the catalytic alkylation of phenols over ion-exchange resins is still limited. This simple and highly productive method should be judged on its merits and given a proper place in industrial practice.

7. ION EXCHANGERS AS CATALYSTS IN POLYMERISATION

Only a little work has so far been devoted to the catalysis of polymerisation by ion exchangers.

From the accumulated data it is quite certain that cation exchangers can only catalyse the polymerisation reactions whose mechanism is protonic, and where there is no concomitant formation of high-molecular-weight molecules.

The sulphonic cation exchanger Wofatit F has been used as a catalyst in the polymerisation of acetaldehyde to paraldehyde[87,88]. The main practical difficulty in this process is the removal of the heat of reaction. An attempt was made to increase the surface of the Wofatit F by depositing it on porcelain Rashig rings or on pieces of copper wire. However, after heating the catalyst in acid and subsequently drying it, the cation exchanger did not remain on the carrier.

Satisfactory results were obtained by introducing a thin layer of the ion exchanger into the reactor by means of acetaldehyde fed from below and partly vaporised during the reaction. This principle forms the basis of a production plant with a daily output of 100 tons[87]. In case where high yields of the final products are obtained (99%) ion-exchange catalysis is greatly superior to the sulphuric acid method, and is more economical on energy (80%). There are no further references in the literature as to the industrial application of ion exchangers as catalysts in polymerisation reactions.

Papers by Odioso[35] and Menyailo and his coworkers[89] contain occasional items of information about the activity of cation exchangers as catalysts in the polymerisation of alkenes. In collaboration with Tulupov, Federov, and Tsekhmister, the author of this review has made a special study[90] of the polymerisation tertiary pentenes and isobutylene in the presence of the KU-2 cation exchanger. According to the authors[90], heating a mixture of 85% 2-methylbut-2-ene and 15% 2-methylbut-1-ene with the anhydrous KU-2 resin at 100° for 2, 24, 107, and 346 h yields 28, 67, 70, and 90% polymer, respectively, calculated on the pentenes introduced. At 150° the conversion of pentenes in 2 h is increased to 45%, but the resin deteriorates considerably due to thermal desulphonation. At the same temperature, but in isopentane solution, the cation exchanger KU-2 is more heat-resistant.

Heating the industrial butane–butene fraction in the presence of the hydrated form of KU-2 resin to 50° results in the selective hydration of isobutene yielding trimethylmethanol. Normal butenes do not react. At 75°, and even more at 100°, polymerisation starts to compete with hydration. The character of reactions catalysed by ion exchangers therefore depends not only on the properties and the physical state of the catalyst, but also on the temperature.

The anhydrous KU-2 cation exchanger catalyses only the polymerisation reaction, which involves isobutene and, to a lesser extent, normal butenes. Polymerisation in the presence of the KU-2 cation exchanger can thus be used for the selective removal of isobutene and the purification of the butane–butene fraction. If a method were found of increasing the selectivity of polymerisation of isobutene, cation-exchange catalysis could be used industrially for pretreating the butane–butene fraction as a raw material for the production of butadiene.

Our own results show that the sulphonic polystyrene cation exchanger catalyses the polymerisation of diene hydrocarbons[91]. The polymerisation of isoprene over an anhydrous cation exchanger proceeds very slowly, and a viscous product of molecular weight 785 is formed.

In the presence of the H-form of KU-2 resin in the state of maximum swelling the chemical transformations of isoprene are much more rapid and complex. In this case,

hydration accompanies polymerisation. Cyclopenta-1,3--diene undergoes similar changes, but less rapidly.

The discovery of the catalytic transformations of isoprene on cation exchangers has considerable relevance to the problem of the mechanism of formation of terpenes and their derivatives during plant metabolism. In this field ion-exchange catalysis has a point of contact with the chemistry of natural products.

8. ION EXCHANGERS AS CATALYSTS IN CONDENSATION REACTIONS

There is an abundant bibliography concerning the application of ion, especially anion, exchangers as catalysts in condensation reactions. The most typical reactions carried out in the presence of ion exchangers are considered below.

(a) Aldol condensation and crotonisation. The condensation of carbonyl compounds occurring as the result of the addition of an hydrogen atom from a methyl or α-methylene group of one molecule to a carbonyl oxygen of another molecule has been termed the aldol condensation:

$$RCH_2CHO + R'CH_2CHO \rightarrow RCH_2CH(OH)CHR'CHO.$$

Under the conditions which favour dehydration of the resulting aldol, unsaturated compounds of crotonaldehyde type are obtained:

$$RCH_2CH(OH)CHR'CHO \rightarrow H_2O + RCH_2CH = CRCHO.$$

This has been termed crotonisation.

In homogeneous media both types of reaction proceed side by side and are accelerated by many acidic and alkaline catalysts, including amines[92]. They are also catalysed by cation and anion exchangers.

Air-dried[93] or anhydrous[94] resins are used as catalysts. Owing to their low thermal stability the strongly basic anion exchangers should be dehydrated *in vacuo*. Precautions should be taken against the inactivation of strongly basic anion exchangers by carbon dioxide from air (owing to conversion of the hydroxyl form into the carbonate form) or by carboxylic acids, which react with the resins according to the scheme[94]:

$$R_4NOH + R'COOH \rightarrow R_4NOCOR' + H_2O.$$

The following techniques are used in the condensation of carbonyl compounds: (*a*) mixing reactants with the resins, followed by the distillation of the unreacted carbonyl compound and (sometimes) subsequent dehydration of the aldol; (*b*) heating the catalyst and the reactant with benzene (in order to remove water in an azeotrope) in an apparatus fitted with reflux condenser and water separator until no more water separates (this method is convenient for aldehydes which undergo condensation with difficulty); (*c*) filtration through a column packed with freshly regenerated resin[93] (used with easily condensed carbonyl compounds).

The aldol condensation may arise between two molecules of the same aldehyde, and between two different aldehydes, as well as ketones. The course and the yield of the reaction depend not only on the nature of the reactants and the catalyst, but also on the temperature and the presence of an inert diluent. In this connection mention should be made of the work of Durr[95], who studied the condensation of acetic and other aldehydes in the presence of various ion exchangers.

The condensation of acetaldehyde in a metal bomb at 130° proceeded vigorously only in the presence of the hydroxyl--form of the weakly basic anion exchanger Amberlite IR-4B. The distillation of the catalysate, obtained from 200 g acetaldehyde in the presence of 10 g anion exchanger gave 32 g acetaldol, 20 g crotonaldehyde and considerable amounts of a resinous residue. At 70° the same catalysate contained 45 g aldol and 12 g crotonaldehyde, since the conditions were less favourable for dehydration. Only a small amount of crotonaldehyde was formed when the strongly basic anion exchanger Amberlite IRA-400 was used, while the strongly acidic cation exchanger Amberlite IR-120 caused the formation of resinous products.

In the cold and in the presence of a sulphonic cation exchanger acetaldehyde undergoes polymerisation, forming 56% paraldehyde in a week. At the same temperature, but in the presence of a strongly basic anion exchanger, methylacrolein and acetaldol are formed in 18.6 and 8% yields, respectively. In the presence of a weakly basic anion exchanger the yields of these products are 8.8 and 19%, respectively. Thus, the strongly basic anion exchangers favour crotonisation, and the weakly basic ones favour aldolisation. The strongly acidic cation exchanger induces the formation of the cyclic paraldehyde[96].

Ueno[96] carried out the aldol condensation of acetaldehyde in ether solution at -2°, using a strongly basic anion exchanger in OH- or CN-forms. Ch'êng Ts'u-hing and his coworkers[97] studied the kinetics of the aldol condensation of acetaldehyde in 10–30% aqueous solutions and showed that the reaction is of the first order, and that the strongly basic anion exchangers are more active as catalysts than those which are weakly basic. According to Ueno and Yamagishi[98] higher yields of aldol are obtained over the CN- than over the OH-form of the strongly basic anion exchangers.

An interesting example of the combined use of a cation and an anion exchanger in the preparation of acetaldol and crotonaldehyde has been described by Mastagli[99]. This author started from paraldehyde, which on heating with a sulphonic cation exchanger was depolymerised to acetaldehyde, which underwent condensation to aldol and crotonaldehyde under the influence of the strongly basic anion exchanger which was also present. The very important conclusion drawn from this work was the independent catalytic action of cation and anion exchangers when present together.

According to Austerweil and Pallaud[100] the aldehydes of relatively low molecular weight are most susceptible to aldol condensation on ion exchangers.

The condensation of butyraldehyde results in the formation of the aldol intermediate, which readily undergoes dehydration to form α-ethyl-β-propylacrolein. According to Durr[101], butyraldehyde does not form the aldol in the presence of the OH-form of a strongly basic anion exchanger. When cold butyraldehyde is passed through a column packed with a strongly basic anion exchanger much heat is released, and the emerging liquid begins to boil. The catalysate obtained from 100 g butyraldehyde contained 38 g α-ethyl-β-propylacrolein and resinous products, but no trace of the aldol[95]. Under static conditions and in the presence of the same anion exchanger a viscous liquid was isolated after three days. It presumably consisted of a butyraldehyde trimer[95]. The weakly basic anion exchanger Amberlite IR-4B is less active under these conditions and forms a large amount of aldol, while the sulphonic cation

exchanger Amberlite IR-120 is inactive in the cold under both static and dynamic conditions. After 3 h at 75°, 10 g Amberlite IR-120 and 200 g butyraldehyde yield 88 g α-ethyl-β-propylacrolein. Amberlite IR-4B and particularly Amberlite IRA-400 are less effective under these conditions, giving 35 and 12 g α-ethyl-β-propylacrolein, respectively [95].

Astle and Zaslovsky [93] made a complete analysis of the catalysate obtained by passing butyraldehyde through a column 60 cm long and 4 cm in diameter. Their results are collected in Table 8 .

As shown in Table 8, the composition of the catalysate depends on the reaction time and on the nature of the catalyst. The formation of aldol alone in the presence of the strongly basic anion exchanger Permutit S is somewhat unexpected. Its dehydration does not occur even in the presence of Zeo-Karb. The conversion of De-Acidite from the hydroxyl- into the acetate-form gives increased activity for the crotonisation. The increase of the catalytic activity of weakly basic anion exchangers sometimes observed in the course of the reaction can be explained as the replacement of the hydroxyl ions in the catalyst by carboxylate ions which are always present in small amounts in aldehydes [93]. It appears that this also explains the increase in yield with increasing contact time.

The majority of authors prefer the weakly basic anion exchangers as catalysts in the condensation of aldehydes. The strongly basic anion exchangers rapidly become inactive [92] and require frequent regeneration even when operating at moderate temperatures.

Although more stable, even the weakly basic anion exchangers lose some of their activity after repeated use.

The decline in the activity of Amberlite IR-4B during the condensation of heptanol is caused by the sorption of the reaction products, blocking the bead surface. The activity of the resin can be maintained in such cases by freeing it from the reaction products by washing it after every run with toluene, benzene, petroleum ether, or some other inert solvent.

The condensation of heptanol over ion exchangers yields heptylideneheptanal [95]. At room temperature this reaction can only be effected by passage through columns packed by Amberlite IRA-400. Amberlite IR-4B is less effective in catalysing this reaction, while the sulphonated cation exchanger Amberlite IR-120 is inactive.

Under static conditions the reaction starts at 90° with Amberlite IR-4B, and at 120°–125° with Amberlite IR-120. At 125° the strongly basic Amberlite IRA-400 is completely devoid of catalytic activity, probably owing to its limited heat-resistance. By raising the temperature from 110° to 125° the yield of heptylideneheptanal in the presence of Amberlite IR-4B rises from 23.9 to 34.8%, but remains unaffected by further temperature increase. The attainment of the limiting yield can be more readily accounted for by the catalyst inactivation and partial solution, than by the reversibility of the reaction, for in the presence of Amberlite IR-120 and at 150°–155° the conversion of heptanal reaches 48.9% after the usual reacting time of 1 h. By increasing the contact time, the yield of the reaction product can be increased, but in no case is the conversion quantitative. The yield of the end product is also affected by the amount of catalyst present. For instance, at the optimal reaction temperature (145°) and after 2 h, the yields of heptylideneheptanal obtained in the presence of 1, 8, and 15 g Amberlite IR-120 per 100 g heptanal were 31.6, 67.4, and 73.9%, respectively.

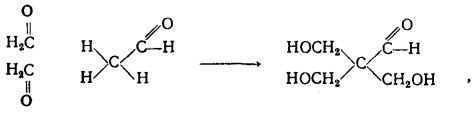
TABLE 8. Effect of the nature of anion exchanger and the contact time on the composition of products in the condensation of butyraldehyde.

Catalyst	Reacting time, h	Weight of catalyst per 100 g butyraldehyde	Yield, %	
			aldol	α-ethyl-β-propylacrolein
De-Acidite acetate	5	35	22	50
De-Acidite acetate	25	30	17	70
De-Acidite acetate	11	20	26	27
De-Acidite	48	30	53	3
Permutit S	20	30	66	0
Amberlite IR-4B	20	30	0	50

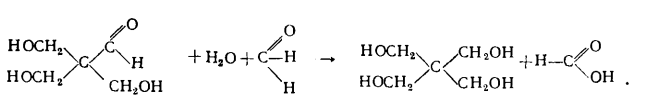
Astle and Pinns made a thorough study of the catalytic properties of sulphonic cation exchangers towards various other aldehydes [102]. They used Dowex-50 and Amberlite IR-120, which after the usual purification they dried in the air, and then *in vacuo* at 60°–65°. These authors disputed the above data of Durr [95] and showed that even at room temperature in the presence of sulphonic cation exchangers various aldehydes, including butyraldehyde, undergo polymerisation to form cyclic trimers and small amounts of dialkylacroleins. At higher temperatures the conditions become more favourable for dehydration, and the yield of dialkylacroleins rises. Dilution of aldehydes, particularly butyraldehyde, by inert solvents such as benzene, lowers the conversion into dialkylacrolein. The addition of water to the mixture of reactant and catalyst has the same effect. For this reason the decline of the resin's activity on repeated use may also be due to the absorption of water, and not solely to thermal decomposition.

Prolonged refluxing of the reaction mixture may reduce the yield of dialkylacroleins although the total conversion remains constant. In such cases the reaction product was found to contain higher amounts of compounds with –C–O–C–O–C– chains, and non-conjugated carbonyl groups [102]. It appears that, in the presence of cation exchangers the aldehydes may form not only cyclic trimers and dialkylacroleins, but also complex products of rather high molecular weight. So far the discussion has covered only the condensation of identical aldehydes, and a brief account of the condensation of two different aldehydes is given below.

The greatest promise is shown by the condensation of formaldehyde and acetaldehyde. The aldolisation of two molecules of formaldehyde and one molecule of acetaldehyde yields a complex aldehyde:



which subsequently undergoes the Cannizzaro reaction with another molecule of formaldehyde, forming pentaerythritol:



The synthesis of pentaerythritol in the presence of the OH-form of a strongly basic anion exchanger has been described in the patent literature [103]. It can, however, be assumed that under stated reaction conditions the catalysts are in fact OH^- ions, driven out into the liquid phase by chloride ions, introduced in the form of NaCl, while the role of the anion exchanger is to bind the formic acid produced in the Cannizzaro reaction. We attach importance to the application of ion-exchange catalysis in the condensation of formaldehyde and acetaldehyde to form acrolein, especially after the recent discovery of a cheap method for the manufacture of acetaldehyde by direct oxidation of ethylene [104].

The condensation of two different aldehydes was investigated by Durr [95,105] and Mastagli [99,106]. Mastagli and his coworkers showed that α-furfurylidenehexanal can be obtained in high yield by the condensation of furfural with hexanal at 118°–120° in the presence of Amberlite IRA-400. Under conditions of homogeneous alkaline catalysis this reaction yields large amounts of by-products. The same catalyst was used in the condensation of furfural with acetone to form monofurfurylidenacetone and small amounts of difurfurylideneacetone [106].

The aldol condensation and crotonisation can also take place between ketones. The weakly basic anion exchangers of types Amberlite IR-4B and IR-45 are, however, incapable of catalysing the condensation of acetone. Only in the presence of a strongly basic anion exchanger is acetone converted into diacetone alcohol [93,107]. The resulting aldol can be dehydrated with high yields to form mesityl oxide if the still of a Soxhlet apparatus is filled with acetone and the sulphonated cation exchanger Zeo-Karb, and the extractor is packed with Amberlite IRA-400. In view of the current availability and low cost of acetone, the practical application of ion-exchange catalysts in the preparation of a very valuable product such as mesityl oxide becomes a possibility.

(b) The Knoevenagel and Pechmann condensations. In its simplest form the Knoevenagel reaction is the condensation of a carbonyl compound with compounds whose methylenic hydrogen atom can easily be substituted by the radicals corresponding to aldehydes and ketones:

$$RR'CO + CH_3COCH_2COOC_2H_5 \rightarrow CH_3COC(=CRR')COOC_2H_5 + H_2O.$$

The Knoevenagel reaction is catalysed by liquid amines and anion exchangers. It is usually effected by heating to 90°–100° the mixture of an aldehyde or ketone and acetoacetic or similar esters with 10% by weight of the resin. After refluxing for 2 h the resin is separated on a Buchner funnel, and the reaction products extracted by ether. In certain cases a cation exchanger is added to the anion-exchanger catalyst [108].

The composition of the product formed in the presence of mixed anion and cation exchangers depends on the ratio of the catalyst's components. Such procedure can yield not only open-chain compounds, but also cyclic derivatives.

In certain cases the role of the cation exchanger is to accelerate the reaction which yields the starting compounds required in the Knoevenagel condensation.

Thus, Mastagli and Lagrange [109] used a cation exchanger as a catalyst of the saponification of heptanacetal and the OH-form of an anion exchanger for the subsequent condensation of the resulting heptanal with ethyl ester of cyanoacetic acid.

In the condensation of isobutyraldehyde and butyraldehyde with ethyl acetoacetate it was shown that [93] the weakly basic anion exchangers (Amberlite IR-4B, De-Acidite in the OH- or CH_3COO-form) are more efficient catalysts of the Knoevenagel reaction than the strongly basic anion exchangers Amberlite IRA-400 and Dowex-1. It is possible, however, that the lower activity of the strongly basic anion exchangers is due to their inactivation by standing in the air or in the presence of acid, *e.g.* CH_3COOH.

Trivedi [110,111] successfully applied the strongly basic anion exchangers, *e.g.* Amberlite IRA-400 to the synthesis of coumarin and 3-cyano-4,6-dimethyl-2-pyridone.

Mastagli and Andric [112] described a method for synthesising 3-acetylcoumarin by reacting salicylaldehyde with ethyl acetate in the presence of anion exchangers. In the cold this reaction took one month. At 75°–85° it lasts 3 h, but the yield of the product is considerably smaller.

Another method for obtaining coumarin derivatives consists in reacting β-ketoesters [112,113] or malic acid with phenols. This is the so-called Pechmann condensation, in which Amberlite IR-120 can be used instead of sulphuric acid. The higest yields of coumarin derivatives are obtained if the reaction is carried out in hexane solution, in which the β-ketoesters are strongly enolised.

(c) Condensation of aldehydes and ketones with alcohols. The condensation of aldehydes with alcohols to form acetals is catalysed by the H-form of cation exchangers. The catalytic efficiency of the cation exchanger depends on its heat-resistance, on the strength of its active groups, and on their position in the resin macromolecule [114].

Acetals are prepared by heating the reactants at 110°–120° in the presence of a sulphonated cation exchanger until no more water separates. The acetal derived from furfural and n-heptanol was obtained in this way [115], and so were the acetals derived from benzaldehyde and butanol, hexanol, or heptanol [116].

The interesting work by Astle and his coworkers [117] deals with a continuous method for the preparation of acetals and ketals from ethylene glycol. Aldehydes react more readily than ketones. The conversion of the aldehyde studied was 60–100%.

The reaction of paraformaldehyde with diethylene glycol in the presence of a sulphonic cation exchanger gave a cyclic acetal, capable of forming wax-like polymers [117].

(d) Certain specific condensations. Strongly basic anion exchangers in the CN-form effectively catalyse the benzoin condensation [94,118]. Benzaldehyde (50 g), ethanol (100 g) and water (40 g) are refluxed for 2 h in the presence of the CN-form of Amberlite IRA-400 (75 ml). The reaction mixture is filtered while still hot, and 39 g benzoin separates on cooling the filtrate (79% yield). This method can also be applied to preparing furoin from furfural and *p*-dimethylaminobenzoin from *p*-dimethylaminobenzaldehyde and benzaldehyde [94].

Anion exchangers have also been used as catalysts in the condensation of aldehydes and nitroalkanes to form nitroalcohols [94,119,120].

Schmidle and Mansfield [94] described the preparation of 1-nitrobutan-2-ol by passage of 58 g propionaldehyde, 91 g nitromethane, and 50 g ethanol through a column packed

with the OH-form of Amberlite IRA-400 at 27° – 30°. The product was obtained by distillation of the filtrate. This simple method gives fairly high yields (up to 70%) and can be used for the synthesis of 2-nitropentan-3-ol, 2-nitrohexan-3-ol, and 1-nitropentan-2-ol. The synthesis of 2-nitroethanol from nitromethane and formaldehyde, however, proceeds with difficulty and the yield is small (up to 9%) [119]. The weakly basic anion exchangers do not catalyse the condensation of nitromethane with formaldehyde and other aldehydes. Nonetheless, the condensation of 2-nitropropane with various aldehydes is more efficiently catalysed by the weakly basic anion exchanger Amberlite IR-4B than by strongly basic resins. The catalytic activity of an anion exchanger is therefore determined not only by its basicity and the type of reaction catalysed, but also by its own steric properties and those of the reactants.

Certain reactions, for example, the condensation of acetone and cyclohexane with nitromethane or nitroethane, have been carried out in the presence of strongly basic anion exchangers with satisfactory yields, but the reactions took several days.

Finally, mention may be made of two more condensation reactions, still in the experimental stage. In one of them, namely the condensation of formaldehyde to form lower sugars [121], an anion exchanger saturated with α-aminoacetophenone was used as catalyst. It should, however, be noted that in this case the anion exchanger was only the carrier of the catalytically active compound, which was bound to it by the van der Waals forces.

The other reaction is of interest as a possible method for the selective extraction of isopentenes from the pentane–pentene cracking fraction. The condensation of tertiary pentenes with paraformaldehyde is catalysed by cation exchangers [79], while in the presence of water-soluble acids it is not so well defined. Isagulyants [79] succeeded in obtaining good yields of isohexyl acetate by condensation of 2-methylbut-2-ene with paraformaldehyde in acetic anhydride solution and in the presence of a cation exchanger. It may be of interest to undertake a detailed study of the Prins reaction using other hydrocarbons, particularly isobutene.

9. ION EXCHANGERS AS CATALYSTS IN CERTAIN OTHER REACTIONS

The above examples demonstrate sufficiently clearly the essential principles underlying ion-exchange catalysis, its merits, and its shortcomings, although they do not exhaust all the possibilities of its practical application. In Table 9 are listed briefly some reactions of addition, cyclisation, structural rearrangement, etc., which can be carried out in the presence of ion exchangers.

It should especially be emphasised that inorganic ion exchangers are beginning to be used as catalysts of organic reactions. Their great chemical and thermal stability [150] distinguishes them favourably from their organic counterparts. Chemists should take notice of these new ion exchangers and do their best to develop methods for their use as catalysts in reactions requiring high temperatures.

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The catalytic action of ion-exchange resins is based on the capacity of mobile ions in their active sites to participate in the formation of unstable intermediate compounds with the molecules of one of the reactants.

Reactions in which the intermediate product is a carbonium-type cation are catalysed by cation exchangers. The anion-exchanging resins catalyse the reactions characterised by the intermediate formation of anionic complexes.

In rare cases, such as the aldol condensation, both cation and anion exchangers are active. Probably, both cationic and anionic complexes can be formed in such reactions.

If in a multistage process one stage yields a cationic complex, and another an anionic complex, a mixed catalyst should be used, consisting of both a cation and an anion exchanger. When both are present, the component reactions proceed independently.

TABLE 9*. Some further examples of the application of ion exchangers as catalysts.

Type of reaction	End product	Type of catalyst	References
Cyclisation	tetrahydropyrans	sulphonic cation exchangers	122
Cyclisation	2,3-dimethylindole	strongly basic anion exchanger	123
Michael reaction	nitro-derivatives	strongly basic anion exchangers	124
Protein hydrolysis	amino-acids	sulphonic cation exchangers	125
Rearrangement	unsaturated ketones	sulphonic cation exchangers	38
Addition	cyanohydrins	strongly basic anion exchangers	94
Addition	4-methoxy-4-methyl-2-pentanone	sulphonic cation exchanger	65
Addition	bis-(2-cyanoethyl) ether	strongly basic anion exchanger	94, 109, 126, 127
Addition	epoxides	inorganic ion exchangers	128
Addition	epoxides	cation exchangers	129
Decomposition	phenol and acetone	sulphonic cation exchangers	130, 131, 132
Decarboxylation and saponification	esters, alcohol, acids	sulphonic cation exchangers	133
Saponification	alcohols and acids	sulphonic and carboxylic cation exchangers	134
Saponification	alcohols and esters	sulphonic cation exchangers	135
Esterification	ethyl glucuronate	anion exchanger	136
Dehydration	isobutene	sulphonic cation exchanger	137
Oxidation	glutaric acids	sulphonic cation exchangers	138
Oxidation and esterification	esters of ω-acyloxyalkyl-ω-hydroxyalkyl carboxylic acids	sulphonic cation exchangers	139
Nitration	various nitro-derivatives	sulphonic cation exchangers	140
Ring-opening	1,3-diols	sulphonic cation exchangers	141
Alkylation	alkylation products of ethers and phenols	sulphonic cation exchangers	142
Alkylation	*p*-t-butylphenol	sulphonic cation exchanger	143
Condensation	mesityl oxide	sulphonic cation exchanger	144
Exchange of functions	acetals, unsaturated ethers	sulphonic cation exchangers	145
Polymerisation	polymers of dienes	sulphonic cation exchangers	146
Polymerisation	isobutene polymers	sulphonic cation exchangers	147
Hydration	t-pentyl alcohol	sulphonic cation exchanger	148
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* This table contains certain data published after the present review was written, and certain reactions not covered by Sections 2–8.

The majority of reactions catalysed by ion exchangers proceed in the ion-exchanger pores, since the reactants and the reaction products diffuse in opposite directions. The velocity of a reaction catalysed by ion exchangers therefore depends on the ratio of the reactant's molecular size and the size of the catalyst's "micropores", and consequently on the structure of the catalyst's lattice. In the selection of the catalyst therefore attention should be paid to the degree of cross-linking in an ion exchanger. Organic reactions involving large molecules should be carried out on ion exchangers with open structures. The important factors in the catalytic activity are also the bead size, swelling, exchange capacity, and the state of bonding of the mobile ion in active sites. In the majority of cases the ion exchangers which are strong electrolytes are more effective as catalysts than the weakly acidic cation exchangers or the weakly basic anion exchangers. The exceptions to this rule can be accounted for by the chemical changes of the catalyst itself giving rise to secondary reactions.

The velocity of a reaction catalysed by ion exchangers is greatly affected by the nature of the solvent. The addition of compounds which have the effect of concentrating the reacting molecules within the ion-exchanger bead increases the rate of conversion.

Slow reactions are usually carried out under static conditions, by agitating the catalyst with the reactants in some sort of reactor, or by refluxing their mixture. The rapid reactions are carried out in the flow of reactants, and the catalyst is fixed either in a Soxhlet extractor, or in a column.

The simplicity of the apparatus for the continuous process, and the ease of the separation of the products from the catalyst are certainly the greatest merits of ion-exchange catalysis. Other advantages are the repeated use of the catalyst, and the ease of its regeneration. Another advantage still is the absence of side-reactions. Reaction products are obtained in high yields and do not require additional purification. Ion exchangers can therefore be used for the processing or the preparation of compounds which are unstable under the conditions of homogeneous catalysis with acids or alkalis. Moreover, the reactions catalysed by ion exchangers are selective, and a fact very important in industry, they simplify the treatment of waste waters compared with that when acid or alkaline liquids are used.

All this has stimulated the development of ion-exchange catalysis into an independent and promising field of organic synthesis.

It should, however, be stressed that the vast potentialities of ion-exchange catalysis are still insufficiently exploited in industry. This is not entirely due to the general attachment to conventional methods, for certain shortcomings of ion-exchanger catalysis are also to blame. Their main shortcoming is their rapid decomposition due to chemical or thermal instability. Their high cost and scarcity are also responsible. Finally, the development of ion-exchange catalysis is retarded by lack of cooperation between theory and practice, which is due to obvious underestimations of its great practical possibilities.

This development will undoubtedly be promoted by lower cost, greater variety, and enhanced stability of ion exchangers.

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THE METAL CHEMISTRY OF VANADIUM

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1. METALLIC VANADIUM

Vanadium occurs in Group V of Mendeleev's Periodic System of the elements. Among the metals of industrial importance, vanadium occupies the seventh position, after chromium, in abundance in the Earth's crust, and in this respect considerably surpasses niobium and tantalum, and also molybdenum and tungsten.

The vanadium atom has an unfilled *d* shell, so that vanadium is a transition metal.

The electronegativity series of the metals (according to the "Project for the Nomenclature of Inorganic Compounds"[1]) vanadium occupies an intermediate position, *i.e.* it can be to equal extents an electropositive metal (with respect to metals following it in the electronegativity series) and electronegative (with respect to metals which precede it). This confers on vanadium a special chemical character, and the variety of its chemical compounds is consistent with its position in the electronegativity series of the metals.

Vanadium is among the most difficult of metals to obtain in a pure form. Owing to its great reactivity at high temperatures it gives a series of stable refractory compounds with non-metals. Metallic vanadium is able to absorb considerable quantities of hydrogen. It is only now, when new methods have been developed for preparing vanadium of the highest purity, containing less than 0.05% of impurities, that its physical and mechanical properties can be regarded as firmly established.

Table 1 gives the chemical composition of various grades of vanadium, including both the ductile metal and the brittle, aluminothermic material. To this table should be added the fact that extremely pure vanadium (99.99%) has recently been produced[2] for some new branches of technology. It is prepared in the form of single crystals by the secondary refining of the 99.5% vanadium by methods involving electrolysis, vessel-free zone melting, electron-beam melting, etc.[2]

TABLE 1. Composition of different grades of vanadium (in wt. %).

Element	Grade of vanadium				
	aluminothermic	chloride (metal sponge)	carbothermic	calciothermic	iodide
V	95.37	90.5—99.6	99.73	99.63—99.8	99.88
O	1.54	0.14—0.57	0.045	0.01—0.1	0.042
N	0.066	0.01	0.020	0.005—0.004	0.008
H	0.002	0.001	—	0.005	0.005
C	—	—	0.20	0.12—0.05	—
Si	0.96	—	—	0.04	0.002
Fe	0.78	0.03—0.1	—	0.001—0.05	0.07
Ca	—	—	—	0.001—0.05	—
Mg	—	0.07—0.20	—	—	—
Al	0.61	—	—	0.01	0.05
Cr	—	—	—	—	0.002
Mo	—	—	—	—	0.005

TABLE 2. Principal properties of vanadium.

Crystal structure up to 1550°	body-centred cubic
Lattice constant, Å	3.034
Specific gravity at 20°	5.8
Melting point, °C	1900 ± 25
Heat of fusion, cal $mole^{-1}$	4185
Entropy of fusion, cal g^{-1} deg^{-1}	2.1
Boiling point, °C	3000
Volatility at the melting point	very low
Specific heat at constant pressure over the temperature range 20°–100°, cal g^{-1} deg^{-1}	0.120
Thermal conductivity, cal cm^{-1} sec^{-1}, at 100°	0.074
Ditto at 500°	0.088
Coefficient of linear expansion (200°–1000°)	8.95×10^{-6}
Electrical resistivity at 20°C, Ω cm	26×10^{-6}
Temperature coefficient of resistivity (25°–100°)	28×10^{-3}
Magnetic susceptibility, c.g.s. unit	1.4×10^{-6}
Vickers hardness	
iodide vanadium	70
cold-rolled iodide vanadium	120
calciothermic vanadium	143
Young's modulus, kg mm^{-2}	14 070
Modulus of rigidity, kg mm^{-2}	4730
Tensile strength, σ_b, kg mm^{-2}	22.2
Proportionality limit, kg mm^{-2}	8.5
Proof stress $\sigma_{so.1}$, kg mm^{-2}	10.7
$\sigma_{so.2}$, kg mm^{-2}	11.6

The physical and especially the mechanical properties of vanadium of varying chemical composition have been described in detail[3]. Table 2 gives the chief properties of vanadium of 99.7–99.9% purity.

The plastic properties of pure metallic vanadium are changed markedly even by oxygen contents as low as 0.05% and nitrogen as low as 0.03%. Therefore the ability of a specimen of vanadium to undergo various types of mechanical working may be regarded as a measure of its purity, since appreciable quantities of oxygen, nitrogen, and hydrogen make it an extremely brittle and hard material.

Pure vanadium has low tensile strength, high plasticity, low specific gravity, high corrosion resistance, and a high melting-point, resembling in this respect titanium and zirconium.

2. METAL CHEMISTRY OF VANADIUM

The solution of the problem of the industrial production of pure vanadium in the 1950s and the demands of various branches of industry for new materials enabled a systematic study to be undertaken of the chemical interaction of vanadium with various elements and of the phase equilibria in metallic systems based on vanadium.

The start of this systematic investigation can be regarded as Rostoker's study[4] of the solubility in vanadium of twenty-one elements of the Periodic System, with suggested equilibrium diagrams for several of the systems investigated. Many investigations have been published recently on equilibrium diagrams of binary and ternary systems based on vanadium, in which pure metals were used.

The problem of the interaction of vanadium with other elements can be worked out on the basis of the general laws governing the formation of metallic solutions and intermetallic compounds, established by Hume-Rothery[5], Ageev[6], Kornilov[7], and others. The formation of solid solutions is determined by the following conditions: (1) similarity in the chemical properties of the metals, following from their positions in the Periodic System and in the electronegativity series of the elements; (2) a small difference in atomic radius between the elements, not exceeding 8–10% for the formation of continuous solid solutions, and 14–18% for restricted solid solutions; and (3) isomorphous crystalline structure for the formation of continuous solid solutions.

As the difference in chemical properties between the elements increases, intermetallic compounds are formed until there is a transition from the intermediate type of semiconducting compounds to compounds of ionic type.

TABLE 3. Difference in atomic diameter between vanadium and the other elements of the Periodic System.

Group	Element	Atomic diameter, %*	Difference, %	Group	Element	Atomic diameter, %*	Difference, %
	Subgroup A			8	Fe	2.54	5.5
				8	Co	2.50	7.05
1	H	1.20	55.3	8	Ni	2.49	7.42
1	Li	3.13	16.3	8	Ru	2.67	0.74
1	Na	3.83	42.6	8	Rh	2.68	0.37
1	K	4.76	71.7	8	Pd	2.75	2.22
1	Rb	5.40	100.7	8	Os	2.70	0.37
1	Cs	5.40	100.7	8	Ir	2.71	0.74
				8	Pt	2.88	7.05
2	Be	2.25	16.3		Subgroup B		
2	Mg	3.20	18.9				
2	Ca	3.93	45.9	1	Cu	2.55	5.2
2	Sr	4.29	59.4	1	Ag	2.883	7.05
2	Ba	4.48	66.5	1	Au	2.877	6.7
2	Ra	—	—				
3	B	1.94	27.9	2	Zn	2.748	22.2
3	Al	2.80	4.08	2	Cd	3.042	13.1
3	Sc	3.02	12.2	2	Hg	3.10	15.2
3	Y	3.62	34.6				
				3	Ga	2.74	1.86
4	Ti	2.93	8.2	3	In	3.138	16.6
4	Zr	3.19	18.8	3	Tl	3.427	27.4
4	Hf	3.17	17.8				
4	Th	3.60	33.8	4	C	1.54	42.8
				4	Si	2.34	13.01
5	V	2.69	—	4	Ge	2.78	3.3
5	Nb	2.94	9.3	4	Sn	3.168	17.8
5	Ta	2.94	9.3	4	Pb	3.494	29.8
6	Cr	2.57	4.46	5	N	1.42	47.2
6	Mo	2.80	4.08	5	P	2.20	18.2
6	W	2.82	4.82	5	As	2.80	4.08
6	U	2.81	4.46	5	Sb	3.228	2.0
				5	Bi	3.640	35.2
7	Mn	2.60	3.3				
7	Re	2.75	2.2				

* *Sic.* It is not clear whether kX or Å is intended. For accepted atomic diameters the reader may consult W. Hume-Rothery, "Elements of Structural Metallurgy", Institute of Metals Monograph and Report Series No. 26, 1961, pp. 38–39 (Ed. of Translation).

Work on the laws governing the formation of intermetallic compounds has been surveyed[8].

The above conditions for the formation of solid solutions and intermetallic compounds have been verified many times in connection with the solubility of elements in iron, nickel, chromium, and titanium[7,9-12]. These same generalisations can be applied to the study of the formation of solid solutions and compounds of vanadium.

Table 3 gives the difference in atomic diameter between vanadium and elements arranged according to their position in the Periodic System. These data are important in determining the nature of the interaction between vanadium and the other elements. Below we shall examine published data on the interaction of vanadium with other elements in the order of their position in the Periodic System.

3 INTERACTION WITH ELEMENTS OF GROUP I

Data are available on the interaction of vanadium only with hydrogen, copper, silver, and gold. The interaction of vanadium with hydrogen has been discussed in a monograph by Mikheeva on the hydrides of the transition metals[13].

Since the absorption of hydrogen greatly increases the hardness of vanadium, several authors have suggested that a solid solution of hydrogen in vanadium is formed, but what type of solid solution is obtained is unknown. Absorbed hydrogen can be removed from the metal by heating in a vacuum to 400°. This indicates the instability of vanadium hydrides as chemical compounds. A vanadium hydride containing 38.6–50 at.% of hydrogen is obtained[14] by reducing V_2O_3 with calcium hydride in a stream of hydrogen at 1175° for 45 min. This hydride is dark grey to black. It was first discovered by Hägg in a study of the adsorption of hydrogen by vanadium on heating[15]. The adverse effect of hydrogen on the physicochemical and mechanical properties of vanadium is noteworthy.

The alkali metals differ greatly from vanadium in chemical properties and in atomic diameter. Therefore vanadium should not interact with them, apart, perhaps, from lithium. It is because they do not interact with vanadium that alkali metals can be used to reduce its compounds and to obtain pure vanadium uncontaminated by these elements

Metals of the copper subgroup (Cu, Ag, Au) are characterised by completion of the *d* electron shell and have a smaller tendency to give solid solutions with metals of the transition groups, including vanadium

Copper forms with vanadium a restricted series of solid solutions. Rostoker and Yamamoto[4] consider the limiting solubility of copper in vanadium to be 5.5–8 at.%. In the copper–vanadium equilibrium diagram it is suggested that a region of liquid immiscibility exists between 20 and 80 wt.% of copper, but these data must be regarded only as tentative[16]. For silver there are only isolated data on the mutual insolubility of the metals in both liquid and solid states[4].

The gold–vanadium equilibrium diagram has been published recently[17] (Fig. 1): the solubility of gold in vanadium is 19 at.% at 1520° and 8 at.% at room temperature. A peritectic reaction between the melt and the α solid solution of gold in vanadium at 1520° yields the compound V_3Au (24 at.% Au), which has a small range of homogeneity. At

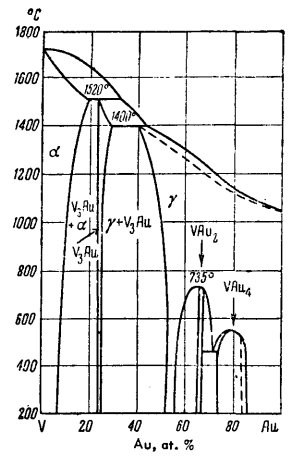

Fig. 1. Equilibrium diagram of the gold–vanadium system.

1400° a solid solution of vanadium in gold is formed by the peritectic reaction:

$$L + V_3Au \rightleftharpoons \gamma\dagger.$$

The gold concentrations in the phases are then: *L* 44, V_3Au 28, and γ 41 at.%. The solubility of vanadium in gold is 59 at.% at 1200°, and 48 at.% at room temperature.

As the temperature falls the γ solid solution yields two intermetallic compounds of Kurnakov type, V_3Au_2 and VAu_4, which are formed at 735° and 565° respectively. Both compounds have regions of homogeneity, and coexist in the eutectoid equilibrium at 460°. The region of the diagram within which both phases exist lies between 56 and 85 at.% gold. VAu_4 has the $MoNi_4$ type of structure with a = 6.39 kX and c/a = 0.622. The structure of VAu_2 has not been established. V_3Au is isomorphous with V_3Co, V_3Ni, and V_3Pd, its lattice constant being 4.87 kX.

4. INTERACTION WITH ELEMENTS OF GROUP II

Group II metals of subgroup A, like the alkali metals, differ considerably from vanadium in chemical properties and atomic diameter, and therefore they should not form solid solutions with it. Beryllium is an exception (the difference in atomic diameter being 16.3%). The limiting solubility of beryllium in vanadium is 0.8 wt.% (4.3 at.%). The equilibrium diagram of the beryllium–vanadium system[4] is of eutectic type, the eutectic point being at Be 49.9 at.%, 1680°. X-Ray examination of this system has revealed a VBe_2 phase, isomorphous with $MgZn_2$ and possessing a hexagonal structure, and a phase VBe_{12}, which belongs to the $ThMn_{12}$ type[18].

Since magnesium and calcium do not interact with vanadium their use is widespread in the development of methods for obtaining vanadium from its compounds such as chlorides, oxides, and sulphides.

The interaction of vanadium with Group IIB elements (zinc, cadmium, and mercury) is not discussed in the literature. In view of the considerable difference in atomic

† Here and subsequently, *L* = liquid phase.

diameter and the great difference in melting point and boiling point, it is difficult to suppose that they can interact with vanadium to form solutions and compounds.

5. INTERACTION WITH ELEMENTS OF GROUP III

Among the elements of subgroup A in Group III, boron, which has a small atomic diameter, is able to yield very dilute solid solutions with vanadium, and to form with it a series of metallic compounds, the borides. The solubility of boron in vanadium does not exceed 2 at.%.[4] Rostoker and Yamamoto have confirmed by X-ray diffraction the existence of the vanadium borides VB (17.52 wt.% B) and VB_2 (29.81 wt.%). VB has an orthorhombic lattice of the CrB type, and is apparently formed[4] by a peritectic reaction between VB_2 and the melt at 1780°. VB_2 has a hexagonal structure and is isomorphous with other diborides (Ti, Zr, Nb, Ta)B_2. Such borides as V_2B_5 (isomorphous with Ti_2B_5, W_2B_5, and Cr_2B_5)[19] and V_3B_4 [20] are known.

A tentative equilibrium diagram for the boron–vanadium system has been suggested recently (Fig. 2)[21]. The starting materials were vanadium containing < 0.5% impurities and boron powder containing B 96, Mg 0.9, Fe 0.14, Si 0.1%, and a considerable amount of oxygen. Alloys were prepared from the powders by sintering under pressure in argon at 1600° for 12 h, and by normal sintering in argon in a tubular tungsten furnace at 1800° for 4 h. Under such treatment the alloys rich in vanadium and those rich in boron melted.

The presence in the vanadium–boron system of the previously known borides VB, V_3B_4, and VB_2 has been confirmed by means of X-rays, and a new compound V_3B_2 has been found. However, the existence of the previously reported compound V_2B_5 was not proved, either in the sintered or in the cast specimens. The concentration range of the homogeneous regions of these borides was not established by the X-ray examination, but it is assumed to be small. Melting-point determinations using a micropyrometer and studies of the microstructure indicate that the compounds V_3B_2, VB, and VB_2 melt without decomposition, whereas V_3B_4 is formed by a peritectic reaction. The eutectic reaction

$$L \rightleftharpoons V_3B_2 + \alpha$$

takes place at 1550° and 15 at.% B. The position of the second eutectic, adjacent to the opposite side of the diagram, has not been determined exactly. Methods for preparing the various vanadium borides and their properties have been reviewed[22].

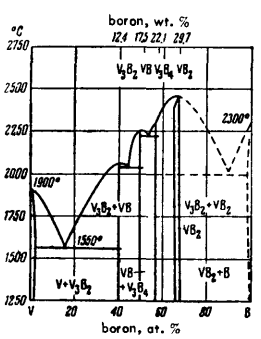

Fig. 2. Tentative equilibrium diagram for the boron–vanadium system.

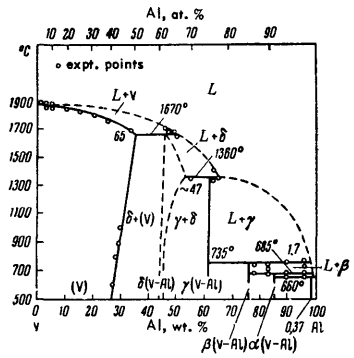

Fig. 3. Equilibrium diagram of the aluminium–vanadium system.

The aluminium–vanadium equilibrium diagram is shown in Fig. 3. The alloys were prepared from ductile vanadium obtained by reduction with calcium. In contrast to Rostoker and Yamamoto's work, in which alloys containing up to 70 wt.% vanadium were studied, later workers[23] investigated thoroughly the whole system, and made additions and corrections to the equilibrium diagrams suggested previously. Thus a new δ phase was discovered, which is formed by a peritectic reaction between the liquid phase and vanadium solid solution at 1670°. It contains 54.2 wt.% (38.5 at.%) vanadium, corresponding to the formula V_5Al_8. This is the only phase which has a wide homogeneity range. Two other phases, γ (VAl_3), melting at 1360°, and β (VAl_6), which melts incongruently at 735°, were described earlier by Rostoker and Yamamoto. They were the first to detect the β phase. A peritectic reaction between the liquid and the β phase at 658° yields a new α phase, which can be given the composition VAl_{11} (14.6 wt.% or 8.3 at.% V). It can also be regarded as a solid solution of VAl_{10} and V_2Al_{21}. The solubility of vanadium in aluminium is low, 0.37 wt.% (0.19 at.%) at 660°. Neither the formation of a compound by a peritectic reaction at 1215°, which had been suggested by Rostoker and Yamamoto, nor the existence of such phases as V_2Al, VAl, V_2Al_3, VAl_7, and VAl_4 could be confirmed[23]. The crystal structure of an α′ phase in an alloy containing 2.5 wt.% aluminium has been studied[24]. The parameters of the monoclinic α′ phase are $a = 25.604 \pm 0.014$, $b = 7.6213 \pm 0.0018$, $c = 11.081 \pm 0.012$ Å, and $\beta = 128°55'$. The composition of the α′ phase was found to be V_7Al_{45} from the density and the volume of the unit cell. Positions are given for all the atoms, together with the interatomic distances and the coordination, and the similarity in structure between the α′ phase and the α and β phases is noted.

The equilibrium diagrams for the systems formed by vanadium with the remaining elements of Group III of the Periodic System, including the lanthanides, are unknown. The fact that pure vanadium is obtained by reducing V_2O_5 with a mixture of lanthanides indicates that these metals do not form appreciable ranges of solid solutions with vanadium. Recently an investigation has been made of the

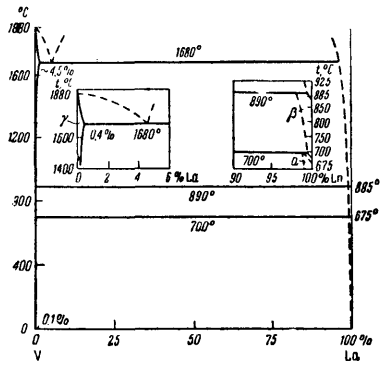

Fig. 4. Equilibrium diagram of the lanthanum–vanadium system.

interaction of vanadium with lanthanum[25]. The alloys were made from carbothermic vanadium (99.3% V) and from lanthanum of purity 98.5% in an arc furnace in an atmosphere of helium (0.5 atm) by remelting four times. Fig. 4 shows the equilibrium diagram for the lanthanum–vanadium system. This diagram has a broad miscibility gap in liquid and solid states. The microstructure of alloys containing 4–99.5% lanthanum showed the presence of two layers, γ rich in vanadium and α rich in lanthanum. Alloys containing $<4\%$ or $>99.5\%$ lanthanum have a two-phase structure. Lanthanum and vanadium form restricted solid solutions. The solubility limit of lanthanum in vanadium is 0.1% at 20°, and 0.47% at 1650°. The solubility of vanadium in α- and β-lanthanum is $<0.5\%$, and also increases with rise in temperature.

Addition of lanthanum to vanadium causes a marked depression of the melting-point of the latter to 1680°, which is a monotectic temperature. At 890° the peritectic reaction $L + \gamma \rightleftharpoons \beta$ results in formation of the β solid solution based on lanthanum. Vanadium raises the polymorphic transformation temperature of lanthanum, a solid solution based on α-La being formed at 700° by the peritectoid reaction $\gamma + \beta \rightleftharpoons \alpha$. The ease of oxidation of alloys containing $>0.5\%$ lanthanum was noted.

Vanadium does not form solid solutions with elements of the IIIB subgroup (gallium, indium, and thallium), in conformity with the difference in chemical properties and the ratio of their atomic diameters. The properties of the intermetallic compound V_3Ga have been described[90]. At 17°K it is superconducting. There is evidence that at 0°K the critical magnetic field of this compound may reach more than 500 000 oersteds.

6. INTERACTION WITH ELEMENTS OF GROUP IV

The elements of subgroup A in Group IV (titanium and zirconium) interact with vanadium to form solid solutions. The nearest neighbour to vanadium in the Periodic System, titanium, has a similar atomic diameter, and at high temperatures its lattice (β modification) is isomorphous with that of vanadium. Hence in this modification it should form a continuous series of solid solutions on crystallisation with vanadium. The equilibrium diagram of the titanium–vanadium system has been thoroughly studied[26,27]. The version in Fig. 5 is based on Adenstedt *et al.*[26] The liquidus has a minimum at 31 at.% V. Vanadium markedly lowers the polymorphic transformation temperature of titanium, and consequently the area of the α phase region is small. The $\alpha + \beta$ two-phase region extends at 650° to 21 at.% vanadium. This equilibrium diagram[26] has been confirmed by other work[4,27], the differences amounting merely to a somewhat different solubility of vanadium in α-titanium.

Titanium–vanadium alloys containing 15–17 wt.% V undergo marked precipitation hardening, which increases appreciably the hardness, diminishes the plasticity, and produces a considerable change in the lattice constant[28].

The X-ray photograph of a titanium–16% vanadium single crystal which had been aged at 460° for 30 min showed reflections due to a new ω phase, the unit cell of which can be assigned to the hexagonal system with constants of $a = 4.60$ Å and $c = 2.82$ Å. The ω phase is a metastable phase. A study has been made of the kinetics of its formation in alloys containing 15 and 17.5 wt.% vanadium[29]. After homogenising in the β region (900°–950°) the specimens were quenched in water, and then maintained at temperatures of 200° to 700°. During this treatment, the ω phase was precipitated. Brief heating of the aged alloys at temperatures above 550° results in almost complete dissolution of the ω phase. When the specimens are maintained a second time at lower temperatures, the ω phase is formed afresh, in smaller amount the longer the specimen had been previously maintained at the temperature of dissolution of the ω phase.

The variation of the modulus of elasticity and of the internal friction with composition of quenched and annealed titanium–vanadium alloys has been investigated[30]. The starting materials were vanadium of 99.5% purity and sponge titanium having $H_B = 130$ kg mm^{-2}.

Fig. 6 shows the concentration dependence of the modulus of elasticity and the internal friction of the alloys at room temperature. Analysis of the curves indicates that the minimum value of the former and the maximum value of the latter for quenched alloys are located in the region of the martensitic α phase, while the maximum Young's modulus occurs within the range of the β phase. The critical concentration for stabilisation of the β phase is 14.5 wt.%

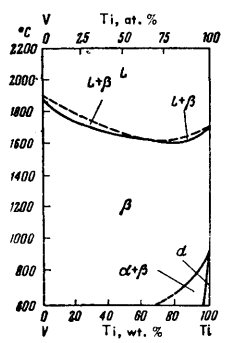

Fig. 5. Equilibrium diagram of titanium–vanadium system.

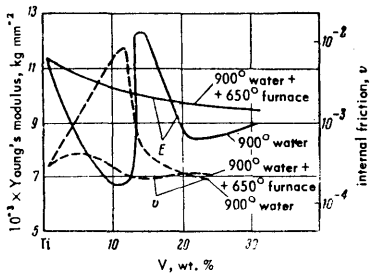

Fig. 6. Variation in Young's modulus E and in internal friction v with composition of titanium–vanadium alloys.

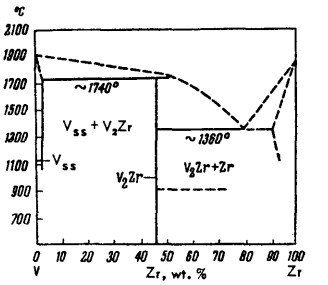

Fig. 7. Equilibrium diagram of the vanadium–zirconium system.

of vanadium[30]. From a study of the temperature dependence of the modulus of elasticity it has been concluded[30] that, with titanium–vanadium alloys having the β structure, the first step in the formation of the ω phase takes place below 280°, the ω phase is formed above 280°, and the equilibrium phase separates above 500°.

With zirconium, vanadium forms restricted solid solutions, in conformity with the great difference in atomic diameter. The limiting solubility of zirconium is less than 1.7 at.% at 1000°, and still smaller at room temperature. Fig. 7 reproduces the equilibrium diagram of the vanadium–zirconium system[4]. Although vanadium and titanium do not form any compounds, the vanadium–zirconium system yields the compound ZrV_2, which is formed by a peritectic reaction between the vanadium solid solution and the melt at 1740°. This compound is in eutectic equilibrium at 1360° with the zirconium solid solution.

No information is available in the literature on the interaction of vanadium with hafnium. From the ratio of the atomic diameters it can be supposed that hafnium, as the closest congener of zirconium,, will give extremely restricted series of solid solution with vanadium. For the same reasons thorium should not dissolve at all in vanadium in the solid state. The vanadium–thorium equilibrium diagram[31] in Fig. 8 shows a simple eutectic type of system. The eutectic is located at V ~ 19 at.%, 1400°.

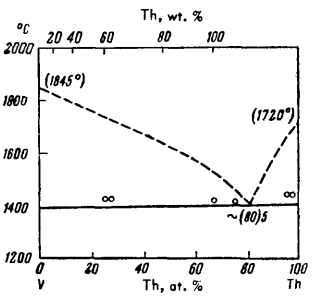

Fig. 8. Equilibrium diagram of the thorium–vanadium system.

Carbon and silicon interact with vanadium to form extremely restricted solid solutions and a series of compounds, of the carbide and silicide types.

Owing to the great difference in atomic diameter, carbon forms extremely restricted solid solutions with vanadium[32,33]. The small atomic diameter of carbon results in the formation, as in its interaction with iron, of solid solutions of interstitial type. According to Schönberg[33], the solubility of carbon in vanadium is 0.2 wt.% (1 at.%) at 1000°.

Much work has been done on the carbide phases of vanadium, and this has been critically reviewed[3,34]. The equilibrium in the carbon–vanadium system has been investigated[4] up to 19 wt.% carbon, the proposed diagram being reproduced in Fig. 9. Schönberg used 99.7% vanadium for preparing vanadium–carbon alloys and reported two carbide phases, V_2C and VC. The hexagonal V_2C phase had a homogeneity range of 8–10.5 wt.% (27–33 at.%). The VC phase had the homogeneity range of 15.1–18.5 wt.% (43–49 at.%) carbon.

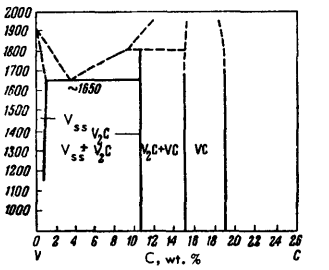

Fig. 9. Equilibrium diagram of the carbon–vanadium system.

Gurevich and Ormont[35] studied the structure of the carbide phases of vanadium containing up to 18 wt.% carbon and 0.14 wt.% oxygen. They concluded that the carbide phases, whatever their mode of preparation, contained a certain amount of oxygen in the form of oxide carbides. Apart from the known carbides V_2C and VC, which these workers[35] regard as oxide carbides, a new phase was discovered having a homogeneity range roughly from $VC_{0.5}O_{0-0.1}$ to $VC_{0.7}O_{0-0.14}$ and a face-centred cubic lattice with constants of 4.115–4.130 kX. The existence of such phases as V_2C and V_4C, which Osawa and Oya[36] found in this system, has been denied[4,34,35].

The solubility of silicon in vanadium is less than 5 wt.% (6.4 at.%) close to the melting point of vanadium, and less than 2.5 wt.% (3 at.%) at 900°. The eutectic reaction

$$L \rightleftharpoons V_{ss} + V_3Si$$

is said[4] to take place in vanadium–silicon melts on the vanadium side at 1840°. A study of the microstructure of the cast alloys showed that, at temperatures above 2000°, a peritectic reaction takes place between the liquid phase and V_3Si with the formation of a new phase, the composition of which was not determined and was tentatively assumed to be VSi. X-Ray structural analysis has established[37] the lattice type and the composition of the unknown silicide, which corresponds to the formula V_5Si_3 and is isomorphous with Ta_5Si_3, β-Nb_5Si_3, Cr_5Si_3, Mo_5Si_3, and W_5Si_3. Kieffer *et al.*[38] confirmed this structure and composition, and gave the silicon–vanadium equilibrium diagram shown in Fig. 10.

A series of papers on silicide systems by the Austrian scientist Nowotny[37,39] are of great value in the search for extra-hard heat-resistant materials. All the vanadium silicides shown on the silicon–vanadium equilibrium diagram were prepared, and the systems formed by the silicides were studied.

Table 4 summarises Nowotny's results on the nature of the interaction between vanadium silicides and those of other metals.

The VSi_2–$TiSi_2$ system has been studied in greater detail[40]. Fig. 11 shows the variation in the physical properties of such alloys, which are very heat-resistant. Their addition to other alloys, which readily oxidise on heating, considerably increases the heat-resistance of the latter.

Table 5 gives the chief properties of the vanadium silicides[34,38,40,41].

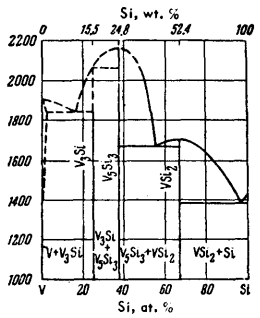

Fig. 10. Equilibrium diagram of the silicon–vanadium system.

TABLE 4.

VSi_2			V_5Si_3		V_3Si	
continuous solid solutions	restricted solid solutions	minimum solubility	continuous solid solutions	restricted solid solutions	continuous solid solutions	restricted solid solutions
$NbSi_2$	$TiSi_2$ $MoSi_2$	$ZrSi_2$	Ta_5Si_3 Nb_5Si_3	Zr_5Si_3	Cr_3Si Mo_3Si	— —

In the vanadium–germanium system, alloys containing 29–83% of vanadium have been studied by X-ray microstructural methods[42]. Apart from the known germanide V_3Ge, which belongs to the Cr_3Si structural type[43], the existence of a new compound V_5Ge_3 was established[42], this having a structure of the $MnSi_3$ type (a = 7.270 kX, c = = 4.960 kX, c/a = 0.676). In rapidly cooled alloys this

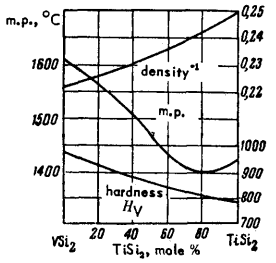

Fig. 11. Variation of physical properties in the VSi_2–$TiSi_2$ system.

TABLE 5. Principal properties of vanadium silicides.

Property	Silicides		
	V_3Si	V_5Si_3	VSi_2
Silicon content, %	15.5	24.8	52.4
Structure	cubic	tetragonal	hexagonal
Lattice constants, kX			
a, Å	4.712	9.41	4.562
c, Å	–	4.74	6.359
c/a	–	0.504	1.394
Density (experimental), g cm^{-3}	5.67	4.80	4.71
Microhardness (100 g load) kg mm^{-2}	1430–1560	1350–1510	1090
Melting point, °C	1730	2150	1670
Electrical resistivity (25°), $\mu\Omega$ cm	–	–	9.5
Temperature of transformation to superconducting state, °K	17.0	–	–
Change in weight on oxidation, kg cm^{-2}, at 1250°	63.0	–7.7	+25
at 1400°	–	–600	–12
Standard heat of formation, ΔH°_{298}, kcal mole^{-1}	–27±9	–96±46	–75±21

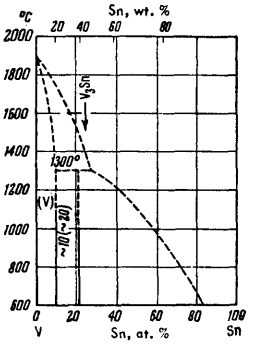

Fig. 12. Tentative equilibrium diagram for the tin–vanadium system.

compound is in equilibrium with germanium and with the compound V_3Ge. Formation of a solid solution of germanium in vanadium is possible on the basis of the ratio of their atomic diameters.

Fig. 12 shows a tentative equilibrium diagram for the tin–vanadium system[44] based on X-ray and microstructural examination of ten alloys which had been annealed at various temperatures up to 1100°. The maximum solubility of tin in vanadium (α solid solution) is approximately 20 wt.% (10 at.%). The compound V_3Sn (47.71 wt.% Sn) has a cubic lattice with the constant[45] a = 4.94 Å, and is formed by the peritectic reaction:

$$L + \alpha \rightleftharpoons V_3Sn.$$

There is no reference in the literature to the interaction of vanadium with lead. From the ratio of the atomic diameters it would appear that solid solutions would not be formed in this system.

7. INTERACTION WITH ELEMENTS OF GROUP V

Niobium and tantalum, Group VA elements, are direct analogues of vanadium, having an isomorphous crystal structure and a small difference in atomic diameter compared with vanadium. It is this which governs their interaction with the latter metal.

One of us predicted, during an investigation of the formation of continuous series of solid solutions of the transition metals, the formation of such solutions of vanadium with niobium and with tantalum[12]. Later experimental work on vanadium alloys containing up to 70 wt.% niobium[4] supported this prediction. Alloys in the neighbourhood of 36 at.% niobium showed, after being annealed at 900°, some signs of a transformation in the solid state. This was ascribed[4] to the formation of a σ phase, which is very characteristic of alloys of transition metals. Later any hypothesis of intermediate phase formation in the niobium–vanadium system was rejected, and an equilibrium diagram with a continuous series of solid solutions was proposed (Fig. 13)[46]. The liquidus curve is characterised by a minimum at 1810° and 35 wt.% niobium.

A study has been made[47] of the heat-resistance, mechanical properties, and corrosion in boiling aqueous media of alloys of vanadium containing 20–50 wt.% niobium. Fig. 14 shows that the addition of niobium to vanadium greatly increases the corrosion resistance in boiling H_2SO_4 and HNO_3. In moist chlorine at room temperature such alloys corrode at a rate of 25 μ per annum. The alloy containing 50% niobium is the most corrosion resistant in all the media examined.

Table 6 shows that alloys based on vanadium possess inadequate resistance to oxidation during prolonged service in air above 700°, although additions of niobium suppress the formation of liquid oxides. However, the relatively simple alloys containing 60% of vanadium and 40% of niobium show such a high corrosion resistance at high temperatures that they are fully able to compete with the best industrial alloys based on iron or nickel, especially if the comparison is made on the basis of specific strength.

A study has been made[4] of alloys containing up to 80 wt.% tantalum, which in the cast state consist solely of solid solution. Alloys within the range 25–80 wt.% tantalum, after being annealed at 900°, contain a second phase, which on the basis of the X-ray diffraction pattern, is ascribed[4] to the family of σ phases.

In an investigation[48] of the structure and properties of tantalum–vanadium alloys undertaken with the aim of constructing the equilibrium diagram of the system, the initial vanadium contained Al 0.5, Fe 0.22%, and an appreciable quantity of oxygen. The alloys were prepared in an arc

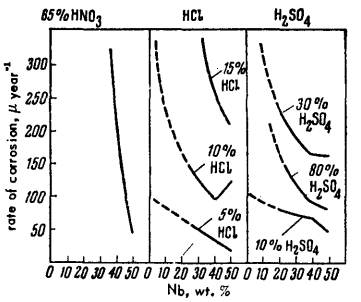

Fig. 14. Corrosion resistance of vanadium–niobium alloys in boiling media.

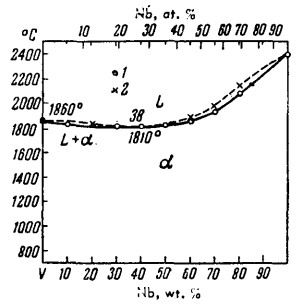

Fig. 13. Equilibrium diagram of the niobium–vanadium system: 1) end of crystallisation; 2) start of crystallisation.

TABLE 6. Corrosion and mechanical properties of vanadium–niobium alloys.

Composition, wt.%	Equilibrium rate of oxidation, mg cm^{-2} h^{-1}			Tensile strength, σ, kg mm^{-2}			Proof stress, $\sigma_{0.2}$, kg mm^{-2}			Elongation, %		
	700°	800°	900°	room temp.	700°	1000°	room temp.	700°	1000°	room temp.	700°	1000°
70 V 30 Nb	14,4	32.6*	—	brittle fracture	88.9	—	—	63.7	—	—	24	—
60 V 40 Nb	9.8	57.4	64.0*	brittle fracture	71.6	24.4	—	63	21.6	—	7.4	8
50 V 50 Nb	8.7	312.0	510.0*	—	—	—	—	—	—	—	—	—

* Some liquid phase observed.

furnace in an atmosphere of argon, the beads being remelted six or seven times in view of the great difference in melting point and density between the components. Alloys containing up to 50 at.% Ta were annealed at 1600°, and those containing more than 50 at.% Ta at 1800° for 3 h. The results (Fig. 15) confirm the formation of a continuous series of solid solutions between vanadium and tantalum. When alloys containing 32.04 and 41.5 at.% Ta were annealed at 1400°, the solid solution broke down with the precipitation of a small quantity of a new phase; as the temperature was lowered the region of breakdown of the solid solution became wider. No conclusions were reached[48] concerning the nature of the new phase. Other workers[49] have found on the melting-point diagram a minimum at Ta 30%, 1820° and also an intermediate β phase (TaV_2, 63.9% Ta), which is formed below 1320°. The two-phase $\alpha + \beta$ region covers the range 27.5–87.5% Ta at 900°.

The elements of subgroup B in Group V differ markedly in chemical properties from vanadium. Whereas the metal congeners in Group V tend to form continuous solid solutions, the elements in subgroup B tend to the same extent to give various kinds of compounds, without appreciable ranges of solid solutions.

The solubility of nitrogen in vanadium is very limited[4]. An alloy containing 1 wt.% (2.9 at.%) nitrogen has a single-phase structure when as-cast, but after being annealed at 900° it has a two-phase structure. Higher nitrogen contents yield vanadium nitride VN, which, like oxides, carbides, and nitrides of other metals, has the sodium chloride structure. The homogeneity range of vanadium nitride is 37.8–49.4 at.% nitrogen, and its melting point is ~2050°.[50]

A new vanadium nitride V_3N has been discovered[50] with a hexagonal structure and a homogeneity range of 27.1–29.9 at.% nitrogen. It can be prepared[51] by heating a mixture of stoichiometric amounts of VN and vanadium powder, compressed into tablets under high pressures, in well evacuated quartz tubes at 1000°–1100° for 24 h.

Powdered vanadium nitrides are greyish brown with a bronze tinge, and are chemically stable, VN more so than V_3N.

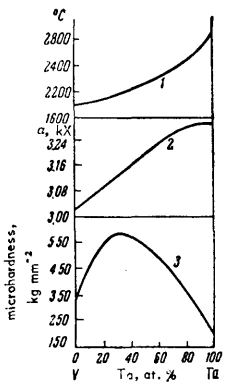

Fig. 15. Property–composition curves of vanadium–tantalum alloys: 1) temperature of crystallisation; 2) lattice constant; 3) microhardness.

Vanadium forms a series of phosphides VP_2, VP, and $VP_{<1}$ (several phases on the phosphorus–vanadium equilibrium diagram)[52]. The most stable among them is VP, which is stable up to 1057°. VP_2 can be obtained from the elements with excess of phosphorus, and VP is obtained by the decomposition of VP_2 in a vacuum at 700°–900°. The vanadium phosphides are dark grey substances, the lower phosphides having a semi-metallic lustre and being resistant to acids. The structure of VP_2 is like that of NbP_2 and TaP_2, and V_3P resembles Cr_3P and $(Fe, Co, W)_3P$ in structure.

The arsenic–vanadium and antimony–vanadium equilibrium diagrams have not been investigated systematically. Nowotny *et al.*[53] suggest that vanadium forms more than one compound with arsenic. They obtained VAs by heating the elements in an evacuated quartz vessel. It dissociates in a vacuum above 1000° to V_2As, which melts at 1345°. They also obtained the compound VSb_2, which is isomorphous with $CuAl_2$.

No information is available in the literature on the interaction of vanadium with bismuth.

8. INTERACTION WITH ELEMENTS OF GROUP VI

Among the elements in subgroup A, chromium and molybdenum form continuous solid solutions with vanadium. This is fully consistent with the conditions stated above for the formation of such solutions, and agrees with the predictions made by one of us[12]. No transformations have been observed in the chromium–vanadium system in the solid state[4,54,55].

The complete equilibrium diagram for the chromium–vanadium system has been published recently[56]. The original vanadium contained Al 1, Fe 0.15, C 0.2, Si 0.35%, and an appreciable quantity of oxygen, the latter affecting the properties of the binary alloys. Addition of the second component has comparatively little effect on the melting point of the alloys, all those in the middle of the diagram melting at ~1700° (Fig. 16). Several properties (hardness and electrical resistivity), however, vary greatly with composition (Fig. 16), the character of the change and the microstructure of the alloys indicating complete solubility of vanadium and chromium in the solid state. The presence of impurities in the vanadium does not prevent complete miscibility of the components; it only raises considerably the hardness and the resistivity, and displaces the maximum in the properties towards vanadium.

The magnetic susceptibility of a solid solution of vanadium and chromium has been studied[57] with the aim of determining its fine structure.

Fig. 17 shows the variation in density, hardness, and magnetic susceptibility with the composition of the alloys. The hardness of alloys prepared from pure materials increases from 90 H_V for pure vanadium to 400 H_V for alloys containing 50% chromium. The hardness of alloys prepared from less pure metals lies about 150 units above the basic curve. The comparatively broad maximum on the magnetic susceptibility curve at 50% chromium is ascribed to the formation of a Kurnakov type of compound, the time for ordering of the solid solution being less than a few seconds. However, no superlattice lines were observed on the X-ray photographs, and if ordering does take place, it occurs to the extent of less than 10%. This phenomenon is quite possible, since vanadium and chromium atoms have

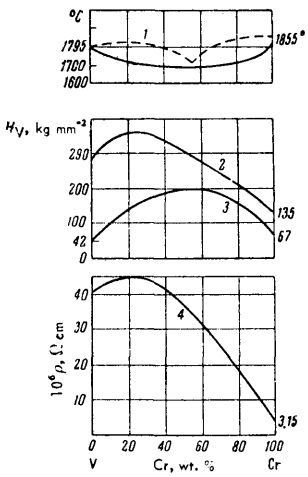

Fig.16. Equilibrium diagram and properties of chromium–vanadium alloys: 1) fusion diagram; 2) hardness in annealed condition; 3) hardness at 1000°; 4) electrical resistivity at 25°.

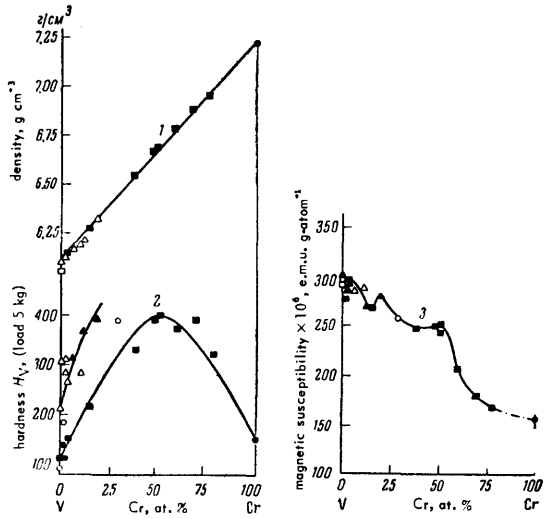

Fig.17. Variation of properties with composition of chromium–vanadium alloys: 1) density; 2) hardness; 3) magnetic susceptibility.

closely similar electrochemical properties and dimensions. The presence of a fine structure in this region has been shown in other work, involving neutron diffraction and specific heat measurements. Fig. 18 shows the molybdenum–vanadium equilibrium diagram with complete miscibility of the components in liquid and solid states[58]. The alloys were prepared from aluminothermic vanadium of 95.5% purity and 99% molybdenum by fusion in an electric arc in argon. Before the properties of the alloy were determined, it was annealed in a vacuum at 1600° for 10 h.

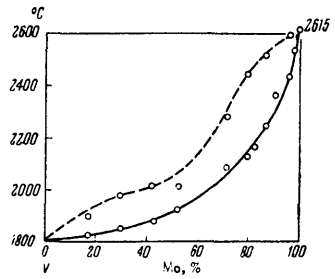

Fig.18. Fusion diagram of the molybdenum–vanadium system.

It is evident from Figs. 19 and 20 that addition of the second component markedly increases the hardness, microhardness, and resistivity of the alloys while diminishing their plasticity.

A vanadium–tungsten equilibrium diagram has been suggested[59,60] which shows complete mutual solubility of the components. Addition of tungsten to vanadium, and especially of vanadium to tungsten, lowers the melting point, the liquidus passing through a minimum at W 4.5 at.%, 1430°.

Apart from determinations of the liquidus and solidus temperatures, several properties of the alloys were studied[60] as a function of their composition (Fig. 21). The alloys were prepared from carbothermic vanadium (98.6%) and from tungsten rods (99.95%) in an arc furnace in an atmosphere of helium, and then annealed at 1100° for 500 h. Additions of tungsten up to 1.25 at.% decrease the hardness and increase the plasticity and compressive strength. The subsequent property–composition curves are typical of systems having unlimited solubility of the components. The alloys oxidised readily in air, and the attack increased progressively with rise in temperature and in the vanadium content of the alloys. It was concluded[60] that at 700°–1000° all the alloys oxidise vigorously, and require protection.

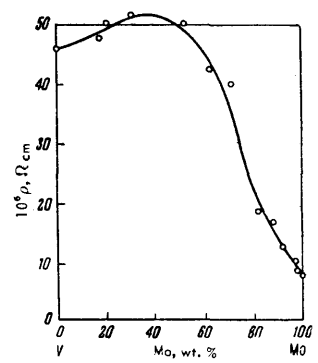

Fig.19. Variation in resistivity in the molybdenum–vanadium system.

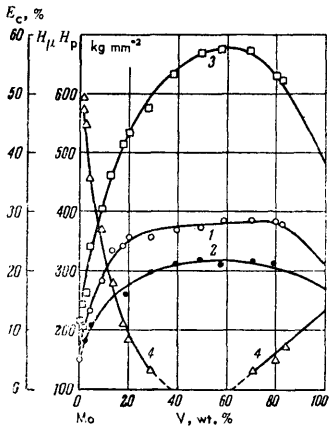

Fig. 20. Variation in mechanical properties in the molybdenum–vanadium system: 1) hardness of as-cast alloys (H_p); 2) hardness of annealed alloys; 3) microhardness (H_μ); 4) plasticity on compression (ϵ_c).

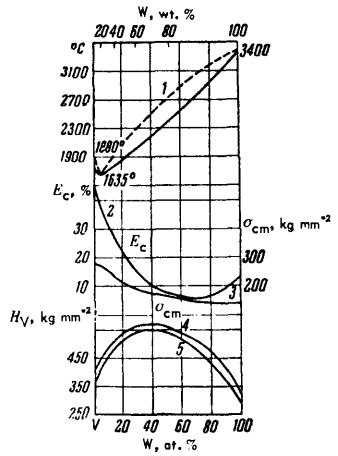

Fig. 21. Equilibrium diagram and properties of tungsten–vanadium alloys: 1) fusion diagram; 2) and 3) plasticity and compressive strength; 4) hardness of as-cast alloys; 5) hardness of annealed alloys.

The equilibrium diagram for the uranium-vanadium system[61] is illustrated in Fig. 22. The alloys were prepared in an electric arc furnace in helium from iodide vanadium and the purest uranium containing at most 0.1% of impurities. The equilibrium diagram is of eutectic type, the eutectic point being at V 18 at.%, 1040°. The temperatures of the allotropic transformations in uranium are lowered by vanadium. The solubility of vanadium in γ-uranium is 12 at.% at the eutectic temperature, falling to 9 at.% at the eutectoid temperature (727°). The solubility of vanadium in the β modification is 2 at.% at 700°, that in the α modification being 1.5 at.% at 600°. The solubility of uranium in vanadium (δ phase) is a maximum at the eutectic temperature, its value being 4 at.% or 15 wt.% uranium.

The equilibrium diagram of the plutonium–vanadium system has recently become known[62]. It is of simple eutectic type (Fig. 23), the eutectic point occurring at V 2.3 at.%, 625°. Additions of vanadium do not affect the polymorphic transformation temperature of plutonium.

The interaction of vanadium with the Group VIB elements, oxygen, sulphur, and their congeners, results in the formation of a series of compounds which have been thoroughly investigated and well described. No data are available on the interaction of vanadium with polonium.

The equilibrium diagram of the oxygen–vanadium system has been studied repeatedly and thoroughly as a result of its great practical importance. The early work, concerned

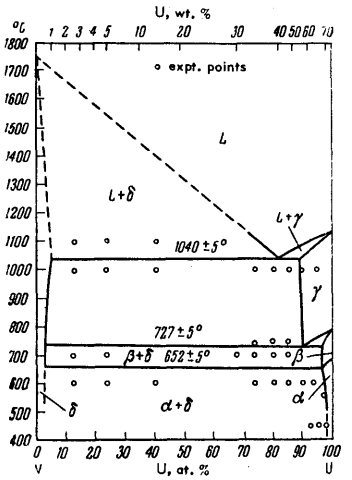

Fig. 22. Equilibrium diagram of the uranium–vanadium system.

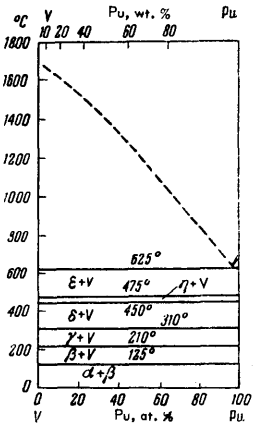

Fig. 23. Equilibrium diagram of the plutonium–vanadium system.

mainly with the oxides of vanadium VO, V_2O_3, VO_2, and V_2O_5, their crystal structure, and the conditions and limits of their existence, has been reviewed by Pearson[63]. Seybolt and Sumsion[64] have established that vanadium undergoes a high-temperature polymorphic transformation at 1500°, and this is reflected in the equilibrium diagram which they proposed for the V–VO_3 system (Fig. 24).

Up to 3.2 at.% oxygen is dissolved by α-vanadium, and up to 35–40 at.% by the high-temperature γ modification. A later paper[65] denies the existence of a high-temperature modification of vanadium, and gives a different V–VO equilibrium diagram (Fig. 25). The alloys were prepared from calciothermic vanadium (total impurities 0.13%) and chemically pure V_2O_5 in an arc furnace. The limiting solubility of oxygen in α-vanadium at temperatures below 900° was found to lie between 0.27 and 0.98 at.%. At 1600° the maximum solubility reaches 3.9 at.%. X-Ray examination has established that at room temperature a β phase, with a body-centred tetragonal lattice, exists over the range 8–40 at.% oxygen. This phase is regarded[65] as a low-temperature allotropic modification of vanadium which is stable at high temperatures in the oxygen–vanadium system.

The $(\alpha + \beta)/\beta$ phase boundary passes from 14.5 at.% oxygen at 900° to 22.1 at.% at 1800°, in agreement with Seybolt and Sumsion's results. Below 1100° a δ phase, the crystal structure of which was not determined, is formed by a peritectoid reaction between the β phase and VO. Between 41 and 56 at.% oxygen is the region of homogeneity of the compound VO, which has the NaCl structure with a lattice constant of a = 4.08 kX.

Investigations were made not only of transformations in the solid state but also of the fusion diagram, which showed a minimum at 30.2 at.% oxygen[65], agreeing with the minimum on the diagram based on Seybolt and Sumsion's data. At the temperature of the minimum it is the β phase which solidifies, not the γ phase as the latter investigators imagined. Over the range 0–50 at.% oxygen the fusion diagram contains two peritectic horizontals on the two sides of the minimum, at the temperatures of which the following reactions take place:

$$L + \alpha \rightleftharpoons \beta \ (1850°) \quad \text{and} \quad L + VO \rightleftharpoons \beta \ (1690°).$$

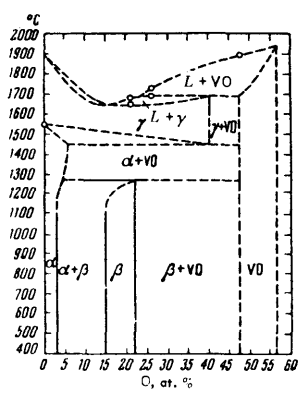

Fig. 24. Equilibrium diagram of the V–VO system according to Seybolt and Sumsion.

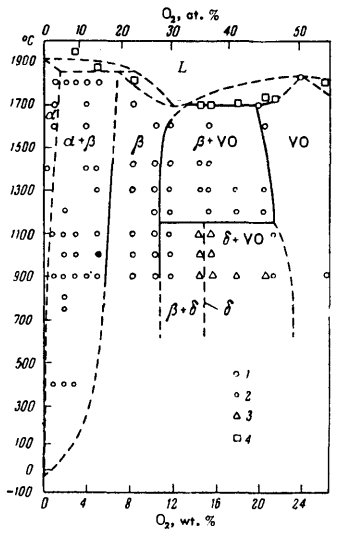

Fig. 25. Equilibrium diagram of the V–VO system according to Rostoker: 1) one phase; 2) two phases; 3) three phases; 4) thermal analysis.

In order to confirm their hypothesis of a low-temperature allotropic modification of vanadium, Rostoker and Yamamoto[65] measured the electrical resistance of a fine vanadium wire as a function of temperature in a vessel containing dry ice and acetone. The curve (Fig. 26) shows a change in resistivity (a break) between -33° and -25°.

Oxygen tends to stabilise the β modification, which has a considerable range of homogeneity in the oxygen–vanadium system. However, doubt has been cast[66] on the existence of a low-temperature modification of vanadium. The curve for the temperature dependence of the electrical resistance of cold-worked vanadium wires containing 99.7 and 99.9% vanadium showed[66] no breaks which would indicate first-order transitions; it is characterised merely by a slight negative deviation from linearity at 73°. The curve representing the temperature dependence of Young's modulus of the vanadium wire showed neither a break nor a deviation from linearity. X-Ray examination indicated only a body-centred cubic lattice.

The following phases have been established[67] in the sulphur–vanadium system: an α phase VS, which is in eutectic equilibrium with vanadium at 1312° and has a nickel arsenide type of structure, a β phase V_2S_3 with an asymmetric structure, and VS_4, which is stable in the presence of sulphur up to 400°. The existence of the previously discovered sulphide V_2S_5 has been denied[67].

A study of the crystal structure of the sulphide richest in vanadium, V_3S, has shown[68] that it exists as two polymorphic modifications, β-V_3S stable above 950°, and α-V_3S stable below 825°; interconversion of these two sulphides occurs between these temperatures. β-V_3S has a body-centred tetragonal structure with lattice constants of a = 9.470 and c = 4.589 Å; α-V_3S has a tetragonal structure with constants a = 9.881 and c = 4.663 Å. The structure of β-V_3S is similar to the Ni_3P type, and the α-V_3S structure is close to that of β-W. A complete crystallographic description of these two forms of V_3S is given.

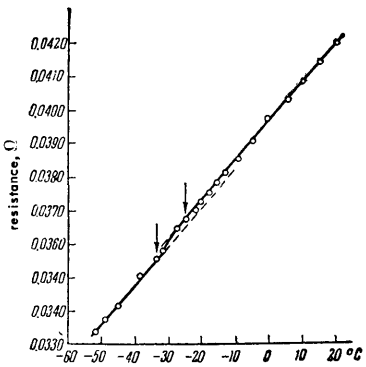

Fig.26. Change in electrical resistance of vanadium wire between -33° and -25°.

The equilibrium diagrams selenium–vanadium and sulphur–vanadium systems are similar in general character[63]. The following phases have been shown by means of X-rays[69] to be present in the selenium–vanadium system: VSe isomorphous with NiAs, V_2Se_3 with a hexagonal lattice of low symmetry, and VSe_2 isomorphous with CdI_2.

The only vanadium telluride known as yet is VTe, which is isomorphous with NiAs[70].

9. INTERACTION WITH ELEMENTS OF GROUP VII

The equilibrium diagrams of vanadium with the metals of Group VII have not been fully studied. Formation of a continuous series of solid solutions between manganese and vanadium is excluded since the crystal structures of the components are not isomorphous and manganese exists in several polymorphic modifications. In conformity, however, with the very slight difference in atomic diameter between the components, manganese shows considerable solubility in vanadium, the limit of which has still not been reached[4] in the alloy containing 14.2 at.% manganese at 900°. The equiatomic alloy has a body-centred cubic structure, and is regarded[71] as an intermetallic compound of vanadium with manganese having the composition VMn.

Manganese-rich alloys contain a σ phase, whose range of homogeneity at 1000° is 13.4–24.5 at.% vanadium[72].

The literature contains a hint of the existence of the compound VMn_2 (33.3 at.% vanadium), melting at 1370°. An alloy having the composition VMn_2 which has been cast and annealed at 1300° and 1200° has a body-centred cubic structure, while those which have been annealed at 1000°, 800°, and 600° are mixtures of two phases, one having a body-centred cubic structure and the other a σ phase structure[31].

Vanadium and rhenium have a slight difference in atomic diameter, which favours the formation of a considerable range of solid solutions, which may contain[73] up to 40 at.% vanadium. No intermetallic compounds have been detected within the range 40–68 at.% vanadium.

It has been established[74] that a σ phase of the composition VRe_3 is formed in the rhenium–vanadium system by a peritectic reaction at 2490° between the melt and the solid solution based on rhenium. The results of X-ray and microstructural analyses indicated the occurrence of a eutectoid breakdown of the σ phase at 1500° with the formation of a mixture of two solid solutions, based on vanadium (α) and on rhenium (β). The lattice constants of the phase are a = 9.36 and c = 4.86 Å.

No data are available on the interaction of vanadium with technetium.

With the halogens, vanadium forms halides of the types $VHal_2$, $VHal_3$, and $VHal_4$. The chlorides and iodides are important as raw materials in the industrial production of pure vanadium.

10. INTERACTION WITH ELEMENTS OF GROUP VIII

Vanadium should interact with all the Group VIII elements to form solid solutions and compounds containing a metallic type of bond. Of the nine elements in this group, equilibrium diagrams are known only for the systems with iron[54,75,76], cobalt[77], nickel[4,72,78], and palladium[79].

With iron, vanadium forms a continuous series of solid solutions, in conformity with the general conditions governing the formation of such solid solutions between metals.

Fig. 27 reproducts the equilibrium diagram for the iron–vanadium system given in Hansen's Handbook[31]. When the α solid solution is cooled, a Kurnakov compound VFe,[76] which dissolves both iron and vanadium, is formed at 1230°. The range of homogeneity of this compound, the σ phase, lies between 37 and 57 at.% vanadium. The plots of hardness and of resistivity against composition for alloys which have been annealed at 900° for 70 h pass through singular minima at 25 and at 50 at.% vanadium, corresponding to the compounds VFe_3 and VFe respectively[80,81]. The binary iron–vanadium system contains a closed region of a face-centred γ solid solution, with a maximum at 1.2 at.% vanadium.

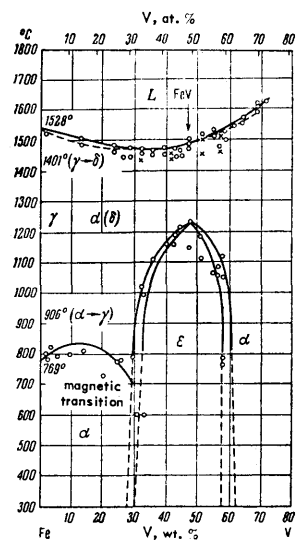

Fig.27. Equilibrium diagram of the iron–vanadium system.

With certain conditions of heat treatment, a second ferromagnetic phase is formed in an iron alloy containing 47% vanadium. High-temperature annealing at 1360° for 60 h with subsequent quenching in alkali is of decisive value in this connection.

A study has been made[83] of the structure of iron alloys containing 28.5, 43.0, 49.5, and 74.0 at.% vanadium, after they have been heated at various temperatures between 1400° and 600° with subsequent quenching in water. All alloys in the temperature range 1400°–1150°consist of a mixture of two phases ($\alpha+\beta$). The second phase, the face-centred cubic β-Fe–V, is regarded[83] as the equilibrium phase in the temperature range above the $\alpha \rightleftharpoons \sigma$ transformation, its amount increasing with increase in the vanadium content. At 800° the alloy containing 28.5% vanadium consists of a single phase, α, whereas alloys containing 43, 49.5, and 74% vanadium consist of two phases, α and σ. At 600° crystals of the α phase disappear from the alloy containing 49.5% vanadium, and its structure consists solely of the σ phase. It is therefore considered[83] that the phase reactions occurring within the range 28.5–74 at.% vanadium when the temperature is lowered from 1400° to 600° are more complicated than would appear from the published iron–vanadium equilibrium diagram.

The analogues of iron — cobalt and nickel — show greater differences from vanadium in atomic diameter, and are not isomorphous with it in crystal structure. This explains the gap in the solubility of cobalt and nickel in vanadium. According to data in the literature[77], the solubility of cobalt in vanadium is 20 at.% at high temperatures and 5% at room temperature.

The equilibrium diagram of the vanadium–cobalt system[77] is shown in Fig. 28. At the eutectic temperature of 1248° the melt is in equilibrium with γ and σ phases, the latter being formed at 1420° by a peritectic reaction between the melt and the vanadium solid solution. The homogeneity region of the solid solution (σ phase) based on the compound VCo lies between 38.5 and 59.5 at.% vanadium[67].

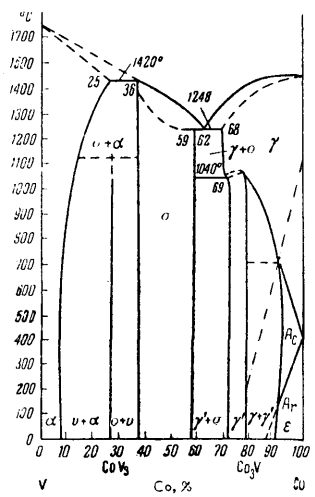

Fig. 28. Equilibrium diagram of the cobalt–vanadium system.

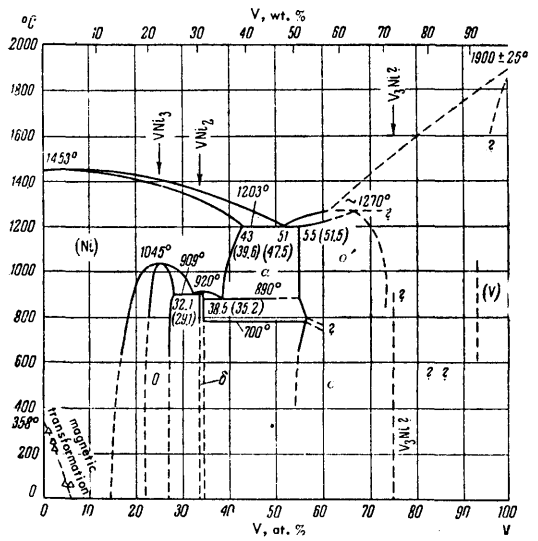

Fig. 29. Equilibrium diagram of the nickel–vanadium system.

An alloy containing 70.7 at.% vanadium undergoes, at temperatures between 1100° and 1150°, a eutectoid reaction between the α and σ phases with the formation of the metallic compound V_3Co, which crystallises with the β-tungsten structure. In the region of the cobalt solid solution at 1070°[84] a new ordered γ' phase based on the compound VCo_3 (a Kurnakov compound) is formed with a homogeneity range of 19.1–26.09 at.% vanadium, on both sides of which are two-phase regions, $\gamma+\gamma'$ and $\gamma'+\sigma$. The X-ray photograph of the ordered phase shows weak superstructural lines. It has a close-packed hexagonal structure containing 24 atoms in the unit cell with lattice constants of a = = 5.032 and c = 12.27 kX.[85]

The solubility of nickel in vanadium is 6–9 at.%.[4] Fig. 29 shows the equilibrium diagram of the nickel–vanadium system[77] up to 60% vanadium. At the eutectic temperature a solid solution of vanadium in nickel, the α phase, is in equilibrium with the σ' phase, which has a considerable range of homogeneity, from 55 to 74 at.% vanadium, and at 760° undergoes the transformation $\sigma' \rightarrow \sigma$, the nature of which is not yet known. X-Ray studies do not distinguish between the σ and σ' phase. The $\alpha/(\alpha+\sigma)$ and $(\alpha+\sigma')/\sigma$ boundaries have been established by means of X-ray studies. At 840° the eutectoid decomposition $\alpha \rightleftharpoons \delta + \sigma'$ takes place, and at 907° $\alpha \rightleftharpoons \theta + \delta$. The δ phase, which has a body-centred orthorhombic lattice, is a solid solution based on the compound VNi_2 (30.27 wt.% vanadium). The θ phase, which has a tetragonal lattice of the $TiAl_3$ type, is a solid solution based on the compound VNi_3, the latter being formed at 1045°.

There are indications[4,86] of the formation of the compound V_3Ni (72.25 wt.% vanadium), having the β-W structure, by a peritectic reaction in the vanadium-rich region at 1380°.

Only restricted solid solutions and intermetallic compounds can be formed between vanadium and the platinum

group elements owing to the absence of isomorphism between the crystal structures. Alloys of vanadium with palladium have been most fully investigated [73,79], while those of vanadium with ruthenium, rhodium, and platinum have been studied to some extent [73]. There is no published information on the interaction of vanadium with osmium or iridium.

The palladium–vanadium equilibrium diagram is of eutectic type (Fig. 30). At the eutectic temperature of 1340° an α solid solution of palladium in vanadium, containing up to 37.5 at.% palladium at this temperature, is in equilibrium with a γ solid solution of vanadium in palladium. At 840° a peritectoid reaction yields the compound V_3Pd having the β-W structure with a = 4.80 kX, isomorphous with V_3Ni. This compound has a narrow range of homogeneity, and has no plasticity. In the region of the γ solid solution the ordering process involves the formation of two intermetallic compounds: VPd_3 at 815°, with a face-centred tetragonal lattice having the parameters a = 3.84, c = 3.87 kX, and c/a = 1.007, isomorphous with VNi_3; and VPd_2 at 905°, with a similar lattice having a = 3.88, c = 3.72 kX, and c/a = 0.962. The eutectoid reaction

$$\gamma \rightleftharpoons VPd_3 + VPd_2$$

occurs at V 28 at.%, 720°. At room temperature the γ phase is homogeneous not only up to 21 at.% vanadium but also between 44 and 50%. The solubility of palladium in vanadium at 500° is 15 at.%.

No definite data are available on the solubility of ruthenium in vanadium. Alloys containing 36, 50, 71, and 82 at.% ruthenium, after being quenched from 1200°, have been studied [73] by means of X-ray diffraction. The 36% Ru alloy has a cubic lattice of the CsCl type with a lattice constant which is very close to that of the solid solution based on vanadium. A phase having a tetragonal lattice was found in the 50% alloy. The solid solution of vanadium in ruthenium contains less than 18 at.% vanadium [73]. The same paper [73] reports an investigation of alloys containing 25, 42, 50, and 60 at.% rhodium after being quenched from 1200°. The compound V_3Rh (42.24 wt.% rhodium), having the β-W type of crystal lattice, has been detected. The alloy containing 60 at.% rhodium contains a second compound having a close-packed hexagonal structure.

The limiting solubility of platinum in vanadium [45] is 8 at.% (25 wt.%), and the solubility of vanadium in platinum is 40 at.%. [73] The compound V_3Pt (43.91 wt.% vanadium), isomorphous with V_3Pd, has been found. A further compound may exist between the platinum-rich solid solution and V_3Pt. [73]

11. TABLE SHOWING INTERACTION OF ELEMENTS OF THE PERIODIC SYSTEM WITH VANADIUM

The theoretical concepts and experimental results discussed enable us to give a general picture of the nature of the chemical interaction of vanadium with all the elements in the Periodic System. By analogy with other metals which we have examined previously [87-89], the interaction of the elements with vanadium can be represented in terms of Mendeleev's Periodic Table. This is shown in Fig. 31 in extended form, vanadium being place above the Table.

The elements can be divided into four classes in relation to vanadium: (1) those forming continuous solid solutions with vanadium; (2) those forming restricted solid solutions and intermetallic compounds; (3) those forming ionic compounds but no solid solutions; and (4) those which do not interact with vanadium.

In Fig. 31, which we shall call the "Table of the Metal Chemical Properties of Vanadium", these classes are separated from one another as shown, and are linked by straight lines with vanadium. It can be accepted that metals which are close to vanadium in the Periodic System will form solid solutions with it. Most of them tend to give intermetallic compounds, which are formed either as a result of reaction in the solid solutions or, as in the case

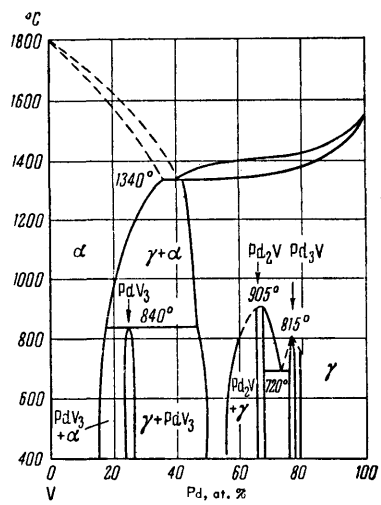

Fig. 30. Equilibrium diagram of the palladium–vanadium system.

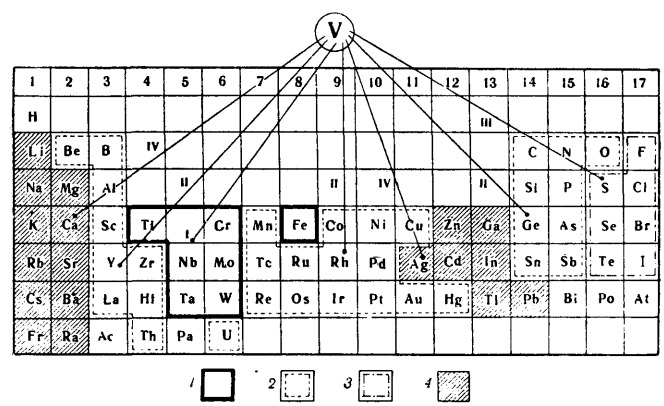

Fig. 31. Metal chemical table of the elements: 1) continuous solid solutions; 2) restricted solid solutions and intermetallic compounds; 3) ionic compounds without solid solutions; 4) no interaction.

of systems having limited solid solutions, directly on crystallisation. Such non-metals as H, B, C, Si, N, and O, which have small atomic diameters, form with vanadium extremely restricted solid solutions of the interstitial or substitutional types. They show a greater tendency to form compounds of the type of the borides, carbides, silicides, nitrides, and oxides of vanadium. With increasing difference in electronic structure and in chemical properties, the tendency to form solid solutions diminishes. With elements which differ markedly in chemical properties, vanadium is unable to give solid solutions, but forms compounds of ionic type. The last class comprises those elements which, owing to an unfavourable size factor or electronic structure, are incapable of interacting with vanadium. It includes the alkali and the alkali-earth metals and, perhaps, several other metals (Zn, Cd, Pb, etc.).

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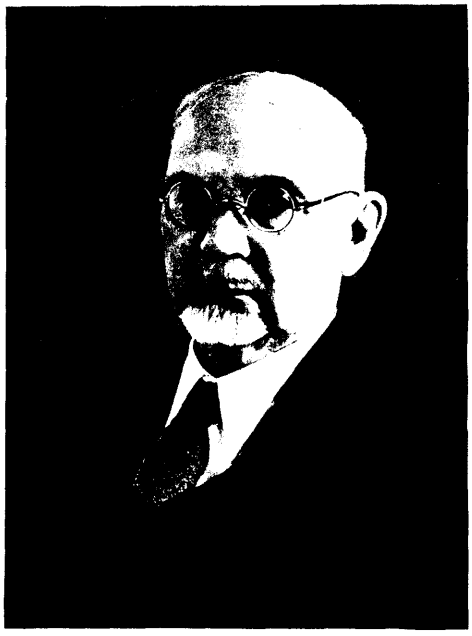

A. E. ARBUZOV

The Editorial Board of the journal Uspekhi Khimii warmly congratulate Aleksandr Erminingel'dovich Arbuzov on celebrating his 85th birthday and completing 60 years of scientific work and wish him good health and progress in his beloved scientific profession.

CHEMISTRY OF VINYLETHYNYLCARBINOLS

S. A. Vartanyan

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INTRODUCTION

Owing to the high activity of the hydroxyl group and the ability of the triple bond to take part in various addition, polymerisation, and condensation reactions, vinylacetylenic

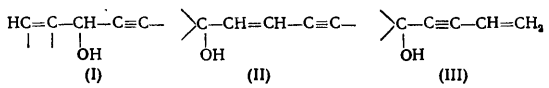
alcohols are important starting materials in the synthesis of a great many compounds. Some of these compounds have emerged from laboratory practice and become important industrial products or intermediates [1,2].

Nazarov's review [1] of the chemistry of vinylacetylenic alcohols covers all the data published prior to 1945. Nevertheless, since this aspect of the chemistry of acetylene is being continually and intensively developed, the need has arisen to collate recently published data. In the present review an effort has been made to gather, and where possible, systematise the extensive information which has accumulated on this subject.

1. SYNTHESIS OF VINYLACETYLENIC ALCOHOLS

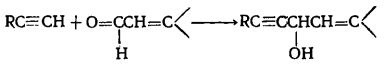
The condensation of acetylene and its monosubstituted derivatives with carbonyl compounds in the presence of alkali, first carried out by Favorskii [3], has been the subject of many investigations in the last few decades [4]. The Favorskii reaction is at present one of the simplest and most accessible methods for the synthesis of a great many acetylenic alcohols.

A further step in the development of this reaction was the preparation of acetylenic alcohols containing a double bond. Three types of such compounds are known:

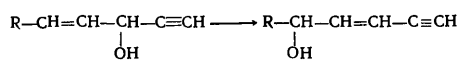


(I) (II) (III)

Carbinols of type (I) are obtained by condensing monosubstituted acetylenic hydrocarbons with $\alpha\beta$-unsaturated aldehydes and ketones [5-19]; condensation by means of sodium in liquid ammonia [20,21] gives satisfactory yields.



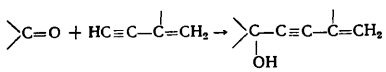
Carbinols of type (II) are obtained by anionotropic isomerisation of carbinols (I) under the influence of acids [5,18]:



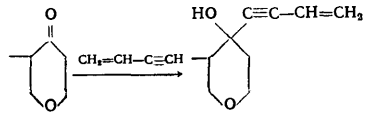
The ease of isomerisation depends on the nature of the carbinol. In many cases the rearrangement goes to completion in the cold during the decomposition of the Iotsich complex with a dilute acid [22,23]. The first member of these carbinols, $CH_2:CH\cdot CHOH\cdot C\vdots CH$, however, does not undergo isomerisation even in the presence of 25% sulphuric acid.

Finally, carbinols of type (III) are obtained by the condensation of vinylacetylene or its homologues with aldehydes or ketones.

In 1938 Nazarov [24] showed that vinylacetylene is also capable of condensation with ketones according to the Favorskii method, forming vinylethynylcarbinols in good yields. The reaction proceeds more rapidly than in the case of acetylene itself. This method was used for the condensation of vinyl- and isopropenyl-acetylene with a series of aliphatic and alicyclic ketones [24,26]:

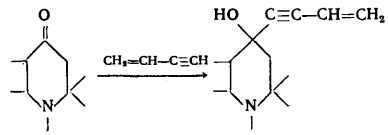


Vinylacetylene reacts with tetrahydro-4-pyrones yielding the expected vinylethynyltetrahydropyran-4-ols [27-29]:

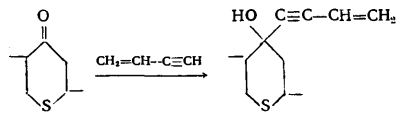


The yield of tetrahydropyranols is small. They are obtained in large yields by the reaction of vinylethynylmagnesium bromide with the corresponding tetrahydropyrones [30].

Nazarov and Raigorodskaya showed, however, that 4-piperidones behave quite differently in these reactions [31-33]. In fact, in this particular case the opposite results are obtained: vinylacetylene reacts with 4-piperidones forming high yields of vinylacetylenic piperidinols, according to the Favorskii reaction. The yields in the condensation of vinylethynylmagnesium bromide with 4-piperidones are small:

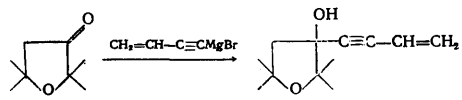


The synthesis of vinylacetylenic tetrahydrothiopyranols was carried out by Nazarov *et al.* [34], who showed that under the conditions of the Favorskii reaction vinylacetylene is capable of undergoing condensation with tetrahydro-4-thiopyrones:

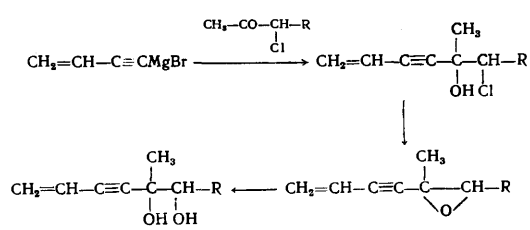


Attempts to condense vinylacetylene with tetrahydro-3--furanones in the presence of powdered potassium hydroxide were unsuccessful, apparently owing to the formation of an alkoxide from the enol form of the furanone, which inhibits further reaction. Certain furanones are known to react with the Grignard reagent only in the enol form, while in the presence of potassium hydroxide they form enolates [35].

3-Vinylethynyltetrahydrofuran-3-ol was obtained in 90% yield by reacting vinylethynylmagnesium bromide with tetrahydro-3-furanones [36]:

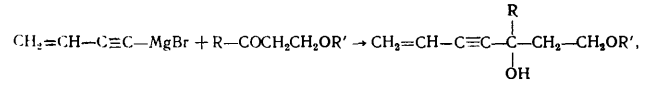


By condensing vinylacetylene with α-chloro-ketones, Perveev and Kudryashova [37,38] obtained the corresponding vinylethynylcarbinols, which, after elimination of hydrogen chloride by means of potassium hydroxide, gave vinylacetylenic epoxides. The condensation of the resulting epoxides with alcohols in the presence of sulphuric and oxalic acids gave α-alkoxy-β-hydroxyvinylacetylenic alcohols:

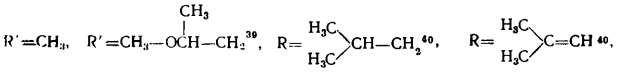


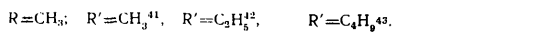
It is interesting that β-alkoxy-ketones completely fail to condense with vinylacetylene in the presence of powdered potassium hydroxide in anhydrous ether, forming instead high-molecular-weight products which cannot be distilled and are insoluble in organic solvents. Moreover, an almost theoretical amount of the alcohol corresponding to the alkoxy-group can be isolated from the ether solution, thus providing evidence that the alkoxy-group is split off during the condensation of β-alkoxy-ketones.

Synthesis of β-alkoxyvinylacetylenic alcohols was effected by reacting vinylethynylmagnesium bromide with the appropriate β-alkoxy-ketones:

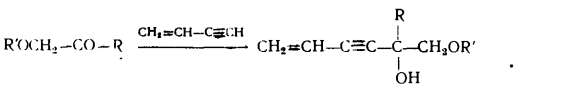


where

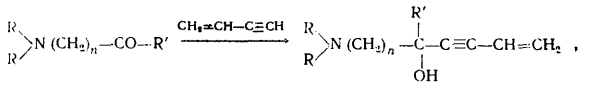




Good yields of vinylethynylcarbinols containing alkoxy--groups were thereby obtained, and their chemical reactions were studied. In contrast to β-alkoxy-ketones, α-alkoxy--ketones are readily condensed with vinylacetylene in the presence of powdered potassium hydroxide in anhydrous ether, forming α-alkoxyvinylethynylcarbinols[44,45]:

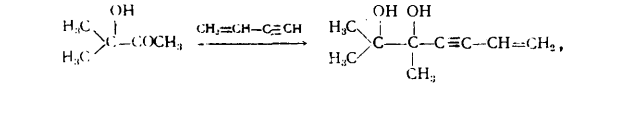


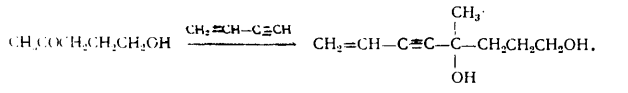
It is interesting that, under the conditions of the Favorskii reaction, amino-ketones condense with vinylacetylene, forming good yields of amino-alcohols of the vinylacetylenic series[46-48]:



where R = CH_3, C_2H_5; n = 1 or 2.

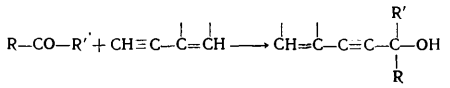
Keto-alcohols can also be condensed with vinylacetylene, forming vinylacetylenic glycols[28]:





As shown above, the synthesis of vinylacetylenic alcohols with unsubstituted vinyl groups was studied in great detail by the Nazarov school, but the synthesis of these alcohols with substituted vinyl groups has so far received little attention.

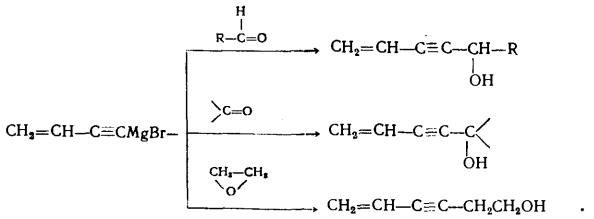
Vinylacetylenic hydrocarbons containing two substituents in the vinyl group require 48 h to condense with ketones, according to the Favorskii–Nazarov reaction, at 30°–35°. At 60°, in anhydrous benzene solution, and in the presence of powdered KOH this reaction lasts 6 h, whereas other acetylenic and vinylacetylenic hydrocarbons undergo condensation at temperatures below zero in the course of a few hours. It was also shown that these hydrocarbons are capable of reacting with ketones in the presence of powdered KOH and without a solvent. A series of vinylacetylenic alcohols with two substituents in the vinyl group were obtained in this way[49]:



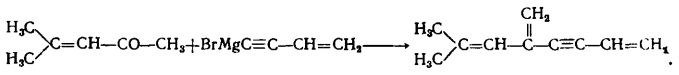
Under the conditions indicated vinylacetylene itself can be condensed with ketones to form the corresponding carbinols[49]. It is worthy of note that despite some data in the literature to the contrary[24,50], vinylacetylene undergoes condensation with ketones even in the presence of powdered NaOH without a solvent, but the reaction is slower[51].

At low temperatures and in the presence of powdered KOH aldehydes can be condensed with vinylacetylenic hydrocarbons to form secondary vinylacetylenic alcohols[49].

Before this method became available, the synthesis of primary and secondary vinylacetylenic alcohols was effected by reacting vinylethynylmagnesium bromide with the appropriate aldehydes and ketones[20,50-60]:



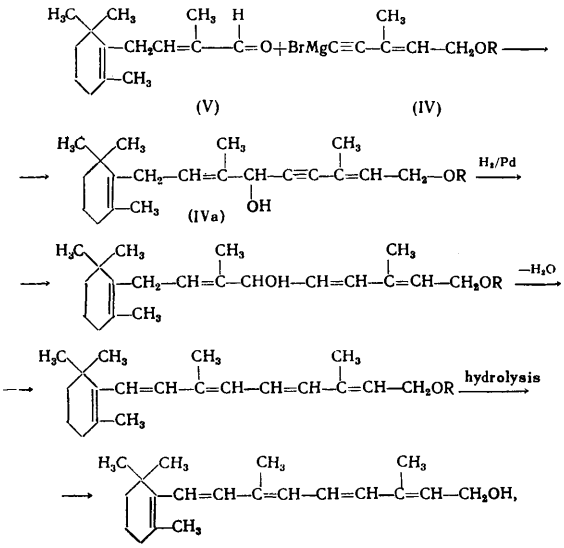
These alcohols could not, however, always be isolated, especially in the case of αβ-unsaturated ketones, since dehydration tended to proceed concomitantly with the decomposition of the Grignard complex. Nazarov and Elizarova[56] showed, for instance, that, unexpectedly, vinylethynylmagnesium bromide reacts with mesityl oxide (4-methyl-3-penten-2-one) forming the corresponding trienyne hydrocarbon:



Of great interest is the condensation of isopropenylacetylene with β-ionone leading to carotenoid compounds[53,54]. Satisfactory results were also obtained by using sodium in liquid ammonia[55], and, even better, by using tertiary potassium alkoxides; this made possible the preparation of acetylenic alcohols from unsaturated ketones, which are very sensitive to alkali.

The Grignard reagents from the vinylacetylenic alcohol (IV, R = H) or from the methyl ether derived from it (IV, R = CH_3) react with aldehyde (V)[61,62] forming the corresponding glycol and glycol monoether, respectively (IVa, R = H, CH_3). By subsequent selective hydrogenation and dehydration, accompanied by an allyl rearrangement, vitamin A methyl ether was obtained, whose hydrolysis

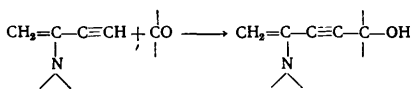
gave the alcohol identical with natural vitamin A [17,18] (in the case of the glycol the primary hydroxy-group should be converted to an ether prior to dehydration):



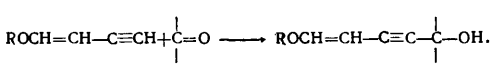
where R = H, CH_3.

It may be noted that all the above methods of preparation of acetylenic carbinols require stoichiometric ratio of the reactants, and at least an equimolar quantity of an alkali metal or one of its active compounds, with the complete exclusion of moisture. The condensation of acetylene and its monosubstituted derivatives with acetone in the presence of aqueous alkali under pressure [63] as catalyst may indeed be considered a major achievement.

Aminovinylacetylenes also condense with ketones under the above conditions, forming aminovinylacetylenic alcohols [64]:



Condensation of alcohols with diacetylene leads to alkoxyvinylacetylenes [65] which, like vinylacetylene, in the presence of alkali can be condensed with ketones to form alkoxyvinylethynylcarbinols [65]:

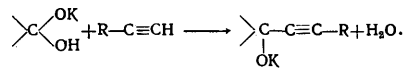


Another, basically new, method for the synthesis of acetylenic alcohols was developed by Reppe. He showed that copper and some other metal acetylides are good catalysts for the condensation of acetylene with formaldehyde in aqueous solution [66]. The reaction rate decreases with the rising molecular weight of the aldehyde. In fact, formaldehyde is the only aldehyde which reacts at a satisfactory rate. The same reaction with ketones has no special merits, since it is very slow and the greater part of the ketone remains unchanged [67].

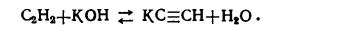
2. MECHANISM OF THE FAVORSKII REACTION

The following mechanism was put forward by Favorskii for the condensation of acetylenic hydrocarbons with ketones: potassium hydroxide unites with the ketone to form the corresponding hydroxyalkoxide; this undergoes condensation with the acetylenic hydrocarbon to form an acetylenic alcohol [68], and liberates potassium hydroxide:

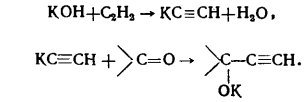
Acetylenic alcohols or glycols formed in this reaction do not pass into the ether solution. It was concluded on the strength of this that the condensation does not yield the alcohol itself, but rather the corresponding alkoxide. Consequently water, not potassium hydroxide, separates in the reaction [69].



It has recently been shown [50,70] that the solubility of acetylene in ether greatly increases on addition of powdered potassium hydroxide. The authors are right in considering that this phenomenon is connected with the formation of potassium acetylide. They carried out the condensation under an acetylene pressure of 5–10 atm in order to shift the equilibrium towards the formation of potassium acetylide:

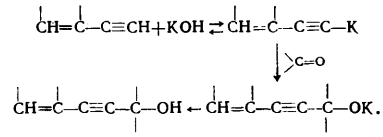


This method gave good yields of a series of secondary and tertiary acetylenic alcohols. Using kinetic methods, Korotkov and Parfenova [50] showed that the condensation of acetylene with carbonyl compounds proceeds *via* the formation of organometallic compounds. Gvertsiteli and Mikadze [71] established that acetylene passed through dry powdered potassium hydroxide is completely absorbed. They also think that potassium acetylide is thereby formed, quoting as evidence the formation from ketones of an acetylenic alcohol by the action of potassium hydroxide through which acetylene had previously been passed at a low temperature:



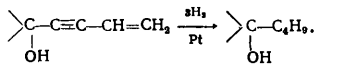
Petrov *et al.* [72] have recently shown that the Favorskii reaction can only be carried out with impure potassium hydroxide, containing traces of iron. On the strength of this, they suggested a chain mechanism for the above reaction.

On mixing 1 mole of α-ethynylcyclohexene with 2–3 moles of potassium hydroxide, the resulting reaction in a few hours yields a solid mass. Only a small amount of the added hydrocarbon can be extracted with ether, but the addition of a ketone leads to the corresponding carbinol in high yield. Apparently in this case also potassium acetylide is formed, which reacts with the carbonyl compound like a Grignard reagent [49]:

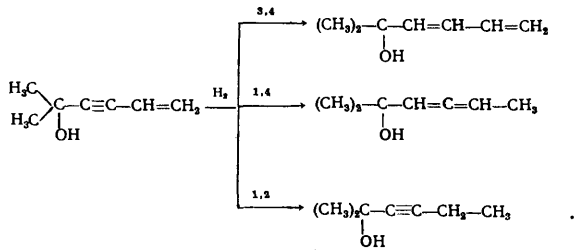


3. HYDROGENATION OF VINYLETHYNYLCARBINOLS

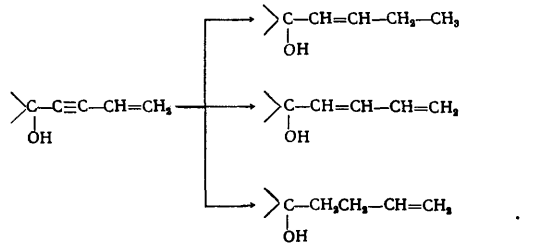
In the presence of platinum vinylethynylcarbinols are readily hydrogenated, forming the corresponding saturated alcohols[73]:



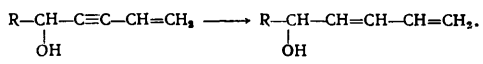
Golovchanskaya[74,75] studied the electrochemical hydrogenation of vinylacetylenic alcohols. The addition of hydrogen occurs in 1,3-, 1,4-, and 3,4-positions. This is the only case reported in the literature of the addition of hydrogen to the vinylethynyl radical in the 3,4-position:



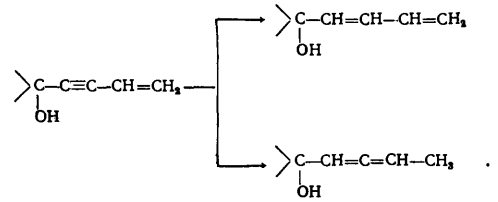
Unlike acetylenic alcohols, vinylethynylcarbinols proved incapable of selective hydrogenation in the presence of either palladium or nickel. For this reason, the addition of one molecule of hydrogen to vinylethynylcarbinols in the presence of these catalysts does not result entirely in 1,3-dienic alcohols, but in a mixture of the initial vinylethynylcarbinol with dienic and olefinic alcohols[76]:



Nazarov worked out a method for the selective hydrogenation of the triple bond to a double bond in vinylacetylenic alcohols. The hydrogenation of vinylethynylcarbinols was carried out by shaking them with a water suspension of zinc powder. This method was used for preparing 1,3-dienic alcohols. During hydrogenation with powdered zinc–copper couple increase in the radical size, R, of secondary vinylethynylcarbinols does not significantly affect the rate or the course of the reaction, which is not the case with tertiary vinylethynylcarbinols[77]:

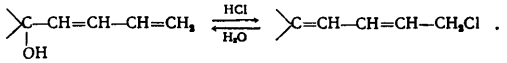


No side-products are formed during hydrogenation of vinylethynylcarbinol, but the hydrogenation rate of methylethyl-, methylpropyl-, and diethyl-vinylethynylcarbinols is slowed down considerably, and hydrogen is added to the vinylethynyl group in the 1,4-position to form the corresponding allenic alcohols[78].

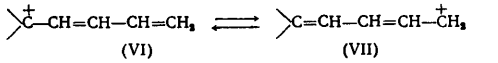


Boroda[79] showed recently that diethylvinylethynylcarbinol undergoes hydrogenation in the presence of colloidal palladium, yielding 95% of diethylbutadienylcarbinol.

1,3-Dienic alcohols are capable of undergoing a reversible anionotropic isomerisation, namely a migration of the hydroxy-group to the opposite end of the diene chain with a simultaneous shift of double bonds, resulting in the formation of a new 1,3-dienic alcohol[80,81]:



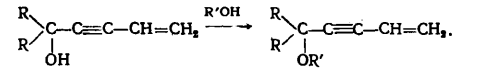
The equilibrium was found to be shifted strongly towards the formation of tertiary alcohols, whereas the opposite was the case with ethers, esters, and halogen derivatives[82-84]. This seems to be connected with the difference in the positive charge on the tertiary ion and on the isomeric primary ion.



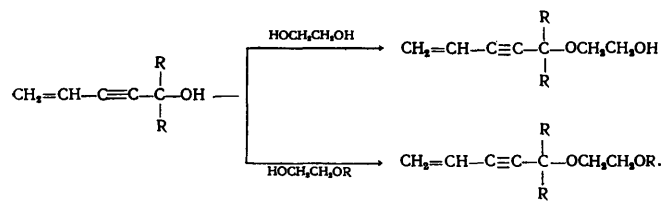
The hydroxide anion unites mainly with the carbonium ion having the tertiary structure (VI), forming tertiary alcohols, while the chloride anion, on the contrary, reacts primarily with the carbonium ion having the primary structure (VII), forming primary chlorides.

4. ETHERS AND ESTERS DERIVED FROM VINYLETHYNYLCARBINOLS

Unlike saturated carbinols, which form ethers only with difficulty, tertiary vinylethynylcarbinols readily form ethers with alcohols in the presence of mineral acids. In the presence of small amounts of sulphuric acid the reaction proceeds even in the cold, and on heating on a water-bath it is complete in a few hours[85].



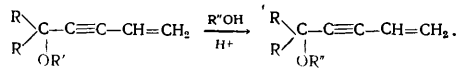
Glycols and ethylene glycol monoalkyl ethers also react with vinylethynylcarbinols in the presence of sulphuric acid to form the corresponding ethers[80-88]:



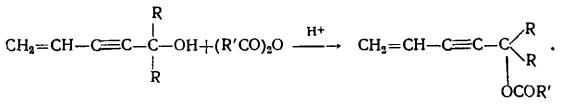
Ethers derived from primary vinylethynylcarbinols are easily obtained by the reaction of vinylethynylmagnesium bromide with α-chloromethyl ethers[89]:

$$CH_2=CH-C\equiv C-MgBr+Cl-CH_2OR \longrightarrow CH_2=CH-C\equiv C-CH_2OR.$$

On heating the resulting ethers with alcohols in the presence of sulphuric acid, a reversible alcoholysis occurs. If the alcohol radical is smaller than the radical of the ether group, alcoholysis proceeds to completion[90]:



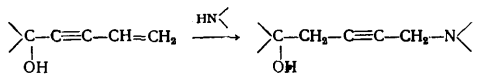
Vinylethynylcarbinols react with acid anhydrides in the presence of trace amounts of sulphuric acid[91], forming up to 80% of the corresponding esters. This reaction proceeds even without a catalyst, but is then considerably slower:



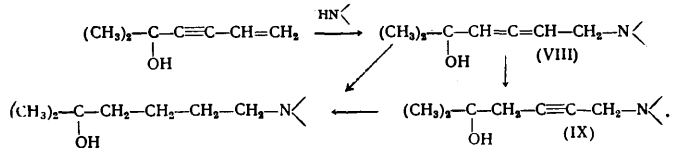
Acylation proceeds readily in the presence of zinc chloride[92]. Polymerisation studies on vinylethynylcarbinols established an interesting correlation between the structure of the starting compound and its polymerisation rate. If the hydroxy-group is esterified, the rate of polymerisation is considerably slower. For instance, esters undergo polymerisation 4–5 times more slowly than the corresponding vinylethynylcarbinols[1].

5. ADDITION OF AMINES AND SILANES TO VINYLETHYNYLCARBINOLS

In 1956 Vartanyan and Badanyan showed that vinylacetylenic alcohols react readily with aqueous solutions of appropriate amines on heating in sealed tubes and form good yields of aminoacetylenic alcohols[93-95]:

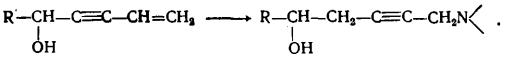


Amines combine with the vinylethynyl group in the 1,4-position; the addition proceeds through the intermediate formation of an allenic amino-alcohol (VIII), which under the effect of the excess of the amine present in the reaction mixture isomerises to the corresponding acetylenic amino-alcohol (IX):

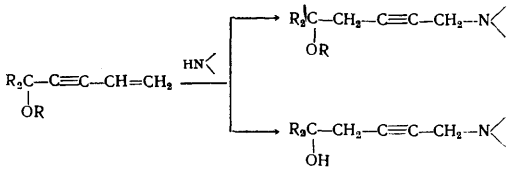


On reducing the reacting time two unsaturated amino-alcohols are obtained, which on hydrogenation yield identical amino-alcohols. Continued heating of the allenic amino--alcohol (VIII) with the aqueous amine solution leads to isomerisation and the formation of β-acetylenic amino--alcohol (IX). The structure of the amino-alcohol (IX) has been established by hydrogenation and oxidation.

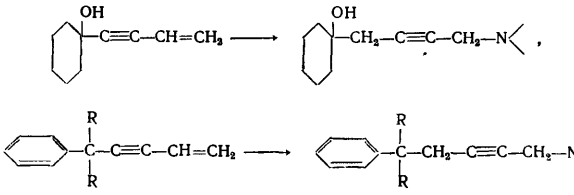
Addition of amines to secondary vinylacetylenic alcohols proceeds similarly:



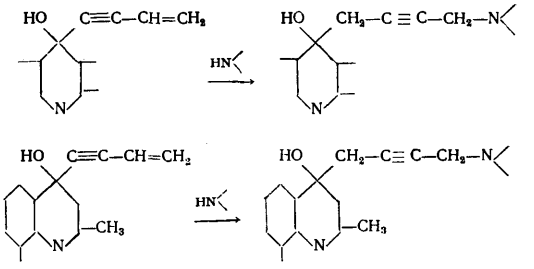
Amines react with vinylacetylenic ethers to form aminoacetylenic ethers[96]. In the case of ethers derived from tertiary vinylacetylenic alcohols, small amounts of the corresponding aminoacetylenic alcohols are obtained in addition to the main reaction product:



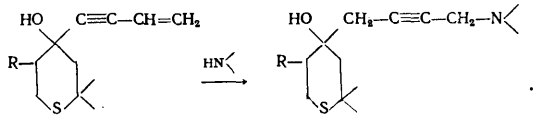
These alcohols are formed by the reaction of amines with the vinylacetylenic alcohol produced by hydrolysis of the vinylacetylenic ethers under the reaction conditions employed. Amines also add readily to secondary and tertiary vinylacetylenic alcohols, containing aliphatic, alicyclic, and aromatic radicals[93-95]:



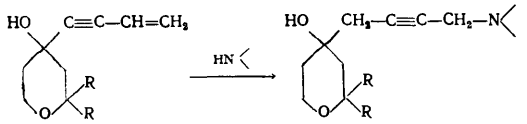
Amines can also combine with vinylacetylenic alcohols containing piperidine, tetrahydrothiopyran, and tetrahydropyran rings. For instance, the reaction of vinylacetylenic piperidin-4-ols with amines results in large yields of the corresponding acetylenic aminopiperidinols[97]:



Addition of amines to vinylacetylenic tetrahydrothiopyran-4-ols proceeds similarly and yields aminoacetylenic tetrahydrothiopyranols[98]:

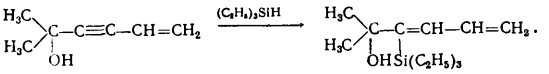


Addition of amines to 4-vinylethynyltetrahydropyran-4-ols yields the aminoacetylenic tetrahydropyranols[29].

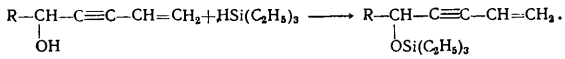


Hydrogenation of aminoacetylenic piperidinols, tetrahydrothiopyranols, and tetrahydropyranols in ethanol in the presence of a platinum catalyst gave the corresponding saturated aminopiperidinols, tetrahydropyranols, and tetrahydrothiopyranols.

It has recently been shown that triethylsilane adds to vinylethynylcarbinols in the presence of platinum and forms the corresponding dienic alcohols[98,99]:

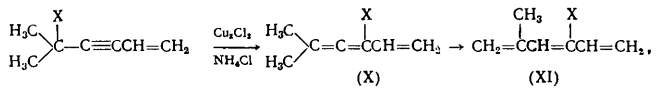


In the presence of $H_2PtCl_6.6H_2O$ this reaction takes 2 h at room temperature, and the yield of dienic alcohols is 55–63%. It proceeds differently with secondary vinylethynylcarbinols, leading to ethers instead:



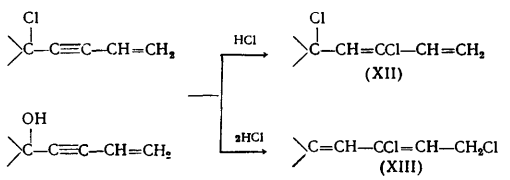
6. HYDROHALOGENATION OF VINYLETHYNYLCARBINOLS

Nazarov and Yanbikov showed that tertiary vinylethynylcarbinols can easily exchange their hydroxy-groups for halogens when acted upon by hydrogen halides[24,100]. On shaking dimethylvinylethynylchloromethane with 1% cuprous chloride and ammonium chloride at room temperature, the acetylene–allene rearrangement occurs resulting in two isomeric chlorine-containing trienes (X, XI):

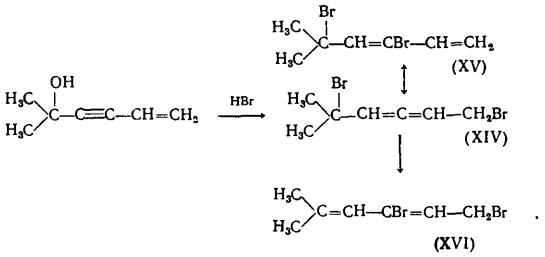


where X = Cl, Br.

Further studies showed that the addition of hydrogen chloride to the conjugated system of a double and a triple bond in tertiary vinylethynylcarbinols does not occur until the substitution of the hydroxy-group has been completed. Thus, by the action of hydrogen chloride on dimethylvinylethynylchloromethane, or by the simultaneous action of two molecules of hydrogen chloride on dimethylvinylethynylcarbinol, two isomeric dichlorides are formed, (XII) and (XIII):

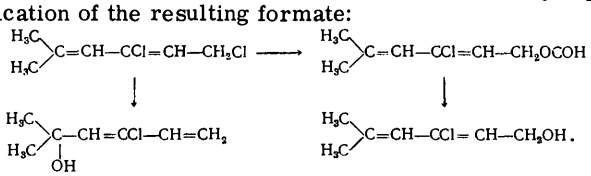


Hydrogen chloride, therefore, as in the case of vinylacetylene[101–103], is added in the 1,4-position of the vinylethynyl group in dimethylvinylethynylcarbinol. The resulting allene dichloride, which contains two mobile chlorine atoms, spontaneously undergoes isomerisation to yield a mixture of diene dichlorides (XII) and (XIII), containing only one mobile chlorine atom. The reaction of four molecules of hydrobromic acid with one molecule of dimethylvinylethynylcarbinol yields a mixture of two diene dibromides (XV) and (XVI),[104] whose structure has been established by oxidation and ozonisation:



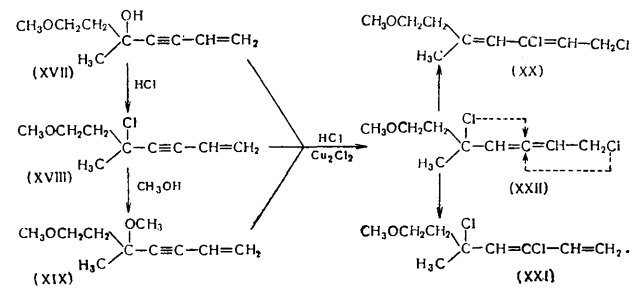
The formation of two isomeric dibromides is interpreted in the following manner: the hydroxyl is substituted by bromine by the action of an excess of hydrogen bromide; simultaneously hydrogen bromide reacts with the vinylethynyl radical in the 1,4-position forming the allene dibromide (XIV), which, since it contains two mobile bromide atoms, undergoes isomerisation to dibromides with conjugated double bonds.

Later work by Nazarov and his coworkers showed[105] that in the reaction of hydrogen chloride with dimethylvinylethynylcarbinol a dichloride containing a primary chlorine atom is formed (XIII), which on hydrolysis in an alkaline solution undergoes a complete diene rearrangement forming a tertiary chlorodiene alcohol. A primary chlorodiene alcohol can be obtained from a primary diene dichloride by treating the latter with formic acid salts followed by saponification of the resulting formate:



This proved that hydrochlorination of dimethylvinylethynylcarbinol yields only one diene dichloride with a primary chlorine atom.

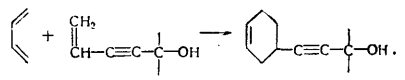
Nonetheless, by shaking methyl-β-methoxyethylvinylethynylcarbinol (XVII), and the monochloride (XVIII) and methyl ether (XIX) derived from it, with concentrated hydrochloric acid in the presence of a catalyst for 1–1.5 h, two isomeric dichlorides are obtained: 1,3-dichloro-5--methyl-7-methoxyhepta-2,4-diene (XX) and 3,5-dichloro--5-methyl-7-methoxyhepta-1,3-diene (XXI).[106] On being heated with concentrated hydrochloric acid in the presence of cuprous chloride, (XXI) is completely isomerised to the primary dichloride (XX). Under similar conditions the carbinol (XVII) undergoes hydrochlorination, forming mainly the dichloride (XX).



Clearly, the methyl ether derived from the carbinol (XIX) is split by hydrogen chloride to form methanol and the chloride (XVIII). The formation of two isomeric dichlorides (XX) and (XXI) may be accounted for by the addition of another molecule of hydrogen chloride in the 1,4-position of the chloride (XVIII), similar to the addition of hydrogen chloride to vinylacetylene. The resulting allyl dichloride (XXII) contains two mobile chlorine atoms and is immediately isomerised into a mixture of dichlorides (XX) and (XXI). Mainly the tertiary chlorine atom migrates, and the mixture chiefly contains the dichloride (XX).

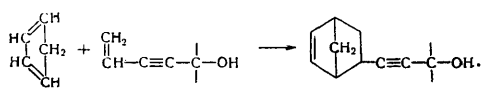
7. VINYLETHYNYLCARBINOLS IN THE DIENE SYNTHESIS

Nazarov and Nagibina[107] showed that vinylethynylcarbinols react with 1,3-dienes at 130°–160° according to the general mechanism of the diene synthesis, forming Δ^3-cyclohexenylethynylcarbinols of various structures. Only the vinyl group participates in this reaction, the triple bond and the hydroxy-group remain intact:



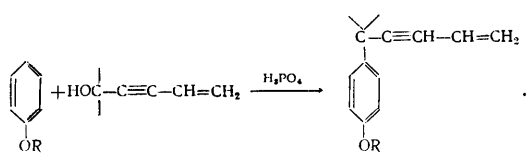
On being heated with powdered potassium hydroxide, Δ^3-cyclohexenylethynylcarbinols are quantitatively decomposed into the corresponding ketones and Δ^3-cyclohexenylacetylenes:

The diene reaction between cyclopentadiene and vinylacetylenic alcohols yields *endo*-methylene-Δ^3-cyclohexenylcarbinols:

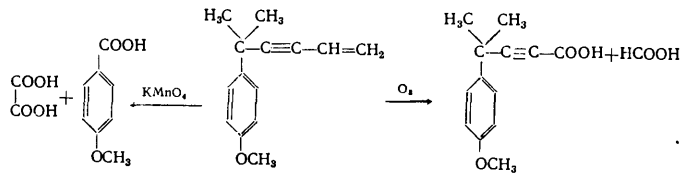


8. ALKYLATION WITH VINYLETHYNYLCARBINOLS

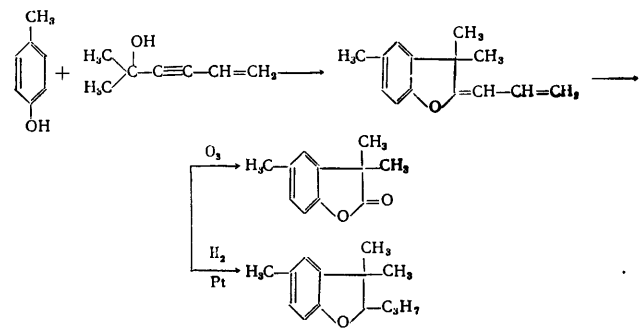
Vinylacetylenic intermediates, particularly the substituted phenols of the vinylacetylenic series, have not so far been studied much, owing to difficulties involved in their synthesis. The development of a suitable method for their preparation would be of practical as well as of theoretical interest, since by the hydrogenation of vinylacetylenic phenols a series of new substituted phenols might be obtained, with possible practical applications. Nazarov and Kuznetsova[108] were the first to show that condensation of phenol with vinylethynylcarbinols in the presence of phosphoric acid yields *p*-substituted phenols:



Condensation of anisole with dimethylvinylethynylcarbinol gave *p*-substituted anisole. The structure of these *p*-substituted phenols was established by oxidation. For instance, heating *p*-substituted anisole with an aqueous potassium permanganate solution gave anisic and oxalic acids, while its ozonisation gave *p*-methoxyphenyldimethyltetrolic acid:

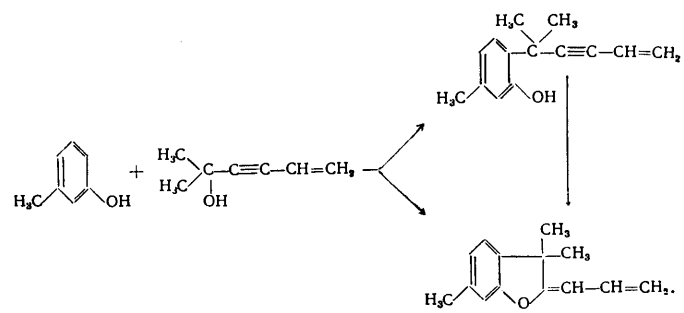


Alkylation of *p*-cresol with dimethylvinylethynylcarbinol under the same conditions proceeds much less readily, yielding instead of the expected *o*-substituted *p*-cresol, its cyclisation product 3,3,5-trimethyl-2-allylidenecoumaran[109]:



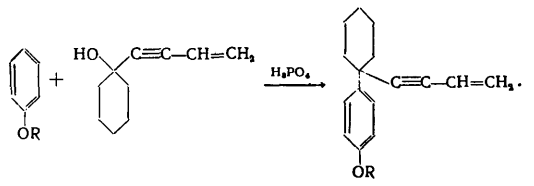
On ozonisation, this cyclic product gave 3-methyl-6-hydroxyphenyldimethylacetic acid lactone, and on hydrogenation 3,3,5-trimethyl-2-propylcoumaran was obtained. Condensation, under above conditions, of *o*-cresol and dimethylvinylethynylcarbinol yields the corresponding *p*-substituted *o*-cresol.

Condensation of dimethylvinylethynylcarbinol with *m*-cresol proceeds vigorously with the evolution of heat, yielding almost equal amounts of the *p*-substituted *m*-cresol, and its cyclisation product, 3,3,6-trimethyl-2-allylidenecoumaran[110]:

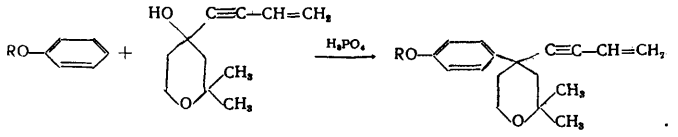


It was shown later that similar reactions occur with alicyclic vinylacetylenic alcohols. Thus, condensation of

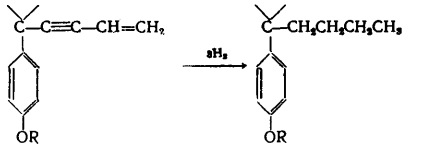
vinylethynylcyclohexanol with phenol and anisole gives high yields of the corresponding phenol derivative [111]:



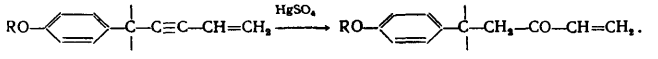
Alkylation by means of 4-vinylethynyltetrahydropyran-4-ol also proceeds according to the above mechanism, yielding the expected *p*-substituted phenol [111]:



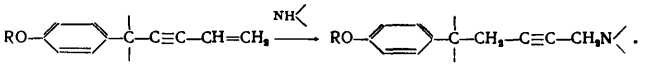
In the presence of a platinum catalyst vinylacetylenic phenols are hydrogenated to saturated *p*-alkylphenols [108,112]:



Vinylacetylenic phenols can be hydrated in an aqueous solution of methanol in the presence of small amounts of mercuric sulphate and sulphuric acid, to form the corresponding vinyl ketones in good yields [113]:

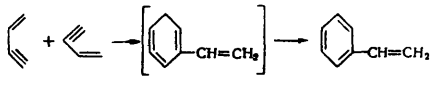


On being heated with vinylacetylenic phenols, secondary amines in aqueous solutions combine with the vinylethynyl group in the 1,4-position, forming acetylenic aminophenols [114]:



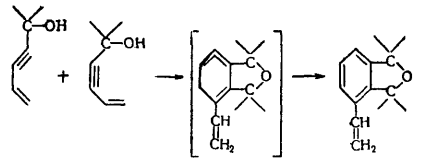
9. CONDENSATION REACTIONS OF VINYLETHYNYLCARBINOLS

Dykstra showed that, on being heated in the presence of acidic reagents (acetic, chloroacetic, malonic, and hydrochloric acids), vinylacetylene undergoes dimerisation to styrene [115]. One molecule of vinylacetylene adds in the 1,4-position to the acetylenic bond of another molecule, and the resulting allene compound isomerises under the experimental conditions to styrene:

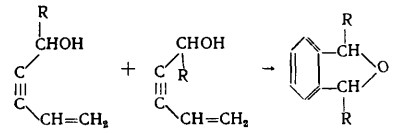


Favorskii and Zakharov showed that vinylacetylene derivatives undergo similar cyclisation on being heated in methanol solution in the presence of glacial acetic acid [116-118]. When heated in benzene in the presence of acidic reagents, or better, ferrous chloride, vinylethynylcarbinols yield a cyclic derivative, isocoumaran [119,120]. This reaction is a unique example of cyclisation by way of the dimerisation of two molecules of vinylethynylcarbinol with the elimination of water and the formation of vinylisocoumarans. This reaction is also of interest because all three functional groups of vinylethynylcarbinol participate in it.

It appears that the formation of the six-membered ring occurs first, and that it is subsequently followed by the isomerisation of the allene compound and the elimination of water:

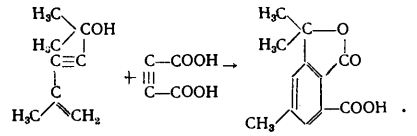


The structure of isocoumarans was established by oxidation and ozonisation. Although tertiary vinylethynylcarbinols undergo ring-closure much more rapidly than secondary ones, the latter can also be condensed to form the corresponding isocoumarans [121]:

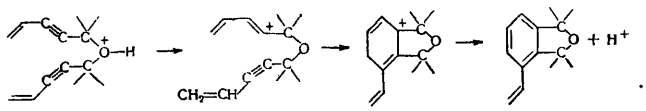


Vinylisocoumarans are colourless liquids which, on heating with benzoyl peroxide, polymerise to a transparent vitreous mass.

Johnson showed that 2,5-dimethylhex-5-en-3-yn-2-ol reacts readily with acetylenedicarboxylic acid in benzene solution and forms 3,3,5-trimethylphthalide-7-carboxylic acid [122].



Torgov and Verkholetova suggested a mechanism for this reaction [123] whereby, in the presence of $FeCl_3$, a hydroxyl is split off from the tertiary carbinol, to a carbonium ion. The carbonium ion reacts with another molecule of carbinol forming an 'onium complex. This in turn undergoes an intramolecular diene condensation and a concomitant migration, to yield an aromatic system.



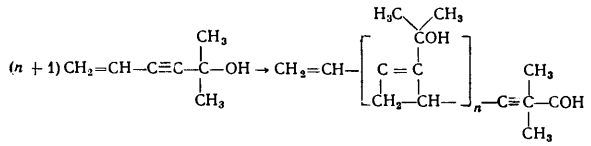
The reaction course is determined by the mobility of the hydroxyl. Vinylethynylcarbinol, where the hydroxyl is the least mobile, is incapable of undergoing ring-closure.

10. POLYMERISATION OF VINYLETHYNYLCARBINOLS

Non-stabilised vinylethynylcarbinols polymerise rapidly, and are gradually converted into a solid vitreous mass [124]. Oxygen, ozone, and peroxides catalyse the polymerisation of vinylacetylenic alcohols, the most efficient catalyst being nitric acid.

Good stabilisers of vinylethynylcarbinols are pyrogallol, hydroquinone, catechol, ammonia, α- and β-naphthylamines, diphenylamine, and agerite†. In the presence of 0.01% of any of these stabilisers vinylethynylcarbinols can be kept up to one year, and in the presence of 0.1% of stabiliser they remain unchanged for years. Tertiary vinylethynylcarbinols polymerise more rapidly than secondary ones, and the corresponding esters, as already mentioned, do so more slowly than the corresponding carbinols. Consequently, the hydroxyl displays a greater activating activity with respect to the enyne system than the alkoxy- or acetoxy-groups.

Vinylethynylcarbinols can also be copolymerised with vinyl and 1,3-diene compounds. Dimethylvinylethynylcarbinol[125] polymerises like vinylacetylene, *i.e.* by the reaction of the triple bond of one molecule and the double bond of another molecule of carbinol, to form cyclobutene rings:

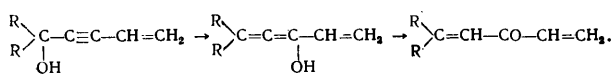


The product of partial polymerisation of dimethylvinylethynylcarbinol, well known as the "carbinol adhesive", is widely used in industry (electrical engineering, aviation, instruments) as adhesive for metals, glass, marble, china, plastics, etc. A mixture of 20–30% chloroprene and the carbinol can be used as adhesive for cementing rubber to metals and other materials mentioned above[1].

Partially polymerised dimethylvinylethynylcarbinol has a high adhesive capacity. It is obtained as a syrup by heating freshly distilled dimethylvinylethynylcarbinol for 20–25 h on a water-bath. In the presence of 0.05–0.1% of benzoyl peroxide the polymerisation time can be reduced to 5–10 h. The carbinol adhesive can be stabilised by 0.25% of agerite, which is added to the 10% solution of the monomer. The stabilised carbinol adhesive can be kept in a cool, dark place for six months. The syrup can be prepared from stabilised carbinol by heating it for 6–10 h in the presence of 0.2–0.3% of benzoyl peroxide.

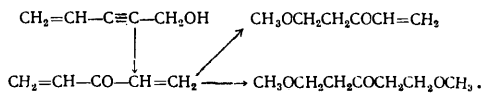
11. ISOMERISATION OF VINYLETHYNYLCARBINOLS

Nazarov first showed that, in the presence of mercuric sulphate in acetone solution, vinylethynylcarbinols isomerise to divinyl ketones[26,127]:

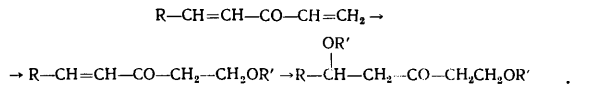


This isomerisation, however, can be readily carried out with the formation of up to 40% of the expected ketone, only in the case of dimethylvinylethynylcarbinol (R = CH_3). Other acetylenic alcohols (R = C_2H_5, C_3H_7, etc.) can only be isomerised with difficulty, and, owing to side-reactions, particularly dehydration of the carbinol, the yields are below 5%.

Further studies showed that vinylethynylcarbinols are very readily isomerised in solutions of alcohols which are capable of addition to divinyl ketones[90,117,128]. The ease of isomerisation in alcoholic media (especially methanol) is explained by the fact that alcohol adds to the resulting divinyl ketones to form alkoxy-ketones which are removed from the reaction sphere. Detailed investigations of the addition of alcohols to divinyl ketones showed that alcohols can unite with the unsubstituted vinyl group even in the absence of a catalyst[128]. Isomerisation of the primary vinylethynylcarbinol under these conditions yields 1-methoxypent-4-en-3-one and 1,5-dimethoxypentan-3-one[129]:

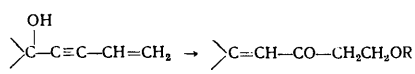


In the presence of mercury salts secondary vinylethynylcarbinols also undergo isomerisation to divinyl ketones, which readily add one molecule of alcohol to the unsubstituted vinyl group and form unsaturated alkoxy-ketones[130]:

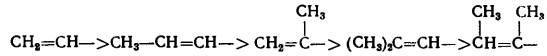


Under the influence of mercury salts (or other catalysts) the β-alkylvinyl group can combine with another molecule of alcohol, to form saturated $\beta\beta$-dialkoxy-ketones.

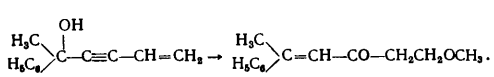
The selectivity observed in the addition of alcohols to $\beta\beta$-dialkyldivinyl ketones is even greater. Here, even in the presence of a catalyst, one molecule of alcohol usually combines with the unsubstituted vinyl group, so that isomerisation of tertiary vinylacetylenic alcohols yields the corresponding unsaturated β-alkoxy-ketones[131]:



According to the rate of addition of alcohols (as well as amines and other compounds) to $\alpha\beta$-unsaturated ketones, vinyl radicals can be arranged in the following series[131–136]:

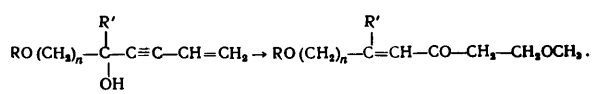


Vinylacetylenic alcohols containing aromatic radicals behave like their aliphatic or alicyclic analogues. For example, methylphenylvinylethynylcarbinol is converted into 1-methoxy-5-phenylhex-4-en-3-one[137]:



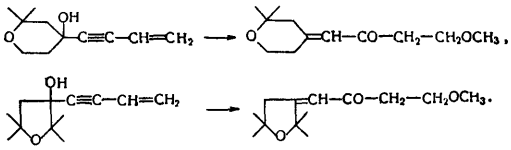
Thus isomerisation of vinylethynylcarbinols in alcohol solutions in the presence of mercury salts is a very simple and convenient method of preparation of β-alkoxy-ketones.

It has been shown that vinylacetylenic alcohols containing one or two alkoxy-groups in the α- or β-positions are also capable of being isomerised to corresponding alkoxy-ketones[39–45]:



† Agerite is *p*-hydroxyphenylbenzyl ether (Ed. of Translation)..

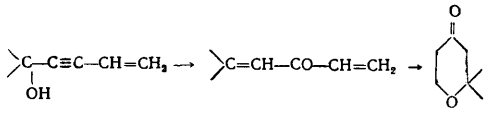
It has recently been shown that isomerisation of vinylethynylcarbinols also occurs in the case of 4-vinylethynyltetrahydropyran-4-ols[27], 3-vinylethynyltetrahydrofuran-3-ols[36], etc.



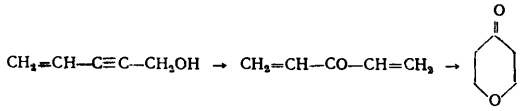
Since they are relatively simple to obtain, it was possible to study their various reactions[138]. Of special interest is the synthesis of vinyl ketones, carried out by the splitting off of the alcohol from β-alkoxy-ketones. A series of very reactive vinyl ketones were thus prepared in satisfactory yields[139,140].

12. HYDRATION OF VINYLETHYNYLCARBINOLS AND THEIR ETHERS AND ESTERS

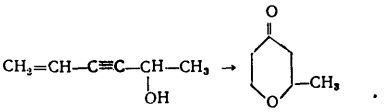
In 1943 Nazarov and his coworkers established that, on heating with dilute sulphuric acid in the presence of mercuric sulphate, vinyl ketones undergo ring-closure, forming tetrahydropyrones[127,141]. It was further shown that under the above conditions vinylethynylcarbinols are isomerised to divinyl ketones. Tetrahydro-4-pyrones can be obtained in one stage by combining the isomerisation of vinylethynylcarbinols to divinyl ketones with their hydration[142]:



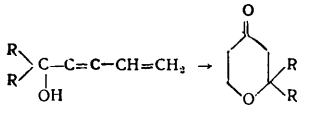
Heating the first member of this series, vinylethynylcarbinol, with dilute sulphuric acid in the presence of mercuric sulphate gave 70% of tetrahydro-4-pyrone. Isomerisation of this carbinol in anhydrous methanol yields 1,5-dimethoxypentan-3-one, which on hydrolysis forms tetrahydro-4-pyrone:



Under similar conditions methylvinylethynylcarbinol also easily undergoes isomerisation and cyclohydration[141], as do other secondary vinylethynylcarbinols or β-alkyldivinyl ketones:

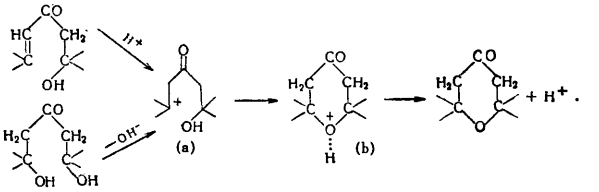


This reaction also proceeds readily with tertiary vinylethynylcarbinols, which form 2,2-dialkyltetrahydro-4-pyrones in good yields[142]:



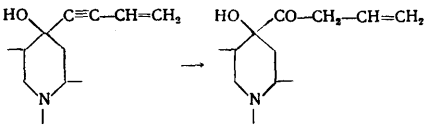
Experiments on the hydration of β-methyl-β-ethyldivinyl ketone in aqueous acetone solution have shown that the first product of hydration of divinyl ketone is an unsaturated β-keto-alcohol, formed by the addition of water to the unsubstituted vinyl group. Under the action of dilute acids the resulting unsaturated β-keto-alcohol undergoes cyclisation to 2-methyl-2-ethyltetrahydro-4-pyrone[143].

Cyclisation of αβ-unsaturated and β-hydroxy-compounds is usually induced by hydrogen ions. In neutral or alkaline media these compounds are either completely stable, or tend to undergo isomerisation in other ways. Nazarov suggested the following mechanism for the formation of tetrahydro-4-pyrones[144]:

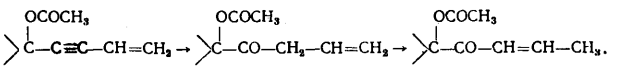


The first stage of the reaction consists of the addition of a hydrogen ion to unsaturated keto-alcohols or the scission of a hydroxide ion from the corresponding ββ-keto-glycols. This leads to the formation of a carbonium ion (a), which cyclises to an oxonium ion (b), which becomes stabilised by splitting off a proton and undergoing conversion into the corresponding tetrahydro-4-pyrone[144].

It is interesting that, in contrast to other vinylacetylenic alcohols, the vinylacetylenic alcohols containing piperidine rings do not isomerise during hydration. Instead, direct hydration of the triple bond occurs, resulting in unsaturated α-keto-alcohols[145]:



All attempts to avoid isomerisation during hydration of vinylethynylcarbinols in order to obtain α-hydroxy-ketones were unsuccessful[92,146-148]. Nevertheless, hydration of vinylethynylmethyl acetates in 75–90% acetic acid in the presence of mercuric acetate at 60°–80° results in the formation of unsaturated α-acetoxy-ketones. The keto-group assumes the α-position exclusively with respect to the acetoxy-group. The resulting dialkyl(vinylacetyl)methyl acetates undergo isomerisation to dialkylcrotonylmethyl acetates[92,146-148]:



At higher temperatures (105°) this reaction yields only the dialkylcrotonylmethyl acetates, whereas at 35°–45° the principal reaction products are dialkyl(vinylacetyl)methyl acetates. On heating (50°–60°) with a solution of *p*-toluenesulphonic acid, sulphuric acid, or with mercury or sodium acetates, the latter compounds isomerise to form dialkylcrotonylmethyl acetates.

The course of hydration of ethers derived from vinylethynylcarbinols is completely different[39]. In contrast to the reaction with esters, water reacts with the triple bond of vinylacetylenic alcohols forming β-keto-derivatives.

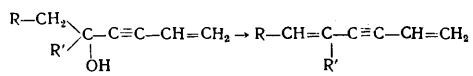
Under the conditions of the Kucherov reaction the resulting divinyl ketones undergo ring-closure, forming tetrahydro--4-pyrones[89]. In methanol solution and in the presence of mercuric sulphate the latter compounds react again, first with water and then with methanol, yielding β-methoxy--ketones[149].

In the presence of sulphuric acid the rate of hydration of ethers derived from vinylethynylcarbinols is considerably enhanced. This is interpreted using the fact that in acid media ethers are capable of forming oxonium compounds, which, on the one hand, increase the polarisability of the triple bond, and, on the other hand, hinder the binding of the catalyst (mercuric sulphate) to the ether. Consequently, methyl ethers of vinylethynylcarbinol cannot be hydrated in dioxane solution owing to the tendency of this solvent to bind acids and acid salts into oxonium compounds.

The course of hydration of the triple bond in esters, which are unable to form oxonium ions, is determined by the vinyl group, which has quite the reverse effect.

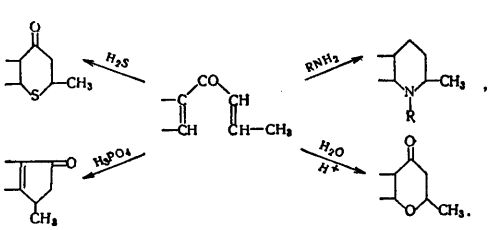
13. DEHYDRATION OF VINYLETHYNYLCARBINOLS

Vinylethynylcarbinols can be readily dehydrated by the usual methods to form the corresponding hydrocarbons of the divinylacetylene series[124]:



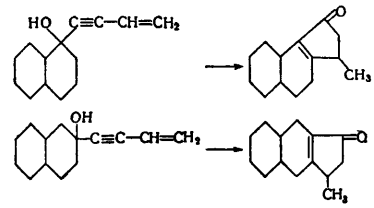
Dehydration is often carried out with 50% sulphuric acid or by distillation over powdered potassium bisulphate. The hydration of divinylacetylenic hydrocarbons in aqueous methanol solution in the presence of mercuric acetate yields divinyl ketones[141,150], which under the action of ammonia and primary amines undergo cyclisation to 4-piperidones[151,152]. These compounds are important in the synthesis of physiologically active products. One of the methylpiperidin-4-ols, called "promedol"‡, has recently found practical use as a morphine substitute[2].

Under the action of hydrogen sulphide, divinyl ketones undergo cyclisation, forming 4-thiopyrones[153-155], while their hydration in the presence of mercuric sulphate yields tetrahydro-4-pyrones[142]. On being heated with phosphoric, formic, and other acids, divinyl ketones can be converted into corresponding cyclopentenones[156]:

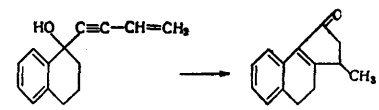


14. CYCLOHYDRATION OF VINYLETHYNYLCARBINOLS

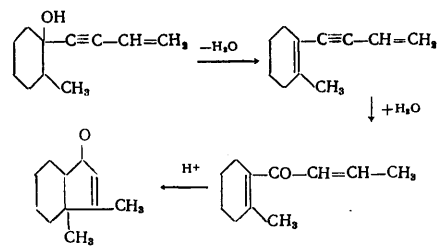
The cyclohydration of vinylethynylcarbinols in the presence of phosphoric acid, resulting in the formation of cyclopentenones, has already been mentioned. Nazarov and Burmistrova showed that, with phosphoric acid at 60°-70°, α- and β-vinylethynyldecalols undergo ring-closure, yielding the corresponding polycyclic ketones[156,157]:



1-Vinylethynyltetral-1-ols similarly gave 3-methyl-4,5--dihydro-6,7-benzoindanone[156]:



Nazarov and Pinkina showed that, on being heated with phosphoric acid, 2-methyl-1-vinylethynylcyclohexanol undergoes cyclohydration, forming 1,8-dimethyl-Δ^1-hexahydro-3-indenone. The same compound was also obtained by dehydration of 2-methyl-1-vinylethynylcyclohexanol to the corresponding dienyne compound, which was subsequently hydrated to form a dienone, and cyclised[158]:



This new type of cyclohydration of vinylethynylcarbinols makes it possible to obtain readily polycyclic ketones containing angular groups, which are normally very difficult to prepare. This is important in the synthesis of steroid compounds.

It is clear from this review that vinylethynylcarbinols are being widely used in a great variety of synthetic processes, and have started a fascinating new chapter of organic chemistry. They are versatile starting materials in the synthesis of complex organic compounds and a series of invaluable products.

‡ 1,2,5-trimethyl-4-phenyl-4-propionoxypiperidine hydrochloride (Ed. of Translation).

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THE REACTIVITY OF ACETALS AND IONIC TELOMERISATION

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1. INTRODUCTION

Acetals are extremely reactive compounds, and have found increasing use during recent years as starting materials in various syntheses. Among the many methods for preparing acetals, an important current technique is their formation from unsaturated ethers based on acetylene and diacetylene. Thus acetals are obtained by the addition of alcohols to unsaturated ethers[1-13]:

$$CH{\equiv}CH \xrightarrow{ROH} CH_2{=}CH{-}OR \xrightarrow{ROH} CH_3{-}CH(OR)_2,$$

$$CH{\equiv}C{-}C{\equiv}CH \xrightarrow{ROH} CH{\equiv}C{-}CH{=}CH{-}OR \xrightarrow{ROH} CH_3{-}C{\equiv}C{-}CH(OR)_2,$$

or by the addition of orthoformic esters[14-16]:

$$CH_2{=}CH{-}OR + CH(OR)_3 \rightarrow (RO)_2CH{-}CH_2{-}CH(OR)_2,$$

$$CH{\equiv}C{-}C{\equiv}CH \rightarrow BrMg{-}C{\equiv}C{-}C{\equiv}C{-}MgBr \xrightarrow{CH(OR)_3} (RO)_2CH{-}C{\equiv}C{-}C{\equiv}C{-}CH(OR)_2,$$

$$CH{\equiv}C{-}CH{=}CH{-}OR \rightarrow BrMg{-}C{\equiv}C{-}CH{=}CH{-}OR \xrightarrow{CH(OR)_3} \rightarrow (RO)_2CH{-}C{\equiv}C{-}CH{=}CH{-}OR$$

$$CH{\equiv}C{-}CH{=}CH{-}SR \rightarrow BrMg{-}C{\equiv}C{-}CH{=}CH{-}SR \xrightarrow{CH(OR)_3} \rightarrow (RO)_2CH{-}C{\equiv}C{-}CH{=}CH{-}SR.$$

In this way various acetals, alkoxyacetals, and diacetals, containing alkoxy-, alkylthio-, or arylthio-groups, and perhaps also double and triple bonds in the carbon skeleton, can be synthesised from vinyl ethers, ethynylvinyl ethers, and sulphides based on acetylene and diacetylene, and also from diacetylene itself.

A great deal of work has recently appeared in the chemical literature on the synthesis of various polyene and polyenyne compounds (for example isoprenoids). Acetals are often employed as starting materials in these syntheses. Furthermore, acetals are able to undergo ionic telomerisation with vinyl ethers and sulphides (this constitutes a new trend in the use of these compounds). Since new unsaturated compounds containing an acetal group are beginning to be employed in these interesting syntheses, it seemed to us profitable to summarise the disconnected experimental results available on this question.

The present review will deal mainly with new or little known reactions of acetals, which are from our point of view the most promising and are of interest for the chemistry of acetals in general.

Acetals can react differently, depending on their structure and the reaction conditions, the carbonyl group, substituents, or multiple bonds being involved in the reaction. Acetals are characterised by many chemical reactions, including hydrolysis, symmetrisation, hydrogenation, condensation, etc., which have been described by various workers[1,10-13,18-28].

2. NON-CATALYTIC AND IONIC REACTIONS OF ACETALS

Non-catalytic reactions of acetals are readily explained in terms of hydrogen bonding[29], the role of which in the formation of acetals has been discussed by Shostakovskii[1,12]. This hypothesis was later supported by optical measurements[30]. A hydrogen bond formed between the oxygen atom of the vinyl ether and the alcoholic hydrogen produces an intermediate compound[30], which can dissociate reversibly under certain temperature conditions, yielding molecules of vinyl ethers and of alcohols containing different radicals. Interaction between vinyl ether and alcohol molecules containing identical radicals results in the formation of symmetrical acetals. Thus the reaction mixture contains all possible acetals.

$$CH_2{=}CH{-}OR + R'OH \rightleftarrows CH_2{=}CH{-}OR \rightleftarrows CH_3{-}CH\begin{matrix}OR\\OR'\end{matrix},$$
$$\vdots$$
$$H{-}O{-}R'$$

$$CH_3{-}CH\begin{matrix}OR\\OR'\end{matrix} \rightleftarrows CH_2{=}CH{-}OR' \rightleftarrows CH_2{=}CH{-}OR' + ROH.$$
$$\vdots$$
$$H{-}O{-}R$$

This concept explains the mechanism of such reactions as the non-catalytic formation of acetals from vinyl ethers and alcohols on heating, and the trans-etherification of mixed into symmetrical acetals on distillation. The thermal decomposition of acetals into vinyl ethers and alcohols, which is often used for preparative purposes[1], must be regarded as a reaction of this type.

Similarly, pyrolysis of an acetaldehyde monothioacetal involves its decomposition with the elimination of an

alcohol molecule and formation of 2-butoxyethyl vinyl sulphide[31]:

$$CH_3-CH\begin{matrix}OC_4H_9\\SCH_2CH_2OC_4H_9\end{matrix} \xrightarrow{\Delta} CH_2=CH-SCH_2CH_2OC_4H_9 + C_4H_9OH.$$

It is interesting that in this case it is the alkoxy- and not the alkylthio-radical of the acetal which is eliminated, indicating the greater lability of the former. Most reactions of acetals, however, take place in the presence of catalysts and by an ionic mechanism.

Among ionic reactions involving exchange of alkoxy--groups in acetals, those with aldehydes and ketones have been described[32]. A redistribution of alkoxy-groups takes place, the reaction being reversible. The reactions of acetals of acetaldehyde with butyraldehyde, benzaldehyde, furfuraldehyde, cyclohexanone, and acetophenone, for example, can be represented by the scheme

$$R-CHO + CH_3-CH(OC_4H_9)_2 \rightleftarrows R-CH(OC_4H_9)_2 + CH_3CHO,$$
$$(R)_2CO + CH_3-CH(OC_4H_9)_2 \rightleftarrows (R)_2C(OC_4H_9)_2 + CH_3CHO.$$

Reactions of acetals of another type are those in which the hydrogen atoms of the aldehyde take part. In an investigation of hydrogen exchange between the diphenyl acetal of acetaldehyde and liquid deuterated ammonia (ND_3) with KND_2 as catalyst[33] it was found that one of the five hydrogen atoms exchanged for deuterium comes from the aldehyde part of the acetal, and in our opinion from the methine group, since hydrolysis of this acetal yielded acetaldehyde containing a deuterium atom attached directly to the carbonyl group[34]:

$$CH_3-CD(OC_6H_3D_2)_2 \rightarrow CH_3-CDO.$$

Hence under certain conditions the methine hydrogen in the diphenyl acetal of acetaldehyde is reactive in solution in liquid deuterated ammonia, which possesses well defined basic properties. It is interesting that exchange does not take place in the dibutyl acetal under these conditions.

When the dibutyl acetal reacts with phenyl vinyl ether in the presence of the boron trifluoride–ether complex, the reaction products include the dibutyl acetal of 3-phenoxybutyraldehyde. This fact does not exclude the possibility that the reaction takes place by exchange of a 2-hydrogen atom of the acetal[34]:

$$\overset{2}{CH_3}-\overset{1}{CH}(OC_4H_9)_2 + CH_2=CH-OC_6H_5 \rightarrow CH_3-\overset{3}{CH}(OC_6H_5)-\overset{2}{CH_2}-\overset{1}{CH}(OC_4H_9)_2$$
$$CH_3-CH(\downarrow OC_6H_5)-CH_2-CHO .$$

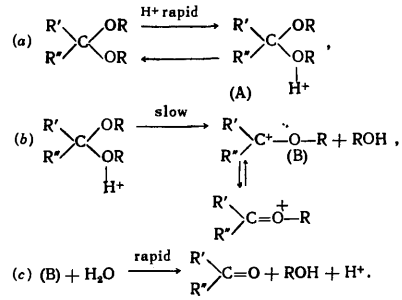
Hydrolysis of acetals is among the most typical ionic reactions of these compounds, on which a great amount of work has been done. This reaction takes place in acid medium and yields the aldehyde and the alcohol[1]:

$$R-CH(OR')_2 + 2H_2O \rightarrow RCHO + 2R'OH.$$

Various acidic reagents are employed for the hydrolysis, depending on the structure of the acetals: oxalic[35], tartaric[36,37] citric[38], benzenesulphonic[39], perchloric[40], trifluoroacetic[41], and acetic[42,43] acids, boron trifluoride[44], and also ion-exchange resins[45].

Investigation of the influence of various conditions and factors on the rate of hydrolysis of acetals has shown that those containing alkyl radicals are readily hydrolysed in the cold, but the rate falls with increase in their molecular weight. This reaction is greatly influenced by polarity, conjugation[47], and steric effects[46]. Kreevoy and Taft[47] studied the rate of hydrolysis of various acetals and ketals in aqueous dioxane at 25°, and found that with acetals of $\alpha\beta$-unsaturated aldehydes conjugation is the main factor in preventing hydrolysis. This is confirmed with acetals of aldehydes containing an enyne grouping, obtained from diacetylene. These acetals and their alkoxy--derivatives are not hydrolysed under normal conditions.

The mechanism of the hydrolysis of acetals in acid medium has now been quite fully investigated, and can be represented by the scheme[48]



In the first stage (*a*) an ether oxygen atom undergoes cationic attack, resulting in the formation of an "oxonium cation" (A), which decomposes slowly into a cation (B) and an alcohol. Stage (*b*) determines the rate of hydrolysis. In the following stage (*c*) the cation (B) is converted *via* the hemiacetal into the final carbonyl compound.

The thermal decomposition of acetals to form a vinyl ether and an alcohol often takes place considerably more readily and more rapidly in the presence of a catalyst. Many investigators[49-53] have studied this reaction with the aim of developing the most effective method for synthesising various vinyl ethers and alkoxybutadienes. The catalysts used for these purposes were sulphates and phosphates of sodium, magnesium, and aluminium, activated charcoal, clay, $BaO.SiO_2$, etc.

Elimination of an alcohol from acetals may take place both in the vapour and in the liquid phase. Makin and Kruptsov[53] worked out a method for synthesising alkoxybutadienes by vapour-phase and liquid-phase methods in the presence of salts of phosphoric acid:

$$CH_2(\overset{|}{OR})-CH-CH(OR)_2 \xrightarrow{-2ROH} CH=C-C=CH-OR.$$
$$R' \quad R'' \; R'''$$

A new and interesting reaction of acetals is their dimerisation and trimerisation, studied by Yufit and Kucherov[44,54-56] with acetals of saturated and unsaturated aldehydes. Dimerisation of the former takes place in the presence of boron trifluoride or zinc chloride and involves the elimination of an alcohol molecule. Thus the diethyl acetal of acetaldehyde dimerises into 1,1,3-triethoxybutane, which was isolated in up to 50% yield:

$$2CH_3-CH(OC_2H_5)_2 \rightarrow CH_3-CH(OC_2H_5)-CH_2-CH(OC_2H_5)_2 + C_2H_5OH.$$

In the case of the interaction of the acetals of two different aldehydes dimerisation also involves a 2-hydrogen atom of one of the acetals, resembling in this

respect the scheme for the reaction of acetals with vinyl ethers:

$$R{-}CH(OC_2H_5)_2+R{-}CH_2{-}CH(OC_2H_5)_2 \rightarrow R{-}CH(OC_2H_5){-}CH(R){-}CH(OC_2H_5)_2+C_2H_5OH.$$

The dimerisation products readily split off alcohol molecules to form unsaturated compounds.

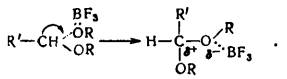
In the opinion of these workers[44], the dimerisation and trimerisation of acetals of $\alpha\beta$-unsaturated aldehydes involves a double bond conjugated with the acetal group and sufficiently active to add on a second and a third molecule of the same acetal:

$$2R{-}CH{=}CH{-}CH(OR)_2 \rightarrow R{-}CH{=}CH{-}\underset{\displaystyle OR}{\underset{|}{CH}}{-}\overset{\displaystyle R{-}CH{-}OR}{\overset{|}{CH}}{-}CH(OR)_2.$$

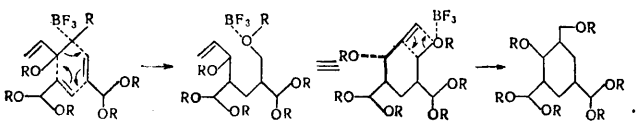
Thus the diethyl acetal of crotonaldehyde readily dimerises under the influence of boron trifluoride, but that of acrolein reacts with greater difficulty, the main product being the trimer.

Yufit and Kucherov[54-56] found that their results for the dimerisation of acetals of $\alpha\beta$-unsaturated aldehydes could not be explained by a mechanism based on the intermediate formation of a carbonium ion. In the low-temperature dimerisation of acrolein acetal under the influence of BF_3 they detected the formation of a cyclic trimer in addition to the normal dimer and a linear trimer. They consider that the classical ionic views of the mechanism of addition and substitution reactions of acetals are not always entirely satisfactory, and that such reactions can be explained in a different way, by cyclic electron transfer[57,58].

Addition of BF_3 to an oxygen atom in the acetal group *via* a lone pair of electrons destroys the electronic symmetry of the group, producing strong polarisation of the C–O bond. This polarisation is intensified by the presence of a double bond in the $\alpha\beta$-position, and can easily be involved, through cyclic electron transfer, in addition and substitution reactions:



The formation of a cyclic trimer in the reaction is explained by the formation of a quasiaromatic complex containing six electrons in the field of six nuclei, this being subsequently stabilised to yield the trimer:



3. EXCHANGE OF ALKOXY-GROUPS IN ACETALS

The most widely known reactions of acetals, which enable them to be used as starting materials in various syntheses, are those involving the exchange of alkoxy-groups. First of all there is the well known Chichibabin reaction[59], which consists in the exchange of an alkoxy-group for the hydrocarbon radical of an organomagnesium complex, to yield the corresponding ether:

$$CH_3{-}CH(OR)_2+BrMgR' \rightarrow CH_3{-}CHR'{-}OR.$$

This reaction has now been extended to many acetals[60,61], and several peculiarities have been found depending on the structure of the radical. In mixed acetals, for example, the heavier alkoxyl exchanges more readily, while in symmetrical acetals the capacity of the alkoxy-groups for exchange decreases in the following sequence:

$$OC_6H_5>OAlK>OCH_2C_6H_5.$$

If the alkoxy-groups of the acetal contain halogen, this is exchanged for the radical of an organomagnesium complex on reaction with the latter. Thus a bis-2-chloroethyl acetal with benzylmagnesium chloride yielded the bis-3-phenylpropyl acetal[62]:

$$CH_3{-}CH(OCH_2CH_2Cl)_2+2C_6H_5CH_2MgCl \rightarrow CH_3{-}CH(OCH_2CH_2CH_2C_6H_5)_2+2MgCl_2.$$

When acetals react with alcohols containing radicals other than those in the acetal, interchange of the radicals takes place[63]:

$$R{-}CH(OR')_2+R''OH \rightleftarrows RCH\begin{matrix}OR'\\OR''\end{matrix} \longrightarrow R{-}CH(OR'')_2.$$

This reaction forms the basis of a well-known method for synthesising various mixed and symmetrical acetals[64]. Mkhitaryan[65] carried out this reaction with pentaerythritol, which under the influence of catalytic amounts of *p*-toluenesulphonic acid reacts with acetals of various aldehydes to form cyclic acetals:

$$2R{-}CH(OR')_2+\begin{matrix}HOCH_2\\HOCH_2\end{matrix}\!\!>\!C\!<\!\begin{matrix}CH_2OH\\CH_2OH\end{matrix} \longrightarrow R{-}CH\begin{matrix}OCH_2\\OCH_2\end{matrix}\!\!>\!C\!<\!\begin{matrix}CH_2O\\CH_2O\end{matrix}\!\!>\!CH{-}R+4R'OH.$$

An interesting reaction is that of acetals with thionyl chloride and phosphorus pentachloride: the alkoxy-group of the acetal is exchanged for halogen, yielding chlorinated alkoxyalkanes. Thus Skoldinov and Protopopova[66] were the first to obtain 1,3-dialkoxy-1,3-dichloropropanes from acetals of malonaldehyde. These are very reactive compounds readily forming a series of derivatives:

$$(RO)_2CH{-}CH_2{-}CH(OR)_2 \xrightarrow{SOCl_2;\ PCl_5} RO{-}CHCl{-}CH_2{-}CHCl{-}OR.$$

We have used this reaction to synthesise alkyl and aryl 1-chloroethyl ethers from the corresponding acetals of acetaldehyde:

$$CH_3{-}CH(OR)_2 \xrightarrow{SOCl_2} CH_3{-}CHCl{-}OR.$$

This reaction goes smoothly when equimolar quantities, for example of the dibutyl acetal of acetaldehyde and of thionyl chloride, are mixed in the presence of catalytic amounts of pyridine at 70°–80°, and results in the formation of the butyl 1-chloroethyl ether, isolated in 72% of theoretical yield.

With alkoxyacetals of the type $RO{\cdot}CH{:}CH{\cdot}C{\vdots}C{\cdot}CH(OR)_2$, based on diacetylene, however, it proved impossible to carry out this reaction under the above conditions. It is probable that here, as in the hydrolysis of these compounds, conjugation in the carbon chain greatly influences the mobility of the alkoxy-groups.

Arnold and Šorm[67-69] have described the formylation of acetals by treating them with dimethylformamide and carbonyl chloride:

$$R{-}CH(OC_2H_5)_2 \xrightarrow[COCl_2]{(CH_3)_2NCHO} [(CH_3)_2N{-}CH{=}\underset{\displaystyle R}{\underset{|}{C}}{-}CH{=}N(CH_3)_2]^+Cl^- \rightarrow$$

$$\rightarrow (CH_3)_2N{-}CH{=}\underset{\displaystyle R}{\underset{|}{C}}{-}CHO \longrightarrow CHO{-}\underset{\displaystyle R}{\underset{|}{CH}}{-}CHO.$$

They carried out this reaction also with vinyl ethers, 1-chloroalkyl ethers, and ketals[68], and used it to synthesise various aliphatic alkylidenedialdehydes. If acetals

of crotonaldehyde are subjected to formylation under these conditions, it is possible to synthesise nicotinic aldehyde[69]:

$$CH_3-CH=CH-CH(OC_2H_5)_2 \xrightarrow[(CH_3)_2NCHO]{-C_2H_5OH} [CH_3=CH-CH=CH-OC_2H_5] \rightarrow$$

$$\rightarrow (CH_3)_2N-CH=CH-CH=CH-CHO.$$

In this case, as also when the acetal of 3-ethoxybutyraldehyde was used as starting material, the reaction involved the intermediate formation of 1-ethoxybuta-1,3-diene.

In this type of exchange reactions can be included the reaction of acetals with alkane- and arene-thiols, which we have recently studied[8,15,70] and which gives a good yield of mercaptals:

$$R-CH(OR')_2+2AlkSH \rightarrow R-CH(SAlk)_2+2R'OH,$$

where $R=CH_3$, $CH_3-C\equiv C$, $CH_3CH(OC_4H_9)-CH_2$; $R'=C_2H_5$, C_4H_9;

$$RX-CH=CH-C\equiv C-CH(OR')_2+R'SH \rightarrow (R'S)_2-CH-CH_2-C\equiv C-CH(SR')_2,$$

where $RX=C_2H_5S$, C_4H_9O; $R'=C_2H_5$.

This reaction can be extended to ketals and orthoformic esters, and a method for synthesising various mercaptals, mercaptols, and thioorthoformic esters was worked out on its basis[71]:

$$\begin{matrix} R \\ R' \end{matrix}\!\!>\!C(OR'')_2+AlkSH \longrightarrow \begin{matrix} R \\ R' \end{matrix}\!\!>\!C(SAlk)_2+2R''OH,$$

$$CH(OR)_3+AlkSH \longrightarrow CH(SAlk)_3+3ROH.$$

Reaction takes place on slight warming in the absence of catalysts. However, it proved difficult to prepare dimercaptals containing aromatic radicals by this method, and in both cases (I) and (II) the reaction stopped at the formation of the mixed mercaptals, probably owing to the low reactivity of the alkoxy-group in the mixed mercaptal under these conditions:

$$CH_3-CH(OAr)_2 \xrightarrow{AlkSH} CH_3-CH\begin{matrix} OAr \\ SAlk \end{matrix}, \quad (I)$$

$$CH_3-CH(OArk)_2 \xrightarrow{ArSH} CH_3-CH\begin{matrix} OAlk \\ SAr \end{matrix}. \quad (II)$$

4. REACTIONS OF ACETALS WITH VINYL ETHERS AND IONIC TELOMERISATION

This type of exchange reaction can be taken to include the interesting and promising reactions of acetals with various vinyl compounds. Among such reactions are those of acetals with vinyl ethers[34,72-77], with 1- and 2-substituted vinyl ethers[78-80], 1-alkoxybut-1-en-3-ynes[81], 1-ethoxyalka-1,3-dienes[22], and vinyl sulphides[23]. The reaction with vinyl ethers was carried out not only with acetals of aliphatic aldehydes but also with those of aromatic aldehydes[24-26,73], dialdehydes[27,78], alkoxyaldehydes, and alkyl(aryl)thio-aldehydes[23] containing a pentenyne carbon chain.

Reactions of acetals with vinyl ethers have become more and more widespread during recent years as a result of the search for new ways of building up carbon chains in the molecules of various unsaturated compounds. For example, reactions of acetals with vinyl ethers are widely employed in the synthesis of isoprenoid chains[73]. Isler and others[75,76] used this method to synthesise β-carotene from β-ionone as starting material. These papers have been discussed in detail in Yanovskaya's reviews[28,82] of the various methods for building up carbon chains, and therefore we shall consider only the later work which is of interest from the point of view of ionic telomerisation.

A thorough study of the condensation of acetals with vinyl ethers was first made by Hoaglin and Hirsh[72], who suggested two possible ways in which this reaction could occur:

$$CH_3-CH(OR)_2+CH_2=CH-OR' \begin{cases} \rightarrow CH_3-CH(OR)-CH_2-CH\begin{matrix} OR \\ OR' \end{matrix} & (I) \\ \rightarrow CH_3-CH(OR')-CH_2-CH(OR)_2. & (II) \end{cases}$$

With ethyl vinyl and butenyl ethyl ethers as examples, they showed that this reaction takes place according to pathway (I).

Later work with acetals and vinyl ethers containing alkyl radicals confirmed the correctness of this scheme. If, however, vinyl ethers containing radicals differing in structure from those in the acetals, for example aryl radicals, are subjected to this reaction, a mixture of substances is obtained, among which are found compounds indicating that the reaction may occur according to pathway (II), *i.e.* by splitting off a 2-hydrogen atom of the acetal. Thus in the reaction of dibutyl acetal with phenyl vinyl ether in the presence of BF_3 we were able[34] to isolate from the reaction mixture 1,1-dibutoxy-3-phenoxybutane, which gave on hydrolysis 3-phenoxybutyraldehyde.

Vinyl ethers interact differently with acetals containing unlike radicals, depending on the reactivity of the ethers and the nature of the aldehydes forming the acetals. Moreover, mixtures are formed in this case also, the separation of which is very difficult, and is aggravated by symmetrisation of the mixed acetals.

The addition of vinyl ethers to acetals is an electrophilic ionic reaction involving the intermediate formation of a complex of the acetal with BF_3, $ZnCl_2$,[72] or $FeCl_3$, decomposition of which liberates a carbonium ion $CH_3\cdot\overset{+}{C}H\cdot OR$ and an alkoxy-group as an anion, which add on to the double bond of the vinyl ether[72].

Study of the conditions and products of reactions between acetals and vinyl ethers showed that reaction does not stop at the addition of one molecule of the ether to the original acetal, the resulting alkoxyacetal adding on the next molecule of vinyl ether, and so on, until various polyalkoxy-alkanes, -alkenes, or -alkenynes have been formed, so that this reaction can be regarded as a telomerisation taking place by an ionic mechanism. The authors of these papers[23,34,72,74] were able, by carrying out this reaction in the presence of various catalysts (BF_3, $ZnCl_2$, $FeCl_3$), to isolate telomeric products of the general formula

$$CH_3-CH(OR)-[-CH_2-CH(OR)-]_n-CH_2-CH(OR)_2,$$

the proportions of which depend on those of the original ether and acetal, and also on the rates of the subsequent stages in the reaction, *i.e.* on the addition of a vinyl ether molecule to the polymeric products.

Telomerisation reactions are now being studied on a broad front, but this applies mainly to radical telomerisation, investigated with various unsaturated hydrocarbons[83,84], sulphur-containing compounds[85], some vinyl esters[86], and ethers with CCl_4,[87-89] and also vinyl ethers in the presence of various radical initiators[90-93].

Investigations of ionic telomerisation have been concerned also mainly with diene hydrocarbons in the presence of $SnCl_4$[94,95].

Little has been published on the ionic telomerisation of oxygen-containing compounds.

Heslinga[96] investigated the ionic telomerisation of styrene with formaldehyde in acetic acid, the reaction being catalysed by concentrated sulphuric acid at room temperature.

Reaction between formaldehyde and styrene under the influence of sulphuric acid was first achieved by Prins[97]. He isolated an equimolar addition product, and assumed it was 2-phenyl-1,3-propanediol, which later workers found to be erroneous. Subsequently it was found[98] that this reaction is telomeric in character, and a fraction containing dimeric acetates of aromatic $\alpha\omega$-glycols having the structure

$$HO-[-CH(C_6H_5)-CH_2-]_n-CH_2OH\ ,$$

was isolated. The same paper describes the ionic telomerisation of styrene with acetic acid and with acetonitrile, esters containing 1–3 styrene molecules, $H[CH_2\cdot CH(C_6H_5)]_n\cdot O\cdot CO\cdot CH_3$, being isolated in the first case, and acyl derivatives of primary amines, identified as $H[CH_2\cdot CH(C_6H_5)]_n\cdot NH_2$, in the second case.

Heslinga[96] studied the effect of varying the conditions of the Prins reaction on the composition of the final products, investigated quantitative aspects of the reaction, and isolated telomers of the general formula

$$CH_3CO-[-CH(C_6H_5)-CH_2-]_n-CH_2OH.$$

He discusses in detail the mechanism of this reaction, and considers that it involves the intermediate formation of a carbonium ion, $C_6H_5\cdot\overset{+}{C}H\cdot CH_2\cdot CH_2OH$, by the interaction of protonated formaldehyde with styrene. This ion adds on a second, etc. styrene molecule, or else terminates chain growth by adding on an acetate ion:

$$CH_2{=}CH(C_6H_5) \xrightarrow{CH_3OH} \overset{+}{C}H(C_6H_5)-CH_2-CH_2OH \xrightarrow{nC_6H_5-CH=CH_2} -[-\overset{+}{C}H(C_6H_5)-CH_2-]_n-CH_2OH \xrightarrow{AcOH}$$

$$AcO-[-CH(C_6H_5)-CH_2-]_n-CH_2OH+H^+.$$

Apart from the above investigations we may mention here a Japanese patent[99] describing the preparation of vinyl polyalkoxyacetals from vinyl ethers in the presence of mixed catalysts, for example $(CH_3COO)_2Hg$ or HgO with BF_3 complexes. From methyl vinyl and ethyl vinyl ethers, they obtained a mixture of products of the general formula $CH_2{:}CH\cdot[CH_2\cdot CH(OR)]_n\cdot CH_2\cdot CH(OR)_2$, from which they isolated compounds having carbon chains up to C_8.

5. IONIC TELOMERISATION REACTIONS OF ALKOXY-ACETALS AND ALKYLTHIOACETALS WITH VINYL ETHERS AND SULPHIDES

Quite recently we have investigated the ionic telomerisation occurring when alkoxyacetals and alkylthioacetals react with vinyl ethers and sulphides in the presence of $ZnCl_2$.[23] In the case of the alkyl vinyl ethers the reaction can be represented by the scheme

$$(C_2H_5O)_2CH-C\equiv C-CH=CH-OR \xrightarrow{CH_2=CH-OC_2H_5} (C_2H_5O)_2CH-$$
$$(SR)$$

$$-[-CH_2-CH(OC_2H_5)-]_n-C\equiv C-CH=CH-OR\ .$$
$$(SR)$$

This reaction leads to the formation of a mixture of telomeric products containing C_{15} and longer carbon chains.

In contrast to the reaction of vinyl ethers with acetals of acetaldehyde, the first molecule of the ether adds on more slowly than subsequent molecules, which is probably due to a decrease in activity of the alkoxy-groups in the initial acetal under the influence of the neighbouring triple bond. This may well explain the more ready formation of higher telomerisation products. In the interaction of ethyl vinyl ether with the butoxyacetal an addition product containing one molecule of the ether and a C_7 carbon chain was isolated, as well as a C_{15} product containing five molecules of the vinyl ether. Of the addition products of the vinyl ether to the ethylthio-acetal, those containing one and three molecules of the vinyl ether, with C_7 and C_{11} carbon chains respectively, were isolated.

The use of vinyl sulphides in this reaction represents the first example of the participation of these compounds in ionic telomerisation. Before the present investigation the addition of ethyl vinyl sulphide to the diethyl mercaptal of acetaldehyde in the presence of the ether complex of BF_3 had been described[100]. Under the reaction conditions employed, however, the reaction did not occur telomerically, but stopped at the equimolar addition of the starting materials, addition of a second molecule of the vinyl sulphide being effected by taking the equimolar addition product as starting material.

Reaction of vinyl sulphides with alkylthio-acetals containing a pentenyne grouping, which we have investigated[23], yields a mixture of telomeric products and occurs according to the scheme

$$RS-CH=CH-C\equiv C-CH(OR)_2 \xrightarrow{CH_2=CH-SR}$$

$$RSCH=CHC\equiv C-CH(OR)CH_2CH\begin{matrix}OR\\SR\end{matrix} \longrightarrow RSCH=CHC\equiv CCH(OR)CH_2CH\begin{matrix}(SR)_2\\(OR)_2\end{matrix}$$

$$\xrightarrow{CH_2=CH-SR}$$

$$RS-CH=CH-C\equiv C-CH(OR)-[-CH_2-CH(SR)]_n-CH_2-CH\begin{matrix}OR\\SR\end{matrix}$$

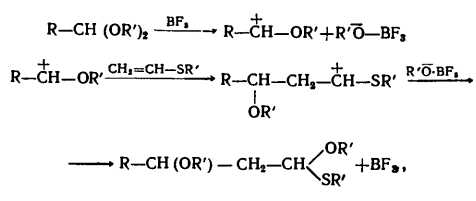
$$RS-CH=CH-C\equiv C-CH(OR)-[-CH_2-CH(SR)-]_n-CH_2-CH\begin{matrix}(SR)_2\\(OR)_2\end{matrix},$$

where $R = C_2H_5$ and $n = 1$ or 2.

Apart from extending the carbon skeleton of unsaturated acetals, this reaction makes it possible to introduce alkylthio-radicals into their molecules, yielding compounds containing sulphur (2 substituent groups).

In the early stages the mechanism of the successive addition of the vinyl sulphide to the unsaturated alkylthio-acetals is probably similar to that of the addition of vinyl ethers to acetals of acetaldehyde, and consists in the splitting off, under the influence of the catalyst, of an alkoxy-group of the acetal as an anion followed by addition of this anion and the resulting cation at the double bond of the vinyl sulphide. The mixed mercaptal which is thus formed reacts in a similar manner with the next vinyl sulphide molecule, and so on, the ion responsible for the subsequent process being the complex cation $RS\cdot CH{:}CH\cdot C{:}C\cdot CH(OR)\cdot[CH_2\cdot CH(SR)]_n\cdot CH_2\cdot\overset{+}{C}H\cdot SR$. The reaction can be terminated by symmetrisation of the

mixed mercaptals, as was proved by the quantitative "mercuric chloride" titration of the telomer end-groups:



where R = $C_2H_5 \cdot S \cdot CH{:}CH \cdot C{:}C-$.

These reactions enabled us to synthesise various polyalkoxy-acetals and polyalkylthio-acetals containing a C_{15} carbon chain, and also alkoxy-mercaptals having a C_{11} chain with a conjugated system of double and triple bonds.

The ionic telomerisation of oxygen- and sulphur--containing unsaturated compounds is a promising field in the chemistry of high polymers. Apart from their intrinsic value for synthetic purposes, the resulting products can serve as models for studying the structure of the end-groups of macromolecular compounds, in particular the polymers of vinyl ethers and sulphides. This is very important also in studying the ionic polymerisation and copolymerisation of many ethers[101-103], for example aryl vinyl ethers, when polymers of low molecular weight whose structure has not yet been adequately elucidated, are obtained.

This investigation of the chemical properties of various unsaturated alkoxy- and alkylthio-acetals, synthesised on the basis of diacetylene, has shown that these compounds are very reactive. Their interaction with vinyl ethers and sulphides under the influence of ionic catalysts results in telomerisation with the formation of various polyalkoxy (or alkylthio)-alkenynes, which are telomeric products having acetal or mercaptal end-groups.

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XYLAN

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1. INTRODUCTION

Xylan is the chief polysaccharide among the hemicelluloses of cereals and many other plant raw materials. Increasing attention has been paid during recent years to the investigation of its structure and properties, and the results obtained have considerably extended our knowledge of the hemicelluloses[1,2].

TABLE. Content of pentosans in plant material.

Raw material	Pentosans, %
Pine[11]	11.0
Fir[11]	12.8
Straw of winter wheat[11]	21.61
Maize stalks[11]	31.50
Seed capsules of wheat grain[12]	35.65
Oat husks[13]	29.40
Barley husks[14]	23.85

The study of xylan is of interest from several points of view, since it forms the structural material of cell walls[3,4], and can be used for the preparation of xylose, xylitol, and other polyhydric alcohols, organic acids, nutrient yeasts, and other products[5,6].

Xylan can be used in the foodstuffs, perfumery, and pharmaceutical industries as a thickening, an emulsifier, and a stabiliser. It can be added to printing inks and paper compositions, and employed in the sizing of textiles and for other purposes[7,8].

The presence of xylan affects the properties of the products resulting from the processing of grain[9] and wood[10].

Various plant materials serve as a source of xylan. Large amounts are contained in the husks, seed capsules, and stems of cereals, and smaller amounts in wood. The xylan content is proportional to the quantity of pentosans indicated in the Table.

2. ISOLATION AND PURIFICATION OF XYLAN

Xylan is obtained in two ways: (1) by removing as much lignin as possible from plant tissue, and subsequently extracting the xylan with dilute alkali from the holocellulose which is formed; and (2) by extracting the hemicelluloses from the raw material with dilute alkali and subsequently precipitating xylan from the latter.

Several methods can be employed for the delignification of the raw material. Zherebov and Paleev treated plant tissue with chlorine, and then extracted the chlorolignin with organic bases[15]. Ritter and Kurth[16] acted on the raw material alternately with chlorine and a mixture of alcohol and pyridine. Later the pyridine was replaced by an alcoholic solution of aminoethyl alcohol[17]. A method was also employed for removing lignin from wood powder by treating it with a solution of chlorine dioxide and sodium sulphite[18,19]. This method has been employed widely[20]. Sodium chlorite[21-24] and acetyl hydroperoxide[25] have been proposed for the delignification of the raw material.

The isolation of hemicelluloses from holocellulose has been studied in several investigations. Jayme and his coworkers employed extraction with 10% caustic soda solution for this purpose. According to Rogovin (Ref. 10, p. 148), the polysaccharide complex dissolves best in 8% caustic soda. The hemicelluloses from the holocellulose of maize stems[26], the stalks of wheat straw[27], bran, and oat husks[28] can be fractionated by dissolving them in alkalis, cuprammonium solution, and dimethyl sulphoxide[29]. Mitchell and Ritter separated the hemicelluloses of the sugar maple into four main fractions according to solubility by successively treating the holocellulose with hot water for 1 h, cold 2% sodium carbonate solution for 48 h, cold 4% caustic soda and hot 1% caustic soda for 1 h[30]. A similar method[31] was used to extract the hemicelluloses of aspen holocellulose.

Several investigators assume[32-38] that no degradation of the hemicelluloses occurs in the preparation of the holocellulose. This is improbable in view of the high degree of branching of the xylan macromolecule and the presence of readily hydrolysable arabinofuranose residues in the side-chains.

Actually, the hemicelluloses isolated by different methods differ in degree of polymerisation. Timell and Jahn[40] observed a decrease in the degree of polymerisation of polysaccharides in the chlorite delignification of birch wood, and Jayme and Hanke[41] found simple sugars, decomposition products of the hemicellulose, in the chlorite extract after delignification. The decomposition of polysaccharides in the production of holocellulose has also been noted in several other papers[42,43].

The method of alkaline extraction has long been used to isolate hemicelluloses directly from plant tissue[44-51]. Thus Allen and Tollens isolated hemicelluloses from straw by treating it first with aqueous ammonia and then with caustic soda solution and precipitating the polysaccharides from solution with ethyl alcohol. This method has been used widely[52-57].

The concentration of the alkali solutions used for the extraction varies from 2 to 16%,[58] the yield of hemicellulose increasing with increase in this concentration[59]. The hemicelluloses can be fractionated by using different concentrations of alkali. Schmidt[60] divides xylan into "readily soluble" and "difficultly soluble". McDonald[61] used a two-stage alkaline extraction, and showed that very dilute alkalis (0.01–0.1 *N*) extract mainly lignin from the raw material, while more concentrated alkalis remove mainly hemicelluloses.

The polysaccharides undergo little degradation during alkaline extraction[39,62], their molecular weight remaining practically unchanged even when they are heated at 100° for 3 h.[63]

The extract contains other hemicelluloses and several impurities as well as the xylan. The xylan is purified by precipitation either by adjusting the pH, for example, to 3.4–4.2 for xylan from maize stems[64], or with alcohols, acetone[65], inorganic salts (for example ammonium sulphate[66-68], copper chloride[69], sulphate[70], or acetate, or Fehling's solution[71]), or the copper–ethylenediamine complex[72].

Polysaccharides containing carboxyl groups have been precipitated from hemicelluloses by acetyltrimethylammonium bromide[73] and by barium hydroxide solution[74].

A combined method has also been suggested, in which, after extraction of straw with 8% caustic soda solution, neutralisation, and precipitation with methyl alcohol, the hemicelluloses are treated with a solution of chlorine dioxide containing a little pyridine[75].

3. STRUCTURE OF XYLAN

Xylose is formed by the hydrolysis of pentans[76], and this monosaccharide in fact forms the main chain of xylan.

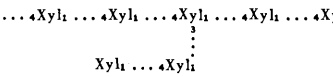
Several xylans are found in plant tissue. Whistler divides them into two types[5], (1) the glycoside type containing D-glucuronic acid, and (2) xylans not containing residues of this acid.

Srivastava[4] distinguishes five types of xylans: (1) true xylans, (2) arabinoxylans, (3) glucuronoxylans, (4) arabinoglucuronoxylans, and (5) complex xylans.

The true xylans, built up solely of D-xylopyranose residues, including the xylans of esparto grass[77,78] and of seaweed (*Rhodymenia palmata*)[79].

The hydrolysis products of esparto xylan have been found to include D-xylose and a small amount of L-arabinose; hydrolysis of the methylated polysaccharide yielded 2,3-di-*O*-methyl-D-xylose and 2,3,5-tri-*O*-methyl-L-arabinose in the proportions 20 : 1. A solution of this xylan shows a negative specific rotation, indicating the presence of β-linkages between the units.

The following formula has been suggested for esparto xylan[80]:



The arrangement of a small quantity of easily removable L-arabinose residues in the xylan macromolecule remained obscure. It was suggested that arabinose forms the end-grouping $Ara_1...{}_4Xyl_1...{}_4Xyl_1...$, but the variability in the number of its residues in the molecule and the dependence of the number on the degree of purification of the xylan suggested that the arabinose is combined with the xylan chain not by a main chemical bond but by forces of association, and is a contaminant.

The presence in the chain of 1,4-linked β-xylopyranose residues proved to be general, and typical of the structure of the main chain of xylans from a wide variety of vegetable sources.

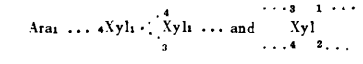
Using methylation and hydrolysis, Whistler and Tu[81] obtained from maize stem xylan a series of oligosaccharides, ranging from xylobiose to xyloheptaose, with the same link between the pyranose units of xylose. They are characterised by the following formula:

$$Xyl_1.[{}_4Xyl_1]_n.{}_4Xyl,$$

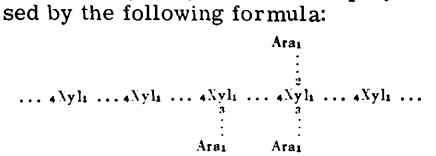
where $n = 0-5$.

In the second group of xylans we can include arabinoxylan, the main polysaccharide of the hemicelluloses in grains of the grass family.

Wheat flour xylan extracted with water comprises 63% xylose and 37% arabinose[82]. On methylation, followed by hydrolysis and chromatography, it gave equal quantities of 2,3,5-tri-*O*-methyl-L-arabinofuranose and 2,3-di-*O*-methyl-D-xylose together with 2-*O*-methyl-D-xylose and free D-xylose, which indicates that the monosaccharide units are linked as follows:



Arabinose units are readily split off from the main chain of the xylan on mild hydrolysis, and this polysaccharide is characterised by the following formula:



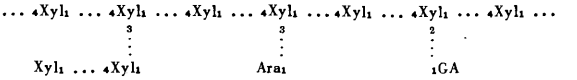
Montgomery and Smith investigated the water-soluble xylans of wheat flour[83,84] and of the seed endosperm, and established the presence of 59% of xylose, 39% of arabinose, and 2% of glucose in the strongly ramified molecule. Considerable branching is characteristic also of the arabinoxylan of barley flour, in the molecule of which the L-arabinofuranose residues add on at the 3 and 2 positions to the xylopyranose units of the main chain[85], as well as of the arabinoxylan of rye flour[86].

The discovery in vegetable materials of molecules built up of xylose and arabinose led to reinvestigation of esparto grass xylan, the fractions obtained during its purification being studied[87]. The esparto xylan was found to be a mixture of two substances, one built up solely of xylose residues, and the other of xylose and arabinose units. The existence of several xylans is probable also with other plant tissues, and their isolation depends on fractionation methods.

The third type of xylan comprises glucuronoxylans built up of D-xylose and D-glucuronic acid or 4-*O*-methyl-D-glucuronic acid units. They include the xylan of beech[88], birch[89], fir[90], peapods[91], and wheat straw[92].

Several investigations have been made of the structure of straw xylan. Aspinall and Mahomed[92] treated wheat straw xylan with 70% ethyl alcohol to remove araban, and showed by methylation and hydrolysis that the xylan is built up of 1,4-linked xylose units and glucuronic acid residues linked to one of every 40–45 xylose units.

Wheat straw xylan was found[93] to contain not only glucuronic acid residues but also arabinose, and to have the structure

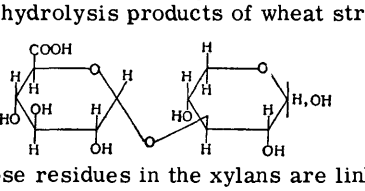


After the same xylan had been purified by reprecipitation of its copper complex, Ehrenthal[94] found xylose, arabinose, and glucose in it.

The variation in the results is probably due to the non-homogeneity of the xylans[80] present in the original plant tissue, which differ in the nature of the side-chains. It is probable that, depending on the method of purification, different kinds of macromolecules can be isolated from the same type of raw material.

The fourth type of xylan includes the arabinoglucuronoxylans, which yield on hydrolysis D-xylose, L-arabinose, D-glucuronic acid, and/or 4-*O*-methyl-D-glucuronic acid. This type of polysaccharide includes one of the xylans of wheat straw, and the xylans of oat and barley straw, maize stalks, and the husks of oats, millet, and barley[95,96].

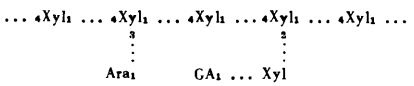
In the arabinoglucuronoxylan molecules the glucuronic acid is directly linked to a xylose unit. This was shown after it had been found that the glycosidic bond linking the uronic acid with the pentose is stable to hydrolysis, and an aldobiuronic acid of the following structure had been isolated from the hydrolysis products of wheat straw xylan:



The arabinose residues in the xylans are linked mainly with the third carbon atom of the xylopyranose unit, as was found by enzymic hydrolysis of the xylans[97]. The enzyme

of *Myrothecium verrucaria* effects selective hydrolysis of a $Xyl_1...{}_4Xyl$ bond and does not hydrolyse an $Ara_1...{}_3Xyl$ bond. Its use made it possible to isolate a series of oligosaccharides built up from arabinoxylose units linked by the latter bond.

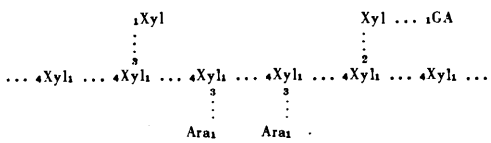
Investigation of the xylans of oat and barley straw[98] showed that their macromolecules are constructed similarly to the xylan of wheat straw:



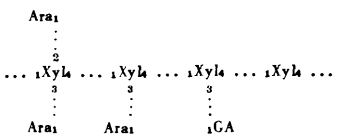
The macromolecule of these xylans is built up of β-D--xylopyranose units, and each unit gives two side branches in positions 2 and 3. Part of the glucuronic acid is present in the form of 4-*O*-methylglucuronic acid.

The xylan isolated from barley husks[99] is built up from xylose and arabinose units in the proportions 6 : 1 with a small amount (4%) of glucuronic acid. Mild hydrolysis splits off 2-*O*-D-xylopyranosyl-L-arabinose from the macromolecule, and after methylation and hydrolysis the products are found to include, among other carbohydrates, 3,5-di-*O*-methyl-L-arabinose and 3-*O*-methyl-2-*O*-(2,3,4--tri-*O*-methylglucuronopyranosyl)-D-xylose.

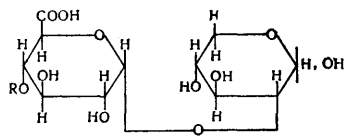
Aspinall and Ferrier give the following structure for the xylan of barley husks:



The xylan of the husks of oats and millet has been shown to have a macromolecule containing the following type of unit[95,96]:



Acid hydrolysis of the arabinoglucuronoxylan of maize stalks yielded three aldobiuronic acids: 2-*O*-α-D-glucuronosyl-D-xylose,



2-*O*-(4-*O*-methyl-α-D-glucuronosyl)-D-xylose, and 4-*O*--α-D-glucuronosyl-D-xylose, and also an aldotriuronic acid[100,101].

Among the neutral oligosaccharides obtained by the partial degradation of xylan, of xylooligosaccharides ranging from xylobiose to xyloheptaose have been isolated[102,103], including 2-*O*-α-*D*-xylosyl-L-arabinose[104]. Hence it follows that the xylan from maize stems has a strongly branched macromolecule. Its main chain is made up of 1,4-linked D-xylose units, while the side-chains consist of D-glucuronic and 4-*O*-methyl-D-glucuronic acids and L-arabinose.

Some fractions of alfalfa hemicelluloses contain considerable quantities of xylose, appreciable amounts of uronic acid, and a small amount of arabinose. Sugar-cane fibres have yielded a hemicellulose fraction containing xylose, arabinose, and glucuronic acid. One of the fractions isolated from the hemicellulose of maize stalks has been shown to contain glucuronic acid, arabinose, and xylose in the proportions 2 : 7 : 19.

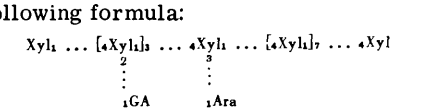
The category of complex xylans comprises polysaccharides having a complex ramified molecular structure and in several cases containing not only uronic acids but also neutral sugars. Srivastava includes among them the xylans from the seed capsules of wheat, maize, the species of pine *Pinus taeda*, fir, flax, and algae.

Analysis of the xylan from the seed capsules of wheat showed the presence of xylose, arabinose, and glucuronic acid[45,105,106]. Hydrolysis of the methylated xylan[107-109] yielded methyl derivatives of L-arabinose, D-xylose, D-galactose, and aldodiuronic acids, containing glucuronic acid.

Mild hydrolysis of the xylan yielded a series of acidic and neutral polysaccharides, including 2-*O*-α-D-glucuronosyl-D-xylose, L-galactosyl-D-xylosyl-L-arabinose, 3-*O*-α-D-xylosyl-L-arabinose[110,111], 5-*O*-D-galactosyl-L--arabinose, and several other polysaccharides[112] showing considerable ramification of the macromolecule, the main chain of which was made up of 1,4-linked xylopyranose units and branches containing arabinose, galactose, and glucuronic acid units. Nevertheless, Adams[106] considers that the xylan from wheat capsules is constructed solely from arabinose, xylose, and uronic acid, and should be included rather among the arabinoglucuronoxylans. The quantity of arabinose reaches 50%.

It was shown in 1953 [113] that the xylan of maize capsules comprises 48% of xylose, 35% of arabinose, 7% of galactose, and 10% of uronic acids. Subsequently *O*-α-D-xylopyranosyl-(1→4)-*O*-D-xylopyranosyl-(1→2)-L-arabinose was obtained, in addition to xylose and arabinose, by the incomplete hydrolysis of this polysaccharide[114]. The structure of the aldobiuronic acids obtained has also been investigated[115].

A glucomannan and a glucuronoxylan have been obtained[116] by the fractionation of the hemicelluloses of western hemlock (*Tsuga heterophylla*); study of the methylated xylan led to the following formula:



A glucuronoxylan and a glucomannan have been isolated from the wood of the black Virginian pine (*Pinus taeda*).[117] Several polysaccharides of this class have been isolated from other kinds of wood[118,119] and from flax.

The xylans from seaweed are characterised by 1→3 in addition to 1→4 xylopyranose links. Thus the xylan of red seaweed (*Rhodymenia palmata*) contains 80% of 1→4 links and 20% of 1→3 links between the β-D-xylopyranose units[79]. Later it was established that only 1→3 links are present in the xylan of green seaweeds.

The degree of homogeneity of the xylans present in the hemicelluloses from the same type of plant material has been inadequately studied. According to some results[80,87], the xylan of esparto grass is a mixture of two xylans differing in their basic unit. It is possible[95,96], by successive extraction with an alkaline solution, to isolate from the husks of oat grains a glucuronoarabinoxylan, an arabinoxylan, and a glucuronoxylan, while from those of millet a glucuronoarabinoxylan can be obtained.

Some investigators [121,122] consider, on the basis of electrophoretic work, that the xylans of wood and of barley straw are homogeneous. It has been established [123], by electrophoresis with periodate oxidation and coloration of the resulting xylan fractions with Schiff's reagent (fuchsin–sulphurous acid solution), that the xylans of the husks of oat, barley, and millet grains are non-homogeneous, differing in the number of fractions and their mobility in the electric field. The results of many investigations make it evident that the macromolecules of the xylans both from Spermatophyta (seed-bearing plants) and from Thallophyta (algae) are comparatively small, being in most cases branched and non-uniform in composition and in the structure of the unit.

The main unbranched chain of xylan is constructed from 1,4-linked β-D-xylopyranose units. The xylans from algae form an exception, containing 1→3 links either along or together with the former type.

The composition and structure of the branched portion of the xylan macromolecules are different for different types of plant material. The side-chains are comparatively short, being made up of one or more monosaccharides (L-arabinose, D-glucuronic, and 4-*O*-methyl-D-glucuronic acids, and D-galactose) in various combinations and proportions.

Hemicelluloses from the same type of raw material may contain xylans differing in the structural unit of the macromolecule. Their isolation depends on the degree of purification and the extent of fractionation of the polysaccharides.

4. PROPERTIES OF XYLAN

Purified xylans are amorphous white substances which are readily soluble in alkalis and cuprammonium hydroxide solution, soluble in hot water, and insoluble in alcohols, ethers, and other organic solvents. Solutions of xylans have a negative specific rotation [32,57,97,124]. When dried slowly, xylan loses moisture and is converted into a dense, horny mass.

Xylans are very hygroscopic compared with cellulose. Konkin [125] found the sorption of water vapour by straw xylan to be characterised by sigmoid isotherms with a hysteresis effect, like that in the corresponding isotherms for cellulose. He determined the integral heat of wetting of xylan with water to be 31.0 cal g^{-1}. Konkin considers that the intensity of intermolecular interaction in xylan is less than in cellulose but greater than in galactan or in agar-agar.

The infra-red spectra of xylan showed the predominance of absorption in the region of 3400 cm^{-1}, which is characteristic of an unstable type of hydrogen bond [126,127]. The proportion of hydroxyl groups involved in the formation of the more stable hydrogen bonds is far smaller in xylan than in cellulose. The X-ray diffraction photographs of straw xylan showed a low degree of ordering of its molecules and a marked difference from cellulose. Apparently, xylan does not crystallise. Partly hydrolysed xylan, having lost the arabinofuranose residues, acquires the ability to crystallise after being heated with water [128]. Its degree of polymerisation varies from 55 for oat straw xylan to 185 for rice straw. Oligosaccharides obtained by further decomposition of xylans crystallise well [129].

Jundt [130,131] obtained microcrystals of partly hydrolysed xylans isolated from barley straw and birchwood and purified by precipitation from alkaline solution with Fehling's solution. The crystals gave typical X-ray diffraction patterns, and were made up of xylose units.

Several workers have determined the molecular weights of xylans. The degree of polymerisation (D.P.) of wheat straw xylan determined osmotically in formamide solution by Huseman [32], is 119, while that of methylxylan in acetone is 113. In order to determine molecular weights by a viscometric method, it has been suggested that $K = 5.0 \times 10^{-4}$. The molecular weight of beechwood xylan reaches 20 000. The degree of polymerisation of the xylans of barley straw and birchwood is 150, and so is that of fir [132]. The work of Nikitin [133] has shown that xylan is degraded by atmospheric oxygen during its isolation from plant tissue. Thus, for example, the degree of polymerisation of rye straw xylan isolated by the usual method was 97, while the value in the absence of oxygen was 237. This makes it necessary to isolate xylan in an atmosphere of nitrogen or other inert gas.

One of the highest degrees of polymerisation (300) has been found for the xylan of wheat capsules. The xylan of wheat straw (flour) is apparently homogeneous, the value of η_{sp}/c remaining constant on fractionation.

Ethers and esters of xylans. Xylans form ethers and esters. The presence of acetyl groups in natural xylan is indicated by the formation of acetic acid on decomposition of holocellulose [134].

Treatment of xylan with acetic anhydride [135], acetyl chloride [136], a mixture of acetic anhydride and pyridine, and other acetylating agents [137,138] yields acetylxylans of different degrees of substitution. The rate of acetylation of xylan exceeds the rate of esterification of cellulose by a factor of 10. Konkin and Rogovin obtained a theoretical yield of diacetylxylan [75] by the acetylation of xylan with acetic acid in the presence of phosphoric acid. Acetic esters of xylan differing in degree of substitution and obtained under different conditions dissolve differently in organic solvents [139]. Nikitin [140] fractionated acetylxylan from rye straw.

Several papers have reported the preparation of nitric [32,135,141,142], sulphuric [143], and also benzoic [135], stearic, oleic [139], and other esters of xylan. Solechnik [142] nitrated xylan with a ternary mixture of sulphuric and nitric acids and water, at 2° and 20°, and observed considerable degradation of the polysaccharide. Breakdown of the xylan can be diminished by effecting nitration with an anhydrous mixture of nitric and phosphoric acids.

The methylation of xylans with methyl iodide and silver oxide [144,145] has been widely used, primarily in the investigation of molecular structure. It is difficult to substitute by this method all the hydroxyl groups, this being accompanied by degradation of the macromolecule. Xylan can be methylated quantitatively by using dimethyl sulphate in alkaline solution. Replacement of caustic soda solution by caustic potash accelerates the process [136,145]. Methylated xylan is hydrolysed at the glycosidic links by the successive action of hydrogen chloride in methyl alcohol and of aqueous hydrochloric acid, yields of up to 90% of methylated monosaccharides being obtained [146]. The action of carbon disulphide on an alkaline solution of the polysaccharide yields xylan xanthates [147,148].

Oxidation of xylans. Xylans are oxidised under various conditions. The oxidative degradation of straw xylan under the influence of atmospheric oxygen in alkaline medium [75,133] and in triethylbenzylammonium solution has

been investigated[149]. In the latter case the rate of such degradation is less than the rate of oxidation of amylose, cellulose, and galactan, owing to the absence of a primary hydroxyl group in the monosaccharide unit. The activation energy for the oxidative degradation of xylan is 8779 cal × × mole^{-1}.

Treatment of xylan with sodium periodate[150] ruptures the bond between the second and third carbon atoms of the monosaccharide residues with the formation of dialdehydes[151].

When xylan is heated with nitric acid, it is hydrolysed and oxidised with the formation of trihydroxyglutaric and other acids[152-156].

Hydrolysis of xylans. Xylan is readily hydrolysed, being converted ultimately into simple sugars. Its treatment with dilute acids at 100° or above yields xylose[157] and other monosaccharides.

The hydrolysis constants of xylans isolated from beech and from cotton pods are about the same. Sharkov[158] investigated the kinetics of the dissolution of xylan in 20% sulphuric acid at various temperatures, and showed that the rate of dissolution increases with rise in temperature, although to a less extent than in the case of amylose, for example. Dudkin[95,96] studied the kinetics of the hydrolysis of xylans from the husks of oats and millet, established that the hydrolysis rate constants are identical, the activation energy for the hydrolysis of oat xylan being 32 000 and that for millet xylan 29 700. The rate of hydrolysis of wheat straw xylan under homogeneous and heterogeneous conditions is greater than that of the hydrolysis of cellulose by a factor of 3.75, the activation energy being 26 600 cal.[159] Yasinskaya made a comparative study of the hydrolysis of xylan[160]. The action of concentrated hydrochloric[161] and sulphuric acids on xylan has been investigated.

Plant tissue contains, in addition to the hydrolysable xylan, a difficultly hydrolysable xylan[162]. This xylan could not be isolated from cellulose[163]. Sharkov considers that the "difficultly hydrolysable" xylan is "walled up" in the cellulose[164].

A study has been made of the thermal decomposition of xylan in a stream of hydrogen[165] and then in a high vacuum[166]: the character of the decomposition is found to be greatly dependent on the nature of the surrounding medium. The reaction goes more completely and more gently in a current of hydrogen than with the usual dry distillation, as a result of which a greater quantity of liquid distillate and a smaller amount of gaseous secondary products are isolated at the same temperature. A reaction mechanism has been suggested, comprising hydrogenolysis of the xylan molecule at the glycosidic linkages, hydrogenolysis of the pentoses at the glycol group, and condensation of the compounds of low molecular weight to polymethylene and aromatic substances.

Heating birch xylan in a high vacuum at 155° and 175° produced cleavage of the macromolecules with formation of new oligosaccharides, owing to rupture of the 1,4-glycosidic linkages at isolated weak sites in the molecules and breakdown of the intermolecular bonds.

The thermographic investigations of Sergeeva and Vaivads[167,168] showed that the thermal degradation of xylan when isolated is different from that in the native state in the overall complex.

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STERIC CONFIGURATION OF PIPERIDINE DERIVATIVES

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The stereochemistry of various alicyclic compounds, particularly cyclohexane derivatives, has been much studied in the last 20–25 years, and the results obtained on the steric configuration of cyclohexane systems have served to a considerable extent as a basis for the "theory of conformational analysis".

The stereochemistry of monocyclic piperidine derivatives, in common with other heterocyclic compounds, has received comparatively little attention. The fundamental work of Fodor and his coworkers on the stereochemistry of heterocyclic compounds was mainly devoted to the spatial configuration of condensed piperidine systems (tropane alkaloids, morphine derivatives, etc.), and there have been comparatively few studies on the stereochemistry of monocyclic piperidine derivatives. The stereochemistry of piperidines is important not only for establishing the rules which determine the steric configuration of these systems, but also in their applications.

Many natural and synthetic nitrogen-containing heterocyclic compounds have a strong physiological action and are used as drugs; in particular, the powerful synthetic analgesics (morphine substitutes), the isomeric prodines, and the isomeric promedols, are piperidine derivatives. Many compounds of this series are powerful local anaesthetics.

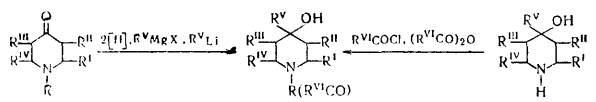
It has often been demonstrated that the effective physiological action of piperidine derivatives depends on their steric configuration: thus, for example, the isomeric prodines (1,3-dimethyl-4-phenyl-4-propionoxypiperidines) differ by a factor of about two in their analgesic activity, and a similar effect is found in the analgesic action of the isomeric promedols (1,2,5-trimethyl-4-phenyl-4-propionoxypiperidines). Similar variation occurs in the local anaesthetic action of compounds containing the piperidine ring: pseudotropine methiodide is more physiologically active than the corresponding *trans*-isomer[1], and the isomeric 1,2,5-trimethylpiperidin-4-olbenzoates have different anaesthetic activities[2].

The necessity for practical utilisation of certain piperidine derivatives as powerful analgesics and anaesthetics was one of the reasons which stimulated the study of the stereochemistry of this group of compounds.

The initial work was primarily preparative. We prepared the ring-substituted piperidines, isolated the stereoisomers predicted by theory, and studied their physiological activity. The most interesting pharmacologically were derivatives of the various piperidin-4-ols, and particular attention was paid to the synthesis of these alcohols and the development of methods for separating them into the individual stereoisomers.

The stereochemical study of piperidin-4-ols was also favoured by their comparative ease of preparation. Convenient methods were developed for preparing various piperid-4-one starting materials.

The piperidinols were prepared by reducing ring-substituted piperid-4-ones, by *N*-alkylating or *N*-acylating the *N*-unsubstituted piperidin-4-ols, or by means of organometallic compounds:



The three 2,5-dimethylpiperidin-4-ol stereoisomers (α, m.p. 97°–98°; β, m.p. 141°–142°; γ, m.p. 86°–87°) were obtained by reducing 2,5-dimethylpiperid-4-one[3,4]: the α-isomer with sodium in alcohol, the β-isomer by catalytic hydrogenation or with sodium ethoxide, and the γ-isomer by catalytic hydrogenation of 1-benzoyl(or acetyl)-2,5-dimethylpiperid-4-one followed by removal of the benzoyl or acetyl radical[2,5,6]. Various *N*-alkylated and *N*-acylated derivatives of secondary 2,5-dimethylpiperidin-4-ol isomers were prepared by alkylation or acylation.

α-1,2,5-trimethylpiperidin-4-ol (m.p. 72°–73°) was prepared by methylating α-2,5-dimethylpiperidin-4-ol and by reducing 1,2,5-trimethylpiperid-4-one. The other two 1,2,5-trimethylpiperidin-4-ol isomers (β, m.p. 77°–78° and γ, b_6 88°) were obtained by methylating the corresponding unsubstituted piperidinols or their derivatives[2,5].

Similar methods were used to prepare α-, β-, and γ-1-benzoyl-2,5-dimethylpiperidin-4-ol (m.p. 136°–137°, 134°–135°, and 159°–160° respectively)[2], α- and β-1-allyl-2,5-dimethylpiperidin-4-ol (b_2 98° and b_4 98°)[7,8], and α- and β-1-(3,3-dimethylallyl)-2,5-dimethylpiperidin-4-ol (m.p. 80°–81° and 68.5°–70°). α- and β-1-phenyl-2,5-dimethylpiperidinol (m.p. 75°–76° and 81°–82°) were prepared by reducing the corresponding piperidone by various methods[9].

To introduce an unsaturated substituent into position 4 of the piperidine ring, piperid-4-ones were condensed with acetylene, vinylacetylene, and phenylacetylene; the corresponding tertiary piperidin-4-ols are also formed in several stereoisomeric forms. α-, β-, and γ-1,2,5-trimethyl-4-ethynylpiperidin-4-ol (m.p. 73°–74°, 113°–114°, and 177°–178°) were obtained by condensing 1,2,5-trimethylpiperid-4-one with acetylene[10-12]; α- and β-1-allyl-2,5-dimethyl-4-ethynylpiperidin-4-ol (m.p. 92°–93° and 78°–79°) and γ- and β-1-(3,3-dimethylallyl)-2,5-dimethyl-4-ethynylpiperidin-4-ol (m.p. 90°–91° and 85°–86°)[13] were prepared analogously.

The condensation of 1,2,5-trimethylpiperid-4-one with vinylacetylene produces two isomers of 1,2,5-trimethyl-4-vinyl ethynylpiperidin-4-ol, which on hydrogenation gave α- and β-1,2,5-trimethyl-4-butylpiperidin-4-ol (m.p. 91°–92° and 111°–112°)[10]; a third isomer (m.p. 69°–69.5°) was obtained from butyllithium and 1,2,5-trimethylpiperid-4-one.[6] Two isomers of 1,2,5-trimethyl-4-phenylethynylpiperidin-4-ol (m.p. 103°–104° and 139°–140°) were isolated from the reaction products of the corresponding piperidone with phenylacetylene[14].

The stereochemistry of tertiary piperidin-4-ols with aryl radicals in position 4 of the piperidine ring is of particular interest. Stereoisomeric piperidinols of this type were first described by Ziering and Lee[15], who reacted 1,3-dimethylpiperid-4-one with phenyllithium to obtain 1,3-dimethyl-4-phenylpiperidin-4-ol stereoisomers, which were then used to prepare the isomeric prodines. Similarly 1,2,5-trimethylpiperid-4-one gave three of the four theoretical isomers of 1,2,5-trimethyl-4-phenylpiperidin-4-ol (α, m.p. 106°–107°; β, m.p. 101°–102°; and γ, m.p. 107°–108°), which are starting materials for the synthesis of the promedol isomers[10,16].

Many tertiary piperidin-4-ols have now been obtained in several isomeric forms: 1,2,5-trimethyl-4-*p*-tolylpiperidin-4-ol (m.p. 113°–115° and 136°–137°); 1,2,5-trimethyl-4-cyclohexylpiperidin-4-ol (m.p. 92°–93.5° and 125°–126.5°); and 1,2,5,6-tetramethyl-4-phenylpiperidin-4-ol (m.p. 99°–99.5° and 126°–127°)[14]. A series of *N*-substituted 2,5-dimethyl-4-phenylpiperidin-4-ol isomers have been prepared: ethyl (m.p. 91° and 100°–101.5°), propyl (m.p. 53.5°–55° and 93°–94°), isopropyl (m.p. 63°–65°, 67°–69°, and 106°–107°), butyl (m.p. 71°–72° and 96°–96.5°), isobutyl (m.p. 27°–29° and 72°–73°), allyl (m.p. 93°–94° and 71°–72°), isopentyl (m.p. 83°–84° and 109°–110°)[17], 3,3-dimethylallyl (m.p. 109.5°–110.5°, 105.5°–106.5°, and 115.5°–116.5°), crotyl (m.p. 97°–98° and 102°–103°), 3-chlorocrotyl (m.p. 132°–133°, 134°–135°, and 110°–111°), and other similar compounds[18].

Only the physical constants of most of these piperidinols are known; their steric configuration has not been determined.

When stereoisomeric piperidinols were isolated, they were given arbitrary designations by Greek letters (α, β, γ), sometimes in order of melting point, the lowest melting isomer being called the α-isomer. When a piperidinol isomer is alkylated or acylated, the designation of the product remains that of the starting compound. The same designation is sometimes given to stereoisomeric piperidinols having various substituents in the piperidine ring on the basis of the comparative physiological activity of their derivatives.

Unfortunately, the accepted designations do not reflect the structure of the isomers. These designations are doubly subjective, and are often a convenience only for the initial workers. Sometimes they cause confusion. As will be shown below, β-prodine and α-promedol have identical steric configurations of the 3- and 4-substituents in the piperidine ring, and they have almost identical physiological activities; they ought therefore to have the same designation. To prevent confusion in naming the isomers, it is convenient (if the structure is known) to use the accepted nomenclature for indicating the position of a substituent; for example, β-prodine should be named, 1,3-dimethyl-4*ax*-phenyl-4-propionoxypiperidine, and α-promedol should be 1,2*eq*, 5*eq*-trimethyl-4*ax*-phenyl-4*eq*-propionoxypiperidine.

The fairly extensive experimental data on the preparation of isomers of a number of piperidine derivatives have served as a basis for studying their steric configuration.

The piperidine ring is not equivalent to cyclohexane, but the principles of conformational analysis as applied to the study of the steric configuration of cyclohexane derivatives can also be used for piperidines. The two ring systems, of course, differ, but the differences do not substantially affect the factors which determine the mutual influence of substituents in each of the rings. In passing from the cyclohexane to the piperidine system, one must consider the influence of the nucleophilic nitrogen atom in the piperidine ring on the steric configuration of the molecule, including the interaction between electrophilic ring substituents and the unshared electron pair of the piperidine ring nitrogen, and the steric position of substituents on the nitrogen.

In *N*-substituted piperidines the substituent may be equatorial or axial. Koczka and Bernáth[19] studied the steric position of the piperidine *N*-methyl group of codeine. Treatment of codeine with benzyl iodide gave an *N*-benzylcodeine iodide of m.p. 178°, and treatment of *N*-benzylnorcodeine with methyl iodide gave a product of m.p. 217°; it was suggested that the compounds differ only in the disposition of the substituents on the piperidine ring nitrogen.

Fodor had earlier studied the stereochemistry of the nitrogen in heterocyclic compounds by the formation of quaternary ammonium compounds from pseudotropine and *N*-ethoxycarbonylmethylnorpseudotropine[20]. Treatment of the former with ethyl iodoacetate and the latter with methyl iodide gave quaternary ammonium compounds differing in the disposition of the substituents on the nitrogen.

On the basis of these studies, it has been suggested that the nitrogen atom is an asymmetric centre, and in consequence that the lone pair of electrons on the nitrogen in tertiary *N*-derivatives occupies a definite tetrahedral position.

A study of the optical anisotropy of piperidine has shown that the molecule has the chair form with the >N–H bond in the axial position[21]; for *N*-substituted monocyclic piperidine derivatives, the nitrogen substituents are most probably (from the point of view of the steric interaction of the ring and nitrogen substituents) in the equatorial position.

The equatorial position of the *N*-methyl group in morphine and α-prodine has been demonstrated by X-ray structure analysis of their crystalline salts. Aroney and Le Fèvre[22] used data on the Kerr effect, refractive indices, dielectric constants, and densities of benzene solutions of 1-phenylpiperidine and 1-*p*-nitrophenylpiperidine to calculate the polarisation, dipole moments, and molecular Kerr constants; comparison of the experimental results with those calculated for the various possible conformations showed that these compounds have the chair-structure with the *N*-phenyl groups in the equatorial position. However, the *N*-substituent of the piperidine ring may, as shown by Closs[23], change its conformation under certain conditions, *i.e.* axial–equatorial isomerism may occur. This was demonstrated by study of the nuclear magnetic resonance spectra of certain tropine and pseudotropine derivatives.

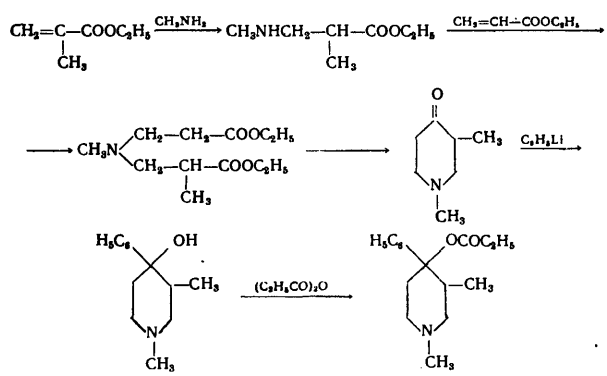
Comparison of the nuclear magnetic resonance spectra of pseudotropine ethiodide, in which the *N*-methyl group is axial, with those of ethyl norpseudotropine methiodide, in which the methyl group is equatorial, showed that the peak at higher field corresponds to the isomer with the equatorial methyl group. Pseudotropine methiodide showed two peaks of equal intensity.

These spectra have been compared with the nuclear magnetic resonance spectra of pseudotropine hydrochloride obtained at various acidities. The spectrum of this compound in aqueous solution at pH 1 has two doublets, which merge into a single peak at pH 6. This has been explained as due to rapid exchange of a proton with the solvent, which is connected with the rapid interconversion of the isomers differing in the position of the *N*-methyl group (axial or equatorial).

In studying the stereochemistry of substituted piperidines, in some cases the possibility of easy inversion of the piperidine ring itself must be taken into account; this causes difficulties in studying the conformation of some piperidines. Naturally, with polycyclic compounds, where the piperidine ring is fixed in a definite steric configuration, the stereochemical problems can be more definitely answered. The tendency of *N*- and *C*-substituted piperidines towards inversion of the piperidine ring and the probability of existence of either conformational isomer are to a large extent determined by the nature and position of the substituents in the piperidine ring [*C*-substituents? (Ed. of Translation)].

The stereochemistry of piperidin-4-ols and their derivatives has recently been studied in particular detail, especially the above-mentioned 1,3-dimethyl-4-phenylpiperidin-4-ol and 1,2,5-trimethyl-4-phenylpiperidin-4-ol isomers and their propionates, *i.e.* the isomeric prodines and isomeric promedols.

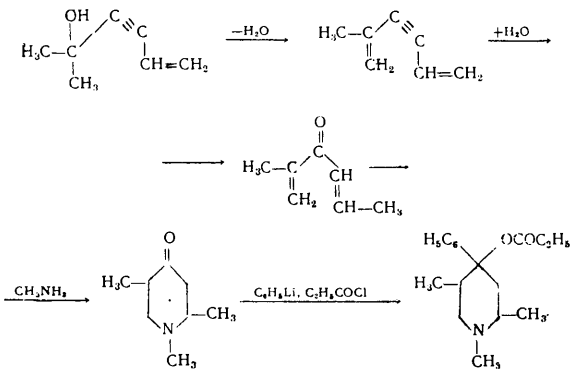
The 1,3-dimethyl-4-phenylpiperidin-4-ol isomers and the corresponding α- and β-prodines have been prepared by Ziering and Lee as follows[15]:



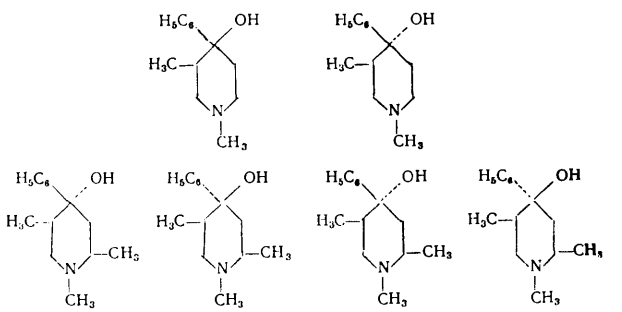
The isomeric prodines are widely used abroad as anaesthetics. Their stereochemistry has been studied by Ziering and Beckett and coworkers (these studies are considered below); they give opposite steric configurations to the α- and β-prodines.

The preparation of the isomeric promedols, which are the main analgesics used in the Soviet Union, was the result of

several years work by Nazarov and coworkers [3,10,16,24-27]. At present the industrial preparation is as follows:



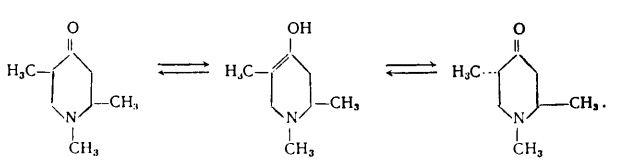
The structures of α- and γ-1, 2, 5-trimethyl-4-phenylpiperidin-4-ol and some of their analogues and derivatives are considered below; these structures are directly related to the configurations of promedol and α-promedol. The 1, 3-dimethyl-4-phenylpiperidin-4-ol molecule has two, and the 1, 2, 5-trimethyl-4-phenylpiperidin-4-ol molecule has three asymmetric carbon atoms; consequently the former can exist in two and the latter in four geometrically isomeric forms:



Establishing the configurations of these analgesics would enable the analgesic action of these substances to be correlated with their steric structure, and might also solve certain problems of the mechanism of the biological action of the analgesics.

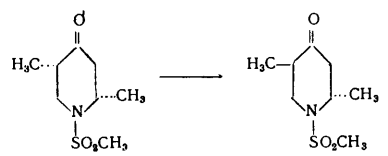
cis- and *trans*-1, 2, 5-Trimethylpiperid-4-one

Two geometrical isomers of 1, 2, 5-trimethylpiperid-4-one are theoretically possible, differing in the steric disposition of the 2- and 5-methyl groups:



They are easily interconverted, and it is therefore difficult to identify the isomers as their derivatives. The existence of *cis*- and *trans*-forms of 1, 2, 5-trimethylpiperid-4-one is definitely shown by the reaction of the piperidone with organometallic compounds, which yields the piperidinols corresponding to both isomeric piperidones [16].

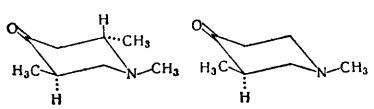
Individual stereoisomers of the 1-acyl-2, 5-dimethylpiperid-4-one series have been isolated and studied [4]. Because of the considerably reduced basic properties of the piperidine ring, interconversion of the 1-acyl-2, 5-dimethylpiperid-4-one isomers takes place unidirectionally and at higher temperatures. For example, 1-mesyl-2, 5-dimethylpiperid-4-one is obtained as two isomers, melting at 76°–78° and 98°–100°. The lower-melting isomer is less stable, and on heating is converted into the more stable isomer of m.p. 98°–100°:



cis-isomer m.p. 76°–78° *trans*-isomer m.p. 98°–100°

The more stable *N*-substituted 2, 5-dimethylpiperid-4-one isomers must correspond with the piperidones with *trans*-equatorial methyl groups, in accordance with the structure of 1, 4-substituted cyclohexanes [28]; it is known that "di- and poly-substituted cyclohexane derivatives usually take up that conformation in which a majority of the substituents are equatorial" [29].

For 2, 2, 6-trimethylpiperid-4-one, the more stable structure is that with the maximum number of equatorial substituents [30]; consequently, the quantitatively predominant isomer of 1, 2, 5-trimethylpiperid-4-one must be the *trans*-isomer with equatorial methyl groups. The 3-methyl group of 1, 3-dimethylpiperid-4-one, the starting material for the preparation of the prodine isomers, is also in the equatorial position:



α-Prodine and Promedol; β-Prodine and α-Promedol

Of the stereoisomers α- and β-1, 3-dimethyl-4-phenylpiperidin-4-ol and γ- and α-1, 2, 5-trimethyl-4-phenylpiperidin-4-ol and their propionate hydrochlorides, the following are analogues in a chemical and pharmacological sense: (a) α-1, 3-dimethyl-4-phenylpiperidin-4-ol and γ-1, 2, 5-trimethyl-4-phenylpiperidin-4-ol and the corresponding propionate hydrochlorides α-prodine and promedol; (b) β-1, 3-dimethyl-4-phenylpiperidin-4-ol and α-1, 2, 5-trimethyl-4-phenylpiperidin-4-ol and the corresponding propionate hydrochlorides β-prodine and α-promedol.

The reaction of phenyllithium with 1,3-dimethylpiperid-4-one and 1,2,5-trimethylpiperid-4-one gives α-1,3-dimethyl-4-phenylpiperidin-4-ol and γ-1,2,5-trimethyl-4-phenylpiperidin-4-ol in about the same predominating quantity (75–80%) as compared with the other isomers of these piperidinols[31,32]. α-Prodine and promedol are very similar in their analgesic action. It has been shown in Mashkovskii's laboratory that promedol is about 2–3 times as effective an analgesic as morphine (tests on rats); α-prodine is also about twice as active as morphine[33].

β-1,3-Dimethyl-4-phenylpiperidin-4-ol and α-1,2,5-trimethyl-4-phenylpiperidin-4-ol are also formed from phenyllithium and the corresponding piperidones in about the same yields, but considerably lower (20–25%) than the piperidinols corresponding to α-prodine and promedol. β-Prodine and α-promedol also have similar analgesic activity: they are about 4–6 times as active as morphine.

These facts are a sufficient basis for the simultaneous consideration of the structures of (a) α-prodine and promedol, and (b) β-prodine and α-promedol.

Comparison of the Steric Configuration of the Prodine and Promedol Isomers with that of the Piperidine Portion of the Morphine Molecule

Morphine occupies a special place in the history of organic chemistry and especially the chemistry of medicinals. The alkaloid was first obtained pure from opium in 1805 by Sertürner[34], but its structure was not determined until 120 years later[35]. Recently morphine has been synthesised[36,37], and this was the decisive proof of Robinson's proposed structure for morphine.

The guiding light in the search for synthetic analgesics has always been the chemistry of morphine and related alkaloids. The morphine molecule has served as the model for hundreds of different compounds, reproducing individual sections of its molecule. Compounds whose molecules reproduce the piperidine portion of the morphine molecule have in fact proved to be fairly effective analgesics.

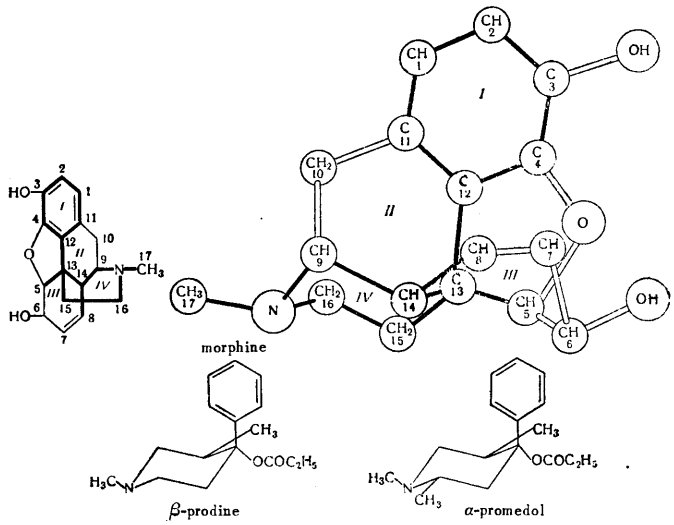
The molecules of the prodines and promedols and the known analgesic Lydol (1-methyl-4-phenyl-4-ethoxycarbonylpiperidine)[38,39] also have structural elements in common with the piperidine portion of the morphine molecule: they all contain an aryl radical and an oxygen-containing group in the 4-position of the piperidine ring.

The steric configuration of the morphine molecule has now been established by various chemical and physicochemical methods, and has been confirmed by X-ray structure analysis of morphine hydriodide dihydrate[40].

The molecule is T-shaped, with the atoms lying in two almost perpendicular planes, one containing the benzene ring *I*, the oxygen-containing ring, and the cyclohexane ring *II*, and the other containing the cyclohexene ring *III* and the piperidine ring *IV*; the last ring has an almost true chair form. The *N*-methyl group is *cis* relative to the C_9-C_{10} bond.

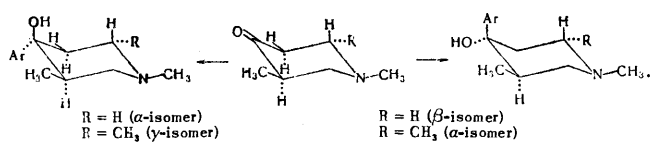
Just as the structure of the morphine molecule has been the foundation for preparative studies on synthetic analgesics, its stereochemistry has to a certain extent been the starting point in the study of the configuration of synthetic analgesics.

Considering the comparatively high analgesic action of morphine, the more active of the isomeric piperidine derivatives which are analgesics would be expected to be the isomer having the spatial configuration which is the same as that of the piperidine portion of the morphine molecule. This is one of the principles underlying the suggestions already made[33] regarding the steric configuration of α- and β-prodine.



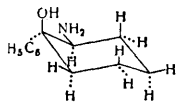
From this point of view β-prodine and α-promedol (the most active analgesics of the compounds under consideration) should have the structure in which the piperidine ring is in the chair form, the 4-phenyl radical is *cis* with respect to the 3-methyl group (or 5-methyl group in the case of α-promedol), and the propionoxy-group is equatorial and the 4-phenyl radical axial.

Influence of Steric Factors on the Reaction of 1,3-Dimethylpiperid-4-one and 1,2,5-Trimethylpiperid-4-one with Aromatic Organometallic Compounds



In the reaction of 1,3-dimethylpiperid-4-one and 1,2,5-trimethylpiperid-4-one with phenyllithium the aryl radical could enter in either the equatorial or axial position, but from the point of view of steric factors it is more probable that the phenyl radical, and other substituents of large size, would enter from the sterically less hindered side, *i.e.* from the peripheral side of the ring. With an axial phenyl radical, there is 1,3-interaction between the phenyl group and the axial hydrogen at C_2 and C_6, and this structure is therefore less favoured than the conformation in which the radical at C_4 is equatorial. This point of view is in full accord with suggestions made about the conformation of cyclohexane derivatives with a large substituent in the ring: the presence of a large substituent prevents the occurrence of any considerable quantities of the conformation having this substituent in the axial position[41].

From a study of the conformation of the isomeric **2**-amino-1-phenylcyclohexanols, it was concluded that "in the presence of a large substituent the predominant conformation is that in which this substituent (*e.g.* the phenyl group) is equatorial and the hydroxy-group axial".



It can be considered a rule that "the more stable chair form sterically, is that in which substituents of high steric requirement occupy equatorial positions and those of low steric requirement occupy axial positions" [28].

Assuming that steric factors determine the relative proportions of α- and β-1,3-dimethyl-4-arylpiperidin-4-ol formed when 1,3-dimethylpiperid-4-one reacts with aromatic organometallic compounds, Beckett and coworkers [42] studied the reaction of this piperidone with various lithium aryls whose structure was expected to hinder or prevent the possibility of the aryl group entering in the axial position. Phenyllithium and *m*- and *p*-tolyllithium were found to give a mixture of piperidinols containing a considerably predominant quantity of one of the isomers. With *o*-tolyllithium, *o*-methoxyphenyllithium, and 2,6-dimethylphenyllithium, the products consisted almost exclusively of only one of the isomeric piperidinols, which, like those formed predominantly in the other reactions, belongs to the α-series. The configurational identity of these piperidinols of the α-series, and similarly of all piperidinols of the β-series, has been proved spectroscopically.

From the above theoretical considerations and experimental results, α-1,3-dimethyl-4-phenylpiperidin-4-ol and γ-1,2,5-trimethyl-4-phenylpiperidin-4-ol have an equatorial phenyl radical and an axial hydroxy-group; β-1,3-dimethyl-4-phenyl piperidin-4-ol and α-1,2,5-trimethyl-4-phenylpiperidin-4-ol have the opposite configuration at C_4.

Becket *et al.* [43] have made a systematic study of the stereochemical directivity of the reaction of 1-(2-phenylethyl)-, 1-(2-phenylethyl)-3-methyl-, 1-(2-phenylethyl)-3-ethyl-, and 1-(2-phenylethyl)-3-n-propylpiperid-4-one with phenyllithium, *o*-, *m*-, and *p*-tolyllithium, *o*-anisyllithium, and 2,6-dimethylphenyllithium; in each case the predominant isomer was the piperidinol with the aryl group in the *trans*-position to the 3-alkyl group. A small amount of the *cis*-isomer was isolated only in the case of 1-(2-phenylethyl)-3-methyl-4-phenylpiperidin-4-ol, by saponification of the corresponding propionic acid ester obtained by fractional crystallisation of the mixed piperidinol propionates. The equatorial position of the propionoxy-group in the ester of the piperidinol of *cis*-structure is shown by its considerably greater ease of saponification in comparison with the ester of the piperidinol of *trans*-structure.

All the piperidinols with the 4-aryl group *trans* to the 3-alkyl group have peaks in the infra-red spectrum at 990–1010 and 1350–1385 cm^{-1}. The corresponding *cis*-piperidinols have a peak at 1040–1050 cm^{-1}.

Similar conclusions on the steric configuration of the isomeric piperidinols were made by Beckett and coworkers [44] in their study of the reaction of phenyllithium with 1-(2-phenylethyl)-2-methyl-, 1-(2-phenylethyl)-2,6-dimethyl- and *cis*-2,6-dimethylpiperid-4-one.

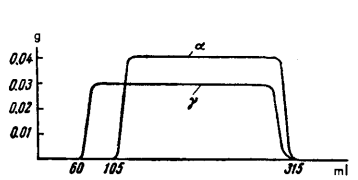
Two stereoisomers of 1-(2-phenylethyl)-2-methyl-4-phenylpiperidin-4-ol were obtained, formed in the ratio 2:1. From a consideration of the stereochemical factors influencing the reaction between the piperidone and the phenyllithium, the study of the infra-red spectra of the piperidinol isomers and their chemical properties, the 1-(2-phenylethyl)-2-methyl-4-phenylpiperidin-4-ol formed in greater quantity was assigned the configuration in which the 2-methyl and 4-phenyl groups are equatorial and the 4-hydroxy-group is axial. The other isomer has the reverse configuration of the hydroxy-group and phenyl radical at C_4.

Three isomers of 1-(2-phenylethyl)-2,6-dimethyl-4-phenylpiperidin-4-ol were isolated, in the ratio 9:2:1. The predominant isomer has equatorial 6-methyl and 4-phenyl groups and axial 2-methyl and 4-hydroxy-groups; the next most frequent piperidinol differs from the first in having an equatorial 2-methyl group, and the third isomer has equatorial 2- and 6-methyl and 4-hydroxy-groups, and the 4-phenyl radical in the axial position.

Thus in all the examples considered, the predominant piperidinol isomer has, as a rule, the 4-phenyl radical in the equatorial position.

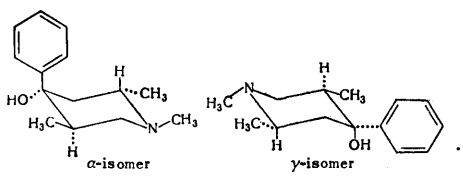
Chromatographic Study of Isomeric Piperidinols

Isomers with polar functional groups behave differently when chromatographed. It has often been demonstrated, particularly with steroids, that alcohols with an equatorial hydroxy-group are more strongly adsorbed, and therefore less easily eluted from a chromatographic column, than alcohols with an axial hydroxy-group [45]. The behaviour of α- and γ-1,2,5-trimethyl-4-phenylpiperidin-4-ol on chromatography has been studied in connection with the stereochemistry of promedol and α-promedol [31,46]; alumina adsorbs the α-isomer considerably more strongly than the γ-isomer. Under comparable conditions (1.5 g of piperidinol, column 50 × 1.5 cm, 69 g of alumina, with chloroform as solvent) the eluate volume is 60 ml for the γ-isomer and 105 ml for the α-isomer. The solubilities of the α- and γ-forms in chloroform are respectively 64 g and 70 g in 100 ml of chloroform at 20°. From these results, it is considered that the hydroxy-group is axial in the γ-isomer and equatorial in the α-isomer.



Elution of the 1,2,5-trimethyl-4-phenylpiperidin-4-ol stereoisomers from a chromatographic column.

In considering the results of the chromatographic analysis of γ- and α-1, 2, 5-trimethyl-4-phenylpiperidin-4-ol the possibility of inversion of the piperidine ring must be borne in mind. This isomerisation clearly does not take place during chromatography. The inverted chair form of the γ-isomer would be extremely unstable, because all the substituents except the hydroxy-group would be axial. More probable would be the formation of the inverted isomer of the α-piperidinol with the equatorial phenyl group. If it be assumed that under the influence of the alumina the piperidine ring of the α-piperidinol undergoes inversion during the chromatography, the inverted form would have an equatorial hydroxy-group, as in the case of the γ-isomer; if this took place, the experimentally observed difference in the behaviour of these alcohols on chromatography would clearly not be found.



In the chromatography of α- and γ-1, 2, 5-trimethyl-4--phenylpiperidin-4-ol, the interaction between the polar groups of the amino-alcohols and the adsorbent must be taken into account. One of the causes of this interaction is the formation of hydrogen bonds between the adsorbent and the piperidinol molecules[47]

Steric factors affect the interaction between the adsorbent and the hydroxy- and amino-groups of the piperidinol isomers to different extents. In the case of the γ-isomer the equatorial position of the large phenyl radical and the position of the methyl group on the nitrogen hinder the interaction between the polar groups and the alumina; in the α-isomer the hydroxy-group and the piperidine nitrogen are not screened in this way. α- and γ-2, 5-Dimethyl-4--phenylpiperidin-4-ol, which on methylation are converted to α- and γ-1, 2, 5-trimethyl-4-phenylpiperidin-4-ol respectively, behave in the same way on chromatography; the α-isomer is more strongly adsorbed by the alumina and is less easily eluted than the γ-isomer.

There are indications that the smallest deviation from the rules of behaviour of isomeric alcohols on chromatography would be expected in partition chromatography[45,48], and Savord found that steroid alcohols with an axial hydroxy--group travel faster on the paper than their equatorial epimers. From this point of view the results obtained by Ziering *et al.*[49] by paper chromatography of the α- and β-1, 3-dimethyl-4-phenylpiperidin-4-ol isomers are of interest. Using t-pentyl alcohol–di-n-butyl ether–water (80:7:13) as solvent, they obtained the following values Rf at the indicated pH values:

	pH 6.3	pH 4.9	pH 3.6	pH 2.2
α-isomer	0.65	0.58	0.46	0.27
β-isomer	0.64	0.48	0.37	0.19

Thus the α-isomer of 1, 3-dimethyl-4-phenylpiperidin-4-ol (the structure analogue of γ-1, 2, 5-trimethyl-4-phenylpiperidin-4-ol) travels faster on paper, and these piperidinols therefore have an axial hydroxy-group.

Esterification of the Isomeric Piperidinols and Saponification of Their Esters

Alcohols with an equatorial hydroxy-group are more easily esterified than alcohols with an axial hydroxy-group, and correspondingly esters with an equatorial acyloxy--group are more easily hydrolysed than those with an axial acyloxy-group. Since β-prodine is more easily hydrolysed than α-prodine, Beckett and coworkers[50] consider the propionoxy-group to be equatorial in the former and axial in the latter. Study of the esterification of α- and γ-1, 2, 5--trimethyl-4-phenylpiperidin-4-ol with propionyl chloride in benzene at 80° led to similar conclusions:

Duration of reaction, min	Yield of 1,2,5-trimethyl-4-phenyl--4-propionoxypineridine, %	
	α-isomer	γ-isomer
15	78	19.4
30	—	19.4
45	84	21.2
60	87.4	22.9

The esterification of the isomers of 1-(2-phenylethyl)--2-methyl-4-phenylpiperidin-4-ol has also been studied[51]. The *trans*-isomer (referring to the relative positions of the methyl and phenyl radicals) of this piperidinol (m.p. 98°) reacts with ketene to form the ester, but the *cis*-isomer (m.p. 79°) is not esterified under these conditions, indicating that the hydroxy-group is equatorial in the former and axial in the latter. *Trans*-1-(2-phenylethyl)-2-methyl-4--phenylpiperidin-4-ol has a peak in the infra-red spectrum at 1030 cm^{-1}, like β-1, 3-dimethyl-4-phenylpiperidin-4-ol, and this confirms that the steric configurations of these piperidinols are identical.

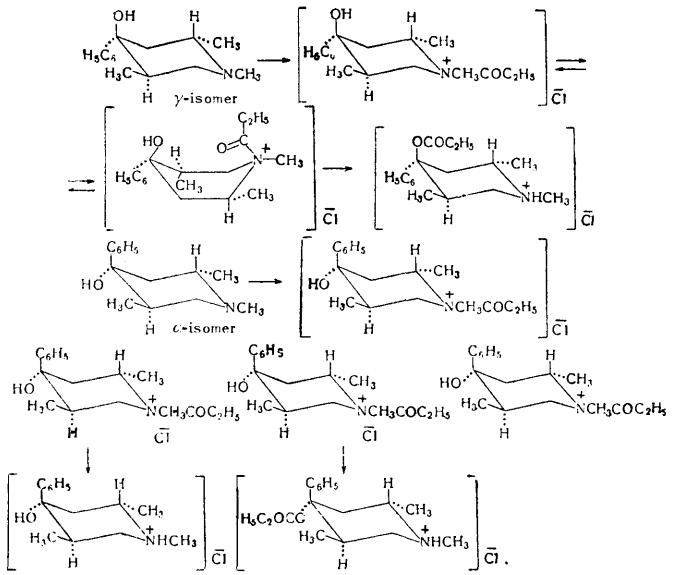
Analogous spectrographic data have been given to prove that *cis*-1-(2-phenylethyl)-2-methyl-4-phenylpiperidin-4--ol and α-1, 3-dimethyl-4-phenylpiperidin-4-ol have the same conformation.

Under comparable conditions α-1, 2, 5-trimethyl-4--phenyl-4-propionoxypiperidine is much more readily saponified than the γ-isomer: the former (α-promedol) is 73% hydrolysed by heating with 5% alcoholic KOH for 15 min at 80°, while the latter (promedol) is not hydrolysed under these conditions. The esterification of α- and γ-1, 2, 5-trimethyl-4-phenylpiperidin-4-ol and the hydrolysis of their esters clearly indicate that the hydroxy-group is equatorial in the α-isomer and axial in the γ-isomer.

Esterification of these piperidinols does not cause inversion of the configuration at C_4. Hydrolysis of promedol and α-promedol gives the initial piperidinols in quantitative yield.

With α- and γ-1, 2, 5-trimethyl-4-phenylpiperidin-4-ol, esterification takes a different course: the γ-isomer produces the corresponding propionate hydrochloride, but the α-isomer, in addition to the propionate hydrochloride, produces a considerable amount (sometimes up to 50%) of the piperidinol hydrochloride. This difference is due to the steric configuration of the isomeric piperidinols. Piperidine bases form salts with organic acid chlorides, and this is evidently the first step in the esterification of the α- and γ-piperidinols. The subsequent migration of the acyl radical towards the hydroxyl oxygen takes place intramolecularly with the γ-isomer and intermolecularly with the α-isomer. Because of this, esterification of γ-1, 2, 5-trimethyl-4-phenylpiperidin-4-ol gives the ester

hydrochloride, while the α-isomer gives the ester hydrochloride and also the piperidinol hydrochloride:



Esterification of α- and γ-1, 2, 5-trimethyl-4-phenyl piperidin-4-ol thus furnishes additional proof of their configuration.

Reaction of α- and β-1, 3-Dimethyl-4-phenylpiperidin-4-ol with Thionyl Chloride

Beckett *et al.*[42] showed that α-1, 3-dimethyl-4-phenylpiperidin-4-ol and 1-methyl-4-phenylpiperidin-4-ol are easily dehydrated by thionyl chloride. This reaction and the ease of elimination indicate that the hydroxy-group of the initial piperidinols is axial, since it is then that conditions for *trans*-elimination are stereochemically realisable.

With thionyl chloride, β-1, 3-dimethyl-4-phenylpiperidin-4-ol gives the corresponding 4-chloro-derivative in high yield; this reaction is only possible if the hydroxy-group of the initial piperidinol is equatorial, the reaction passing through the intermediate formation of a compound of the piperidinol with the thionyl chloride, the intermediate then decomposing to form the chloro-compound; it is known that this does not cause inversion of configuration[52-56].

Dehydration of α- and γ-1, 2, 5-Trimethyl-4-phenylpiperidin-4-ol

Observations on the dehydration of α- and γ-1, 2, 5-trimethyl-4-phenylpiperidin-4-ol[57] without study of the kinetics or the reaction mechanism can hardly give reliable data for deciding the configuration of these compounds. It is well known that many dehydration and dehydrohalogenation reactions produce an unsaturated compound which does not correspond in configuration to the initial compound, since the elimination often takes place with a change of configuration at one of the carbon atoms participating in the reaction[58]. Thus on dehydration α- and γ-1, 2, 5-trimethyl-4-phenylpiperidin-4-ol yield the same 1, 2, 5-trimethyl-4-phenyl-Δ¹-tetrahydropyridine, so that in one case there is inversion at the asymmetric centre at C_4.

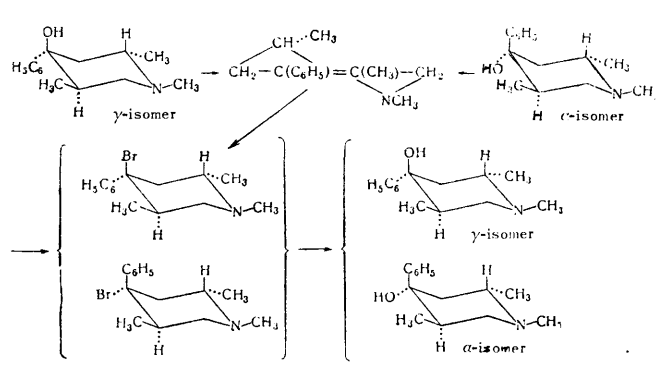
Study of the *N*-acyl → *O*-acyl rearrangement of α- and γ-1-acetyl-2, 5-dimethyl-4-phenylpiperidin-4-ol has shown that inversion occurs in the case of the α-isomer. This gives grounds for assuming that it is also the α-form which inverts when α- and γ-1, 2, 5-trimethyl-4-phenylpiperidin-4-ol are dehydrated. Consequently, α- and γ-1, 2, 5-trimethyl-4-phenylpiperidin-4-ol are dehydrated by different routes, and without kinetic investigation of the mechanism of the conversions, comparison of the quantitative results obtained in the dehydration of the piperidinol isomers under identical conditions is insufficient for any conclusions to be drawn in respect of their configuration.

Interconversions of α- and γ-1, 2, 5-Trimethyl-4-phenylpiperidin-4-ol

These have been studied in connection with the stereochemistry of promedol and α-promedol[57,59]. Treatment of γ-1, 2, 5-trimethyl-4-phenylpiperidin-4-ol for 40 h with hydrogen bromide in glacial acetic acid at 100° and then with water gave the piperidinol dehydration product in 87% yield and a mixture of the α- and γ-piperidinols in 13% yield. This can give no definite information regarding the steric configuration of the initial piperidinol, because the reactions involve a number of successive stages the stereochemical nature of which is not yet known.

Heating γ-1, 2, 5-trimethyl-4-phenylpiperidin-4-ol with hydrogen bromide or chloride causes dehydration, and it is important to note that the same 1, 2, 5-trimethyl-4-phenyl-Δ⁴-tetrahydropyridine is formed as when the α-piperidinol is dehydrated. The later reactions in the above series can thus give no indication of the steric configuration of the initial γ-1, 2, 5-trimethyl-4-phenylpiperidin-4-ol.

The subsequent addition of hydrogen bromide to the 1, 2, 5-trimethyl-4-phenyl-Δ⁴-tetrahydropyridine may be *cis*- or *trans*-addition, and since the resulting bromides may undergo hydrolysis either with or without inversion at the asymmetric centre at C_4, the formation of a mixture of α- and γ-1, 2, 5-trimethyl-4-phenylpiperidin-4-ol is fully to be expected. It is known that in successive addition and elimination reactions only the occurrence of steric rearrangement in one of the steps can be established[60]:

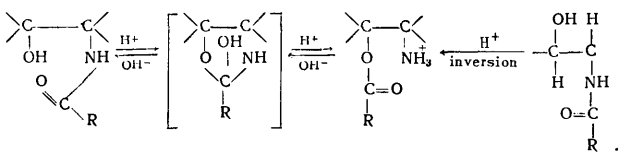


Consequently, the experimental results obtained in these conversions cannot be used to deduce the steric configuration of the γ- and α-piperidinols. Since α- and γ-1, 2, 5-trimethyl-4-phenylpiperidin-4-ol are dehydrated to form the same 1, 2, 5-trimethyl-4-phenyl-Δ⁴-tetrahydropyridine, the conversions can be regarded as those of γ-isomer to α-isomer, γ-isomer to γ-isomer, α-isomer to γ-isomer, and α-isomer to α-isomer.

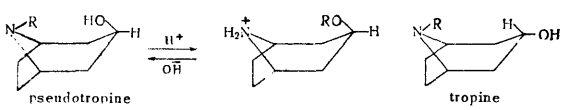
The observations of Cornubert and coworkers[61] on the reactions of *cis*- and *trans*-2-methylcyclohexanols illustrate the complexity of the processes taking place in the reaction of cyclic alcohols with hydrohalic acids. Heating the *trans*-alcohol with hydrochloric acid gave a mixture of 1-chloro-1-methylcyclohexane with *trans*- and *cis*-1--chloro-2-methylcyclohexanes, and also 1-methylcyclohexene and 3-methylcyclohexene. Under the same conditions the *cis*-alcohol gave as the main product (85%) 1-chloro-1-methylcyclohexane and 1-methylcyclohexene. It was suggested that dehydration of the methylcyclohexanol isomers first takes place, followed by addition of hydrogen chloride.

The Stereoisomers α- and γ-2, 5-Dimethyl-4-phenylpiperidin-4-ol, α- and γ-1-Acetyl-2, 5-dimethyl-4-phenylpiperidin-4-ol, and α- and γ-1, 2, 5-Trimethyl-4-phenylpiperidin-4-ol. *N*-Acyl ⇌ *O*-Acyl and *N*-Acyl → *O*-Acyl Rearrangements of γ- and α-1-Acetyl-2, 5-dimethyl-4--phenylpiperidin-4-ol

A method based on stereospecificity has been used in the study of the structure of certain tropane alkaloids and *cis*- and *trans*-amino-alcohols[62]. It is known that "N → O migration of an acyl group proceeds readily and reversibly with the *cis*-isomer, but in the case of the *trans*-compound this process takes place only with simultaneous inversion of configuration of the carbon atom carrying the hydroxy--group. With O → N migration such inversion cannot occur"[63]:



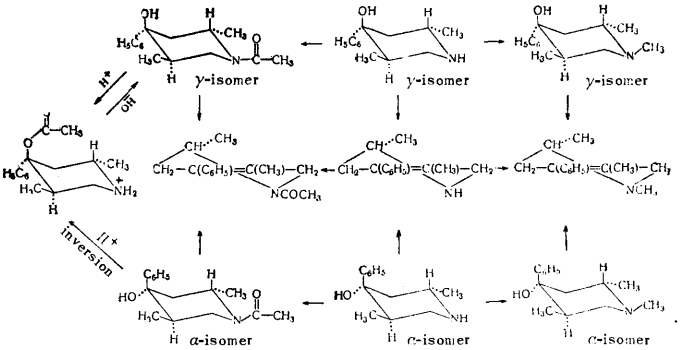
In this way, by studying the *N*-acyl ⇌ *O*-acyl rearrangement of *N*-acyl derivatives of nortropine and norpseudotropine, Fodor and Nador obtained data on the steric configuration of tropine and pseudotropine[64]:



The *cis*-position of the nitrogen bridge and the equatorial hydroxy-group in pseudotropine, and consequently their *trans*-relationship in tropine[65] have also been demonstrated by other methods, *e.g.* by measuring the rates of hydrolysis of their esters[66], and by comparison of the calculated and experimental dipole moments of tropine and pseudotropine[67].

Fodor[68] and others[69] consider the N → O acyl migration process to pass through the intermediate formation of a cyclic compound of the ortho-acid derivative type.

To use this method of conformational analysis for studying the structures of α- and γ-1, 2, 5-trimethyl-4--phenylpiperidin-4-ol, the isomers α- and γ-2, 5-dimethyl--4-phenylpiperidin-4-ol were prepared[31]. Their methylation and acetylation gave two series of genetically related stereoisomers: α- and γ-1, 2, 5-trimethyl-4-phenylpiperidin-4-ol and 1-acetyl-2, 5-dimethyl-4-phenylpiperidin-4-ol.



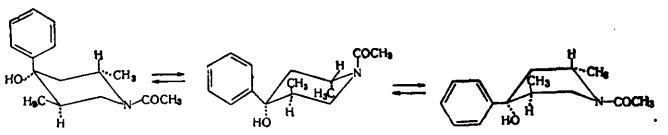
γ-1-Acetyl-2, 5-dimethyl-4-phenylpiperidin-4-ol, the steric configuration of which is identical with that of the γ-isomers of 1, 2, 5-trimethyl-4-phenylpiperidin-4-ol and 2, 5-dimethyl-4-phenylpiperidin-4-ol, readily undergoes *N*-acyl ⇌ *O*-acyl rearrangement, which indicates the *syn*-position of the hydroxy-group relative to the nitrogen atom of the piperidine ring, *i.e.* the axial position of the hydroxy-group. The reversibility of the rearrangement indicates the absence of inversion at C_4 during the process.

Under more severe conditions α-1-acetyl-2, 5-dimethyl--4-phenylpiperidin-4-ol undergoes *N*-acyl → *O*-acyl rearrangement, but the same 2, 5-dimethyl-4-phenylpiperidin--4-ol acetate is formed (as the hydrochloride) as in the *N*-acyl → *O*-acyl rearrangement of the γ-isomer. The reverse *O*-acyl → *N*-acyl rearrangement with the formation of the initial α-1-acetyl-2, 5-dimethyl-4-phenylpiperidin--4-ol does not occur: the γ-isomer is formed. Consequently, in the case of the *N*-acyl → *O*-acyl rearrangement of the α-isomer, there is inversion of the configuration at C_4.

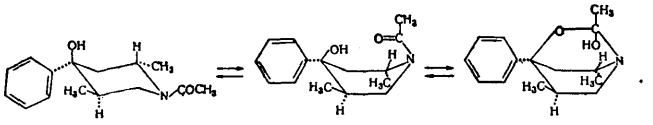
An analogous inversion of configuration of α-isomer to γ-isomer is found in the reaction of α- and γ-1-acetyl-2, 5--dimethyl-4-phenylpiperidin-4-ol with acetyl bromide[31]. These conversions of α- and γ-1-acetyl-2, 5-dimethyl-4--phenylpiperidin-4-ol indicate that the hydroxy-group is equatorial in the α-isomer and axial in the γ-isomer, and that the hydroxy-group has the same configuration in the genetically related α- and γ-1, 2, 5-trimethyl-4-phenylpiperidin-4-ol and 2, 5-dimethyl-4-phenylpiperidin-4-ol.

A necessary condition for the *N*-acyl → *O*-acyl rearrangement is the close proximity of the 4-hydroxy-group to the *N*-acyl radical. This condition is realised if the 4-hydroxy-group is axial and the *N*-substituent equatorial. This must be kept in mind, since under the conditions of N → O acyl migration α-1-acetyl-2, 5-dimethyl-4-phenylpiperidin-4-ol may be in various conformations. Of course the *N*-acyl → *O*-acyl rearrangement is only possible in the conformation with an axial hydroxy-group. However, in this conformation of the α-isomer the *N*-acyl group must be axial, on the opposite side of the ring to the hydroxy-group, so that in the boat form produced from this conformer of the α-piperidinol, the hydroxy- and acetyl groups are also at a considerable distance from one

another, and the necessary conditions for *N*-acyl → *O*-acyl rearrangement are not realised:



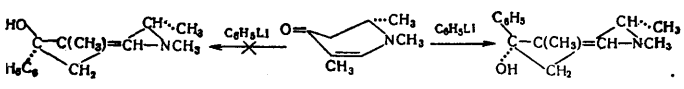
With γ-1, 2, 5-trimethyl-4-phenylpiperidin-4-ol the spatial disposition of the hydroxy- and acyl groups is such as to facilitate N ⇌ O acyl migration:



Preparation of α-1, 2, 5-Trimethyl-4-phenylpiperidin-4-ol by the Catalytic Hydrogenation of 1, 2, 5-Trimethyl-4--phenyl-Δ⁵-tetrahydropyridin-4-ol

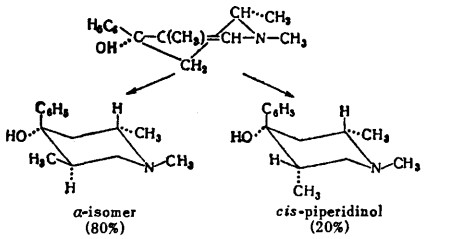
Shvetsov and Kucherov[57] have described the preparation of α-1, 2, 5-trimethyl-4-phenylpiperidin-4-ol from 1, 2, 5-trimethyl-Δ⁵-tetrahydropyrid-4-one. Reaction of this pyridone with phenyllithium gave only one of the possible isomers of 1, 2, 5-trimethyl-4-phenyl-Δ⁵-tetrahydropyridin--4-ol. From the steric point of view, this reaction should give predominantly or only the isomer of 1, 2, 5-trimethyl--4-phenyl-Δ⁵-tetrahydropyridin-4-ol having the 4-phenyl and 2-methyl radicals in the *trans*-position. In the 1, 2, 5-trimethyl-Δ⁵-tetrahydropyrid-4-one molecule all the atoms except C_2 lie almost in one plane.

The steric factor which determines the direction of attack of phenyllithium on the carbonyl group is the presence of the 2-methyl group; the *trans*-position relative to this methyl group is naturally less sterically hindered to the entry of the phenyl radical:

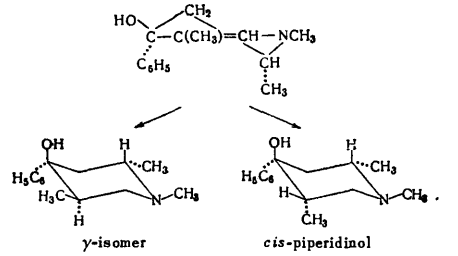


The structure of the 1, 2, 5-trimethyl-4-phenyl-Δ⁵-tetrahydropyridin-4-ol obtained was not given. Catalytic hydrogenation of the tetrahydropyridinol gave two isomers of 1, 2, 5-trimethyl-4-phenylpiperidin-4-ol: the α-isomer is known to have *trans*-methyl groups, and the β-isomer to have *cis*-methyl groups. The hydrogenation was found to give **80%** of the α-isomer and 20% of the β-isomer, undoubtedly because of steric factors which influence the adsorption of the initial tetrahydropyridinol by the catalyst and the direction of addition of the hydrogen.

Catalytic hydrogenation is known to effect *cis*-addition of hydrogen to a double bond. Hydrogenation of the 1, 2, 5--trimethyl-4-phenyl-Δ⁵-tetrahydropyridin-4-ol, which on theoretical grounds should be formed solely or predominantly in the phenyllithium synthesis (with the 4-phenyl and 2-methyl radicals in the *trans*-position), could produce two isomers of 1, 2, 5-trimethyl-4-phenylpiperidin-4-ol, the methyl groups being *trans* or *cis*:



It is not difficult to see that the adsorption of the initial 1, 2, 5-trimethyl-4-phenyl-Δ⁵-tetrahydropyridin-4-ol by the catalyst and the addition of hydrogen will be considerably hindered from the side of the ring carrying the large phenyl radical; the opposite side of the ring is not so hindered, and consequently the piperidinol with *trans*-methyl groups should be produced in predominant quantity, as was found experimentally. From this point of view, in the hydrogenation of the second, less probable isomer of 1, 2, 5--trimethyl-4-phenyl-Δ⁵-tetrahydropyridin-4-ol (having the 4-phenyl and 2-methyl radicals in the *cis*-position) the steric factors would favour the adsorption of the tetrahydropyridinol and the direction of addition of hydrogen such as to produce in predominant quantity the 1, 2, 5-trimethyl-4--phenylpiperidin-4-ol with *cis*-methyl groups; in this case conditions are unfavourable for the production of the piperidinol with *trans*-methyl groups. However, as indicated above, experiment showed the reverse.



In connection with these hydrogenation reactions of unsaturated tetrahydropyridinols, the observations of Plisov and Bogatskii on the hydrogenation of crotonic and isocrotonic acids are not without interest: *cis*-isocrotonic acid is hydrogenated more rapidly than *trans*-crotonic acid[70].

The data reviewed above confirm that α-1, 2, 5-trimethyl-4-phenylpiperidin-4-ol has an equatorial hydroxy--group.

Spectroscopic Study of the Isomeric α- and β-1, 3-Dimethyl--4-phenylpiperidin-4-ol

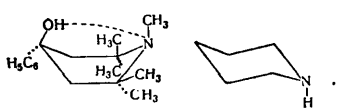
The only work which apparently contradicts the view put forward in this article on the structure of α- and β-prodine and hence of their analogues promedol and α-promedol, is that of Ziering *et al.*[49], who made a spectroscopic study of α- and β-1, 3-dimethyl-4-phenylpiperidin-4-ol (the piperidinols corresponding with α- and β-prodine) in the infra-red. The spectral characteristics in the region 3700–3510 cm^{-1} were used to estimate the degree of association of the alcohols. It was found that the α-isomer is more associated than the β-isomer. The data were interpreted by analogy with the results obtained by Smitt[71], who showed that

pentan-3-ol and 2-methylpentan-3-ol are associated to differing extents, the latter being considerably less associated than the former, and it was concluded that the presence of a methyl group adjacent the hydroxy-group limits the possible formation of an intermolecular hydrogen bond. Unfortunately, the orientation of the methyl radical relative to the hydroxy-group was not taken into account.

These considerations were used by Ziering *et al.* to determine the configurations of the α- and β-piperidinols from their degree of association. The more associated piperidinol, in their opinion, should have the 4-hydroxy- and 3-methyl groups in the relative positions which would preclude any screening effect by the methyl on the hydroxy--group, *i.e.* the *trans*-position. Assuming this α-1,3--dimethyl-4-phenylpiperidin-4-ol must contain an equatorial hydroxy-group and an axial phenyl radical. The β-isomer, which according to the results obtained is less associated, must have the reverse configuration at C_4. This contradicts numerous observations which have been made and are partially set out above.

It must be said that comparison of the abilities of aliphatic alcohols and cyclic amino-alcohols to associate (the comparison made by Ziering and coworkers) can only be relative. The association of aliphatic alcohols is due to the formation of intermolecular hydrogen bonds between the hydroxy-groups of different alcohol molecules, but with amino-alcohols the amino-nitrogen can also take part in hydrogen bonding. When considering cyclic amines, intramolecular association, *i.e.* the formation of an intramolecular bond between the hydroxy-group and the nitrogen of the piperidine ring, must also be taken into account. A necessary condition for this is for the hydroxy-group and the piperidine nitrogen to be in the *syn*-position. Intramolecular association is possible in the isomer of 1,3--dimethyl-4-phenylpiperidin-4-ol having an axial hydroxy--group. A second condition for this intramolecular association is the presence of the boat conformation. The ratio of the chair and boat conformations in piperidine derivatives is determined by the nature and position of the ring substituents. There has been a recent publication of data on the stereochemistry of 1,2,2,6,6-pentamethyl-4--phenylpiperidin-4-ol, which is an illustration of the case where the boat conformation of the piperidine ring is more stable than the chair conformation.

The chair form of 1,2,2,6,6-pentamethyl-4-phenylpiperidin-4-ol is less favoured because the molecule has three opposed axial substituents (the 2- and 6-methyl groups and the 4-hydroxy-group), and it may therefore be assumed that the conversion of the chair form to the boat form has a low energy barrier. 1,2,2,6,6-Pentamethyl--4-phenylpiperidin-4-ol is exceptionally stable towards esterification and dehydration reactions. Its chemical properties and spectroscopic data indicate that in the solid form and also in solution 1,2,2,6,6-pentamethyl-4-phenylpiperidin-4-ol exists to a considerable extent in the boat form, stabilised by intramolecular hydrogen bonding[72]. An example of the opposite case is piperidine, for which the main configuration is the chair form.



Between these two extremes lie a series of intermediate cases, in which each conformation exists to a greater or lesser extent.

Smissman and West studied intramolecular hydrogen bonding in a number of β- and γ-piperidinols by infra-red spectroscopy[73], and showed that with piperidin-3-ol and 1-methylpiperidin-3-ol the bonded and non-bonded forms are in equilibrium, since only conformations with an axial hydroxy-group form intramolecular hydrogen bonds.

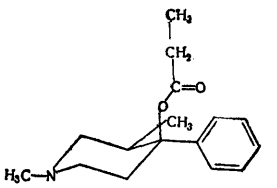
The spectrum of 1-methyl-3-phenylpiperidin-3-ol does not exhibit the frequency corresponding to a free hydroxy--group, since the preferred conformation has an axial hydroxy-group. In the case of 1-methylpiperidin-4-ol no intramolecular hydrogen bonding is observed, indicating that the hydroxy-group is equatorial.

Ziering and coworkers determined spectroscopically the total degree of association of the 1,3-dimethyl-4-phenylpiperidin-4-ol isomers; part of this is intramolecular association, but at the concentrations used (6.28% solution of piperidinol in chloroform) it is impossible to determine the intramolecular association by spectroscopic analysis, since this requires very low concentrations[74].

It may be assumed that of α- and β-1,3-dimethyl-4--phenylpiperidin-4-ol, the isomer which can form an intramolecular bond will be associated to a greater extent, *i.e.* the α-isomer, since this has an axial hydroxy-group.

X-Ray Structure Analysis of α-Prodine

A recent study dealing with the conformations of α- and β-prodine is that of Ahmed *et al.*[75], who studied single crystals of *dl*-α-prodine hydrochloride and hydrobromide by X-ray crystallography. They showed that the 3-methyl and 4-phenyl radicals are in the *trans*-position, and that the phenyl radical is equatorial and the propionoxy-group axial. The piperidine ring is in the chair form:



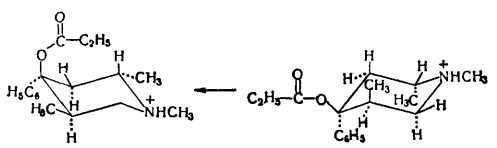
The X-ray structure data are a convincing proof that the conformations of α- and β-prodine and promedol and α-promedol determined from their chemical conversions are correct.

Anomalies in the Melting Points of Promenol and α-Promedol

Promedol (γ-1,2,5-trimethyl-4-phenyl-4-propionoxypiperidine hydrochloride) is produced in quantitative yield by treating the piperidinol with propionyl chloride in benzene, preferably in molar ratio 1:2.5.[76] Usually one recrystallisation of the technical product from a mixture of acetone and alcohol gives crystals with a distinct melting point at 198°–199°. However, on further heating the melt solidifies and begins to melt again above 215° (usually at 217°–219°). If the product of m.p. 198°–199° is subjected to further crystallisations (heating in acetone or alcohol), promedol of m.p. 221°–222° is obtained. Analytically the samples melting at 198°–199° and 221°–222° are identical, both being 1,2,5-trimethyl-4-phenyl-4-propionoxypiperidine

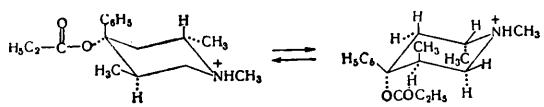
hydrochloride; on hydrolysis they yield γ-1,2,5-trimethyl-4-phenylpiperidin-4-ol, and, what is particularly important, they all have identical analgesic activity and toxicity.

The reason for the anomaly in the melting point of promedol may be that in addition to the main conformation, with equatorial phenyl and methyl groups, there exists a considerably less stable conformer in which these groups are axial; on heating, this isomer is converted into the more stable form with equatorial phenyl and methyl radicals.



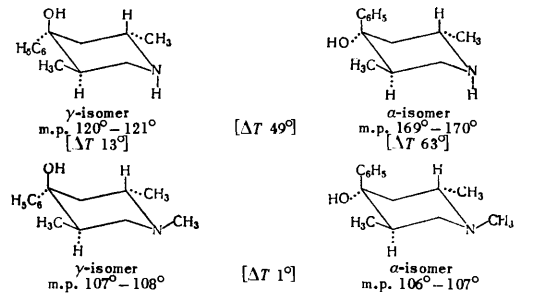
There is a particularly clear anomaly in the melting point of α-1,2,5-trimethyl-4-phenyl-4-propionoxypiperidine hydrochloride, *i.e.* α-promedol. Up to the present α-promedol has not been characterised by an accurate melting point. Samples prepared by the esterification of α-1,2,5-trimethyl-4-phenylpiperidin-4-ol with propionyl chloride in benzene usually have a low (in comparison with promedol) and diffuse melting point (98°–102°, 102°–106°, 104°–106°, 108°–112°, 132°–140°, 153°–154°). Unlike promedol, α-promedol is soluble in benzene and toluene; recrystallisation from benzene has given a sample of α-promedol melting at 153°–154°, but after being kept molten for some time, it later melted at 116°–123°.

As with promedol, the various samples of α-promedol are analytically identical, and on hydrolysis they all give α-1,2,5-trimethyl-4-phenylpiperidin-4-ol; they are all equivalent in analgesic activity and toxicity. In the same way as with promedol, with α-promedol there apparently exists, in addition to the conformation with equatorial methyl groups and an axial phenyl group, the inverse conformer with axial methyl groups and an equatorial phenyl radical. This conformation apparently exists to a greater extent in α-promedol than in promedol, and there is a state of dynamic equilibrium, which is not found with promedol. The large size of the phenyl radical in the axial position and its 1,3-interaction with the hydrogens at C_2 and C_6 favour the formation of the inverse conformer having an equatorial phenyl radical:



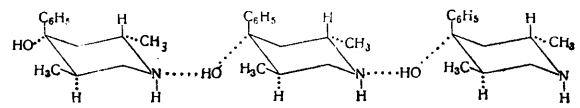
Structure and Melting Points of the Isomeric α- and γ-1,2,5-Trimethyl-4-phenylpiperidin-4-ol and 2,5-Dimethyl-4-phenylpiperidin-4-ol

α- and γ-1,2,5-Trimethyl-4-phenylpiperidin-4-ol have very close melting points (α-isomer, m.p. 106°–107°, γ-isomer, m.p. 107°–108°), but α- and γ-2,5-dimethyl-4-phenylpiperidin-4-ol melt at very different temperatures (α-isomer, m.p. 169°–170°, γ-isomer, m.p. 119°–121°), and there are also large differences in the melting points of the 2,5-dimethyl-4-*p*-tolylpiperidin-4-ol and 2,5-dimethyl-4-benzylpiperidin-4-ol isomers.



On passing from the piperidinols with a secondary amino-group to those with a tertiary nitrogen atom, there is a fairly large change in melting point in the α-series and a comparatively small change in the γ-series.

The higher melting point of α-2,5-dimethyl-4-phenyl piperidin-4-ol (and also of the analogous piperidinols of the α-series) in comparison with the γ-isomer may be due to this conformation, with an equatorial hydroxy-group and an unscreened piperidine nitrogen (the hydrogen on the nitrogen being axial), favouring intermolecular association, which is considerably more in evidence in the α-isomer than in the γ-isomer.



The steric configuration of the γ-isomer, with an axial hydroxy-group, hinders intermolecular association, and intramolecular association is evidently present only to a slight extent. This causes the large difference in melting point between these isomeric alcohols.

Intermolecular association due to hydrogen bonding between the hydroxy-group of one piperidinol molecule and the piperidine nitrogen of another is greatly weakened if the hydrogen on the nitrogen is replaced by an alkyl radical, and hence, there is a large change in melting point on passing from α-2,5-dimethyl-4-phenylpiperidin-4-ol to α-1,2,5-trimethyl-4-phenylpiperidin-4-ol. This is not observed in the analogous conversions in the γ-series.

From what has been said above, we may consider the question of the steric configuration of the efficient analgesics promedol and α-promedol to be solved. The task now is to obtain stereochemical analogues of α-promedol and β-prodine, which should prove to be highly effective analgesics.

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ELECTROLYTIC REDUCTION OF ACETYLENIC BONDS

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1. INTRODUCTION

The hydrogenation of acetylenic bonds in organic compounds takes place stepwise and can in general be represented as follows:

$$-C\equiv C- \xrightarrow{2H} -CH=CH- \xrightarrow{2H} -CH_2-CH_2-$$

By choosing certain conditions, the hydrogenation can be stopped at the stage at which the ethylenic compound is produced. Reduction of acetylenic to ethylenic compounds is important in preparative organic chemistry and much research [1] has been devoted to a study of this reaction. However, the problem of the selective hydrogenation of acetylenic to ethylenic bonds has not yet been solved satisfactorily.

One of the possible ways of both partial and complete hydrogenation of acetylenic bonds is their electrochemical reduction. Since a considerable amount of work has been devoted to this electrochemical reduction, it is useful to discuss the prospects of employing electrolysis for carrying out reactions of this type.

2. MECHANISM OF THE ELECTROLYTIC REDUCTION OF ACETYLENIC BONDS

The mechanism of the electrolytic reduction of acetylenic compounds depends, to a considerable degree, on their general structure. Isolated acetylenic bonds (not conjugated with ethylenic bonds or with electron-accepting functional groups) are easily reduced by catalytically activated hydrogen. In such cases the electrolytic reduction process does not differ in principle from catalytic hydrogenation [2]. Study of the reaction mechanism for catalytic and electrolytic reduction of acetylenic alcohols by the charging-curve method showed that their electrolytic reduction takes place at more negative potentials than the discharge of hydrogen ions and cannot therefore be brought about by protons [3,4].

With the mechanism discussed, the electrolytic reduction takes place at cathodes of platinum, palladium, nickel, cobalt, and other metals which possess a low hydrogen overpotential.

The mechanism of electrolytic reduction at copper and silver cathodes did not receive a careful examination, but it has been suggested that intermediate organometallic complexes play an active part in this process [5-8]. One piece of evidence for this hypothesis is, for example, the formation of an organo-copper compound in the electrolytic reduction of dimethylethynylmethanol at a copper cathode. This compound decomposes and separates out as a precipitate of composition C_5H_7OCu when the solution obtained on reduction is saturated with carbon dioxide [6]. In the light of these ideas, the decreased tendency of phenylethynylmethanol to electrolytic reduction at a copper cathode is explained by the instability of the copper complexes it yields.

Acetylenic compounds containing double bonds or electron-accepting functional groups conjugated with the acetylenic bonds are reduced on metals with a high hydrogen overpotential (lead, mercury) by an electronic mechanism. Such compounds (which we shall designate as having "activated acetylenic bonds") are reduced at a dropping mercury cathode; this permits a detailed study of the mechanism of their electrolytic reduction [10-17]. For example, in the reduction of phenylacetylene and diphenylacetylene in aqueous dioxane at a dropping mercury cathode one four-electron wave, independent of the pH, is observed; this indicates that under these conditions the reduction takes place in one step with complete saturation of the acetylenic bond. The mechanism can be expressed thus:

$$R + e \rightleftharpoons R^- \text{ (potential-determining stage)},$$

$$R^- + e \longrightarrow R^{2-},$$

$$R^{2-} + 2H_2O \longrightarrow RH_2 + 2OH^- \text{ (fast)}.$$

The ethylenic compound formed requires for its reduction a less negative potential and is immediately reduced, by a similar scheme, to the saturated compound.

The reduction mechanism changes somewhat when some non-aqueous solvents, *e.g.* dimethylformamide, are used [10,11,18]. In this solvent reduction takes place with the formation of intermediate radical-anions as shown by the presence of two one-electron waves in the polarogram.

For example, the reduction of diphenylacetylene can be expressed as follows:

$$\text{first wave } C_6H_5C\equiv CC_6H_5 + e \rightarrow [C_6H_5\dot{C}=\dot{C}C_6H_5]^- \text{ (slow)},$$

$$\text{second wave } [C_6H_5\dot{C}=\dot{C}C_6H_5]^- + e \rightarrow [C_6H_5\dot{C}=\dot{C}C_6H_5]^{2-} \text{ (slow)},$$

$$[C_6H_5\dot{C}=\dot{C}C_6H_5]^{2-} + 2H^+ \rightarrow C_6H_5CH=CHC_6H_5.$$

The stability of the free radical-anion is confirmed by the fact that electrolytic reduction of diphenylacetylene in the presence of carbon dioxide is accompanied by the formation of diphenylmaleic anhydride and diphenylfumaric acid. The formation of the latter can be described by the following scheme [10]:

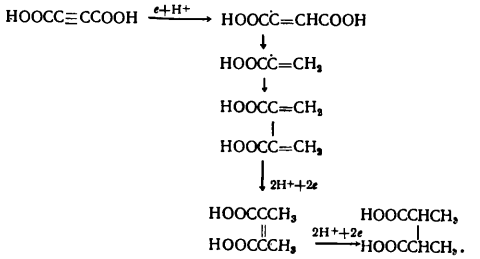
$$[C_6H_5\dot{C}-\dot{C}C_6H_5]^- + CO_2 \rightarrow C_6H_5C(COO^-)=\dot{C}C_6H_5,$$

$$C_6H_5C(COO^-)=\dot{C}C_6H_5 + e \rightarrow C_6H_5C(COO^-)=\dot{C}C_6H_5,$$

$$C_6H_5C(COO^-)=\dot{C}C_6H_5 + CO_2 \rightarrow C_6H_5C(COO^-)=CC_6H_5(COO^-).$$

The reduction of acetylenedicarboxylic acid takes place by a similar scheme, but the corresponding free radical-anion is unstable and becomes decarboxylated [15]; the

radicals formed dimerise and the dimeric product is reduced at the same potential:



3. EFFECT OF ELECTROLYSIS CONDITIONS

a. Electrode material. The nature of the reduction products is determined to a considerable extent by the cathode material used. At platinum, platinised platinum, palladium, nickel, and cobalt cathodes reduction usually takes place without stopping at the ethylenic compound stage, a mixture of both ethylenic and saturated compounds being formed[6,9,19-25]. However, since the ethylenic and acetylenic bonds are electrolytically hydrogenated at different rates and at somewhat different potentials on platinum-group metals[8,20], it is possible to achieve selective hydrogenation of the acetylenic bond on these metals using electrolysis at a controlled potential.

The most generally useful electrode materials for selective hydrogenation of acetylenic to ethylenic compounds are copper, silver, and copper–silver alloys[6,7,9,20-22,24,26-43].

Preparation of the cathode surface plays a big part in successful electrolytic reduction. Preliminary oxidation by heating in a burner flame is recommended for creating an active surface on a copper cathode. During the work the activity of the copper electrode is quickly lost and it must be renewed by oxidation before each operation. Silver and copper–silver electrodes possess considerably greater stability. The latter are most conveniently prepared by immersing a purified copper cathode in dilute aqueous silver nitrate for some minutes. Such a cathode can be used in several successive operations without any additional treatment. However, even with copper–silver cathodes it is apparently impossible to secure prolonged working of the electrode without activation.

As previously noted, compounds having "activated" acetylenic bonds are reduced at a mercury cathode[12-15,18], complete saturation of the acetylenic bond taking place. These compounds are also reduced by alkali metal amalgams[26]. In work with a mercury cathode the formation of heavy organomercury compounds as well as reduction products is observed[6,9,21,22].

In addition to a mercury cathode, it is possible to use other metals with a high hydrogen overpotential, for example zinc, for the electrolytic reduction of compounds with "activated" acetylenic bonds. A zinc cathode also loses its activity quickly, and for stable working addition to the solution of a zinc salt and the periodic removal of the zinc sponge precipitated on the cathode are recommended.

b. Current density. At a platinum cathode an increase in current density favours formation of a saturated compound[46]. In the hydrogenation of vinylacetylene at a copper amalgam cathode, raising the current density from 1 to 2 A dm^{-2} considerably increases the formation of tarry products which settle on the cathode surface and lead to a reduction in the yield of hydrogenation products from 45 to 36% (based on the reagent). When the current density is doubled, the product yield in the reduction of dec-5-yne at a rotating nickel cathode falls from 75 to 50%.[47]

A reduced yield of reduction products with increasing current density was observed in the electrolytic reduction of butynediol at a copper–silver cathode[43]. The authors explain this by a rise in the cathode potential and give the following dependence of the yield of butenediol on that potential:

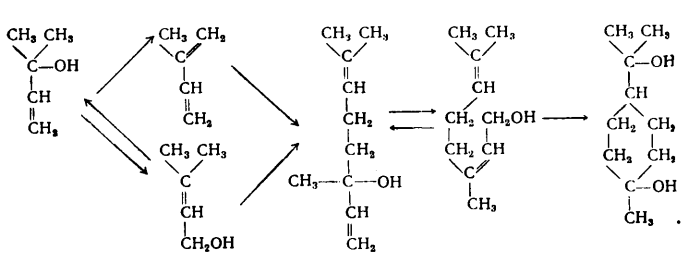
Cathode potential, V	Current yield of butenediol, %
1.50	55.0
1.40	57.5
1.30	65.8
1.20	73.7

In connection with what has been written the selective hydrogenation of acetylenic compounds is usually carried out at current densities not exceeding 1–2 A dm^{-2} (100–200 A m^{-2}), namely:

	A dm^{-2}
Dimethylethynylmethanol	0.5–1.0[28]
	0.77[31]
Dimethyl(vinylethynyl)methanol	0.5–2.0[38]
Methylcyclopropylethynylmethanol	0.5–1.0[39]
Diacetylene glycols	0.8[41]
1-Ethynylcyclohexanol	0.5–0.6[42]
Butynediol	0.05–1.5[33]
Vinylacetylene	1–1.5[34]

c. Choice of electrolyte and solvent. There is no essential difference in the use of an alkaline or acidic electrolyte for hydrogenation of a triple bond[47,48]. For example, acetylene is hydrogenated to ethylene to the same extent both in 10% sulphuric acid and in 10% sodium hydroxide solution[47].

However many ethylenic compounds are unstable in acidic solutions and undergo further changes. For example, in the electrolytic reduction of acetylene in 65% sulphuric acid the ethylene formed is absorbed by sulphuric acid with the formation of ethyl hydrogen sulphate, which hydrolyses to ethyl ether[46]. Even more complex changes are observed in the electrolytic reduction of acetylenic alcohols in acidic solutions[49,50]. Thus, in the electrolytic reduction of dimethylethynylmethanol, apart from an ethylenic alcohol, there is partial formation of geraniol, linaloöl, and terpene hydrate, the formation of which can be represented by the equations



Therefore to avoid possible secondary processes, the electrolytic reduction is usually carried out in a weakly alkaline medium, using as electrolyte dilute aqueous sodium hydroxide[6,7,24-26,30,32,35,36,40,41], potassium hydroxide[20,33,43], or sodium bicarbonate[19,28,37-39,42].

Aqueous sodium chloride can also be used as electrolyte and the anodic process can then be employed for the simultaneous production of elementary chlorine[51].

Since most acetylenic compounds are weakly soluble in water, addition of a solvent, usually ethanol, to the electrolyte is recommended[7,26,30,32,35,39,41]. For polarographic measurements, aqueous ethanol[13], aqueous dioxane[11,12,14], and anhydrous dimethylformamide[10,18] have been used.

d. Concentration of substance being electrolysed. Although, for the maximum rate of reduction and for avoiding concentration phenomena, it is desirable to work with the highest possible concentrations of organic substances, secondary processes leading to a fall in the yield of reduced compounds are observed at high concentrations. Thus, in the electrolytic reduction of dimethylethynylmethanol the following dependence of yield of dimethylvinylmethanol on the reactant concentration is found[9,3]:

Dimethylethynylmethanol concentration, g litre^{-1}	Yield of dimethylvinylmethanol, %
50	78.3
100	72.6
150	73.0
200	69.5

Although the highest rate of hydrogenation is observed with a concentration of 150 g litre^{-1}, a reduction in the concentration of the substance being reduced favours formation of dimethylvinylmethanol.

An increase in the concentration of butynediol in solution reduces the yield of butenediol[43].

In most researches the effect of reactant concentration on the reduction process was not studied, and dilute solutions, not exceeding 5–10%, were used[1,7,26,28,30,32,33,41,42]. Stirring of the solution is said to favour the reduction process[3].

e. Temperature. In most cases a change in temperature has almost no effect on the course of the reduction process. Thus, the composition of the products in the reduction of dimethylethynylmethanol does not vary significantly on changing the temperature from 15° to 50°,[28] in the reduction of butynediol on passing from 0° to 80°,[33] and in the reduction of acetylenic hydrocarbons at a spongy nickel cathode on passing from 20° to 80°.[47] However, at higher temperatures evaporation losses of the substance being hydrogenated increase significantly and formation of tarry products is observed[9]. Therefore to obtain pure substances it is desirable to use low temperatures.

4. EFFECT OF THE STRUCTURE OF THE ORGANIC SUBSTANCE ON THE ELECTROLYTIC REDUCTION PROCESS

Results for the electrolytic reduction of various acetylenic hydrocarbons are given in Table 1. The compounds studied were mainly those with "activated" acetylenic bonds, *i.e.* hydrocarbons in which the acetylenic bond adjoins a benzene ring or is conjugated with an unsaturated carbon–carbon bond. In the latter case reduction starts at the acetylenic bond and is evidently not very selective because a complex mixture of products is formed in the electrolytic reduction of divinylacetylene on various electrode materials[26].

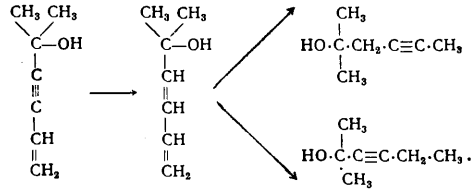
A more complicated carbon skeleton in the acetylenic compound and especially branching of the carbon chain leads to some increase in the reduction potential of the acetylenic bond, which is apparently due to steric hindrance[14].

The electrolytic reduction of acetylenic alcohols and their ethers has been studied in most detail (see Table 2). All the compounds studied can be reduced to ethylenic alcohols sufficiently selectively and, apart from the necessity of choosing a suitable solvent for substances not readily soluble in water, the structure of the compounds being reduced does not affect substantially the course of the electrochemical process.

The experiments on the electrolytic reduction of butynediol at a copper–silver cathode with a controlled potential, in which an exceptionally pure hydrogenation product was obtained[20,43], deserve special attention.

When the alcohol molecule being reduced contains two conjugated acetylenic bonds or an ethylenic bond conjugated to an acetylenic bond, the composition of the reduction products is substantially more complicated. The intermediate products are diene compounds which undergo intramolecular rearrangements; dehydration processes are also possible. All things considered, these secondary processes lead to the formation of a complex mixture of products.

Thus, for example, in the hydrogenation of vinylethynyldimethylmethanol the corresponding diene alcohol is formed and, on account of its instability, is partially isomerised, a mixture of at least three isomeric products being formed[5]:



Similar transformations, complicated by dehydration, are observed in the electrolytic reduction of 2,7-dimethyl-2,7-dihydroxyocta-3,5-diyne[41].

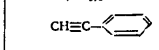
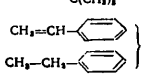
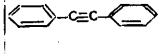
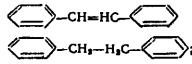
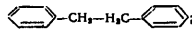
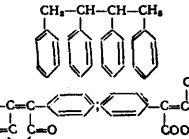
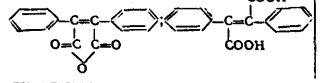
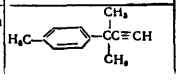
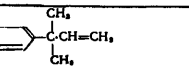
The reduction of other acetylenic compounds has been little studied (see Table 3). Acetylenic bonds activated by polar groups (COOH, > CO, CH_2Br) are reduced at a dropping mercury cathode at considerably more positive potentials than enyne hydrocarbons.

Interesting hydrodimerisation processes are observed in the electrolytic reduction of acetylenedicarboxylic acid and its monoethyl ester[15]. The mechanism of this reaction has been discussed previously.

5. INDIRECT USE OF ELECTROLYSIS IN THE REDUCTION OF ACETYLENIC COMPOUNDS

A number of processes have been described in which the indirect use of electrochemical processes was proposed for the selective reduction of acetylenic to ethylenic compounds. For example, it is proposed to use electrolysis to

TABLE 1. Electrolytic reduction of acetylenic hydrocarbons.

	Acetylenic compound	Reduction product	Cathode material	Electrolyte	Solvent	Current density, A dm^{-2}	Reduction potential, $E_{1/2}$	Yield, % acc. to substance	Yield, % acc. to current	References
1	2	3	4	5	6	7	8	9	10	11
C_3	$HC\equiv CH$	$CH_2=CH_2$; $CH_3\cdot CH_3$	Pt	acid; alkali						48,60,61
		$C_6H_4OSO_3$	Pt	65% sulphuric acid						46
		$CH_2=CH_2$	Co,Ni	alkali						25
		$CH_2=CH_2$	Zn							45
C_4	$CH_2=CH-C\equiv CH$	$CH_2=CH-CH=CH_2$	Cu(Pt)	Na_2CO_3		1 : 1.5		95.8		34
		$CH_3-CH=CH-CH_3$	Cu(Pt)					100.0		27
		$CH_2-CH_2\cdot CH=CH_2$	Hg	$(C_2H_5)_4NBr$			—2.23			12
		$CH_3-CH_2\cdot CH=CH_2$	Hg	$(C_4H_9)_4NI$	75% dioxane		—2.4			14
	$CH\equiv C-C\equiv CH$	$CH_3-CH_2-C\equiv CH$	Hg	$(C_2H_5)_4NBr$			—2.27			12
C_5	$CH_2C\equiv C-CH=CH_2$	$CH_3\cdot CH_2\cdot CH_2\cdot CH=CH_2$	Hg	$(C_4H_9)_4NI$	ditto		—2.63			14
	$CH\equiv C-C(CH_3)=CH_2$	$CH_3-CH_2-C(CH_3)=CH_2$	Hg	$(C_4H_9)_4NI$	»		—2.51			14
	$CH\equiv C-CH=CH-CH_3$	$CH_3\cdot CH_2\cdot CH=CH\cdot CH_3$	Hg	$(C_4H_9)_4NI$	»		—2.61—2.62			14
C_6	$CH_2=CH\cdot C\equiv C\cdot CH=CH_2$	$CH_2=CH-CH=CH-CH=CH_2$	Cu	5% NaOH	alcohol	2			20	26
		$CH_2=CH-C=CH-CH=CH_2$								
		$CH_2=CH-C\equiv C-CH_2-CH_3$	CuHg	ditto	»	2			42	26
		$CH_2-CH=C=CH-CH_3$	Ni	»	»				20—22	26
			Hg	»	»					
			Hg	$(C_4H_9)_4NI$	dioxane		E_1=—2.07 E_2=—2.55		42	26 12
			Hg	$(C_4H_9)_4NI$	dimethyl-formamide		E_1=—1.74 E_2=—2.23			18
	$CH_2\cdot CH_2\cdot C\equiv C\cdot CH=CH_2$	$CH_2\cdot CH_2\cdot CH_2CH_2\cdot CH=CH_2$	Hg	$(C_4H_9)_4NI$	75% dioxane		—2.60—2.61			14
	$CH_2\cdot C\equiv C\cdot C(CH_3)=CH_2$	$CH_2\cdot CH_2\cdot CH_2\cdot C(CH_3)=CH_2$	Hg	$(C_4H_9)_4NI$	ditto		—2.80			14
	$CH\equiv C\cdot C(CH_3)=CH-CH_3$	$CH_2\cdot CH_2\cdot C(CH_3)=CH-CH_3$	Hg	$(C_4H_9)_4NI$	»		—2.56—2.55			14
C_7	$CH\equiv C\cdot C_4H_{11}$	$CH_2=CH\cdot C_4H_{11}$	Ni	H_2SO_4; KOH	96% alcohol				65	47
C_8	$C_4H_9C\equiv C\cdot CH=CH_2$	$C_4H_9\cdot CH_2\cdot CH_2\cdot CH=CH_2$	Hg	$(C_4H_9)_4NI$	75% dioxane		2.56			14
	$CH\equiv C-C(CH_3)=CH_2$	$CH_3\cdot CH_2\cdot C(CH_3)=CH_2$	Hg	$(C_4H_9)_4NI$	ditto		—2.58—2.59			14
			Ni	H_2SO_4; KOH	95% alcohol					47
			Hg	$(C_4H_9)_4NI$	70% dioxane		—2.376			11,12
	$C_6H_7C\equiv C\cdot C_6H_7$	$C_6H_7\cdot CH=CH\cdot C_6H_7$	Ni	H_2SO_4; KOH	95% alcohol				80	47
C_9	$CH_3-C\equiv C-C(CH_3)=CH_2$	$CH_3\cdot CH_2\cdot CH_2\cdot C(CH_3)=CH_2$	Hg	$(C_4H_9)_4NI$	75% dioxane		—2.83—2.84			14
C_{10}	$C_4H_{10}-C\equiv C-CH=CH_2$	$C_4H_{11}CH_2\cdot CH_2\cdot CH=CH_2$	Hg	$(C_4H_9)_4NI$	ditto		—2.55—2.54			14
	$C_3H_6C\equiv C-C(CH_3)=CH_2$	$C_3H_7\cdot CH_2\cdot CH_2\cdot C(CH_3)=CH_2$	Hg	$(C_4H_9)_4NI$	»		—2.82			14
	$C_4H_9C\equiv C\cdot C_4H_9$	$C_4H_9CH=CHC_4H_9$ (*cis*)	Ni	H_2SO_4; KOH	95% alcohol				75	47
			Ni	H_2SO_4; KOH	ditto				80	47
			Hg	$(C_4H_9)_4NI$	80% alcohol		—2.195			11,12
			Hg	$(C_4H_9)_4NI$	75% dioxane					10
	+CO_2		Hg	$(C_4H_9)_4NI$	ditto					10
C_{11}			CuAg	NaOH	alcohol			80		7

obtain highly active zinc sponge, which is employed as a reducing agent for a number of acetylenic compounds[52]. It is thought possible to use sodium amalgam, which is easily obtained electrolytically, for reducing vinylacetylene to butadiene[26]. However the most effective selective reducing agent for acetylenic bonds is chromium(II) chloride[1]. The reduction of acetylene, for example, with this reagent can be represented by

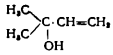
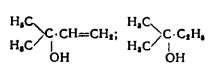
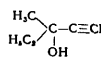
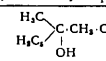
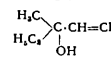
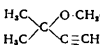
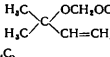
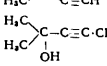
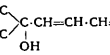
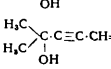
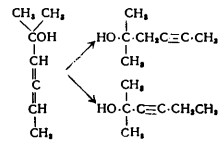
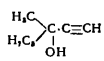
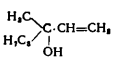
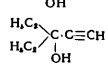
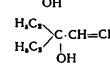
$$2CrCl_2+2HCl+C_2H_2 \rightarrow 2CrCl_3+C_2H_4.$$

The chromium(II) chloride is converted into the corresponding compound of tervalent chromium from which a bivalent compound is easily regenerated electrochemically. Construction of an electrolysis cell, in which the cathodic process results in the regeneration of the bivalent chromium,

$$2CrCl_3+2H \rightarrow CrCl_2+2HCl,$$

and the anodic process in the production of chlorine gas, has been proposed. The electrodes are graphite rods. At

TABLE 2. Electrolytic reduction of acetylenic alcohols and their ethers.

	Acetylenic compound	Reduction product	Cathode material	Electrolyte	Solvent	Current density, A dm^{-2}	Reduction potential	Yield, % acc. to substance	Yield, % acc. to current	References
1	2	3	4	5	6	7	8	9	10	11
C_4	$HOCH_2C{\equiv}C{\cdot}CH_2OH$	$HOCH_2CH{=}CH{\cdot}CH_2OH$	Ag CuAg	NaOH 2% KOH		1.0	1.2		90	33 20,43
C_5			Cu CuAg any metal covered with silver Ni sponge PtPt	Na_2CO_3		0.5—1.0		95 87		6,9,21, 22,28 31 24,39 3,6
		 geraniol, linaloöl, terpene hydrate	Cu	H_2SO_4						49,50
C_6			PtPt					46		6
			CuAg	Na_2CO_3				59.6— —63.4		9
C_7			CuAg Cu	NaOH	alcohol					40
			Cu CuAg	Na_2CO_3	»			80—90		35 5
			Cu	Na_2CO_3	0.5—2.0			57—60		19,38
			CuAg	NaOH				75—80		37
			CuAg	NaOH	alcohol			80—82		32
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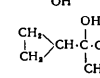
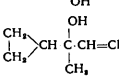
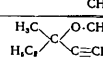
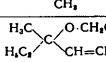
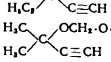
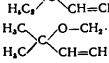
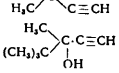
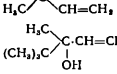
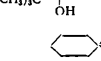
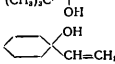
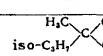
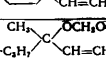
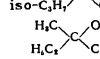
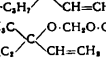
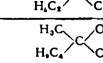
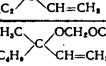
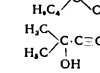
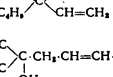
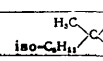
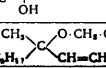
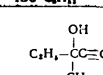
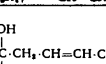
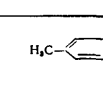
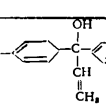
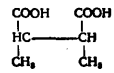
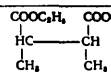
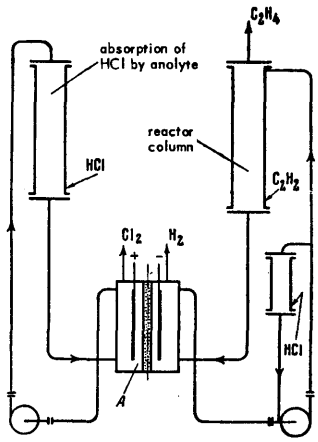
			Cu	$NaHCO_3$		0.1—0.05		60—70		39
C_8			Cu AgCu	1% NaOH	»					40
			Cu AgCu	1% NaOH	»					40
			CuAg	1% NaOH	»			52		30
			Cu	1% $NaHCO_3$	»			88—83		36,42
C_9			CuAg	1% $NaHCO_3$	»					40
			CuAg	1% $NaHCO_3$	»					40
C_{10}			CuAg	1% $NaHCO_3$	»					40
			CuAg							
			Cu	NaOH	»					34,41
C_{11}			CuAg	1% $NaHCO_3$						40
C_{12}			CuAg							5 7
C_{16}			Cu AgCu	NaOH						

TABLE 3. Electrolytic reduction of other acetylenic compounds.

	Acetylenic compound	Reduction product	Cathode material	Electrolyte	Solvent	Current density, A dm^{-2}	Solution pH	Reduction potential	Current yield, %	References
C_3	$CH_2BrC{\equiv}CH$		Hg	buffer solutions	50% alcohol		5.45 9.10	—0.84 —0.91		13
C_4	$HOOCC{\equiv}CCOOH$		Hg							15
C_8	$C_2H_5OOC{\cdot}C{\equiv}C{\cdot}COOH$		Hg							15
C_9	$C_2H_5OOC{\cdot}C{\equiv}C{\cdot}COOC_2H_5$	$C_2H_5OOC{\cdot}CH_2{\cdot}CH_2{\cdot}COOC_2H_5$	Hg							15
C_9	$C_6H_5C{\equiv}C{\cdot}CHO$		Hg	buffer solutions	50% alcohol		1.3 4.9 7.2 8.6	—0.64 —0.84:—1.30 —0.95:1.25 —1.25		13
C_{15}	$C_6H_5C{\equiv}C{\cdot}CO{\cdot}C_6H_5$		Hg	ditto	ditto		1.3 4.9 7.2 8.6	—0.53: 0.96 —0.74: 1.06 —0.89: 1.08 —1.08: 1.57		13
C_{17}	$C_6H_5C{\equiv}CCOC{\equiv}CC_6H_5$		Hg	»	»		1.3 7.2 8.6 11.3	—0.39 —0.73 —0.85 —0.93		13



a cathodic current density of 7.8–9.3 A dm^{-2} and a temperature of 20°–25° the chromium salt is reduced with a current yield up to 90%.[53-56]

A scheme for the technical reduction of acetylene to ethylene is shown in the Figure. The electrolytic cell *A* is a sealed chamber divided by a porous diaphragm. The anolyte is circulated, by a pump, through an absorption column where the loss of chloride owing to liberation of chlorine gas is made up by absorption of HCl. The catholyte similarly passes through another absorption column where sufficient HCl is absorbed to compensate for its loss by migration to the anolyte through the diaphragm. The catholyte is supplied by the pump to the reactor where acetylene is continuously reduced by chromium(II) chloride, and then, with a lowered chromium(II) chloride content, is returned to the electrolytic cell. This method has been used to reduce acetylene to ethylene[53,57], and to reduce diacetylene[58] and vinylacetylene[59] to butadiene. However, the low rate of reaction of the chromium(II) chloride with acetylenic compounds does not allow a sufficiently effective apparatus to be set up, and hence the method has not found any appreciable industrial application.

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This review shows that many acetylenic compounds can be reduced electrochemically, both to ethylenic and to saturated derivatives.

From the preparative viewpoint the possibility of accomplishing partial hydrogenation of an acetylenic to an ethylenic bond electrochemically at a silver or copper–silver cathode at a controlled potential deserves special attention.

Electrolysis can be applied successfully to the regeneration of chromium(II) compounds, which are effective in the selective reduction of acetylenic bonds.

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THE METHOD OF MOLECULAR ORBITALS AND SPIN DENSITY IN PARAMAGNETIC RESONANCE

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INTRODUCTION

The development of the technique of electron paramagnetic resonance and of nuclear magnetic resonance has made it possible to investigate the behaviour of a large number of molecules and free radicals in a magnetic field. Quantum chemistry and one of its techniques, the molecular orbital method, play an important part in the theoretical interpretation of paramagnetic resonance spectra. Application of this method to the study of organic free radicals, molecules in which an unpaired electron is linked with the whole system, *i.e.* is regarded as located in a molecular and not an atomic orbital, can give valuable information about the structure of these compounds.

A large number of free radicals have been studied by the electron paramagnetic resonance method[1-3], and it is of interest to give a theoretical explanation based on the molecular orbital method of new characteristics such as spin density, the magnitude of which can be judged from the hyperfine structure of the electron paramagnetic resonance spectra.

Let us examine briefly the origin of hyperfine structure in the spectra of paramagnetic substances. In an external magnetic field the spin of an unpaired electron is known to acquire two orientations, either in the same or in the opposite direction to the field, corresponding to two energy states, $-\frac{1}{2}g\beta H_0$ and $+\frac{1}{2}g\beta H_0$ (where H_0 is the external magnetic field, β the Bohr magneton, and g the spectroscopic splitting factor, the so-called "g-factor", which for a free electron has a value of 2.0023). When a high-frequency field is applied, transitions from one energy level to the other may occur if the condition of resonance is satisfied, *i.e.* if the energy quantum of the high-frequency field is equal to the difference between the energy levels: $h\nu = g\beta H_0$, where h is Planck's constant and ν the frequency of the field (Fig. 1). In any system a larger number of electrons are present in the lower, ground level than in a higher level, and therefore more transitions will occur from the lower level: energy will be absorbed from the high-frequency field, and a resonance absorption line will be produced.

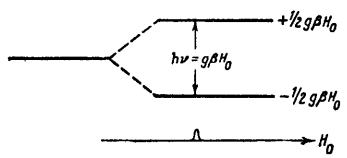


Fig. 1.

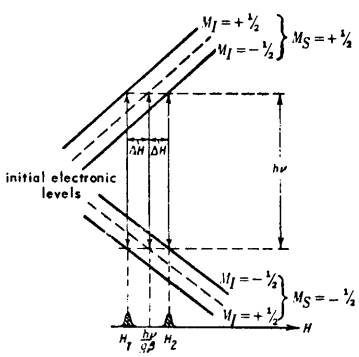


Fig. 2. Hyperfine splitting produced by coupling with one proton.

If the unpaired electron is located in a molecular orbital embracing one or more nuclei having magnetic moments, the energy levels of the electron will be split owing to interaction of the electron with these nuclei. In the particular case of interaction with one proton (nuclear spin $I = \frac{1}{2}$) two spin orientations of the proton are possible, parallel and antiparallel to the electron spin and the direction of the field; *i.e.* each electronic level is split into two. Since an electronic transition is not accompanied by a change in orientation of the nuclear spin, the selection rule is written $\Delta M_I = 0$, *i.e.* transitions will take place between states having identical components of the nuclear spin. The values of the magnetic field at which absorption of energy from the high-frequency field will occur will then be

$$H_1 = \frac{h\nu}{g\beta} - \Delta H,$$

$$H_2 = \frac{h\nu}{g\beta} + \Delta H \text{ (Fig. 2).}$$

Thus interaction with the proton results in two lines instead of one. This is termed "hyperfine splitting", and the complex structure of the spectra is termed a "hyperfine structure". The number of components of the hyperfine structure is $2I + 1$, where I is the nuclear spin. When an electron interacts with one nucleus, all components of the hyperfine structure are separated from one another by the same distance, which is termed the "hyperfine coupling constant". When an unpaired electron interacts with more than one nucleus, it is necessary to introduce several hyperfine coupling constants.

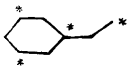
Since the hyperfine splitting is caused by interaction of the electron with the nucleus, the constant should clearly depend on the unpaired-electron density on the given nucleus. In 1956 McConnell suggested[4] that in aromatic hydrocarbon radicals there is a direct relation between the proton splitting a_H and the unpaired-electron density ρ_C on the carbon atom adjacent to the proton: $a_H = Q\rho_C$, where Q is a constant. (The theoretical derivation of this relation and the origin of a hyperfine structure in aromatic free radicals will be discussed in Section 1.)

Subsequent work by Weissman, de Boer, and others showed that the McConnell relation is obeyed quite accurately with positive and negative ions of naphthalene[5,6], anthracene[6-8], and also many other aromatic hydrocarbon radicals. Theoretical values can be calculated for the unpaired-electron density in these compounds by the simple Hückel molecular orbital method[9]. Since, when one unpaired electron is present in a hydrocarbon radical system, the total density $\sum_{i=1}^{N} \rho_{iC}$ is unity (N being the number of carbon atoms in the radical), it is evident from the above equation that the constant Q is identical with the total proton splitting. The overall width of the spectrum with the ions of naphthalene and anthracene and in some other aromatic radicals is about 28 oersteds: *i.e.* the constant Q has a value of 28 oersteds.

As experimental data accumulated, it became clear that by no means all the results could be explained on the basis of McConnell's hypothesis about the relation between hyperfine structure and unpaired-electron density. Thus, for example, the total proton splitting in the negative pyrene ion[6] and that in perinaphthenyl[10] are far larger than 28 oersteds (32 and 49 oersteds respectively).

Similarly, theoretical calculations of the unpaired-electron density by the Hückel method cannot explain, either

qualitatively or quantitatively, the spectra of alternant hydrocarbons containing an odd number of carbon atoms. The atoms in the molecule of an alternant hydrocarbon can, by definition, be divided into two groups, such that a member of one group, say an atom marked by an asterisk, has only atoms of the other system (without an asterisk) as neighbour:



If the molecule contains an odd number of carbon atoms, the Hückel theory predicts that the coefficients for the atomic orbitals of the atoms without asterisks are zero, and hence zero unpaired-electron densities for these atoms.

Brovetto and Ferroni[11] pointed out that hyperfine interaction may be either positive or negative, and in general, therefore, it is necessary to calculate not the unpaired-electron density but the spin density, which may be positive or negative depending on the polarisation of the z-component of the electron spin. In this case the total splitting of the resonance spectrum is $Q\sum_i \rho_C$, *i.e.* the sum of the moduli taking into account negative values of the spin density may be greater than unity, and therefore the splitting itself becomes greater than 28 oersteds. Negative spin densities can be obtained in the valence bond method. In particular, if all the $2n + 1$ carbon atoms in an alternant hydrocarbon are numbered from 1 to $2n + 1$, the valence bond method predicts the presence of negative spin densities at the even-numbered atoms[12,13] (the atoms without asterisks in Hückel's theory). Up to the present this method has been used to investigate the distribution of spin density in a large number of compounds: triphenylmethyl[11,14], benzyl[15], dimesitylmethyl[16], diphenylpicrylhydrazyl[17], 1- and 2-methylnaphthenyls[15], cyclopentyl and cyclohexyl[18], and the polystyrene radical[19].

In order to obtain negative spin densities by the molecular orbital method, it proved necessary to carry out the calculations not by the simple Hückel method but including the interaction of the electrons with one another. Under the influence of the unpaired electron (which has a definite spin direction), orbitals with previously balanced spins become partly uncoupled, *i.e.* an electron density appears having a spin opposite to that of the unpaired electron. In this way, owing to the different projections of the spins, the electrons have densities of opposite sign. For a detailed examination of the appropriate methods of calculating spin densities and comparing theoretical and experimental results, we must first attempt an analysis of hyperfine structure in aromatic radicals and a theoretical definition of spin density.

1. CONCEPT OF SPIN DENSITY

As already remarked, the cause of the complicated structure of the electron paramagnetic resonance spectra of polyatomic free radicals is the hyperfine interaction between the unpaired electron and magnetic nuclei within the molecule. To a first approximation this coupling is in effect that between the spin magnetic moments of the electron and nucleus and the electric field of the electron and the quadrupole moment of the nucleus. In free radicals, however, the latter coupling can be disregarded, since the nuclei usually investigated, ^1H, ^{13}C, and ^{14}N, have either small or zero quadrupole moments.

The hyperfine coupling energy between the magnetic moments of the electron and the nucleus can be represented, in the form of a Hamiltonian, as the sum of two parts[20]:

$$\hat{H} = \hat{H}^{(1)} + \hat{H}^{(2)} \tag{1.1}$$

(the strong magnetic field is directed along the z-axis), where

$$\hat{H}^{(1)} = \mu_0 \sum_{k,n} \frac{\mu_n \sigma_{zk} \sigma_{zn} (1 - 3\cos^2 \Theta_{kn})}{|\vec{r}_k - \vec{r}_n|^3}, \tag{1.2}$$

$$\hat{H}^{(2)} = -\frac{8\pi}{3} \mu_0 \sum_{k,n} \mu_n \sigma_{zk} \sigma_{zn} \delta(\vec{r}_k - \vec{r}_n). \tag{1.3}$$

Here μ_0 is the Bohr magneton and μ_n the magnetic moment of nucleus n, σ_{zn} and σ_{zk} are Pauli operators for the z-component of the spin of the nucleus n and the electron k respectively, $\vec{r}_n$ and $\vec{r}_k$ are the radius vectors of nucleus n and electron k, Θ is the angle between the z-axis and $(\vec{r}_k - \vec{r}_n)$, and δ is the Dirac delta function.

The first part $\hat{H}^{(1)}$ of this Hamiltonian represents dipole-dipole coupling of the magnetic moments, leading to a hyperfine structure dependent on the orientation of the magnetic moments of electron and nucleus in the external magnetic field. This type of hyperfine structure can be observed in single crystals. Since, however, most free radicals are studied in liquid solutions or glasses, the anisotropic splitting $\hat{H}^{(1)}$ averages out at zero owing to rapid molecular rotation, and therefore makes no contribution to the hyperfine structure[21]. Thus with free radicals the greatest interest attaches to the term $\hat{H}^{(2)}$, the so-called Fermi contact term[22], which represents isotropic splitting. It is evident from Eqn. (1.3) that the contribution made by isotropic coupling with the nucleus is proportional to $\sum_k \sigma_{zk} \delta(\vec{r}_k - \vec{r}_n)$. The mathematical probability of this quantity is termed the spin density at $\vec{r}_n$:[23]

$$\rho(\vec{r}_n) = (\Psi \left| \sum_k \sigma_{zk} \delta(\vec{r}_k - \vec{r}_n) \right| \Psi), \tag{1.4}$$

i.e. it is a spin-weighted charge density. Here Ψ represents the complete wave function of the paramagnetic molecule.

A convenient unit for spin density is that at the proton in a hydrogen atom in its 1*s* state. Many theoretical calculations of density are based on this unit.

Since the δ-function occurs in Eqns. (1.3) and (1.4), it is clear that it will differ from zero only if the amplitude of the wave function of the molecular orbital of the unpaired electron differs from zero at the point where the given nucleus is situated. If the odd electron is located in a π orbital, it has zero density at the nucleus, and therefore only σ-type orbitals, which have their maximum amplitude at the nucleus, can given isotropic hyperfine splitting. In aromatic free radicals the unpaired electron is in a π orbital, while the aromatic ring lies in the nodal plane, where the odd-electron density is zero. It could therefore have been expected that the unpaired electron would not couple with the ring protons. However, this clearly contradicts experiment, which shows that a distinct hyperfine structure occurs in such compounds as the radical-ions of benzene, naphthalene, and other hydrocarbons, which contain no magnetic nuclei other than ^1H, and therefore the hyperfine structure can arise only from the ring protons. Several writers have explained this apparent anomaly by taking into account $\pi-\sigma$ configurational interaction at the carbon atom[24-26]. Weissman[24] used molecular orbital theory to

discuss proton hyperfine splitting in an aromatic system (a detailed account of his method will be found in the book by Ingram [1]). A simpler discussion of this question is given by McConnell [25].

Let us consider, following McConnell, the C–H part of an aromatic system. Fig. 3 gives a diagrammatic representation of one of the C–H bonds (side-view). We assume that the bond is localised and consists of a hydrogen 1*s* orbital (*s*) and a carbon hybridised sp^2 orbital, which we shall denote by σ, directed towards it. Perpendicular to the plane of the σ bond is the p_z orbital of the carbon atom, which contains the unpaired electron. The other two hybridised sp^2 orbitals of the carbon atom are disregarded to a first approximation, and are not shown in Fig. 3. We are thus dealing with a three-electron system in which one electron is located in the orbital *s*, another in the hybridised orbital σ, and the third in a p_z orbital. The orbital part of the wave function is then written

$$\Theta(1,2,3) = p_z(1)\,\sigma(2)\,s(3), \tag{1.5}$$

and the spin–orbital configurations of the ground state

$$\begin{aligned} \Phi_1 &= A\,\Theta(1,2,3)\;\alpha\alpha\beta, \\ \Phi_2 &= A\Theta(1,2,3)\,\alpha\beta\alpha, \\ \Phi_3 &= A\Theta(1,2,3)\,\beta\alpha\alpha. \end{aligned} \tag{1.6}$$

Let us form linear combinations of these spin–orbital configurations:

$$\varphi_1 = 1/\sqrt{2}(\Phi_1 - \Phi_2), \tag{1.7}$$

$$\varphi_2 = 1/\sqrt{6}(\Phi_1 + \Phi_2 - 2\Phi_3). \tag{1.8}$$

One of the combinations φ_1 is associated with the singlet C–H state (the ground state), while the linear combination φ_2 represents an excited triplet state. The combined wave function of the ground state becomes, according to perturbation theory,

$$\varphi_1' = \varphi_1 + f\varphi_2, \tag{1.9}$$

where $f = -H_{21}/\Delta W$, $H_{21} = \langle \varphi_2 | H | \varphi_1 \rangle$, and $|f| \ll 1$, H being the complete three-electron Hamiltonian.

Exact calculation shows that

$$H_{21} = -\left(\frac{\sqrt{3}}{2}\right)(J_{p\sigma} - J_{ps}), \tag{1.10}$$

where

$$J_{p\sigma} = \int p_z(i)\,\sigma(j)\,e^2/r_{ij}\,p_z(j)\,\sigma(i)\,d\tau_i\,d\tau_j, \tag{1.11}$$

$$J_{ps} = \int p_z(i)\,s(j)\,e^2/r_{ij}\,p_z(j)\,s(i)\,d\tau_i\,d\tau_j. \tag{1.12}$$

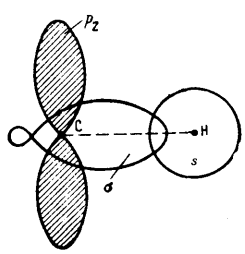


Fig. 3.

Neglecting J_{ps} in comparison with $J_{p\sigma}$, we obtain

$$f = \frac{\sqrt{3}}{2}(J_{p\sigma}/\Delta W).$$

The two-electron exchange integral $J_{p\sigma}$ can be estimated from atomic spectra by the Slater method [27]. ΔW is calculated by finding the energies W_1 and W_2 corresponding to φ_1 and φ_2.

The above position corresponds to an idealised C–H bond system, in which the odd electron is entirely located in the p_z orbital. In aromatic free radicals this odd electron is delocalised over the whole set of carbon atoms, *i.e.* the spin density at a C atom in this C–H system is not unity. The wave function of the ground state must then be written

$$\Psi_j = \varphi_1 + \rho_j f_j \varphi_2, \tag{1.13}$$

where ρ is the spin density, while the subscript j refers to the C and H atoms, and indicates that it is usually necessary to employ different Ψ for different C–H bonds in the aromatic system.

Let us examine the hyperfine coupling in such a system. The energy of first-order hyperfine interaction with the proton j for a doublet electronic state having spin $s = \frac{1}{2}$ is

$$\varepsilon_j(+1/2) = \langle \bar{\Psi}_j | \hat{H} | \Psi_j \rangle = 2\,\rho_j f_j \langle \varphi_1 | \hat{H} | \varphi_2 \rangle, \tag{1.14}$$

where $\hat{H}$ is defined by Eqn. (1.3) and

$$\varepsilon_j(+1/2) = -(\rho_j f_j/\sqrt{3})\,8\pi/3\;\mu_0\mu_I\,|s(0)|^2\,I_z.$$

Since $\epsilon_j(-\frac{1}{2}) = -\epsilon_j(+\frac{1}{2})$, $I_z = \pm\frac{1}{2}$ for the proton, and $\Delta I_z = 0$ for the electronic spin transition, the hyperfine interaction with the proton j produces the splitting $a(H_j)$, which is given by

$$a(H_j) = 2/\sqrt{3}\,(\rho_j f_j)\,\frac{8\pi}{3}\,\mu_0\,\mu_I\,|s(0)|^2, \tag{1.15}$$

$$a(H_j) = 2/\sqrt{3}\,(\rho_j f_j)\;1420\ \text{Mc/s}. \tag{1.16}$$

If we assume that f_j is constant for all C–H bonds, we obtain on denoting the constants by Q

$$a(H_j) = Q\rho_j \quad \text{(McConnell equation)}. \tag{1.17}$$

Hence we see that from the hyperfine proton couplings we can determine the odd-electron spin densities on the carbon atoms.

The constant Q was first calculated by Jarrett [28] by the valence bond method for hyperfine splitting due to one proton, on the hypothesis that the odd electron is located the whole time on one carbon atom (*i.e.* $\rho_C = 1$). The numerical value of $|Q| = 28$ oersteds showed excellent agreement with experiment. Later work by McConnell and Chesnut and the most recent investigations [12,29,30] have confirmed the proposed mechanism of hyperfine coupling, and have shown that Q is negative. Physically this means that, if the resultant electron spin is parallel to the applied field, electrons in the vicinity of protons will have a spin which is antiparallel to the field; and conversely. A theoretical basis was also provided for the hypothesis of negative spin density. Let us again examine Eqn. (1.4), but for convenience determine the spin density at the point (x, y, z):

$$\rho(x,y,z) = \left(\bar{\Psi}\left|\sum_k \sigma_{zk}\,\delta(r_k)\right|\Psi\right), \tag{1.18}$$

where, as previously, Ψ is the complete wave function of the paramagnetic molecule. When Ψ is expressed in terms

of normalised molecular orbitals Φ_i, then $\rho(x, y, z)$ can be expressed as the molecular-orbital density matrix $\rho_{ij} \equiv \bar{\rho}$:

$$\rho(x, y, z) = \sum_{ij} \bar{\rho}_{ij} \Phi_j^* \Phi_i. \quad (1.19)$$

If Ψ is given in terms of a set of atomic orbitals, which have not necessarily been normalised, the atomic-orbital density matrix $\rho_{\lambda\mu} \equiv \rho$ can be determined

$$\rho(x, y, z) = \sum_{\lambda,\mu} \rho_{\lambda\mu} \Phi_\mu^* \Phi_\lambda, \quad (1.20)$$

where $\Phi\mu$ and $\Phi\lambda$ are atomic orbitals. When the molecular orbitals Φ_i are expressed as linear combinations of atomic orbitals (LCAO):

$$\Phi_i = \sum_\lambda a_{\lambda i} \Phi_\lambda, \quad (1.21)$$

the matrices ρ and $\bar{\rho}$ can be correlated with one another:

$$\rho_{\lambda\mu} = \sum_{i,j} \bar{\rho}_{ij} a_{\mu j}^* a_{\lambda i}. \quad (1.22)$$

In the simple molecular orbital theory disregarding electron correlation, when the complete wave function is written as one configuration, all the non-diagonal terms $\bar{\rho}ij$ are zero, while all diagonal terms are positive. Thus the spin density function is everywhere positive. The diagonal elements $\rho_{\lambda\mu}$ are in this case positive, but the non-diagonal elements may be negative. However, this does not mean that the density is negative at this point, since $(\rho_{\lambda\mu}\sigma_{\mu\lambda} + \rho_{\mu\lambda}\sigma_{\lambda\mu})$, where $\sigma_{\lambda\mu} = <\Phi_\lambda\Phi_\mu>$ is the overlap, defines the total spin between the atoms, and cannot be ascribed to only one of the neighbouring atoms.

A description by the simple molecular orbital method of a free radical having $(2k + 1)$ electrons shows that each orbital, in conformity with the Pauli principle, is occupied by not more than two electrons. The lower orbitals are occupied in pairs, while the odd electron occupies one of the lower orbitals remaining free or a higher orbital. Electrons having different spins in the same orbital interact with one another. This phenomenon (the correlation effect) may be taken into account by writing the wave function of the system in terms of molecular orbitals including different configurations. As a result of the introduction of correlation interaction, the $\bar{\rho}ij$ matrix is now non-diagonal, and any of its elements (diagonal or non-diagonal) can be zero. Moreover, in the $\rho_{\mu\lambda}$ matrix the diagonal elements can be negative, which means that the spin density function $\rho(x, y, z)$ can be negative at the given atom. Spin densities have been calculated by the molecular orbital method with configurational interaction for allyl[31,32] and the negative pyrene ion[33].

Below we shall examine other ways of describing free radicals which similarly yield states having negative spin density at the carbon atoms.

2. SPIN DENSITY IN THE SIMPLE HÜCKEL MOLECULAR ORBITAL THEORY

In Hückel's molecular orbital method (the simple LCAO–MO method) charge densities at any atom in a system can be calculated by means of the atomic orbital coefficients according to the relation[9]

$$q_i = \sum_j n_j c_{ij}^2, \quad (2.1)$$

where n_j is a number (0, 1, or 2) representing the extent to which the orbital is occupied, and c_{ij} are coefficients of the atomic orbital i in the molecular orbital j.

As already noted in the Introduction, the charge density is not in general identical with the spin density. In some regions, where there is a high charge density, the spins may be paired, and thus the spin density may be zero. If, however, the projection of the spin on a fixed axis z does not vanish, for some free radicals the spin densities are, to the simple LCAO–MO approximation, proportional to the squares of the Hückel coefficients in the orbital of the odd electron. In this case Eqn. (2.1) is in fact identical with Eqn. (1.22).

Use of this simple molecular orbital theory to find spin densities and calculate hyperfine structural constants gave surprisingly good agreement with experiment for several positive and negative radical-ions of alternant hydrocarbons containing even numbers of carbon atoms. As indicated above, this theory proved valid for naphthalene[5,6] and anthracene[6–8], and also for naphthacene[8], biphenyl[7], perylene[8,34,35], α-methylstyrene[36], pentaphenylcyclopentadienyl[37], and for compounds containing heteroatoms — the tetracyanoethylene anion[38], the cation of p-phenylenediamine[39], the ions of semiquinones[40–42], and for several metal ketyls[43].

The spin density was determined experimentally from the hyperfine structure of the spectra by means of McConnell's equation $a_H = Q\rho_C$. The constant Q is usually given the empirical value -22.5 oersteds, obtained from the spectrum of the benzene minus ion, although the theoretical value of -28 oersteds is sometimes used.

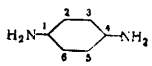
McConnell's equation has been derived to determine spin densities from hyperfine proton splitting in aromatic rings. But the protons of amino- and methyl groups also often contribute to the hyperfine structure. Bersohn[40] investigated several ions of methylated semiquinones by the molecular orbital method, and calculated the spin densities on the protons of the methyl groups, taking into account the delocalisation of the odd electron in these groups. Comparison of his calculated spin densities with experimental values in various quinones gives Q - 25 oersteds. McLachlan[44] showed that, in the case of methylated semiquinones and for the hyperfine couplings of amino-group protons, we can use an equation analogous to $a_H = Q\rho$, but with Q = -28 oersteds for the ring protons and Q = +25 oersteds for protons of methyl or amino-groups, ρ denoting in the latter case the density at the nitrogen nucleus. This agrees with Bersohn's calculations[40].

Bolton and Carrington[45] used the molecular orbital theory to explain the hyperfine structure in the spectra of the anions of toluene and p- and m-xylenes. The methyl group was regarded as an electropositive substituent, exerting an inductive effect on the aromatic ring carbon atom to which it was linked. The form selected for the Coulomb integral of such a carbon atom was α - 0.13β, where α is the Coulomb integral for all the other carbon atoms in the ring and β is the resonance integral of the C–C bond. Values of the hyperfine coupling constants of

the ring protons, calculated from the McConnell equation with Q = 22.5 oersteds, gave good agreement with experiment.

For the hyperfine splitting due to the fluorine nuclei in fluorinated semiquinones Anderson *et al.*[46] derived the relation $a_F = -39.3\rho_C$, where ρ_C is the density at the carbon atom adjacent to the fluorine atom. The equation was obtained on the assumption that the configurational interaction in the ·(C–F) bond is the same as in the ·(C–H) bond and that ρ_C, the total spin density, is the same in the tetrahydrosemiquinones and the fluorosemiquinones. Confirmation of the correctness of this relation was provided by a recent study of the negative ion of *p*-fluoronitrobenzene[47]. The results differed only by 20% from those of the previous paper. Agreement is obtained with experiment when Q = = -47.5 oersteds.

As an example of the use of the basic equation with different values of Q, let us consider in greater detail the positive ion of *p*-phenylenediamine[39]:



The observed electron paramagnetic resonance spectrum gives the following values for the isotropic hyperfine coupling constants:

$$a_N = 5.29 \text{ oersteds},$$
$$a_H(NH_2) = 5.8 \text{ oersteds},$$
$$a_H(\text{ring}) = 2.13 \text{ oersteds}.$$

The McConnell equation (with Q = 28 oersteds) gave spin densities of $\rho_C = 0.07$ at the carbon atoms numbered 2, 3, 5, and 6. A simple calculation was made of the molecule by the LCAO–MO method, in which all the resonance integrals β were taken as equal, while the Coulomb integral for the nitrogen atom α_N was represented by a parameter defined in such a way that it corresponded to the value found for ρ_C. This value was $\alpha_N = \alpha_C + 0.85\beta$, where α_C is the Coulomb integral for the carbon atom. Using this parameter, the odd-electron density in the p_z orbital of the nitrogen atom was calculated to be $\rho_N = 0.236$. If Q is taken as -25 oersteds, we obtain from the equation $a_H(NH_2)$ = = -5.9 oersteds, in excellent agreement with the constant obtained empirically.

It is more difficult to explain the isotropic hyperfine coupling at the ^{14}N nitrogen nucleus. In the paper under consideration hypotheses were put forward as to possible mechanisms for the formation of the hyperfine structure. Such a structure requires the presence of odd-electron density in a 2*s* orbital at the N nucleus. Transfer of odd-electron density to the σ system, and thus to a 2*s* orbital at the nitrogen atom, can, in the opinion of these authors, take place in two ways: (1) by π–σ coupling at the neighbouring carbon atom, transferring spin density to the C–N bond, or (2) by π–σ coupling at the nitrogen atom, transferring the spin density to all three σ bonds of the nitrogen. The ratio $a_N/a_H(NH_2)$ can be calculated on the assumption that the second mechanism is responsible both for the hyperfine splitting due to the nitrogen nucleus and for the splitting caused by protons in the amino-groups:

$$\frac{a_N}{a_H} = 0.0723\frac{|\varphi_N(0)|^2}{|\varphi_H(0)|^2} \qquad (2.2)$$

It is postulated that the ion has a planar configuration and sp^2 hybridisation at the nitrogen atom. The three hybrid σ orbitals are approximately orthogonal linear combinations of the atomic orbitals $(2s)_N$, $(2p_x)_N$, and $(2p_y)_N$. Assuming the (N–H) bond to be non-polar, we write it as

$$\psi_\sigma = \frac{1}{\sqrt{2}(1+\Delta)^{1/2}}\{(sp^2)_N + (1s)_H\}, \qquad (2.3)$$

where Δ is the overlap integral. Remembering that the main contribution at the nitrogen nucleus is made by the 2*s* function, we write

$$\frac{a_N}{a_H} = -0.0723\frac{|2s_N(0)|^2}{|1s_H(0)|^3}. \qquad (2.4)$$

The negative sign arises from the fact that a particular polarisation of electron spin at the nitrogen nucleus produces a polarisation of opposite sign at the proton[48].

Estimating $|2s_N(0)|^2$ by the Hartree–Fock method and $|1s_H(0)|^2$ from the Schrödinger function $(\pi a_0^3)^{-1}$, we have

$$|2s_N(0)|^2 = 33.4 \times 10^{24} \text{ cm}^{-3}, \qquad (2.5)$$
$$|1s_H(0)|^2 = 2.15 \times 10^{24} \text{ cm}^{-3},$$
$$a_N/a_H = -1.12. \qquad (2.6)$$

Experiment gives 0.9. Thus in this ion mechanism (2) does actually provide the main proportion of the hyperfine splitting due to the nitrogen nucleus. For this splitting we can then use an expression of the McConnell type, where the quantity Q_N = 22.4 oersteds satisfies the experimental data when the simple molecular orbital theory is applied. However, the mechanism of hyperfine coupling at the nitrogen nucleus is far more complicated. As Karplus and Fraenkel[49] have recently shown, a complete discussion of the splitting due to the nitrogen atom requires consideration of the effect not only of 2*s* but also of 1*s* electrons (see Section 3, below).

Hyperfine splitting due to the nitrogen nucleus and spin densities have been computed empirically also in phenazine semiquinone (spin density at the nitrogen nuclei of the NH groups $\rho_N = -0.256$) and in other semiquinones containing nitrogen[50,51]. Bersohn[52] made a theoretical calculation of spin densities at the nitrogen atoms in diphenylpicrylhydrazyl by the simple LCAO–MO method. The estimated spin densities at the two central nitrogen atoms were ρ_1 = = 0.1416 and ρ_2 = 0.1518. Holmberg *et al.*[53] calculated spin densities using experimental data on isotropic and anisotropic hyperfine splitting in diphenylpicrylhydrazyl, and obtained values of ρ_1 = 0.274 and ρ_2 = 0.605 (or 0.396). Two values are given for ρ_2 because of uncertainty in the choice of the hyperfine coupling tensor.

3. HYPERFINE SPLITTING DUE TO THE ^{13}C NUCLEUS

Several papers have dealt with the distribution of spin density in hydrocarbons in which a considerable proportion of the ^{12}C atoms have been replaced by the ^{13}C isotope, which has non-zero spin, and which can therefore yield information on the spin density in a molecule not only from the proton splitting but also from that caused by the ^{13}C nucleus.

Tuttle[54] suggested for the spin distribution in the negative naphthalene ion containing ^{13}C atoms the empirical equation

$$a_i = k_i\rho_i + \sum_j k_{ij}\rho_j, \qquad (3.1)$$

where a_i is the hyperfine splitting in position i due to ^{13}C, ρ_i the density of the unpaired π electron in this position, and ρ_j the unpaired π electron density at the neighbouring carbon atoms.

Reitz *et al.*[55] used this equation to determine spin densities in semiquinones by means of the ^{13}C splitting. The value of k_i is known for the proton splitting k_{C-H} (*i.e.* Q in the McConnell equation), while values of k_{C-C} were taken from Tuttle's calculations for ^{13}C splitting in the α- and β-positions in the negative naphthalene ion. The results show good agreement with Bersohn's calculations[40]:

Spin density according to Bersohn	Spin density according to Reitz
$\rho_0=0.206$	$\rho_0=0.221$
$\rho_1=0.090$	$\rho_1=0.078$
$\rho_2=0.113$	$\rho_2=0.123$

The spin density at the ^{13}C nucleus was determined in benzonitrile[56] in which 64% of the carbon atoms in the nitrile group had been replaced by the isotope. The ^{13}C splitting was 6.4 oersteds, and the spin density at the ^{13}C carbon nucleus was 0.051 compared with the hydrogen atom in the 1*s* state.

In triphenylmethyl[6], in which the methyl carbon had been replaced by ^{13}C, the splitting in liquid solution was 26 oersteds, the corresponding spin density at the ^{13}C nucleus being $\rho_{^{13}C} = 0.22$. Similarly, we can determine the spin density at the protons (from the total proton splitting of 35 oersteds) as $\rho_H = 0.068$ and the total density at the carbon atoms numbered 2, 3, 4, 5, and 6 as $\rho_C = 1.57$.[57] The value of $\rho_{^{13}C}$ calculated from the McConnell equation, with Q taken as the isotropic splitting in the negative naphthalene ion, is 0.68, which is close to the spin density calculated theoretically (for one of the configurations of triphenylmethyl the valence bond method[57] gives $\rho_{^{13}C} = 0.616$).

The empirical equation (3.1) has received theoretical justification[30]. The hyperfine coupling constant for a ^{13}C nucleus linked to three other carbon atoms was found to be represented by the relation

$$A_C = Q_1\rho_0^\pi + Q_2(\rho_1^\pi + \rho_2^\pi + \rho_3^\pi), \qquad (3.2)$$

where ρ_0^π is the spin density at the atom having the ^{13}C nucleus, ρ_1^π, ρ_2^π, and ρ_3^π are the spin densities at the adjacent carbon atoms, and the Q are $\pi-\sigma$ configurational interaction constants. This equation was used to determine the hyperfine structural constants in the negative naphthalene ion having the natural content of the ^{13}C isotope[58]. The agreement with experiment is quite good, but some discrepancies are inevitable, since some quite crude assumptions were made in deriving Eqn. (3.2).

Ward[59] used this equation to determine the constants Q_1 and Q_2 in the negative bipyridyl ion. Spin densities at the nitrogen and carbon atoms were calculated by Hückel's molecular orbital method, the resonance integrals being put equal for all the bonds, while the Coulomb integral for the nitrogen atom was chosen as $\alpha_N = \alpha_C + \beta h$, where α_C is the Coulomb integral for the carbon atom, β the resonance integral, and h a parameter which is adjusted to give the best agreement with experiment. When $h = 0$, the spin densities in the negative bipyridyl ion coincide with those in the biphenyl ion. The simple LCAO–MO method then leads to values of $\rho_N = 0.159$, $\rho_o = 0.019$, $\rho_m = 0.089$, and $\rho_p = 0.123$ for the spin densities at the nitrogen atom and in the *ortho-*, *meta-*, and *para*-positions respectively. The experimental values of ρ_o and ρ_m are 0.02 and 0.10 respectively. Application of Eqn. (3.2) to these spin densities and the experimental splitting due to the nitrogen nucleus yields $Q_1 = 19$ and $Q_2 = 9.5$ oersteds. With these values of Q the Hückel theory can be used to estimate the hyperfine coupling constants in other nitrogen-containing ions. In particular, Ward's estimate of the hyperfine splitting due to the nitrogen atom in the negative phenazine ion agreed well with experiment.

However, Eqn. (3.2) does not always yield results agreeing with experiment. In order to examine hyperfine splitting due to ^{13}C (or ^{14}N) nuclei, the effect of the inner, coupled 1*s* electrons must be taken into account[49]. The 2*s* and 2*p* electrons are involved in the formation of molecular orbitals extending throughout the molecule. It is supposed that the contribution of the 1*s* electrons to the hyperfine coupling arises primarily from their transition to antibonding molecular orbitals. For the lowest doublet state of the carbon atom in the CH_3 radical, for example, the wave function is written as a determinant of the form

$$\Psi_0 = (9!)^{-1/2}|\,1s(1)\alpha(1)\,1s(2)\beta(2)\,\sigma_1(3)\alpha(3)\,\sigma_1(4)\beta(4)\times \times\sigma_2(5)\alpha(5)\,\sigma_2(6)\beta(6)\,\sigma_3(7)\alpha(7)\,\sigma_3(8)\beta(8)\,\pi(9)\alpha(9)|, \qquad (3.3)$$

where 1*s* and π represent 1*s* and π orbitals of the carbon atom, while the σ_i (i = 1, 2, 3) represent bonding molecular orbitals of the type

$$\sigma_i = N\{3^{-1/2}[(2s + \sqrt{2}(2p\sigma_i)] + \ldots\}. \qquad (3.4)$$

Here the $2p\sigma_i$ orbitals are directed along the σ_i bond, the leader denoting orbitals of the neighbouring atoms. They need not be discussed in detail, since they do not overlap the 1*s* orbitals.

After transfer of a 1*s* electron to the antibonding molecular orbital

$$\sigma_i^* = N\{3^{-1/2}[(2s) + \sqrt{2}(2p\sigma_i)] - \ldots\},$$

the excited state is written

$$\Psi_i = (9!)^{-1/2}|\,\sigma_i^*(1)\alpha(1)\,1s(2)\beta(2)\,\sigma_1(3)\alpha(3)\ldots\sigma_3(8)\beta(8)\,\pi(9)\alpha(9)|\,. \qquad (3.5)$$

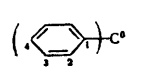
The contribution of the 1*s* electrons to the spin density at the nucleus, which is proportional to that at the atom containing the nucleus, can then be determined exactly by means of perturbation theory. This contribution can be written $S^C\rho^\pi$, and from the atomic model for CH_3, we have $S^C = -12.7$ oersteds.

The final expression obtained by Karplus and Fraenkel[49] for the hyperfine splitting due to the ^{13}C nucleus in an atom linked to three other atoms X_1, X_2, X_3 (sp^2 hybridisation) is of the form

$$a^C = \left(S^C + \sum_{i=1}^{3} Q^C_{CX_i}\right)\rho^\pi + \sum_{i=1}^{3} Q^C_{X_iC}\rho_i^\pi, \qquad (3.6)$$

where ρ^π is the spin density at the carbon atom and ρ_i^π the spin density at the atom X_i. The contribution of the 1*s* electrons is determined by the value of S^C, while those of the 2*s* electrons are determined by $Q^C_{CX_i}$ and $Q^C_{X_iC}$, the former Q determining the hyperfine splitting due to the nucleus of the carbon atom C and the transfer of spin density to the CX_i bond, while $Q^C_{X_iC}$ governs the contribution

TABLE 1.

Radical	Position of atom	Spin density ρ_i^π	Value of a_i^C	
			calc.	expt.
Methyl		1.000	43.8	±41±3
$\overset{2}{\underset{1}{(HOOC)_2}}\overset{0}{CH}$	0	0.892	31.8	33.0
	1	0.0	−12.4	
(radical of malonic acid)	2	0.05		
Negative naphthalene ion	α	0.2087	7.38	±7.1
	β	0.0786	−1.20	±1.2
	γ	−0.0746	−7.06	
Negative benzene ion		0.1667	1.30	±2.4
Negative cyclooctatetraene ion		0.1250	0.97	±1.3
Triphenylmethyl	0	0.68	26.2	26
	1	−0.1299		
	2	0.1067		
	3	−0.0468		
	4	0.1168		

to the hyperfine splitting of the spin densities at the atoms X_i and the transfer of spin density to the X_iC bond. These contributions are of opposite signs.

It is evident from Eqn. (3.6) that knowledge of the $\pi-\sigma$ interaction parameters (Q and S^C) and of the π-electron spin densities ρ_i^π is necessary in order to estimate theoretically the hyperfine splitting due to the ^{13}C (or ^{14}N) nucleus. Karplus and Fraenkel obtained theoretical values (in oersteds) for the CHC_2 radical of $S^C = -12.7$, $Q^H_{CH} = 19.5$, $Q^C_{CC'} = 14.4$, and $Q^C_{C'C} = -13.9$.

These quantities, together with values of ρ_i^π obtained either by the Hückel method or from the proton splitting by means of the McConnell equation, have been used to determine the constants a^C for the methyl radical, the radical of malonic acid, the negative ions of naphthalene, benzene, and cyclooctatetraene, the ion of *p*-benzosemiquinone, and triphenylmethyl. In calculating spin densities by means of the McConnell equation, a value of -23.72 oersteds was used for the $\pi-\sigma$ configurational interaction constant Q^H_{CH}. This value was obtained by examining the contribution of 2*s* electrons to the ^{13}C splitting by the valence bond method.

Table 1 compares the experimental constants a^C with values calculated by means of Eqn. (3.6). It is seen that the two results are in excellent agreement.

4. SPIN DENSITY IN THE SELF-CONSISTENT FIELD METHOD

McLachlan[60] has recently shown that the self-consistent field theory may give the best values for the spin density in both alternant and non-alternant π-electron radicals. The wave function in radicals is usually written as a determinant:

$$\chi_0 = \| \psi_1^2 \psi_2^2 \ldots \psi_n^2 \psi_0^\alpha \|, \qquad (4.1)$$

in which the $2n$ electrons occupy the Ψ_n orbitals in pairs, while the odd electron with spin α occupies the orbital Ψ_0. This function is not self-consistent in the full sense, since, in contrast to self-consistent wave functions, it can combine with excited doublet configurations χ_i^r:

$$\chi_i^r = \| \psi_1^2 \ldots \psi_i \psi_r \psi_n^2 \psi_0 \| \frac{1}{\sqrt{6}} (2\alpha\alpha\beta - \alpha\beta\alpha - \beta\alpha\alpha). \qquad (4.2)$$

where one electron from the orbital i passes to the vacant orbital r. The matrix element between these states is the exchange integral

$$\langle \chi_0 \hat{H} | \chi_i^r \rangle = -\frac{3}{\sqrt{6}} \iint \psi_0^* \psi_r(1) \frac{e^2}{r_{12}} \psi_i^* \psi_0(2)\, d\tau_1\, d\tau_2. \qquad (4.3)$$

Some workers have suggested using a different form of wave function in radicals. Hoijtink[61] took as the function for the ground state

$$\Psi = \chi_0 + \sum_{i,r} \lambda_{ir} \chi_i^r, \qquad (4.4)$$

instead of χ_0, and regarded the exchange energy as a small perturbation. But, as McLachlan points out, here the calculations are complicated, especially with large molecules, where there are many excited configurations.

Pople and Nesbet[62] suggested a self-consistent wave function of the type

$$\Phi = \| \psi_1^\alpha \psi_1'^\beta \ldots, \psi_n^\alpha \psi_n'^\beta \psi_0^\alpha \|, \qquad (4.5)$$

in which electrons with spins α and β occupy independent sets of orbitals Ψ_0, Ψ_1, ..., Ψ_n; Ψ_1', ..., Ψ_n'.

The spin densities in the Pople–Nesbet function

$$\rho = |\psi_0|^2 + \sum_i \{ |\psi_i|^2 - |\psi_i'|^2 \}, \qquad (4.6)$$

may be negative at the nodes of Ψ_0 if $|\Psi_i'|^2$ exceeds $|\Psi_i|^2$.

The spin density may be negative also in the Hoijtink function

$$\rho = \rho_0 + 2 \sum_{i,r} \lambda_{ir} \langle \chi_0 | \rho | \chi_i^r \rangle. \qquad (4.7)$$

In the case of radical-ions McLachlan suggested applying Pariser and Parr's semiempirical method[63] to the Pople–Nesbet function. The LCAO–MO coefficients for the two sets of orbitals

$$\psi_0 = C_{0r}\Phi_r, \quad \psi_i = C_{ir}\Phi_r; \quad \psi_i' = C_{ir}'\Phi_r, \qquad (4.8)$$

are then defined by the equations

$$\left.\begin{aligned} &\sum_s F_{rs} C_{is} = E_i C_{ir} \\ &\sum_s F'_{rs} C''_{is} = E'_i C_{ir} \\ &\sum_s F_{rs} C_{0s} = E_0 C_{0r} \quad \sum_s F^0_{rs} C_{0s} = E_0 C_0 \end{aligned}\right\} \quad s = 1 \ldots\ldots 2n+1, \qquad (4.9)$$

The quantities F, F', and F^0 represent the self-consistent field for electrons having spins α and β and for the odd electron, and they depend on the bond orders and electron densities for the electrons with spins α and β, which are defined as

$$P_{rs} = \sum_{i=1}^{n} C_{ir} C_{is} \quad P'_{rs} = \sum_{i=1}^{n} C'_{ir} C'_{is} \quad P^0_{rs} = C_{0r} C_{0s}. \qquad (4.10)$$

The operators F and F' can then each be written as a sum of three terms:

$$F = V + K - J, \qquad (4.11)$$

$$F' = V + K - J', \qquad (4.12)$$

where V is the field of the nucleus and the σ electrons, K the Coulomb field of all the π electrons, J and J' represent the exchange field for π electrons having spins α and β,

and F^0 is the field due to all the electrons other than the odd electron; F^0 is obtained from F by omitting terms proportional to P^0:

$$V_{rs} = \beta_{rs} - \delta_{rs} \sum_{t \neq r} \gamma_{rt}, \quad (4.13)$$

$$K_{rs} = \delta_{rs} \sum_{t} (P_{tt} + P'_{tt} + P^0_{tt}) \gamma_{rt}, \quad (4.14)$$

$$J_{rs} = (P_{rs} + P^0_{rs}) \gamma_{rs}, \quad (4.15)$$

$$J' = P_{rs} \gamma_{rs}. \quad (4.16)$$

Hence it can be seen that the difference between F and F' arises from the exchange field $J - J'$ of the odd electron. In Eqn. (4.13) the resonance integral β_{rs} is a non-diagonal matrix element, which is zero for atoms r and s not directly linked to one another and has the value β for all C–C bonds; the Coulomb integral β_{rr} is a diagonal matrix element with respect to the one-electron integral containing the kinetic energy; and γ_{rs} is the Coulomb electrostatic coupling of the electrons in Φ_r and Φ_s.

With neutral radicals the spin density can be estimated by the molecular orbital method taking into account perturbation theory. Self-consistent orbitals are taken as the starting point, while the exchange interaction of the odd electron with other, coupled electrons is regarded as a perturbation. If the unperturbed molecule is alternant, $P_{rr} = P'_{rr} = \frac{1}{2}$. Furthermore $P_{rs} = P'_{rs}$, and these vanish if the atoms r and s belong to the same set. The operator F is then

$$F(0)_{rr} = \beta_{rr} + 1/2 \gamma_{rr}, \quad (4.17)$$

$$F(0)_{rs} = \beta_{rs} - P(0)_{rs} \gamma_{rs}. \quad (4.18)$$

The first correction to $F(0)$ is given by $F^0(1)_{rs} = F^0(0)_{rs}$.

$$K(1)_{rs} - K(0)_{rs} = \sum_{t} P^0(0)_{tt} \gamma_{rt} \delta_{rs}, \quad (4.19)$$

$$J(1)_{rs} - J(0)_{rs} = P^0(0)_{rs} \gamma_{rs} = G_{rs}, \quad (4.20)$$

$$F^0(1)_{rs} = F^0(0)_{rs}. \quad (4.21)$$

Here G_{rs} is the exchange potential of the odd electron. Even to this first approximation the orbital of the odd electron and the total electron density are found not to vary, while the change in spin density is caused entirely by the exchange term G_{rs}. The exchange potential G of the odd electron affects the spin density by changing the effective values of the Coulomb integrals α_r and the resonance integrals β_{rs} for electrons having a spin α. The method of Coulson and Longuet-Higgins[64], which takes into account the coefficients of mutual polarisability $\pi_{rs,tu}$, gives for the perturbed spin density

$$\rho_{rs} = \rho(0)_{rs} - \frac{1}{2} \sum_{t,u} \pi_{rs,tu} G_{tu}. \quad (4.22)$$

Equating the γ_{rr} and replacing $\pi_{rs,tu}$ by π_{rs} (since the polarisabilities of the atomic bonds are zero if t and u are located in different systems), we have

$$\rho_r = C^2_{0r} - \frac{1}{2} \gamma \sum_{s} \pi_{rs} C^2_{0s}, \quad (4.23)$$

where π_{rs} is the mutual polarisability of the two atoms. It is calculated from the expression

$$\pi_{rs} = -4 \sum_{i} \sum_{j} \frac{C_{ri} C_{sj} C_{si} C_{rj}}{E_j - E_i}, \quad (4.24)$$

where i and j are occupied and vacant orbitals, and E_i is the energy of the Hartree–Fock parameters.

From a comparison of the results obtained for spin density calculated by means of self-consistent orbitals and the Hückel orbitals used in Eqn. (4.23), McLachlan concludes that the latter can give almost the same result as the former if the right value is chosen for the resonance integral.

According to the self-consistent field theory, the resonance integral is given by

$$\beta_{rs(\mathrm{eff})} = \beta_{rs} - \frac{1}{2} P_{rs} \gamma_{rs}, \quad (4.25)$$

where P_{rs} is the overall bond order. Using the Pariser and Parr parameters $\gamma = 10.53$ eV, $\beta_{12} = -2.39$ eV, $\gamma_{12} = 7.30$ eV, and β about -4.5 in most cases, we obtain

$$1/2 \gamma/\beta \simeq -1.2 = -\lambda. \quad (4.26)$$

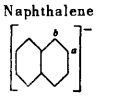
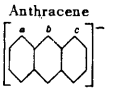
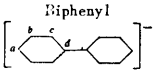
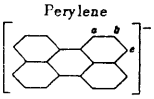
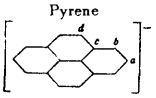
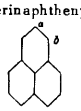
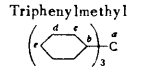
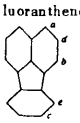
Thus we can replace (4.23) by

$$\rho_r = C^2_{0r} - \lambda \sum_{s} \pi_{rs} C^2_{0s}, \quad (4.27)$$

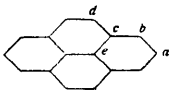
where π_{rs} is a numerical quantity, and the only parameter which must be aribtrarily chosen is λ.

McLachlan calculated the hyperfine structural constants on the assumption that each constant depends not only on Q but also on λ. The latter varies only slightly on passing from one compound to another, while Q is constant, its value being -24.2 oersteds. Although the simple Hückel theory proved successful for many hydrocarbons, the spectrum of the negative pyrene ion can be explained only by

TABLE 2.

Free radical	Spin densities		
	expt.	Hückel method	Hartree – Fock method
Naphthalene 	*a* 0.076 *b* 0.203	0.069 **0.181**	0.055 0.211
Anthracene 	*a* 0.230 *b* 0.113 *c* 0.064	**0.193** **0.036** 0.048	**0.256** 0.118 0.032
Biphenyl 	*a* 0.227 *b* 0.019 *c* 0.113 *d* 0.085	0.159 0.019 0.089 0.123	0.208 —0.023 0.105 0.128
Perylene 	*a* 0.128 *b* 0.019 *c* 0.146	0.083 0.013 0.108	0.115 —0.031 0.145
Pyrene 	*a* 0.054 *b* 0.240 *d* 0.054		—0.052 0.187 0.092
Perinaphthenyl 	*a* 0.008 *b* 0.327		—0.098 0.247
Triphenylmethyl 	*a* 0.68 *c* 0.124 *d* 0.062 *e* 0.124		0.516 0.101 —0.041 0.087
Fluoranthene 	*a* 0.215 *b* 0.161 *c* 0.054 *d* 0.000		0.227 0.157 0.037 —0.023

means of the self-consistent field theory. On the Hückel theory the orbital of the odd electron has nodes at atoms *a* and *e*, and hyperfine splitting should be caused by the protons in positions *b* and *d*:



The spectrum should then consist of 25 lines. Experiment gives 75 lines, which indicates the presence of considerable spin density at position *a*. The self-consistent field method predicts the presence of negative spin density at this position, and gives a good numerical estimate.

Non-alternant ions as well as alternant radical-ions were studied in this work. In the former the electronic states are not coupled as in the alternant type, and this affects to some extent the calculations of spin density, although for simplicity the equations derived for alternant ions were utilised. The negative acenaphthylene ion, the negative fluoranthene ion, and the positive and negative acepleiadylene ions were investigated. The spectra of the two acepleiadylene ions are quite different, and for them neither the Hückel theory nor the self-consistent field theory agrees with experiment. Spin density was calculated also for the neutral radicals triphenylmethyl, perinaphthenyl, allyl, and benzyl. Table 2 compares experimental and theoretical values of spin densities calculated by the Hückel molecular orbital method and by the self-consistent field method.

5. SPIN DENSITY IN ALIPHATIC RADICALS

In contrast to aromatic free radicals, comparatively little study has been made of aliphatic free radicals by electron paramagnetic resonance, and hardly any work has been done on the theoretical determination of their spin density distributions. The difficulty in investigating aliphatic radicals is that they are usually obtained either during irradiation or by being trapped in solids, and it is often difficult to identify the spectrum of the resulting radical, since rupture of bonds may take place at different points. Sometimes anisotropy must also be taken into account, since most work on aliphatic radicals is not done in solution.

Whereas in aromatic free radicals the total extent of the spectrum is independent of the number of protons involved in hyperfine coupling, for aliphatic radicals the total width of the spectrum is sensitive to the number of protons.

Chesnut[65] gave a molecular orbital treatment of aliphatic radicals, the ethyl, isopropyl, and t-butyl radicals being considered. Hyperfine coupling in these radicals can be explained by means of the theory of hyperconjugation[66,67] which, although a very crude approximation, nevertheless gives comparatively good qualitative agreement with experiment.

It is supposed that combinations of the atomic orbitals of hydrogen form hydrogen group orbitals of the type

$$\chi_1 = \frac{\Phi_1 + \Phi_2 + \Phi_3}{(3 + 6S_{HH})^{1/2}}, \qquad (5.1)$$

$$\chi_2 = \frac{2\Phi_1 - \Phi_2 - \Phi_3}{(6 - 6S_{HH})^{1/2}}, \qquad (5.2)$$

$$\chi_3 = \frac{\Phi_2 - \Phi_3}{(2 - 2S_{HH})^{1/2}}. \qquad (5.3)$$

If the wave functions of the methyl carbon atom [in the ethyl radical (Ed. of Translation)] are denoted by sp_1, p_2, and p_3, the one of the hybridised sp_1 orbitals forms a σ bond with χ_1, while the p_2 and p_3 orbitals form bonds of π type with χ_2 and χ_3 respectively. The second carbon atomic sp_1 orbital is utilised for a σ bond with the other atom (see Fig. 4).

If the methyl group adds on to a π system, the hydrogen group H_3 can be regarded as a speudoatom X, contributing one electron to the total pseudo-π and the hyperconjugated system. Thus if ψ_i denotes a π orbital at the atom i, the molecular wave function for the energy level k is written

$$\Phi_k = \sum_i C_{ik}\psi_i. \qquad (5.4)$$

where in the case of hyperconjugation some of the ψ_i will be π orbitals of the methyl carbon atom with the pseudoatom X.

The condition for normalisation of the wave function Φ_k allowing for overlap of the atomic orbitals $S_{ij} = \langle \psi_i | \psi_j \rangle$ is represented by

$$1 = \langle \Phi_k | \Phi_k \rangle = \sum_{ij} C_{ik}C_{jk} \langle \psi_i | \psi_j \rangle = \sum_{ij} C_{ik}C_{jk}S_{ij} = \sum_i C_{ik}Y_{ik}, \qquad (5.5)$$

where $Y_{ik} = \sum_j C_{jk}S_{ij}$.

If Φ_0 is the wave function of the odd electron, its density at atom k is given by the expression[68,69]

$$q_k = C_{k0}Y_{k0}. \qquad (5.6)$$

In this case this definition of odd-electron density is the same as McConnell's definition of spin density[12]. Here

$$\rho_k = \langle \Phi_0 | \Delta_k | \Phi_0 \rangle = \sum_{ij} C_{i0}C_{j0} \langle \psi_i | \Delta_k | \psi_j \rangle = C_{k0}Y_{k0}, \qquad (5.7)$$

where the operator Δ_k satisfies the equation

$$\Delta_k \psi_j = \delta_{jk}\psi_j, \qquad (5.8)$$

δ_{jk} being non-zero only if the electron k is in orbital j. To this approximation the spin density should always be positive, which, as has been remarked several times, is not always the case.

Chesnut calculated the isotropic hyperfine coupling and the distribution of spin density for ethyl radicals using different values of the parameter p, which is taken as the ratio of two resonance integrals

$$p = \gamma_{ij}/\gamma_0, \text{ where } \gamma_{ij} = \langle \psi_i | \hat{H} | \psi_j \rangle \qquad (5.9)$$

and

$$p = \frac{\gamma_{ij}}{\gamma_0} = \frac{S_{ij}}{S_0}.$$

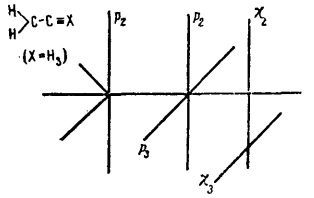


Fig. 4. Hyperconjugation in the ethyl radical.

Here S_{ij} is the overlap of the atomic orbitals i and j, while S_0 and γ_0 relate to values of these quantities for unsubstituted benzene [67]. The results of Chesnut's calculations are given in Table 3.

Table 3 shows that the hyperfine coupling constant does not decrease a great deal if more than one methyl group is involved in the hyperconjugation. This explains the dependence of the width of aliphatic radical spectra on the number of protons producing hyperfine splitting. The width of the spectrum can then be expected to increase with the number of groups involved in hyperconjugation at the carbon atom having the odd electron. The density ρ_C at the central carbon atom varies little for a given value of p, and the hyperfine splitting is, to a good approximation, proportional to this spin density.

A series of radicals was studied experimentally by Symons [70], the spin densities being calculated by means of the McConnell equation, although Symons himself points out that the application of this equation is not entirely justified with aliphatic radicals when ρ is large and both α and β hydrogen atoms couple with the odd electron. Spin densities were estimated in this paper for the radicals $\cdot CH_3$, $\cdot C(CH_3)_3$, $\cdot CH_2CH_3$, and $\cdot CH(CH_3)_2$, and a series of radicals derived from alcohols: $\cdot CH_2OH$, $\cdot CH_2C(CH_3)_2OH$, $\cdot CH(CH_3).C(CH_3)_2OH$, $\cdot CH(CH_3)CH(CH_3)OH$, etc.

In a study of irradiated malonic acid [the $\cdot CH(COOH)_2$ radical] McConnell *et al.* [48] estimated the hyperfine splitting from the isotropic and anisotropic coupling and also estimated the spin density. They showed that Q in the equation $a_H = Q\rho_C$ should be negative, as had previously been predicted theoretically, since it is only then that agreement is obtained between theoretical values of the hyperfine splitting and the experimental data.

This work was extended to a study of succinic acid [71] [the $.CH(COOH)CH_2COOH$ radical]. Here, as in Chesnut's work, consideration was given to the hyperfine coupling of the odd π electron with a "π proton", *i.e.* with a proton situated near the aliphatic carbon atom in a plane above or below the plane in which the π-electron spin density is distributed. In this work, however, anisotropic splitting of the "π protons" was determined experimentally for the case in which there was no free rotation of these protons.

It is postulated that, similarly to the equation $a_N = Q\rho_N$ for σ protons, the isotropic hyperfine coupling at the N nucleus with the "π proton" is directly proportional to the spin density at the adjacent unsaturated carbon atom:

$$b_N = R(\theta)\rho_N. \tag{5.10}$$

The coefficient of proportionality depends on θ, the angle of rotation of the alkyl group attached to the unsaturated carbon atom. The angle θ is defined so that $\theta = 0$ corresponds to the "eclipsed" configuration of the C–H bond relative to the axis of symmetry of the π orbital of the odd electron, whereas $\theta = \frac{1}{2}\pi$ corresponds to the proton situated in the nodal plane of the odd-electron orbital. Thus when $\theta = \frac{1}{2}\pi$ the proton of the alkyl group is a "σ proton". It is shown in the paper that the hyperfine splitting of the "π proton" is almost isotropic, and therefore the mean value of $R(\theta) - < R >$ can be estimated. In the case of the radical $\cdot C(CH_3)_2OH$ the splitting amounts to 56 Mc/s, [72] which is probably the best value of $< R >$ at the present time. The angular variation of $R(\theta)$ can be approximately represented by the equation.

$$R(\theta) = A + B\cos^2\theta. \tag{5.11}$$

Theoretical calculations of hyperfine coupling of the protons of methyl groups [73] indicate that, when $\theta = \frac{1}{2}\pi$, $R \simeq 0$, and hence that $A = 0$. The experimental value of B is then as follows

$$< R(\theta) > = {}^1/_2 B = 56 \text{ Mc/s},$$
$$B = 112 \text{ Mc/s}. \tag{5.12}$$

Isotropic splitting of the order of 112 $\cos^2 30^\circ$ = 84 Mc/s can be expected in this case for the "π protons" in succinic acid, provided that the two protons are oriented exactly as in the non-irradiated molecule of the acid.

TABLE 3.

Radical	Coupling constant of methyl protons	Spin densities	
		ρ_C	ρ_X
$p = 0.7$			
Ethyl	16.9	0.9160	0.0815
Isopropyl	15.5	0.8433	0.0743
t-Butyl	16.2	0.7825	0.0684
$p = 0.93$			
Ethyl	27.8	0.8577	0.1307
Isopropyl	24.2	0.7568	0.1137
t-Butyl	21.5	0.6807	0.1008

6. APPLICATION OF THE ALTERNANT ORBITAL METHOD

Papers have recently appeared in which the distribution of spin density is calculated by Löwdin's so-called alternant orbital method (AOM) [74–76]. The wave function with which the matrix elements of the spin density operator are calculated is obtained by applying the double state projection operator to the determinant

$$T_0 = |(a\Phi_1 + b\Phi_1')(a\Phi_2 + b\Phi_2')\ldots(a\Phi_n + b\Phi_n') \times$$
$$\times (a\bar{\Phi}_1 - b\bar{\Phi}_1')(a\bar{\Phi}_2 - b\bar{\Phi}_2')\ldots(a\bar{\Phi}_n - b\bar{\Phi}_n')|; \tag{6.1}$$
$$a = \cos\theta,\ b = \sin\theta,\ a^2 + b^2 = 1.$$

Here Φ is the wave function with spin α, $\bar{\Phi}$ the wave function with spin β, θ a parameter which combines the excited configurations and the lowest molecular configurations, the Φ representing bonding orbitals, and Φ' antibonding orbitals.

According to Löwdin, the projection operator for N particles having a spin of $\frac{1}{2}$ is

$${}^{2l+1}O = \prod_k^{k\neq l} (s^2 - k(k+1))/l(l+1) - k(k+1)). \tag{6.2}$$

The spin operator s^2 has the eigenvalues $l(l+1)$ where $l = \frac{1}{2}N$, $\frac{1}{2}N - 1$, ..., 0 or $\frac{1}{2}$ depending on whether N is even or odd, and the product is to be taken over all $k \neq l$ from 0 or $\frac{1}{2}$ to $\frac{1}{2}N$.

Application of ${}^{2l+1}O$ to T_0 gives

$${}^{2l+1}OT_0 = \sum_{k=0}^{n} C_k' T_k, \tag{6.3}$$

and for the cases of lowest and highest multiplicity ($l = 0$ and n):

$${}^1OT_0 = C_0^{(0)} \sum_{k=0}^{n} (-1)^k \binom{n}{k}^{-1} T_k, \tag{6.4}$$

$${}^{n+1}OT_0 = C_0^{(n)} \sum_{k=0}^{n} T_k, \tag{6.5}$$

where $T_k = n(2k+1) - 2k^2$ is the sum of the determinants obtained by k changes in the spin functions in T_0 between the two original groups of orbitals Φ_i and Φ_i'. The value of C_0 is $\frac{2}{3}$ for three electrons, and $\frac{1}{2}$ for five electrons.

Application of the doublet operator yields

$$
\begin{aligned}
{}^2OT_0 = C_0 \sum_{k=0}^{n} (-1)^n \binom{n+1}{k} T_k = a^{2n} |\Phi_1\Phi_2 \ldots \Phi_n\Phi_0\overline{\Phi}_1\overline{\Phi}_2 \ldots \overline{\Phi}_i \ldots \overline{\Phi}_n| + \\
+ \left(\frac{2}{3}\right)^{1/2} a^{2n-1}b \sum_{i=1}^{n} \frac{1}{(6)^{1/2}} \{|\Phi_1\Phi_2 \ldots \Phi_i' \ldots \Phi_n\Phi_0\overline{\Phi}_1 \ldots \overline{\Phi}_n| - \\
- |\Phi_1\Phi_2 \ldots \Phi_i \ldots \Phi_n\overline{\Phi}_0\overline{\Phi}_1\overline{\Phi}_2 \ldots \overline{\Phi}_i' \ldots \overline{\Phi}_n| + \\
+ 2|\Phi_1\Phi_2 \ldots \Phi_i \ldots \Phi_n\overline{\Phi}_0\overline{\Phi}_1 \ldots \overline{\Phi}_i' \ldots \overline{\Phi}_i' \ldots \ldots \overline{\Phi}_n|\} - \\
- \frac{(12)^{1/2}}{3} a^{2n-2}b^2 \sum_{i>j} \frac{1}{(12)^{1/2}} \{2|\Phi_1\Phi_2 \ldots \Phi_i\Phi_i'\Phi_n\Phi_0\overline{\Phi}_1\overline{\Phi}_2 \ldots \overline{\Phi}_j' \ldots \overline{\Phi}_j \ldots \overline{\Phi}_n| + \\
+ 2|\Phi_1\Phi_2 \ldots \Phi_j' \ldots \Phi_j\Phi_n\Phi_0\overline{\Phi}_1\overline{\Phi}_2 \ldots \overline{\Phi}_i \ldots \overline{\Phi}_j' \ldots \overline{\Phi}_n| - \\
- |\Phi_1\Phi_2 \ldots \Phi_i' \ldots \Phi_j' \ldots \Phi_n\Phi_0\overline{\Phi}_1\overline{\Phi}_2 \ldots \overline{\Phi}_i\overline{\Phi}_j \ldots \overline{\Phi}_n| + \\
+ |\Phi_1\Phi_2 \ldots \Phi_i' \ldots \Phi_j \ldots \Phi_n\Phi_0\overline{\Phi}_1\overline{\Phi}_2 \ldots \overline{\Phi}_i\overline{\Phi}_j' \ldots \overline{\Phi}_n| + \\
+ |\Phi_1\Phi_2 \ldots \ldots \Phi_i \ldots \ldots \Phi_j' \ldots \Phi_n\Phi_0\overline{\Phi}_1\overline{\Phi}_2 \ldots \overline{\Phi}_i\overline{\Phi}_j \ldots \overline{\Phi}_n| - \\
- |\Phi_1\Phi_2 \ldots \Phi_i \ldots \Phi_j \ldots \Phi_i' \ldots \Phi_j' \ldots \overline{\Phi}_n|\} - \\
- a^{2n-2}b^2 \sum_{i=1}^{n} \{|\Phi_1\Phi_2 \ldots \ldots \Phi_i' \ldots \Phi_j \ldots \Phi_n\overline{\Phi}_1\overline{\Phi}_2 \ldots \overline{\Phi}_j'\overline{\Phi}_j \ldots \overline{\Phi}_n|\}.
\end{aligned}
\tag{6.6}
$$

For normalisation, this function must be divided by $N^{\frac{1}{2}}$, where

$$N = a^{4n} + (2n/3)\, a^{4n-2}b^2 + a^{4n-4}b^4 (2n^2 + n)/3. \tag{6.7}$$

On calculating by means of the expectation value of the spin density operator

$$1/m_s \sum_{\mu} \delta(r - r_\mu) S_{\mu z}$$

for the molecular-orbital spin density, we obtain

$$
\begin{aligned}
\rho(r) = N^{-1} \left\{ a^{4n}\delta_{00} + \frac{4}{3} a^{4n-1}b \sum_{i=1}^{n} \delta_{ii'} + \frac{1}{9} a^{4n-2}b^2 \times \right. \\
\left. \times \sum_{i=1}^{n} [4\delta_{ii'} - 2\delta_{00} + 4\delta_{ii}] + \left(\frac{8}{9}n + \frac{4}{9}\right) a^{4n-3}b^3 \times \sum_{i=1}^{n} \delta_{ii'} + [(2n^2+n)/3]\, a^{4n-4}b^4\delta_{00} \right\},
\end{aligned}
\tag{6.8}
$$

where

$$\delta_{00} = \Phi_0^2(r), \quad \delta_{ik} = \Phi_i(r)\,\Phi_k(r), \quad \delta_{ii'} = \Phi_i(r)\,\Phi_i'(r).$$

If we pass to atomic-orbital spin density and represent by ρ_A the spin density at the starred atoms, and by ρ_B the density at the non-starred atoms, we obtain the following relations:

$$\rho_A = (N')^{-1} \left\{ C_{0A}^2 Y + \frac{2}{3}\tan\theta + \frac{4}{9}\tan^2\theta + [(4n+2)/9]\tan^3\theta \right\} \chi_A^2(r), \tag{6.9}$$

$$\rho_B = (N')^{-1} \left\{ -\frac{2}{3}\tan\theta + \frac{4}{9}\tan^2\theta - [(4n+2)/9]\tan^3\theta \right\} \chi_B^2(r), \tag{6.10}$$

$$N' = 1 + (2n/3)\tan^2\theta + [(2n^2+n)/3]\tan^4\theta, \tag{6.11}$$

$$Y = 1 - \frac{2}{3}\tan\theta - [(2n+4)/9]\tan^2\theta - [(4n+2)/9]\tan^3\theta + [(2n^2+n)/3]\tan^4\theta. \tag{6.12}$$

It can be shown that $\tan\theta$ is always positive, so that the sign of ρ_B will depend on that of the right-hand expression. In Eqns. (6.9)–(6.12), $\chi_A(r)$ represents an atomic orbital centred on a starred atom A, while $\chi_B(r)$ represents an atomic orbital on a non-starred atom B.

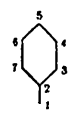
These formulae were used to calculate spin densities in alternant hydrocarbon radicals containing an odd number of carbon atoms: triphenylmethyl, perinaphthenyl[75], and allyl[76].

In the triphenylmethyl calculation terms of the order of b^2 were neglected, so that

$$\rho_A = \left(1 - \frac{2}{3}\tan\theta\right) C_{0A}^2 + \frac{2}{3}\tan\theta,$$

$$\rho_B = -\frac{2}{3}\tan\theta.$$

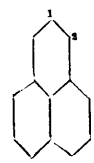
The parameter θ was calculated from the experimental value of the spin density at a non-starred atom, its value was substituted in ρ_A, and the result was compared with experiment. Reitz showed that for triphenylmethyl[77] $|\rho_3| = |\rho_5| = 2|\rho_4|$. It follows from Adam and Weissman's work[57] that the sum of the absolute spin densities at all the carbon atoms linked to a proton is $\rho = 1.57$. On comparing the results, we obtain



$$3\{2|\rho_3| + 2|\rho_4| + |\rho_5|\} = 24|\rho_4| = 1.57, \quad |\rho_4| = 0.065,$$
$$\rho_4 = -0.065.$$

Then $\rho_3 = \rho_5 = 0.137$.

For the perinaphthenyl radical[10], the measured spin density is $|\rho_1| = 0.098$. According to the alternant orbital method, $\rho_1 = -0.098$, whence $\rho_2 = 0.2477$ (the experimental value is $\rho_2 = 0.327$).



With the allyl radical the spin densities obtained by the alternant orbital method showed good agreement with those calculated by the configurational interaction method[32]:

AOM	Configuration interaction
$\rho_1 = 0.6388$	$\rho_1 = 0.6363$
$\rho_2 = -0.2645$	$\rho_2 = -0.2334$
$\rho_3 = 0.6588$	$\rho_3 = 0.6363$

7. SPIN DENSITY AND NUCLEAR MAGNETIC RESONANCE

As McConnell[12] has shown, the magnitude and sign of the spin density can be judged from the chemical shift developed in the proton magnetic resonance of paramagnetic substances. The chemical shift ΔH at the proton and the spin density ρ_C at the carbon atom adjacent to the proton are related as follows:

$$\Delta H = Q\rho_C(\gamma_e/\gamma_H)\, g\beta S(S+1)/6kT, \tag{7.1}$$

where Q is the proportionality constant in the McConnell equation, γ_e and γ_H represent the gyromagnetic ratio for the electron and the proton respectively, g is the spectroscopic splitting factor, β the Bohr magneton, k the Boltzmann constant, T the absolute temperature, and S the spin of the odd electron. A paper by Lefebvre[78] gives a theoretical derivation of this equation and discusses the form of the proton resonance line in polycrystalline radicals.

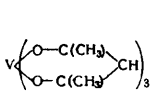
Eqn. (7.1) was first used to estimate spin densities in the organometallic compounds vanadocene, chromocene, and nickelocene [79,80]. In contrast to nickelocene, in which the spin density at the carbon atoms in the ligands is positive, that in the ligands of vanadocene and chromocene was found to be negative with values of ρ_C = -0.06 and -0.12 respectively. The sign of the spin density is determined by the direction of the chemical shift at the proton. If the spin of the proton is polarised in the direction of the external magnetic field, the shift takes place towards lower fields. If the proton spin is in the direction opposite to the applied magnetic field, the proton shift occurs at higher values of the magnetic field.

Nuclear magnetic resonance made it possible to determine spin densities in diphenylpicrylhydrazyl [17,81]. The resonance line of this radical consisted of two partly resolved components of equal intensity but different widths, one being shifted to increasing field by 2.95 oersteds, while the other is shifted in the opposite direction by 1.75 oersteds. As already remarked, the spin polarisation of the proton is opposite to that of the adjacent carbon (or nitrogen) atom [48]. Therefore the sign of the proton shift should be the same as that of the spin density ρ_C, as is reflected in Eqn. (7.1) (Q = -22.5). If one line (up the field) is assigned four *ortho*- and two *para*-protons, while the narrower line is given six *meta*-protons, the shift agrees with calculations on diphenylpicrylhydrazyl by the valence bond method, according to which the spin densities in the *ortho*- and *para*-carbon positions are positive, while those in the *meta*-position are negative. These results confirm not only the existence of negative and positive spin densities, but also the sign of the equation $a = -22.5\rho_C$.

Anderson *et al.* [82] studied the shifts in nuclear magnetic resonance of the negative pyrene ion in its potassium compound, and estimated the isotropic hyperfine coupling constants. The values obtained were very close to those obtained from experiments on electron paramagnetic resonance. Some divergence in the values of the constants was partly due, in the opinion of the authors, to a change in the odd-electron density distribution in the ion under the influence of the crystal lattice, accompanied by corresponding changes in the $\pi-\sigma$ exchange, giving isotropic hyperfine splitting. The difference may be due also to the anisotropy observed in the proton resonance lines.

An interesting confirmation of the fact that the spin density at protons of the methyl group in the C–CH_3 bond is opposite in sign to the spin density at the proton in the C–H bond (in electron paramagnetic resonance this is reflected in the sign of Q = 25 oersteds for the former, and of Q = = -22.5 oersteds for the latter case) is given in a paper by Forman *et al.* [83], who investigated the proton shifts for vanadium acetylacetonate. Compared with the diamagnetic cobalt acetylacetonate, the vanadium compound exhibits a shift towards lower fields.

When the hydrogen in the third position in



is replaced by a methyl group, the shift is changed markedly, owing to the change in the distribution of spin density at this position. Since the shifts are opposite, it is clear that the spin densities at the protons in the C–CH_3 and C–H groups have different signs.

Similar results were obtained for the distribution of spin density in the ligands of nickel chelates [84]. Changes in the distributions of spin density in such compounds produced by the introduction of heteroatoms (S and O) into the system of conjugated bonds, and by –NH– and –N : N– groups have been determined by nuclear magnetic resonance [85].

Thus the distribution of spin density may also be successfully studied in inorganic molecules. The use of nuclear magnetic resonance for this purpose has started comparatively recently, but from the work which has been done up to the present time it can already be concluded that further investigations by this method on paramagnetic compounds, in particular on paramagnetic aromatic complexes of metals, will undoubtedly be of great value in elucidating their electronic structure.

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THE MULTIPLET THEORY OF CATALYSIS. STRUCTURAL FACTORS IN CATALYSIS

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Catalysis forms the basis of modern heavy chemical industry and biochemistry, and the elaboration of a theory of catalysis is of great importance. At present there exist three main theories of catalysis, which are mutually complementary: the intermediate surface compound, the multiplet, and the electronic theories. On their basis we can start to construct a unified theory of catalysis. This will solve the problem of the choice of catalysts[1], which will provide great opportunities for controlling chemical reactions[2].

1. FUNDAMENTAL PRINCIPLES OF THE MULTIPLET THEORY

The revolution in physics at the beginning of the twentieth century led to the modern theory of the structure of matter, on which the multiplet theory of organic catalysis[3,4] is based, and has evolved gradually[5-8] as the former has grown. The present state of the multiplet theory is described below. The multiplet theory generalises the experimental results on the basis of the configurations of molecules and solid lattices, as well as bond lengths and energies, and up to the present time it is the only theory in which actual catalytic reactions are considered systematically at the atomic level from this point of view.

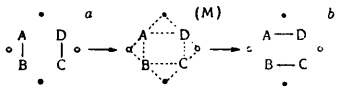
The theory of the structure of matter is based on electronic theory and quantum mechanics, and therefore these also constitute a basis of the multiplet theory; the lengths and energies of bonds represent a stable set of electronic properties of importance in catalysis[9].

The multiplet theory starts from the fact that catalysis is a chemical phenomenon. Chemical valence forces are characterised by potential curves representing the mutual potential energy of two atoms as a function of the distance between them. The bottom of the well in these curves corresponds to the bond length d and the bonding energy (allowing for the zero-point energy). The potential well is narrow and has steep sides. This implies that the atoms interact chemically when they are practically in contact, *i. e.* when they approach to the distance d. Bond lengths and energies are measured by X-ray and electron diffraction, spectroscopically, thermochemically, and by other modern physical methods. A far reaching additivity of bond lengths and also of bond energies is observed, which is of importance in their practical application.

Owing to the small range of action of chemical valence forces, catalytic reactions involve not entire molecules but individual atoms in them, which according to the above considerations should be in contact with one another (not necessarily at the same time). This principle of contact makes it easy to establish which atoms in a molecule touch

one another during each reaction step. A group of such atoms is termed an indicial group; it is the analogue of a functional group in organic chemistry. According to the principle of contact, the reactant atoms should, at some instant, be in contact also with the catalyst[5].

According to the multiplet theory, the simplest and most frequently encountered reactions are duplet reactions[10,11]:



(1.1)

Here A, B, C, and D are the atoms involved in the reaction [substituents not indicated in Eqn. (1.1) may be attached to them]. They are located (not necessarily simultaneously) on the catalyst surface. The atoms of the catalyst, the centres of which are indicated by dots and by small circles, may be of different types. Attraction to the catalyst is effected by chemical forces, under the influence of which the bonds A–B and C–D become weaker. This results in the form M, the multiplet, active complex, which is unstable and tends to pass into a more stable state, which can be either the initial state *a* or the final state *b*, depending on the thermodynamic conditions. The role of atoms denoted by dots and by circles is the same. Therefore forward and reverse reactions pass through the same complex M in opposite directions. The dots imply that, under the given conditions, thermodynamics requires that reaction shall go in the direction of rupture of the vertical bonds in *a* and formation of horizontal bonds in *b*. In this way microreversibility is observed; the distances between the dots in Eqn. (1.1) may be different from those between the centres of the circles.

Scheme (1.1) can be simplified in various ways: we can omit the circles and leave only dots associated with A, B, C, and D; sometimes we enclose the reactant atoms in a frame. The most concise way is to indicate only the atoms and the bonds of the indicial group, arranged in such a way that reaction involves the rupture of two vertical bonds with the formation of two horizontal bonds. Then the scheme (1.1) as a whole is represented by the group

(1.2)

The bonds A–B and C–D may belong either to two molecules or to the same molecule (for example in a cyclisation); therefore the group (1.2) represents not only double decompositions but also decompositions and cyclisations, as well as additions when it contains a multiple bond, for example A=B. If bonds other than those written above are present in the indicial group, they are preserved during the reaction (as are also substituents attached to A, B, C, and D).

A more complicated example is the triplet reaction having the indicial group

(1.3)

This reaction results in the rupture of three bonds A–B, C–D, and E–F with the formation of the bonds B–C, D–E, and F–A.

There is also the sextet type (see later). It is a singular fact that duplet, triplet, and sextet reactions practically exhaust the whole wealth of heterogeneous catalytic reactions known in organic chemistry. At present reactions in which the valency of the indical atoms changes are not included in the multiplet theory. However, they are few compared with the total number of reactions.

Scheme (1.2) and other schemes of the multiplet theory have a definite physical meaning. In order to elucidate it, we must consider the theory of the structure of matter, and in particular the theory of the solid state.

The faces of the crystal lattice of the catalyst contain projections corresponding to the lattice atoms (Fig. 1). Comparison of the electron and X-ray diffraction patterns shows that the surface and inner layers of a solid usually differ little in structure. Furthermore, the closest packing, for example of three identical rigid atoms, should be an equilateral triangle whether the atoms are situated within the lattice or at the surface. This permits us to apply to the surface (with some approximation) the mean additive bond lengths known for the bulk phase.

Apart from projections of atomic dimensions, the crystal faces will obviously contain indentations (*V*) between the projections (see Fig. 1). The distances between the indentations (d_1) are equal to those between the projections (*d*). Atoms entering the indentations are attracted especially strongly, for the same reason that atoms of a metal undergoing crystallisation tend to arrange themselves with the closest packing: here the potential energy is a minimum owing to the possibility of interaction with several surrounding atoms. Crystal growth takes place at sites where the atomic arrangement is especially favourable, at the so-called growth points and centres of crystallisation (see, for example, Ref. 12).

If atoms of a different substance having a similar atomic radius enter the indentations *V* or the deeper gaps *V'* (Fig. 1), crystal growth can also take place, a solid solution being formed (under certain conditions). We shall have a case of isomorphism. In crystal chemistry and in the study of alloys atomic (and ionic) radii are in everyday use (*cf.* Goldschmidt's rule). An example of a general rule applicable to alloys is that metals of atomic radius 2.2–3.0 Å show the greatest tendency to form substitutional solid solutions (Kornilov[13]). Structural conformity plays a great part also in the field of clathrate compounds[14] and molecular sieves[15].

With certain geometrical relations, the lattice of one substance can also be continued in a regular manner by that of another substance. This will be a case of epitaxy, in which crystal-chemical conformity exists at the boundaries between the solid phases (*cf.* Dankov[16] and Seifert[17]).

In oriented adsorption the parts of the molecule in contact with the adsorbent lattice can also be in crystallographic correspondence with the latter. This is none other than stereospecific adsorption.

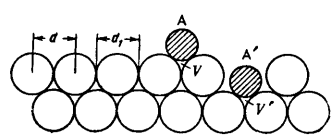


Fig. 1. Section through catalyst surface.

In the case of heterogeneous catalysis the reactant atoms A, B, C, D, etc. fall into the depression *V* between the surface atoms of the catalyst. We are dealing here with a kind of monolayer surface alloy. In this way several atoms of the catalyst are in contact with the reactant atoms (the indicial group), forming the multiplet.

Parts of the molecules extraneous to the catalyst need not in general bear any relation to the catalyst surface. On the other hand, those parts in contact with the catalyst, entering depressions of atomic dimensions in it, must show surface isomorphism with the catalyst. Hence follows the principle of structural conformity between reactant molecules and catalyst. From the above, it is to be expected that the active centres for catalysis will be provided by points on the surface which are active in crystallisation, *i. e.* growth centres and crystal nuclei.

In enzymic catalysis, not only the indicial atoms but also extraindicial substituents should be in contact with the catalyst. The structural conformity must be still more precise, which explains the great specificity of enzymes (see Section 8). With some variation, the same applies to antimetabolites (Section 8) and probably to antibodies[18].

We now have a continuous series of phenomena in which structural conformity plays an important part, these phenomena relating to such different branches of science as crystal chemistry, the study of alloys, epitaxy, stereospecific adsorption, heterogeneous catalysis, enzymes, antimetabolites, and immunology. In the field of epitaxy, similar views have recently been expressed by Seifert[19].

2. THE MULTIPLET THEORY AND OTHER THEORIES OF CATALYSIS

One of the main differences between the multiplet theory and Kobozev's *ensemble* theory[20], which considers that it is an amorphous phase which possesses catalytic activity, is that, according to the multiplet theory, catalysts can be either crystalline or amorphous; most often they are microcrystalline.

For structural conformity, it is important in the multiplet theory that there should be a definite mutual arrangement of atoms in the catalytically active centre, which contains a small number of atoms, and it is not usually necessary that a definite atomic arrangement should be repeated millions of times in the vicinity of this centre (although such replication may influence the properties of the active centres). Therefore active centres may be not only crystals but also certain small parts of large molecules, such as macromolecular amino-acids in enzymic catalysis, and isolated fragments of a crystal lattice, which are amorphous to X-rays and which contain six atoms in the case of sextets and still fewer with duplets and triplets. The multiplet theory discusses crystal lattices because their constants can be used to find atomic radii and the probable arrangement of atoms in the multiplet (*cf.* above).

Incidentally, although the concept of active centres appeared earlier (Constable[21], Taylor[22]), the question of the *structure* of the active centres was first raised in the multiplet theory[3].

Let us now consider what happens to the reactant atoms A, B, C, and D. At the very start the initial materials undergo molecular adsorption (and at the end of the reaction the molecularly adsorbed reaction products are desorbed). The multiplet theory assumes that in the next stage, that of catalytic adsorption, the bonds A–B and C–D [see group (1.2)] become weakened and distorted, and in the limiting case may undergo complete rupture[5,10] into chemisorbed atoms (or radicals). The new bonds A–D and B–C begin to link up in the multiplet active complex even before the original bonds are completely broken.

A completely analogous principle[23] exists in the theory of absolute reaction rates[24]: the reaction path from A–B and C–D to A–D and B–C does not pass over an elevated plateau, corresponding to complete dissociation (A + B + + C + D), but over a lower col.

On the other hand, the theory of intermediate surface compounds assumes that at first there is activated adsorption, and then the catalytic reaction. By this theory (see, for example, Rideal[25]), we imply a modernised version of Sabatier's theory, in which the bulk intermediate compounds of the latter have been replaced by the reactants which have undergone activated adsorption — adsorption accompanied by complete rupture of the bond A–B with attachment of the atoms to the surface. Thus in the formation of ethylene from alcohol on aluminium oxide, for example, it is supposed that the alcohol molecule combines chemically with the surface atoms, with the formation of an intermediate surface alkoxide, which then decomposes to yield the reaction products. Nothing is said, however, about the mechanism of the decomposition of this intermediate compound (*i. e.* the mechanism, in the terminology of the multiplet theory, of the rupture of the bond C–D and the formation of the bonds A–D and B–C).

The appearance of the multiplet theory was soon followed by Polanyi's theory of catalysis[26]. The conclusions reached by this worker, being based on quantum-mechanical considerations, are very similar to those of the multiplet theory, and can be represented in essence[10] by the indicial group (1.2). In Polanyi's theory the intermediate state is one in which the bonds A–B and C–D have been ruptured, and the atoms A, B, C, and D are combined chemically with the surface valences (Fig. 2). Polanyi points out correctly[27] that the state depicted in Fig. 2 is none other than Taylor's activated adsorption. In this respect the intermediate state is the same as in the intermediate surface compound theory, differing, however, in that here the atoms C and D also have undergone activated adsorption.

Later Eyring and Polanyi suggested the transition state theory, which was then developed in detail by the former[24]. It follows from this theory that rupture of the bonds A–B and C–D should not be complete in the intermediate state corresponding to Fig. 2, which is in agreement with the view of the multiplet theory (see above). The following comment may be made as to whether the multiplet theory regards adsorption not only at the bond A–B but also at C–D as always necessary.

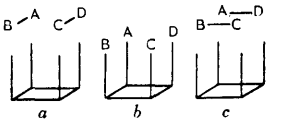


Fig. 2. Polanyi's scheme for catalysis.

Cases of purely duplet, etc. reactions have been examined above. There are, of course, other possibilities, which can also be readily explained. Bonds requiring activation must be in contact with the catalyst. If in a duplet reaction, for example, one part of the indicial group does not need to be activated, it can react without coming into contact with the catalyst. Such a "semi-duplet" scheme was suggested by the present writer[28] for esterification in solution. Hence there is a transition from heterogeneous to homogeneous catalytic reactions and, in the limit, when neither bond of the duplet group requires activation for reaction to occur, to non-catalytic reactions.

In general, however, the quite widely held view, that catalysis often takes place on impact of a molecule of the second component from the gas phase on an adsorbed molecule of the first component, should be treated with great caution. Although such cases may occur, for example with an incomplete duplet (see above), a more thorough examination usually shows that the molecules of the second component must be adsorbed too. Hinshelwood[29] holds the same opinion. It is more correct to regard impact from the gas phase as an adsorption stage which is so rapid that it does not limit the overall reaction.

A further difference between the multiplet and the intermediate surface compound theories is that, according to the former, an intermediate state is followed by a fork in the reaction path. When catalysis is then by far the more rapid, we are dealing, as Roginskii[30] puts it, with presorption catalysis; when, however, the process goes far more rapidly in the direction of activated adsorption, the impression is created that the latter precedes catalysis. The intermediate surface compound theory, on the other hand, assumes that chemisorption precedes catalysis (see above).

According to the multiplet theory, the atom A of scheme (1.1) in Fig. 1 may be located in the hollow *V* between two catalyst atoms, while atom B of the indicial group (1.1), from which A has not yet completely separated, may lie at an angle [11] to the plane of the diagram on the surface. If another atom D is present on the surface (in general at a different angle), a new bond A–D may form under favourable thermodynamic conditions. Thus in this case the position of the atom A is favourable for catalysis. However, A may roll down from *V* into a deeper recess *V'* and occupy position A', where it will have a larger number of catalyst atoms as neighbours. The potential energy at A' will be lower than that at A. The position A' will be more stable, and the energy evolved during such adsorption may be sufficient for complete rupture of the bond A–B, which corresponds to activated adsorption. When under changed conditions (for example with rise in temperature) the hollows *V* also become capable of activated adsorption, they will be poisoned for catalysis, by being filled with firmly held atoms adsorbed in this way. The hollows *V* between the catalyst atoms considered in the multiplet theory correspond to what in several theoretical papers are denoted by free valences[26] or by asterisks[31].

The adsorption responsible for catalysis must be stronger than van der Waals adsorption, since it is produced by chemical forces. Therefore a large amount of energy must be expended in order to remove the adsorbed atom A of the molecule (the atom formed by complete rupture of the bond A–B) from the hollow *V'* between the catalyst atoms. However, this does not mean that the adsorbed atoms must be fixed at a given site on the surface. It all depends on the height of the potential barrier between two neighbouring hollows. The condition necessary for relative freedom of movement is that this barrier should not be high. Migration of the atom (or radical) is then possible along Lennard-Jones valleys, *i. e.* valleys of minimum potential energy situated between projecting parts of atoms and ions forming the crystal face.

Although activated adsorption does not necessarily precede catalysis, its study, and also that of the adsorption, infra-red spectra, and magnetic properties of chemisorbed molecules, are of importance for catalysis. It is likewise important to study bulk chemical compounds similar to the supposed surface compounds, for example alkoxides in the dehydration of alcohols. From this point of view, the properties of nitrides, carbides, hydrides, and analogous compounds must also be studied. All this is necessary to enable us to assess the development of chemical forces under conditions resembling catalysis. It must not be forgotten, however, that such information is indirect, since it relates not to the actual catalytically active centres but to a larger surface, and not to the activated complex but to more stable compounds formed with the catalyst. In this respect a more direct method for the study of catalysis is the kinetic method, which has lately been enriched by the use of labelled atoms and by the stereochemical method.

Summarising the relations between the multiplet and the intermediate surface compound theories, we can say that they resemble one another in that both regard catalysis as due to chemical forces, under the influence of which several intermediate structures are obtained. The main difference is that .... [line missing in the Russian original (Ed. of Translation)] atomic radii, bond energies, etc. Other differences have been considered above. The deformation of reactant molecules and bonds is a concept from the deformation theory of catalysis due to Mendeleev, Zelinskii, and Bodenstein, developed and refined on the basis of modern data.

During recent years an electronic theory of catalysis[32-35] has been successfully developed, the achievements of which include the predictions (subsequently confirmed) that catalytic activity is linked with electrical conductivity and with the work function, of the action of illumination on catalysis, and of the effect of the valency of added ions on their effectiveness as promoters.

There must necessarily exist an intrinsic connection between the multiplet and the electronic theories of catalysis, since both theories are based on that of the structure of matter. The attraction of molecules by the lattice of a solid during adsorption and catalysis occurs as a result of coulombic and quantum-mechanical interaction between electrons and nuclei. All formulae representing these interactions contain a distance. Thus the spatial factor, which is fundamental to the structural aspect of the multiplet theory, should be important for the electronic theory. And conversely, the electronic interactions considered in the electronic theory are determined by bonding energies, a knowledge of which is necessary in order to apply the multiplet theory. It was now time to apply electronic interpretations to the theory of catalysis. Thus Vol'kenshtein writes: "The electronic mechanism of chemisorption does not at all exclude these (geometrical) factors, but emphasises their significance; it retains the geometrical schemes of the multiplet theory" [36]. Schwab[37], a spokesman for the electronic theory, recognises the value of the geometrical stereochemical factor, and says that "the main theory based on the geometrical factor has been up till now Balandin's multiplet theory". Papers have already

appeared in which the electronic and the multiplet theories are applied together (see later).

The application to heterogeneous catalysis of the theory of absolute reaction rates[24] proves to be the closest of all to the multiplet theory. This was first done by Temkin[38] on the simplifying hypothesis that the partition functions of species on a surface are unity. The theory of absolute reaction rates, based on quantum mechanics and statistics, demonstrated[24] that during adsorption, attachment of diatomic molecules (of hydrogen) to two atoms of the catalyst (carbon or nickel) is energetically more advantageous than attachment to a single atom. It showed that the actual energy of activation on solid surfaces should be small, and that for an endothermic process the activation energy should be almost equal to the heat of reaction. The theory discusses the real arrangement of atoms and the mutual energy of their valence electrons. As yet, there have been only a few applications of the theory of absolute reaction rates to actual catalytic reactions, among them being the dehydrogenation of alcohols on copper. As the present writer has shown[39], with reactions of this type, application of the theory of absolute reaction rates to the model given by the multiplet theory yields results which agree with experiment.

Thus calculation shows that the rate constant for dehydrogenation of primary alcohols k_d is, with the model illustrated in Fig. 5,

$$k_d = \frac{kT}{h} \frac{\prod_3 \left(2\pi kT \frac{I_{\neq}^{1/2}}{\theta_{\neq}^{1/2}}/h\right) \prod_3 \left(2\pi kT \frac{m_{\neq}^{1/2}}{\kappa_{\neq}^{1/2}}/h\right) f_{i_{\neq}}^{3n-7}}{\prod_3 \left(2\pi kT \frac{I_a^{1/2}}{\theta_a^{1/2}}/h\right) \prod_3 \left(2\pi kT \frac{m_a^{1/2}}{\kappa_a^{1/2}}/h\right) f_{i_a}^{3n-7}} e^{-\Delta H/kT}, \quad (2.1)$$

where I represents a moment of inertia, m a mass, θ a torsional modulus, and κ a modulus of elasticity, the subscript a denoting the adsorbed molecule, and the double cross the active state. Here the partition functions are no longer unity. The rate of dehydrogenation proves to be constant with different alcohols, in conformity with experiment.

In principle, application of the theory of absolute reaction rates should enable the velocities of catalytic reactions to be calculated from molecular models based on the multiplet theory (see preface in Ref. 24). In this way the multiplet theory is linked by stages with other theories of catalysis.

3. CONSEQUENCES OF THE MULTIPLET THEORY

Several consequences, which have been confirmed experimentally, follow from the above principles of the multiplet theory (Section 1). Some of these consequences have already been mentioned above (Section 2).

1. Catalysis takes place in a monolayer on the catalyst surface. This is consistent with the results of Langmuir's fundamental work[40].

2. The substrate molecules are oriented with their reactive groups towards the catalyst surface. This is confirmed by the very similar activation energies for different compounds in reactions having the same indicial groups, for example in the dehydrogenation of primary alcohols on copper (Constable[21] and others), the dehydration of normal primary alcohols on bauxite and on aluminium oxide[41-43], and also the present author's recent work (see Section 4).

In general it might be supposed that the catalyst combines with the molecule at a distance from the reactive atoms, and that its influence is transmitted along the hydrocarbon chain, producing increased activity at the other end of the molecule (the inductive effect). However, it is known from organic chemistry (see, for example, Ref. 44) that the inductive effect falls off very rapidly along a saturated chain. The above constancy of the activation energy disproves this hypothesis, and demonstrates that the indicial group is oriented towards the catalyst, as required by the multiplet theory.

3. Inert substituents, the extraindicial parts of the molecule, remain unchanged during catalysis, and have little influence on the course of the reaction. This is true when the substituents do not readily displace the electrons in the indicial group, which thus comprises the most important part of the reactant molecules. From this point of view, the hydrogenation of ethylene and that of an unsaturated fatty acid do not differ fundamentally from one another. However, since any substituents, even alkyl groups, somewhat displace electrons in the atoms of the indicial group, they introduce quantitative differences which, in the case of strongly electron-donor or electron-acceptor groups, may be sufficient to produce a qualitative change in the nature of the reaction. Therefore the same catalysts should correspond to the same indicial groups. This is broadly confirmed by experiment.

4. Different catalysts should correspond to different indicial groups, since different atoms in the indicial group have different affinities for the atoms of the catalyst. Therefore catalysis should be selective. This is confirmed by our entire knowledge of organic catalysis. The multiplet theory enables us to classify reactions by systematically replacing atoms in the indicial group, for example of a duplet reaction (see Section 8).

5. Ideally, all the atoms in the indicial group should be in contact with the catalyst, although not necessarily at the same time. We shall see a confirmation of this in the dehydrogenation of hydrocarbons. In fact, in the reverse reaction (hydrogenation) nickel should, according to Sabatier, give an intermediate nickel hydride; on the other hand, the olefine, too, should be adsorbed on the nickel through its carbon atoms, as is now generally accepted (see, for example, Refs. 45, 46, etc.). Obviously all these atoms should be in contact with the nickel during dehydrogenation as well. Investigation by a tracer method (deuterium exchange and hydrogenation with deuterium) shows that different hydrogen atoms and the olefine are adsorbed in a definite sequence, yielding a so-called semi-hydrogenated form and hydrogen atoms adsorbed on the surface (see Section 4).

6. Enhanced catalytic activity may be developed if some of the atoms in the indicial group are attracted to surface atoms of one kind, while other indicial atoms are attracted to atoms of a different kind on the surface. As Schwab[48] has pointed out, this enables the multiplet theory to explain the action of mixed catalysts. It can therefore be expected that catalysts consisting of different solid phases may be especially active along the interphase boundaries (lines). This has been confirmed in a series of papers from the author's laboratory (see Section 7).

7. The multiplet theory is able to explain the gradual increase in activity of a catalyst produced by the addition of

a promoter and, after a maximum has been reached, the subsequent fall in activity due to poisoning of the catalyst. Actually, if, for example, a sulphur atom is introduced into the nickel lattice, it deforms the lattice in its immediate neighbourhood, diminishing the Ni–Ni interatomic distances, and the resulting values may prove to be more favourable for catalysis. If, however, too much sulphur is present, it will screen the nickel surface, and the activity of the latter will fall.

8. Poisoning of a catalyst results from screening of its surface, the molecule of the poison preventing the reactants from coming into contact with the catalyst. Since chemical forces have a small range of action, the catalytic effect cannot develop. Maxted's remarkable investigations[49,50] serve to illustrate this principle. As Garner has pointed out[51], Maxted's results are explained by the multiplet theory.

9. The multiplet theory envisages the adsorption of molecules at two points, the deformation of bonds accompanying adsorption resulting, in the limit, in their dissociation. Taylor's discovery of activated adsorption, which has played such a large part in the theory of catalysis, has in essence confirmed this prediction. However, such far reaching adsorption does not always assist catalysis (see above).

10. Since the indicial atoms are not attached to the catalyst at the same time, free radicals formed as a result of too great a deformation of the bonds may migrate from one hollow to another if the activation barriers to migration are not too high. The migration of radicals may lead to the establishment of surface chain reactions. These will be especially probable in the case of the more stable free radicals, such as the methylene radical $:CH_2$ (see Section 5).

11. Another possible molecular movement along the catalyst surface is that of the intermediate activated complex, *i. e.* of the distorted molecule together with atoms of the catalytically active centre, either as a whole or in part. The conditions necessary for such motion were examined in Ref. 52. When the complex breaks down, the material of the catalyst proves to have been transported to another point on the surface, where new crystals with new faces (although with the same lattice) may be formed on crystallisation. It is evident from this mechanism that such transport can take place only during a catalytic reaction, but not when the catalyst is heated in an inert atmosphere to the temperature at which the catalytic reaction occurs. This phenomenon had been known previously[46,53,54] and was termed "catalytic corrosion" by Roginskii *et al.*[55], who investigated it by means of the electron microscope. Thus the multiplet theory also explains catalytic corrosion.

12. Since the surface of the catalyst is non-uniform, different portions of it should possess different catalytic and adsorptive activities. This conclusion follows from the multiplet theory (*cf.* Section 1).

Sites of maximum catalytic activity should not coincide with those of maximum adsorptive activity (for details see Ref. 56, crater-shaped curves). Therefore the particular fact that in an electron microprojector the last traces of gas can be removed from the metal only under a very high vacuum, while catalysis takes place at a higher pressure[32], does not contradict the multiplet theory. It does not at all follow from these experiments that the whole surface is covered with a gas film, but only that there are portions of the surface which are most difficult to free from adsorbed gas. However, such portions should play practically no part in catalysis, which is effected by other sites exhibiting less strong adsorption.

13. According to all that has been said above, several layers must be distinguished[11,57] in the multiplet active complex (Fig. 3). Starting from the catalyst outwards, these layers will be: (I) catalyst atoms surrounding the active centre; (II) catalyst atoms forming the multiplet; (III) atoms of the indicial group, within which the valence bonds are redistributed from the position characteristic of the starting materials to the position characteristic of the reaction products; (IV) extraindicial substituents, groups which remain unchanged during the reaction and in general are not in contact with the catalyst; (V) molecules adsorbed on the catalyst by van der Waals forces; and (VI) the adjacent layer of solvent (in the case of solutions), or in general the layer within which the starting materials and the reaction products diffuse to and from the catalyst respectively. The interface passes between layers II and III, which govern the course of the catalytic reaction. Layers I and IV exert symmetrical effects on the reaction, which are due to the influence of neighbouring atoms on the reactant atoms: in layer I the influence of the nature, number, and rearrangement of the atoms adjacent to those of the active centre of the catalyst, and in layer IV the influence of the nature and structure of the extraindicial side-chains.

14. The most important consequences following from the premises of the multiplet theory are the principles of structural and energetic conformity between reactant molecules. These principles enable us to obtain the most concrete results.

4. STERIC FACTORS. STRUCTURAL CONFORMITY

a. Duplet Reactions

Exchange of deuterium and hydrogenolysis. The simplest duplet reactions are those involving hydrogen: the high-temperature *ortho–para* conversion [group (4.1)], the reaction $H_2 + D_2 = 2HD$ [(4.2)], and exchange of deuterium with ammonia [(4.3)] and with hydrocarbons [(4.4)]:

$$\begin{matrix} H & H \\ | & | \\ H & H \end{matrix} \quad (4.1); \qquad \begin{matrix} H & D \\ | & | \\ H & D \end{matrix} \quad (4.2); \qquad \begin{matrix} N & D \\ | & | \\ H & D \end{matrix} \quad (4.3); \qquad \begin{matrix} C & D \\ | & | \\ H & D \end{matrix} \quad (4.4)$$

[*cf.* group (1.2)]. Of the three mechanisms suggested for reactions (4.1) and (4.2) (the Bonhoeffer–Farkas, Langmuir–Hinshelwood, and Eley–Rideal mechanisms) the

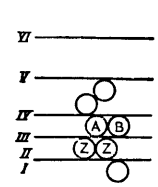


Fig. 3. Layer structure of activated complex.

second[58], which is consistent with the multiplet theory[59] (*cf.* Ref. 60), is the most probable according to the most recent kinetic data.

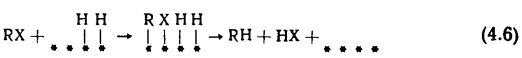
Exchange of deuterium with ammonia is effected by an indicial group analogous to (4.2) with H replaced by N. Owing to the pyramidal shape of NH_3, the remaining two hydrogen atoms should not, according to the multiplet theory, be in contact with the surface, and the molecule must be rotated for them to be exchanged for deuterium.

In the exchange of deuterium with saturated hydrocarbons, the indicial group (4.4) is closest[23] to the Farkas mechanism[61] (corrected for deformation of the molecules). The extraindicial substituents can vary. Thus we have investigated[62] the exchange of deuterium in cyclohexane on Pt and on Cr_2O_3; according to the multiplet theory, the ring is involved here at only one carbon atom. For a detailed review of deuterium exchange in hydrocarbons see Kemball[63].

A further complication of the indicial group (4.1) will be that of hydrogenolysis, in which not one but now two atoms are different from hydrogen. Thus the indicial group for hydrogenolysis of the C–C bond is

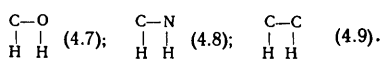
(4.5)

Incidentally, we may note that Burwell's scheme[31] for hydrogenolysis

 (4.6)

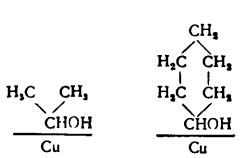
is the same as (4.5), the asterisks corresponding to the hollows V and W (*cf.* Fig. 5).

Dehydrogenation. Dehydrogenation reactions also involve two hydrogen atoms in the indicial group, as well as an additional, horizontal bond (which is converted into a double bond during the reaction); the reaction is unimolecular, and therefore more convenient for kinetic study. Such reactions have been investigated in the author's laboratory[7]. The indicial groups for the dehydrogenation of alcohols, amines, and hydrocarbons by the duplet mechanism are respectively

 (4.7); (4.8); (4.9).

The role of molecular orientation and interatomic distances has been studied in these catalytic reactions.

The rate of dehydrogenation of primary alcohols on precipitated and reduced copper has been shown[64] to be almost independent of chain length, in agreement with previous investigations[21,65-67]. However, it differs for primary and for secondary alcohols. As had been found earlier[68], isopropyl alcohol and cyclohexanol, which differ only in the "superstructure" of the latter, were dehydrogenated at similar rates, indicating that they have the same orientation:



A benzene ring greatly affects the reaction velocity. All this is consistent with theory[69].

A change in the nature of the metal catalyst (having the lattices A1 and A3) greatly influences the rate of dehydrogenation and the activation energy ϵ. The latter is found to depend on the interatomic distance or atomic radius, as is to be expected from the multiplet theory. This relation proves to be linear (see Fig. 4).

In agreement with the multiplet theory, experiment shows that, on oxide catalysts as well, alcohols are oriented with their reactive group >CHOH [see indicial group (4.7)] towards the dehydrogenating catalyst. This is evident from the identity of the true activation energies of dehydrogenation ϵ, and also of the relative adsorption coefficient z of primary alcohols, and the identity of ϵ and z for secondary alcohols. This question has been dealt with most thoroughly in Refs. 70–77. Thus the values of ϵ for primary alcohols of the normal series are (in kcal mole^{-1}): C_2H_5OH 15.9, C_3H_7OH 15.6, C_4H_9OH 16.3, $C_5H_{11}OH$ 15.4, $C_6H_{13}OH$ 15.6, $C_7H_{13}OH$ 15.3, $C_8H_{15}OH$ 15.6, and $C_9H_{17}OH$ 15.3; the corresponding values for secondary alcohols are: isopropanol 12.8, butan-2-ol 11.3, 2,4-dimethylpentan-3-ol 11.5, and octan-2-ol 13.2.

The present writer has suggested[6,10] for the dehydrogenation of alcohols a duplet stereochemical model, which is suitable also for other duplet dehydrogenations, those of amines and hydrocarbons, and also the reverse reactions on Pt, Pd, Ni, etc. As an example, Fig. 5 shows a scale model for the dehydrogenation of primary n-butyl alcohol on Cu; both the reactant molecule and catalyst lattice are represented in accordance with what is known about them from the theory of the structure of matter. In conformity with the multiplet theory, the indicial atoms >CHOH [*cf.* (4.6)] are in contact with the catalyst, the extraindicial substituent C_3H_7 being oriented perpendicular to the surface. During catalysis the indicial atoms fall into hollows between the copper atoms arranged in the (111) phase of the A1 lattice. Fig. 5 shows the instant when one hydrogen atom has already split off from the carbon and passed into the adjacent hollow. The residue forms the so-called semi-hydrogenated form. The second hydrogen atom performs stretching vibrations along the C–H bond parallel to the surface, which, if their amplitude exceeds a certain limit, result in this atom being split off and subsequent combination with the first hydrogen atom. The splitting off of the second hydrogen corresponds to the energy barrier of the overall reaction of dehydrogenation;

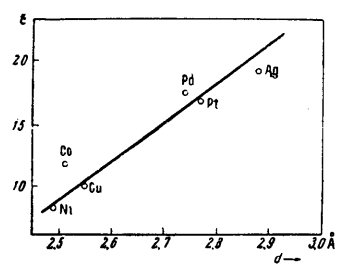


Fig. 4. Interatomic distances d and activation energies ϵ in the dehydrogenation of propan-2-ol.[69]

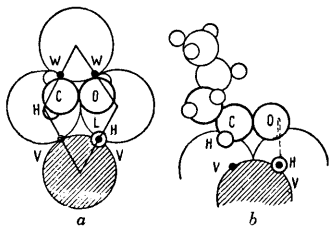


Fig. 5. Model of activated complex in the duplet dehydrogenation of n-butanol on nickel: *a*) viewed from above; *b*) side view.

in Fig. 5 it is shown as a broken line, and is represented by Eqn. (2.1). In general, one of the catalyst atoms may differ from the others. The hollows will then also differ, and may be denoted by V and W (see Fig. 5). The separate stages in the reaction are represented schematically by the equations

$$\left.\begin{array}{ll} (a) & RHCHOH + V_2W_2 = RHCHOV + HW + VW, \\ (b) & RHCHOV + VW = RHVOV + HW, \\ (c) & RHCVOV + 2HW = RHCO + H_2 + V_2W_2. \end{array}\right\} \quad (4.10)$$

Eqns. (4.10) suggest complete rupture of the bonds, but this is a limiting case. The falling of the indicial atoms into the deeper pit L (Fig. 5) corresponds to activated adsorption. The model illustrated by Fig. 5 satisfies the principle of constancy of bond angle (see p. 597), enables calculations to be made on the basis of the theory of absolute reaction rates, and gives a good indication of the various features of the theory of hydrogenation based on the multiplet theory[78-83].

The present writer and Vasyunina[84-86] investigated the kinetics of the dehydrogenation of aliphatic amines to ketimines, which they had discovered:

$$R_1R_2CHNH_2 \rightarrow R_1R_2C{=}NH + H_2. \quad (4.11)$$

The reaction takes place over Pt, Ni on Al_2O_3, and over ThO_2; ϵ also remains quite constant on a given catalyst. Thus the values of ϵ for 1-methylhexylamine, 1,3-dimethylbutylamine, 1-isopropyl-2-methylpropylamine, and *NN*-dimethyl-1-methyltetramethylenediamine are respectively (in kcal mole^{-1}): 9.72, 9.92, 9.14, and 11.4 over Pd, and 9.37, 9.55, 8.68, and 10.73 over Ni. This indicates an identical orientation of the indicial group $\rangle$CHNH towards the catalyst.

The present writer and Brusov[87] were the first to discover the ability of oxides (Cr_2O_3 and MoO_2) to effect the dehydrogenation of cyclohexane in high yield, above 70% (Lazier and Vaughen[88] had previously found that this reaction occurs to the extent of 3% on Cr_2O_3). Cyclohexene is first formed[87], and is then further dehydrogenated, yielding benzene as the final reaction product. The presence of cyclohexene, first detected from the decolorisation of bromine and permanganate[87], was then demonstrated by converting the compound into 2-methoxycyclohexylmercuric chloride[89]. A thorough investigation of the duplet dehydrogenation of cyclohexane over Cr_2O_3 was carried out by Herington and Rideal[90]. That cyclohexene is an intermediate and not a side product was first demonstrated by the fact that, with rise in temperature, its yield increases and then falls[91,92]. In this respect a rise in temperature is to some extent analogous to a decrease in the reaction time. The intermediate character of the formation of cyclohexene has been finally demonstrated quite recently by tracer experiments (using ^{14}C).[93] This work showed that at least part of the benzene formed in the dehydrogenation of cyclohexane over chromium oxide results from dehydrogenation of the intermediate cyclohexene (the rest of the benzene is formed on crystalline Cr_2O_3 by the mechanism discussed at the end of subsection *b*.). Hence in these cases cyclohexane is dehydrogenated by a duplet mechanism in conformity with the indicial group (4.8). A model of the duplet dehydrogenation of cyclohexane is illustrated in Fig. 6.

Kinetic studies[94-96] have shown that substituted cyclohexanes are dehydrogenated in a similar manner to the unsubstituted compound, with very similar activation energies. This indicates edgewise orientation of the ring with the indicial group towards the catalyst. Thus the values of ϵ for cyclohexane, methylcyclohexane, and 1,3-dimethylcyclohexane over Cr_2O_3 are respectively (in kcal mole^{-1}) 25.9, 23.7, and 22.2, the values for tetralin and 1,2,3,4-tetrahydro-6-methylnaphthalene being 29.7 and 30.4.

Five-membered rings as well as six-membered rings are capable of dehydrogenation by an edgewise duplet mechanism. The present writer and Fedorov[97] showed that, on chromium oxide, cyclopentane is dehydrogenated under the same conditions as cyclohexane. After this it was natural to study the dehydrogenation of open-chain alkanes and alkenes, as well as of alkylbenzenes over chrome catalysts, which reactions were investigated in our laboratory. Products of these reactions are important as monomers for the synthesis of rubber from petroleum gases. Similar reactions had been studied for several years before this in the USA (for a review, see Ref. 98). In contrast to this work, however, we were successful in achieving higher yields, studying the kinetics, and effecting the first catalytic preparation of several monomers (the early work is reviewed in Ref. 99). The model for the dehydrogenation of butane, for example, is analogous to that for the duplet dehydrogenation of cyclohexane (Fig. 6, but without the upper two carbon atoms). The indicial group is in all cases the same [(4.9)]. Such reactions include the preparation of butene from butane and similar reactions[100-102], of butadiene from butene[103-114], isoprene from isopentenes[115,116], isopentenes from isopentane[117], of piperylene[118], vinylcyclohexane[119], etc.

We have also studied[120-137] the preparation of styrene and its analogues: *o*-, *m*-, and *p*-divinylbenzenes, trivinylbenzene, isopropenylbenzene, *p*-diisopropenylbenzene,

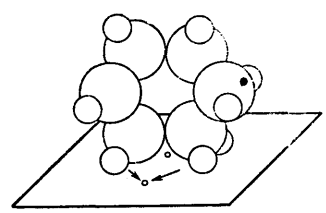


Fig. 6. Edgewise orientation of cyclohexane during dehydrogenation.

p-methylstyrene, mono- and di-butenylbenzenes, 1,1-diphenylethylene, stilbene, etc. We have recently extended these reactions to the preparation of monomers containing oxygen, sulphur, and what is especially interesting, silicon: *o*-vinylphenol, *o*-isopropenylphenol, *o*-isobutenylphenol, 2-vinylthiophen, 2-isopropenylthiophen, 1-methyldichlorosilyl-2-vinylphenylethane, etc.[138-141] It is interesting that the presence of an unsaturated bond or an aromatic ring outside the indicial group markedly changes the character of the dehydrogenation and the nature of the catalysts required. Conjugation energy is playing a part here. It must be noted that the ring takes no part in any of these reactions, and consequently is not superposed on the duplet.

The opposite reaction to hydrogenolysis is dehydrogenation accompanied by formation of a C–C (or other similar) bond between two molecules having the indicial reaction group

$$\begin{matrix} C & C \\ | & | \\ H & H \end{matrix} \qquad (4.12)$$

An example is provided by the formation of biphenyl from benzene:

$$2C_6H_6 = C_6H_5{\cdot}C_6H_5 + H_2. \qquad (4.13)$$

If both C atoms in the above indicial group form part of the same molecule, we have dehydrocyclisation, an example being the formation of fluorene from diphenylmethane over platinum[142].

A special case is the dehydrocyclisation of paraffins, which is a complicated process analogous to the preceding reaction, involving the formation of aromatic hydrocarbons by dehydrogenation of intermediate six-membered rings[143-146]. Recently, dehydrocyclisation has been extended to the formation of five-membered rings from paraffins with the production of cyclopentadiene hydrocarbons[147,148]. For the mechanism of these reactions, see Section 4*b*.

The aromatisation of branched paraffins, involving the transient formation of five-membered rings, has been considered from the point of view of a duplet mechanism[149].

Hydrogenation. A reaction which is opposite to dehydrogenation is the hydrogenation of unsaturated bonds. The indicial group for the hydrogenation of an olefinic bond is

$$\begin{matrix} C & H \\ \| & | \\ C & H \end{matrix} \qquad (4.14)$$

The multiplet reaction model is the same as in Fig. 5, but the stages take place in the reverse sequence.

A very interesting rule was found in the hydrogenation of olefines — the principle of conservation of bond angle. The principle states that, when one bond of a C=C link chemisorbed on two catalyst atoms Z is opened (see Fig. 7*a*), the bond angle should be close to the tetrahedral value $\theta = 109°$. Since the C–C and C–Z distances are known from the atomic radii, the optimum interatomic distance Z–Z of the catalyst can be calculated on this basis. This is found to correspond to metals from Pt to Fe, including not only metals crystallising in the A1 and A3 systems but also those in A2 and other systems. These metals are indeed catalytically active in the hydrogenation of the C=C bond.

Twigg and Rideal, in enunciating[150] the principle of conservation of bond angle, regarded it as applying to the final state, the paraffin hydrocarbon. The present writer and Eidus[151] showed that this principle should apply to the intermediate activated complex, and that it is completely

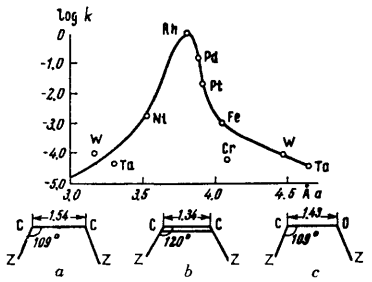


Fig. 7. Reaction velocity constant k and lattice constant a of metal catalysts in the hydrogenation of ethylene[153]. Interatomic distances in the hydrogenation of different types of bond: *a*) olefinic; *b*) acetylenic; *c*) carbonyl.

derivable from the multiplet theory, providing an important confirmation of the principle of structural conformity in the latter.

For the dehydrogenation and hydrogenation of hydrocarbons, the oxygen atom in the activated complex shown in Fig. 5 should be replaced by carbon. If on the resulting diagram the centres of the right-hand and left-hand catalyst atoms are joined with the centres of the carbon atoms in contact with the catalyst, and if the straight lines C–C and Z–Z are drawn, it is readily seen that the same trapezium is obtained as in Fig. 7*a*. Its upper angles will also be 109°, although the plane of the trapezium will be inclined to that of Fig. 5. Thus the model illustrated in Fig. 5 also satisfies the principle of conservation of the bond angle.

Beeck *et al.*[152] investigated the kinetics of the hydrogenation of ethylene on films of various metals condensed on the surface of a quartz tube, and found a relation between the lattice constant (which is proportional to the interatomic distance) and the logarithm of the rate constant for the hydrogenation. Fig. 7 shows a maximum at rhodium. As Beeck points out[153], this result supports the multiplet theory. Recently Sokol'skii[154] has discovered a similar maximum at rhodium for metallic promoters in the liquid-phase hydrogenation of cinnamic acid on Ni containing additives.

Beeck[153] considered, on the basis of electron diffraction patterns, that the (110) faces were the most active in catalysing the hydrogenation of ethylene. Later, however, Sachtler *et al.*[155], using an improved technique, showed that the (110) faces in Beeck's metallic mirrors were adjacent to the quartz, while the (111) [and to some extent the (100)] faces are turned towards the gas; this is consistent with the multiplet model in Fig. 5.

The principle of constancy of bond angle was subsequently applied by several workers, mainly English and American (see Balandin and Eidus' review[156] and also Refs. 157 and 158). Herington[158] carried out for acetylene geometrical calculations similar to those for ethylene, the bond length between the carbon atoms being smaller in the former than in the latter, while the bond angle is greater (Fig. 7*b*). The calculated activity maximum no longer occurred at rhodium but at nickel. According to Herington[158], this agrees with experiment.

From the Rh–Rh distance, which is optimum for the hydrogenation of the C=C bond, we have calculated[159] the optimum distance d_{opt} for hydrogenation of the carbonyl bond C=O, which is shorter than with C=C (Fig. 7*c*):

$$\begin{array}{l} \text{C—C } 1.54 \\ \text{C—O } 1.43 \\ \hline \Delta = 0.11\text{Å} \end{array} \quad \begin{array}{l} \text{Rh—Rh } 2.69 \\ \Delta = 0.11 \\ \hline d_{opt} = 2.58\text{Å} \end{array} \qquad (4.15)$$

Among metals which are insoluble in acids, ruthenium with d = 2.65 Å (*cf.* Table 2) approaches this optimum most closely. Thus the calculated maximum activity for hydrogenation of the C=O bond now occurs at ruthenium. This result has been confirmed experimentally, and provides a theoretical basis for the hydrolytic hydrogenation of cellulose[159,160]. The process consists in the consecutive hydrolysis and hydrogenation of cellulose to sorbitol, and of pentosans to xylitol, with a ruthenium catalyst in acid medium (yield up to 95%). We subsequently showed that lignin can also be hydrogenated over ruthenium in alkaline solution in this case, up to 35% of phenols being obtained[161]. This opens a new field in the chemical processing of wood[162,163] which is abundant in our country (*cf.* Ref. 164). From sorbitol[165] and xylitol[166], glycerol can be obtained by hydrogenolysis over nickel.

It has been shown experimentally[167] that rhodium is especially suitable for the hydrogenation of olefines and aromatic rings, and ruthenium for C=O bonds, in particular one formed by the hydrolysis of disaccharides; the higher polysaccharides were not considered. Thus this paper[167], printed a little after our first publication on ruthenium[159], supports our conclusions.

Dehydration. Let us now examine the dehydration of alcohols to olefines, for which the indicial group is

$$\begin{array}{cc} \text{C} & \text{C} \\ | & | \\ \text{H} & \text{O} \end{array} \qquad (4.16)$$

There probably exist three types of catalytic dehydration reactions. One type, the heterolytic, involves the intermediate formation of a carbonium ion[168], where the hydrogen ion acts as the catalyst. Thus phosphoric acid is the classic catalyst for the preparation of ethylene from alcohol. Incidentally, we were the first to use phosphoric acid on activated carbon[169,170], a procedure which has now become widespread.

TABLE 1. Comparison of atomic and ionic reaction mechanisms.

Reactant	Atomic exchange, %*	Ionic exchange	
		k	ϵ, kcal mole^{-1}
CH_3I	0.03	1200	15.4
$(CH_3)CH_2I$	0.05	65	19.0
$(CH_3)_2CHI$	1.4	10	20.5
		Atomic exchange	
CH_3CH_2OH		28.4*	20.2
$CH_3CH_2CH_2OH$		55.4*	18.3
$(CH_3)_2CHCH_2OH$		52.7*	16.4

* At 350°.

According to Hansford[171], the carbonium ion on the surface is not free, but is "merely a strongly polarised part of the catalytic complex". This suggests deformation and that the steric factor is important in such cases also, but the question has not yet been elucidated.

Another mechanism is the homolytic, where aluminium oxide and similar oxides act as catalysts. It is supported by the following facts. As is now known, the catalytic cracking of hydrocarbons is effected on portions of the catalyst which possess the properties of a Brønsted or Lewis acid, the catalytic activity with respect to cracking and the acidity varying together. Topchieva and Yung-p'ing[172] found that, in mixed $Al_2O_3-SiO_2$ catalysts of various compositions, the catalytic activity for the cracking of cumene and that for the dehydration of alcohol do not vary together, cracking being quite a feeble reaction on pure Al_2O_3. Hence the dehydration of alcohol is not due to the acidic properties of Al_2O_3.[172] Another argument is based on the finding of Neiman *et al.*[173], in an investigation of exchange reactions using radioactive halogens,

$$R\,Br + Br^{*-} = R\,Br^{*} + Br^{-}, \qquad (4.17)$$

$$RI^{*} + I^{-} = R^{-} + I^{*}I, \qquad (4.18)$$

that as the radical R becomes more complicated, the reaction velocity constant k falls and ϵ increases in the case of the heterolytic reactions (4.17), whereas k increases and ϵ decreases in the homolytic reactions (4.18). Comparison[52] with Bork and Tolstopyatova's results[43,174] shows (see Table 1) that dehydration on Al_2O_3 belongs to the homolytic, not the heterolytic, type of reactions, since k increases and ϵ decreases in this case.

The third mechanism, which is observed under special conditions at low pressures probably involves free radicals (see Section 5).

We shall consider only the second mechanism here. Unfortunately, the mechanism of dehydration has not yet been sufficiently elucidated for it to be possible to give a model similar to that illustrated in Fig. 5. It is probable that, just as dehydrogenation passes through a semi-hydrogenated form, so also dehydration goes through a similar unstable form. According to Topchieva[175], this is a surface alkoxide, which is converted into ether or ethylene depending on the conditions. The fact that the intermediate product in the formation of ethylene is not bulk aluminium ethoxide, as Sabatier[176] supposed, was demonstrated by the present writer and Shchekin[23]: aluminium ethoxide decomposes under different conditions, and yields different products, from those observed with alcohol on catalysis on Al_2O_3.

In the opinion of several workers, the primary product (observed at lower temperatures) of the dehydration of ethyl alcohol on Al_2O_3 is ethyl ether, which is then converted into ethylene (observed at higher temperatures). Other workers assume that formation of ethylene and ether takes place simultaneously (for review, see Ref. 177). A tracer method using ^{14}C atoms has shown[178] that ethylene can be formed from alcohol by two pathways, directly at high temperatures, and *via* ether at lower temperatures; quantitative relations have been found between the corresponding reaction velocities. In this way a long-standing controversy between different groups of investigators has been settled.

The fullest data on the effect of the structure of alcohols on their dehydration (on Al_2O_3) were obtained by Bork and

Tolstopyatova[43,174]. As with dehydrogenation, ϵ is constant for the dehydration of primary alcohols, its value being 18.0 kcal mole^{-1}. This indicates that the indicial group >CHCO has the same orientation towards the catalyst.

Similar results have now been obtained for W_2O_5 [179] (the earlier data of Adadurov and Krainii[180] for W_2O_5 have been corrected), and also for CeO_2 [181] and ThO_2.[182]

The activation energy shows great constancy also in the dehydration of secondary alcohols over $MgSO_4$. Cyclohexanol, cyclopentanol, pentan-2-ol, and propan-2-ol were investigated, their percentage dehydration at 370° being 17.7, 17.8, 18.0, and 18.8, while the values of ϵ were 15.0, 14.4, 15.2, and 14.8 kcal mole^{-1} respectively. This also suggests an identical orientation of the molecules, with the indicial group >CHCO towards the catalyst[183].

We have investigated[184-186] the influence of β-rays, emitted by isotopic impurities ^{35}S and ^{45}Ca in $MgSO_4-Na_2SO_4$ and $MgSO_4-CaCl_2$ solid catalysts, in the dehydration of cyclohexanol. The catalytic activity of $MgSO_4$, already an active dehydration catalyst, was almost doubled thereby. During the discussion of this work[187] at the Second International Congress on Catalysis it turned out that similar results had been obtained at the Oak Ridge National Laboratory of the U.S.A.E.C.[188] As we had found, the increase in catalytic activity caused by radioactivity becomes smaller as the latter falls (Fig. 8) not only because of change in the concentrations of ^{35}S and ^{45}Ca introduced, but also because of decay of an existing additive. Exposure to high-energy fast electrons (1.5 MeV) of high intensity has no effect. The present writer has suggested[189] the following explanation for the observed facts. Fast electrons release electrons from the catalyst atoms by impact, and the electron current increases like an avalanche. If the electrons are moving from the solid through the surface, this cascade passes into the gas phase, and the surface acquires a positive charge. This favours the formation of carbonium ions on the surface, and consequently accelerates catalytic dehydration (by a heterolytic mechanism). If the electrons are moving in the opposite direction,

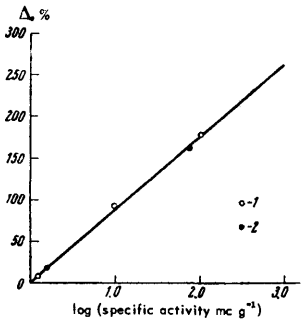


Fig. 8. Increase in degree of dehydration (Δ, %) of cyclohexanol and logarithm of the specific radioactivity of catalysts:
1) experiments with different contents of ^{35}S introduced during preparation;
2) experiments with an ^{35}S content which has decreased owing to radioactive decay (after 314 and 184 days)[185].

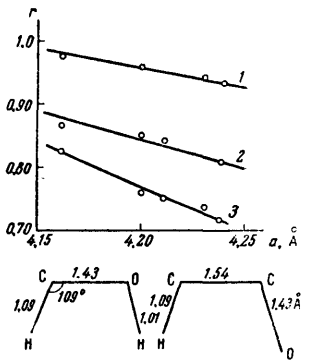


Fig. 9. Above: ratio r of percentage dehydrogenation to sum of percentage dehydrogenation and dehydration of n-butanol as a function of the lattice constant a of MgO: 1) 400°; 2) 440°; 3) 460°.[190] Below: interatomic distances in the catalytic reactions of alcohols: dehydrogenation on the left, and dehydration on the right-hand side.

almost the whole cascade remains within the solid, and the charge on the catalyst does not change. Therefore the reaction velocity is unaffected.

Rubinshtein carried out a remarkable kinetic and X-ray diffraction investigation of the catalysis of alcohols on MgO,[190] the main reactions being dehydrogenation and dehydration. The MgO (with an NaCl type of structure) had a lattice constant a which varied somewhat with the method of preparation. It was found that for greater a, *i.e.* the distance between the catalyst atoms, dehydration was more marked relative to dehydrogenation (Fig. 9, upper part). The interatomic distances in the indicial groups are greater for dehydration than for dehydrogenation (Fig. 9, lower part). There exist optimum interatomic distances for these reactions. In this way we have here an important confirmation of the principle of structural conformity in the multiplet theory.

A similar phenomenon was observed[191] for the catalysis of alcohols on the pentoxides of vanadium, niobium, and tantalum. The increase in atomic radius in the sequence vanadium (1.36 Å), niobium (1.47 Å), tantalum (1.49 Å) is accompanied by an increase in dehydration relative to dehydrogenation.

Recently Rubinshtein *et al.*[192] have observed a maximum, analogous to that observed previously[190] for the dehydration of isopropyl alcohol over Ni on Al_2O_3.

In concluding the section on duplet reactions, let us consider an example of work in which the ideas of the multiplet and the electronic theories of catalysis are applied together.

Dowden *et al.*[193] investigated deuterium–hydrogen exchange on zinc oxide. According to their results, a lattice defect possesses four F-centres, which are able to adsorb both hydrogen and deuterium, this being the condition for catalytic activity. Fig. 10 shows the chemisorption of hydrogen and deuterium on an F-centre of zinc oxide, where the missing oxygen ion has been replaced by two electrons. Due to an increase in the number of defects,

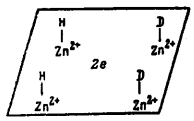


Fig. 10. Catalytically active F-centre in the exchange of deuterium and hydrogen on zinc oxide[193].

the oxide becomes increasingly n-type, which increases the electrical conductivity and promotes catalysis, in agreement with experiment.

The present writer and Sokolova[194] investigated the catalysis of alcohols by tungsten bronzes which have a defect structure. An X-ray structure analysis was also made. In spite of the presence of a defect structure, the tungsten bronzes showed little catalytic activity, in contradiction to the electronic theory of catalysis. However, the catalytic activity decreases as the bronzes are reduced and as lithium is added, in conformity with this theory; the number of defects in the structure also falls at the same time. The electron-diffraction patterns and the B.E.T. data show that the surface of the bronzes remains practically unchanged during reduction. On the other hand, the multiplet theory explains the low activity of the bronzes by the fact that structural conformity is not particularly well satisfied (the difference amounts to 16%). Fig. 11 shows how the molecule fits (the C–C of the alcohol as in ThC_2, the H of the alcohol in the Na defect, and the O of the alcohol replacing the reduced O of the bronze). Simultaneous application of the multiplet and the electronic theories of catalysis enables most of the facts observed here to be explained.

Natta[195] discovered stereospecific polymerisation, leading to the formation of isotactic chain polymers of α-olefines, in the presence of heterogeneous catalysts and activators, and explained it by oriented adsorption. But the latter is a necessary requirement of the multiplet theory, according to which the reactant atoms should be in contact with the surface, and substituents should all be located on the same side, away from the surface[9,196]. According to Natta the electronic structure — the work function and other electronic properties — also plays a large part in stereospecific polymerisation.

Electron, geometrical, and structural considerations are combined also in crystal field theory and in its recent promising application to catalysis[197].

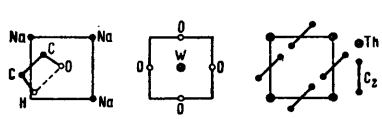
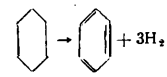


Fig. 11. Lattice of tungsten bronze and arrangement of reactant atoms on it during the dehydration of alcohol. On the right: the (100) face of the ThC_2 lattice.

Triplet reactions are known in catalysis (it is sufficient to recall the 1,4-addition of hydrogen to some dienes), but we shall not consider them here, since little work has been done on them.

b. Sextet Reactions

A sextet model was first developed in the multiplet theory for the dehydrogenation of cyclohexane and its derivatives,



(4.19)

discovered by Zelinskii[198]. The reaction takes place over metallic catalysts at about 300°. A sextet model is illustrated in Fig. 12, which shows it in perspective and in plan. Migrations of hydrogen atoms are indicated by arrows. There is a correspondence between the symmetry elements of the molecule and of the catalyst; the six-membered ring is laid flat on the face with the atoms arranged in equilateral triangles, thus satisfying principles similar to those indicated above. The reaction product, benzene, has a planar configuration, and therefore at some instant during its formation the ring must become planar; according to the sextet model this flattening occurs during the formation of the activated complex in the dehydrogenation of cyclohexane. The model for the reverse reaction, the hydrogenation of benzene at lower temperatures, has a similar form.

The model suggests that only metals (not metalloids) and then only those crystallising in the cubic (face-centred cubic, lattice A1) and in the hexagonal (lattice A3) systems, can act here as catalysts, since it is only on the octahedral faces of the former and on the basal pinacoid faces of the latter that the required arrangement of atoms, in the form of equilateral triangles, is found. Moreover, the shortest interatomic distances in the catalytic metals, which are equal to the atomic diameter d, should lie within definite limits. Otherwise, as a geometrical calculation shows[3], the hydrogen atoms in the cyclohexane will either be too distant from the catalyst atoms which are attracting them, or will not allow the ring to lie on the lattice face. Table 2, compiled[199] from recent data[200], gives a list of the elements crystallising in the A1, A2, A3, and A4 systems with an indication of their shortest interatomic distances (elements crystallising in more complicated systems, and also forms crystallising above 800° where the catalysts are known to sinter, are omitted from Table 2).

It is seen from Table 2 that elements which are known catalysts for the dehydrogenation of cyclohexane and its

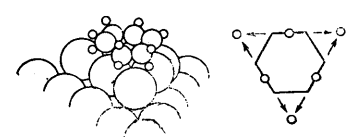


Fig. 12. Sextet model for the dehydrogenation of cyclohexane.

TABLE 2. Types of crystal lattice and minimum interatomic distances (atomic diameters) d in Å.

Face-centred cubic lattice A1	Body-centred cubic lattice A2	Hexagonal lattice A3	Diamond lattice A4
α-Ca 3.947	Cs 5.309	β-Sr 4.32; 4.324	α-Sn 2.8099
Yb 3.880	Rb 4.95	α-La 3.739; 3.770	Ge 2.4498
γ-Ca 3.877	K 4.544	Nd 3.628; 3.658	Si 2.3517
Ac 3.756	Ba 4.347	Gd 3.573; 3.636	C 1.5445
β-La 3.745	γ-Sr 4.20	Y 3.551; 3.647	
Ce 3.650	Eu 3.989	Tb 3.525; 3.601	
α-Pr 3.649	Na 3.7157	Dy 3.503; 3.590	
α-Th 3.595	β-Tl 3.362	Ho 3.486; 3.577	
δ-Pu 3.279	ε-Pu 3.150	Er 3.468; 3.559	
Sc 3.212	Li 3.0390	Tm 3.447; 3.538	
Ag 2.8894	Ta 2.86	α-Te 3.4076; 2.4566	
Au 2.8841	Nb 2.8584	Lu 3.435; 3.503	
Al 2.8635	W 2.7409	α-Po 3.345;	
Pt 2.7746	Mo 2.7251	Sc 3.256; 3.309	
Pd 2.7511	V 2.6224	Mg 3.1971; 3.2094	
Ir 2.714	Cr 2.4980	α-Zr 3.1790; 3.2313	
Rh 2.6901	γ-Fe 2.4823	α-Hf 3.1275; 3.1947	
Cu 2.5560		Cd 2.9788; 3.2933	
Co 2.5061		α-Ti 2.8956; 2.9505	
Ni 2.4916		Re 2.741; 2.760	
		Tc 2.703; 2.735	
		Os 2.6754; 2.7354	
		Zn 2.6649; 2.9129	
		Ru 2.6502; 2.7058	
		α-Be 2.2260; 2.2856	

derivatives are in fact solely metals having lattices of types A1 and A3, with d lying between 2.7746 Å (Pt) and 2.4916 Å (Ni). These elements are enclosed in frames in Table 2. Theory is seen to be fully vindicated. Table 2 shows why Ni, Co, Cu, Rh, Ir, Pd, Pt, Ru, Os, and Re are catalysts for the hydrogenation and dehydrogenation of six-membered ring hydrocarbons, while Ca, Ce, and Fe, for example, are not.

The frames in Table 2 include rhenium, the lattice structure of which was not yet known when the original table[3] was compiled. The prediction of the multiplet theory that rhenium should dehydrogenate cyclohexane, since it is within the frame, has been verified experimentally by Balandin *et al.*[201-203] who also investigated other reactions of this element. The activity of technetium, which is also located within the frame, has not yet been checked.

Whether copper, which is located within a frame in Table 2, catalyses the dehydrogenation of cyclohexane and the hydrogenation of benzene, has given rise to controversy[204,205]. A recent investigation by Erofeev and Nikiforova[206] using infra-red spectroscopy has shown that copper is actually a catalyst for both reactions. This supports the sextet model. The feeble activity of copper is explained by other factors, not structural but energetic[6].

The list of sextet dehydrogenation catalysts contains a smaller number of metals than does the list of metal catalysts whose activity is governed by the principle of constancy of bond angle. In agreement with theory, cyclohexane cannot be dehydrogenated to benzene over manganese, which possesses the more complex structure A12;[207] an olefinic bond is hydrogenated over manganese.

That a reduced iron catalyst, which is active in the hydrogenation of ethylene, is unable to effect the hydrogenation of benzene or the dehydrogenation of cyclohexane has been shown by many investigators, for example in Refs. 208–210. Actually, iron is located outside the frames in Table 2 (for iron films, see below).

According to the sextet model, benzene can be hydrogenated also on solid solutions with an increasing content of one of the metals, but only so long as the required structure (and d) are present. This has been confirmed by simultaneous kinetic and X-ray diffraction measurements on solid solutions of Ni, Co, Fe, Pd, and Ag.[208,209]

Thus the 74.9% Co + 21.7% Fe alloy with an A1 lattice is still active, while the 50% Co + 50% Fe and 24.2% Co + + 75.8% Fe alloys with the A2 lattice are not. Copper formed an apparent exception (see above). Not so long ago Rienäcker and Unger[210] made especially detailed and careful investigations of this type, with X-ray analysis and adsorption measurement of the surface; the results supported the requirements of the multiplet theory. Quite recently Rienäcker and Porubszky[211] found that, in the hydrogenation of propene (which proceeds according to the model in Fig. 5) as well, binary alloys of Ni and Fe of varying composition are active only as long as the nickel structure, *i.e.* A1, is present, which agrees with the multiplet theory.

An important confirmation of the sextet model was obtained by Rubinshtein *et al.*[212], who found that the catalytic activity for the dehydrogenation of benzene falls regularly with decrease in the intensity of the X-ray reflections from the (111) faces of platinum on carbon.

It is not yet clear why iron and tungsten films condensed from the vapours are active in the hydrogenation of benzene, as reported by Anderson and Kemball[213]. This is probably due to different reaction mechanisms on films and on reduced catalysts. Such differences have in fact been observed in other reactions (see Ref. 214 and the note by the editor of the translation in Ref. 213). A duplet mechanism is probably operative here, as in the already known case of the dehydrogenation of ethane on Pd at high temperatures[87,215].

According to the sextet model, the cyclohexane, which is adsorbed flat on the surface, is converted into benzene by all six hydrogen atoms being split off in such a way that the six-membered ring does not leave the active centre until it has been converted into a benzene ring. Therefore no cyclohexene or cyclohexadiene will be present in the gas phase.

The mono- and poly-substituted derivatives are dehydrogenated like cyclohexane itself. It is necessary that all substituents should be oriented on the same side of the plane of the ring. One or more carbon atoms of the six-membered ring may be replaced by nitrogen. Polycyclic systems should behave similarly. All these deductions are confirmed experimentally[216,217]. For the work of Linstead and his collaborators in this field, see Section 6.

Some workers have supposed[218] that cyclohexane is first dehydrogenated to cyclohexene, followed by a far more rapid disproportionation of the hydrogen in the latter, by Zelinskii's so-called irreversible catalytic reaction

$$3\,C_6H_{10} = 2\,C_6H_{12} + C_6H_6. \qquad (4.20)$$

to yield benzene. This is supposed to explain the absence of cyclohexene among the products of the catalysis. Data are now available which refute this view. It has recently been shown[202] that the irreversible catalysis over rhenium takes place more slowly than does the dehydrogenation of cyclohexane to benzene, which disproves a dehydrogenation mechanism involving irreversible catalysis for this case. The fact that cyclohexene is not an intermediate in the dehydrogenation of cyclohexane on rhenium has been shown by

direct radiochemical experiments in which labelled ^{14}C is added as cyclohexene[93]. In view of the similarity of dehydrogenation processes occurring on rhenium and on metals resembling platinum, reaction (4.20) becomes altogether unlikely.

Dehydrogenation of six-membered cycloalkanes (other than geminal forms) to aromatics is greatly favoured thermodynamically, since aromatic compounds are particularly stable owing to the presence of resonance energy (36 kcal mole^{-1} in the case of benzene[219,220]). Therefore six-membered rings can be dehydrogenated at lower temperatures (about 300°) than can other hydrocarbons.

On this basis, Taylor[221] first rejected the sextet mechanism, but later accepted it, and in his article[222] in the book "Chemical Architecture" gives a scheme involving this mechanism together with results obtained by Eyring, Beeck, Rideal, and Pauling. Trapnell[223] has devoted a review to the multiplet theory, in which he gives a detailed and generally correct account of the structural side of the theory, but does not consider its energetic aspects. However, his statement that in this theory the adsorption is supposed to be of van der Waals type is incorrect. His suggested modification of the sextet model was considered by the present writer as early as 1929 (variant III in Fig. 2 in Ref. 3 — see Fig. 13), but was rejected, since there was no longer room geometrically for the hydrogen atoms of the cyclohexane, and therefore the latter could not be superimposed on the catalyst atoms. This can be seen by constructing a three-dimensional model.

An interesting demonstration of the edgewise and planar orientation in different cases was obtained by the present writer and Isagulyants[224]. As we have seen, cyclohexane is dehydrogenated on Ni by a sextet mechanism, and on Cr_2O_3 by a duplet mechanism. This applies also to decalin. It was found that on Ni cyclohexane is dehydrogenated more rapidly than is decalin, which with the planar arrangement occupies more room on the surface (Fig. 14); this proves the planar orientation of the rings on Ni. On chromium oxide cyclohexane and decalin are dehydrogenated at the same rate: here the mechanism is no longer planar but edgewise. With cyclohexane and decalin the values of ϵ are identical both on Ni (12.5) and on Cr_2O_3 (26 kcal mole^{-1}).

Although the aromatic properties of benzene could explain why six-membered, but not other, rings can be dehydrogenated at 300°, this cannot explain why Pt and other similar metals are active in the dehydrogenation of cyclohexane, which is what the sextet model explains. In this connection the sextet mechanism can be tested in another way, by dehydrogenation of seven- and five-membered rings with the formation of non-benzenoid aromatic compounds.

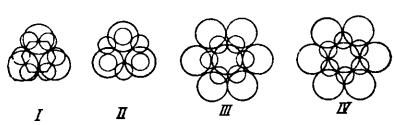


Fig. 13. Four types of planar arrangement of a six-membered ring on the (111) face of an Al lattice[3].

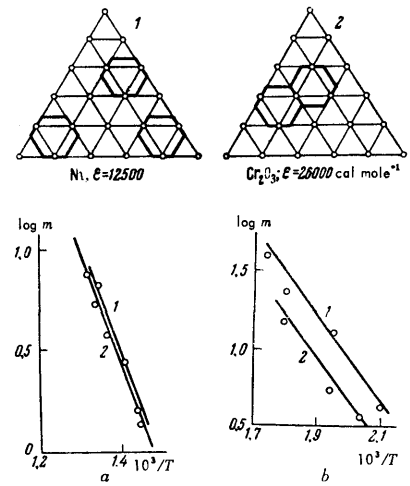
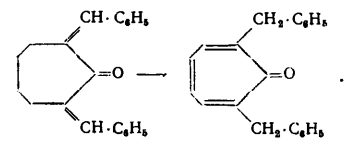


Fig. 14. Arrangement of molecules on the (111) faces of an Al lattice. Arrhenius plots for dehydrogenation on (*a*) Ni and (*b*) Cr_2O_3 of (1) cyclohexane and (2) decalin[224].

It was found recently[225] that over Pd at 290°, 2,7-dibenzylidenecycloheptanone, is 16% converted, by isomerisation and dehydrogenation, into 2,7-dibenzyltropone, in which the seven-membered ring is aromatic in character:

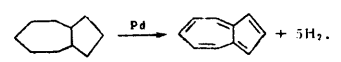


(4.21)

Derivatives substituted in the phenyl groups behave similarly. One H_2 molecule is split off, so that dehydrogenation proceeds here by a duplet mechanism. Incidentally, the isomerisation which precedes dehydrogenation is also a duplet reaction, which is known to occur on Pd; it has the indicial group

(4.22)

A remarkable confirmation of the sextet model is that bicyclo[5, 3, 0]decane is dehydrogenated over Pd to give only low yields of the aromatic hydrocarbon azulene:[226]



(4.23)

Most of the substance decomposes, and azulene is obviously formed by dehydrogenation involving a duplet mechanism. Thus aromatic character, although it does affect catalysis to a certain extent, is nevertheless unable by itself to bring about smooth dehydrogenation, such as takes place in the case of cyclohexane. In order that catalysis should occur, structural conformity is also necessary. Bicyclo[5,3,0]decane, in contrast to cyclohexane, has no symmetry elements in common with the Al lattice of palladium, and cannot be superimposed on the latter.

The following criteria are available for deciding, in any particular case, by what mechanism, sextet or duplet, dehydrogenation will take place. Firstly, the duplet mechanism operates at higher temperatures. Secondly, formation of cyclohexene is observed with the duplet mechanism. It must not be assumed that at 300° cyclohexene cannot still be present in appreciable amount in equilibrium with cyclohexane. In several of our experiments with a specially prepared rhenium catalyst up to 1.5% of cyclohexene was detected in the dehydrogenation of cyclohexane at about 300°. Thirdly, the true activation energy is higher in duplet reactions (on oxides) than in sextet reactions, reaching 20–40 kcal mole^{-1} compared with 13–18 kcal mole^{-1}. Fourthly, the constant a in the compensation effect[7] is greater with duplet than with sextet dehydrogenation of hydrocarbons (~3.5 compared with ~2.5).

It would be incorrect to suppose that all rings must lie flat on the surface during catalysis. We have already had (Section 4*a*) many examples of edgewise orientation of rings, and of cases in which the rings are not involved, or are only partly involved, in the reaction. The number of such reactions is increased if we consider the dehydrogenation of nicotine and pyrrolidine on platinum,[227] in which a five-membered ring is dehydrogenated by a duplet mechanism; the formation of biphenyl from benzene is another example (*cf.* above).

On the other hand, a case has recently been observed[228] of a new planar orientation of cyclohexane undergoing dehydrogenation on a specimen of chromium oxide which was shown by X-ray diffraction to differ from those studied previously in being crystalline. Here the activation energy is low (13 kcal mole^{-1}), and cyclohexene is not detected, a radiochemical method showing that it is not an intermediate product, since when added at the start it does not react. The reaction model is a variant of the sextet model examined by the present writer as long ago as 1929,[3] without a central metal atom (variant IV in Fig. 13, or, what is the same, Fig. 2 in Ref. 3); in the case of metals variant I in Fig. 2 of Ref. 3, illustrated in expanded form in Fig. 12 of the present review, was preferred.

5. FREE RADICALS ON THE SURFACE

The multiplet theory envisages another orientation of cyclohexane[3] (Fig. 15*a*) in addition to those considered above. The CH_2 parts of the molecule are drawn down into the deepest hollows, situated on the (111) face of the Al lattice, which conform to the CH_2 links in the ring. According to the above, this should lead to activated adsorption, which is often accompanied by bond rupture. Bonds are ruptured here too, and free $:CH_2$ radicals are formed, which can migrate along Lennard-Jones valleys. The $:CH_2$ radical is quite stable, approaching molecules in this respect. Nitrogen-containing rings, such as piperidine and piperazine[3], undergo scission still more readily.

The $:CH_2$ radical was detected experimentally by Zelinskii and Shuikin[229], who obtained from cyclohexane, over nickel under severe conditions, methylcyclohexane, toluene, etc. Eidus and Zelinskii[230] detected methylcyclohexane and toluene in the production of Synthole from water gas in the presence of cyclohexane and benzene, thereby confirming the hypothesis put forward by Orlov, and later by Fischer and Tropsch, that Synthole is formed *via* $:CH_2$ radicals. With hydrogen, $:CH_2$ gives CH_4, and with water CO_2 (or CO) and H_2. According to the multiplet theory[231]

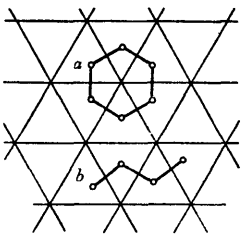


Fig. 15. Arrangement of molecules during their scission into $:CH_2$ radicals on nickel: *a*) cyclohexane; *b*) n-butane.

similar decomposition, for example of butane, with the formation of $:CH_2$ radicals, is represented by the model illustrated in Fig. 15*b*, which is analogous to that in Fig. 15*a*.

The $:CH_2$ radical is obviously also an intermediate in a peculiar type of simultaneous dehydrogenation of hydrocarbons and water discovered in the present writer's laboratory[232]. In this reaction there is a gradual shortening of the hydrocarbon chain by one unit (as in the progressive hydrogenolysis of hydrocarbons[233–235]). This shortening is checked by any structural peculiarity in its path, for example a quaternary carbon atom or a benzene ring; the final reaction products are CO_2 and H_2. Slovokhotova and the present writer[232] showed that such reactions, occurring between organic vapours and water vapour over Ni and other catalysts, are almost as general as, for example, the complete combustion of organic compounds. Reactions occurring under the influence of water vapour which have been studied are chain-shortening in isooctane, isoheptane, and isohexane, the demethylation of xylene, toluene, α-picoline, 2-methylthiophen, and *p*-cresol, the conversion of cyclopentylbenzene into benzene, the decomposition of cyclohexane and piperidine, etc.[236–244] Reactions of a similar type between hydrocarbons and CO_2 have also been studied[245].

The concept of the formation of surface free radicals has been used also to explain isomerisation. As an example, we can cite Burwell's attempt[31] to explain some exceptions to the rule of *cis*-addition (*cf.* Section 6).

Free radicals are probably formed in the dehydration of alcohols (under a pressure of a few millimetres) on $MgSO_4$, as was found from the *ortho–para* conversion of H_2 admitted to the system during the dehydration[246]. As Schwab and Agallidis showed[247] long ago, solid free radicals, such as 1,1-diphenyl-2-picrylhydrazyl[248], can effect the *ortho–para* conversion. It is probable that dehydration of the third kind given above occurs under these conditions.

The formation of radicals can also explain the exchange of a radioactive tracer (^{14}C), occurring on aluminium oxide, between methyl ether (and also methyl alcohol) and, on the other hand, isopropyl, benzyl, and octyl alcohols, ethyl ether, acetone, and ethylene, but not toluene or acetonylacetone, which can serve as a method for preparing labelled compounds[249,250].

A radical mechanism is probable in the addition of organosilicon compounds to olefines[251,252] and in the alkylation of olefines and paraffins under high pressure[253] (for the start of this work, see Refs. 254–258).

Since radicals are formed in such reactions, chain processes may be expected. The presence of surface chains in catalytic reactions is probable in syntheses from water gas[259] and in the hydrocondensation of CO with olefines[260,261].

Radical-like species are probably formed also during dehydration of the third kind, and perhaps a chain reaction takes place. Thus the present writer together with Vasserberg and Georgievskaya[262-265] have investigated the dehydration of alcohols on $MgSO_4$ in a monolayer, at degrees of surface coverage not exceeding 20%. This work has shown that the rate of dehydration of an alcohol is always diminished on addition of another alcohol, which is dehydrated less rapidly, whereas the rate of dehydration is either increased or decreased, when a less stable component is added.

Surface chain reactions in catalysis, which were still unknown not long ago, should be correctly interpreted in terms of the theory of Voevodskii *et al.*[266] which is based on electronic concepts. It is clear from all that has been said above that it needs to be supplemented by structural considerations. The latter are considered by the multiplet theory.

6. STERIC HINDRANCE AND ASYMMETRIC CATALYSIS

Hydrogenation on Pt and other metals of compounds containing a triple bond yields overwhelmingly *cis*-olefines, not the *trans*-compounds. This takes place in spite of the fact that the *trans*-olefines are thermodynamically more stable. According to the multiplet theory, the reason for such behaviour of substituted acetylenes is that, with the triple bond adsorbed at two points, both substituents are forced away from the surface.

For the same reason, the *cis*-forms of olefines are more readily hydrogenated than the *trans*-forms. This phenomenon is well known in catalytic synthesis. The *trans*-forms can fit the plane of the catalyst only on two sides, whereas the *cis*-forms fit on three sides.

The multiplet theory explains the results obtained in the extensive stereochemical work of Linstead and his collaborators[267,268] on the hydrogenation of phenanthrene derivatives over platinum. Almost exclusive formation of *cis*–*syn*–*cis*-forms takes place, atoms being added on one side of the plane of the rings (for a more detailed amount, see Ref. 196). From his work, Linstead reaches the following conclusions: (1) hydrogen is added on the side towards the catalyst (and not from the liquid or gas phase); (2) aromatic rings are arranged flat during hydrogenation on platinum; and (3) steric hindrance between catalyst and substrate plays a considerable part during hydrogenation. These results are readily seen to be in complete agreement with the multiplet theory.

Waldeland, Zartman, and Adkins (1933) attempted to hydrogenate on nickel 2,6,2′,6′-substituted derivatives of biphenyl, in which the substituents prevent free rotation of the rings, the planes of the latter being perpendicular to one another. Hydrogenation of such compounds does not take place, probably owing to steric hindrance: the molecules cannot lie flat on the catalyst surface[267].

According to the multiplet theory, the hydrogenation of disubstituted benzenes should yield *cis*-forms. Investigations with the isomeric xylenes and the eight isomers of dimethylcyclohexene have shown that this is in fact observed under mild conditions[269]. Under more severe conditions, however, the *trans*-forms appear as well. Burwell explained this phenomenon by the formation of free radicals (*cf.* Section 5).

Ehrenstein and Bunge found that derivatives of *cis*-decahydroquinoline and of *cis*-decalin are more readily dehydrogenated than the corresponding *trans*-forms; according to them, their results are consistent with the multiplet theory[270].

For steric hindrance in stereospecific polymerisation, see Section 4*a*.

At low temperatures and high pressures the adsorbed molecules are oriented in the form of a Langmuir array (see, for example, Ref. 271). Rideal and his school[272] have carried out interesting new work on chemical reactions in such oriented monolayers on a liquid surface. As an example, we can cite the lactonisation of 4-hydroxystearic acid[272]. At high surface pressures (high concentrations) only the carboxyl group is in contact with the acid solution, and lactonisation does not take place since the OH group is not in contact with the catalyst (HCl). At low pressures the hydroxyl also is in contact with the solution, and reaction takes place.

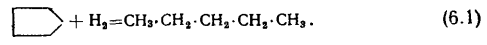
Other methods are used to determine molecular orientation in catalysis by solid surfaces, involving comparison of the chemical structure of the reactant molecules with (1) the activation energy and (2) the adsorption coefficients, which are found from the form of the decrease in reaction velocity due to displacement by foreign substances (see above[7]).

The adsorption coefficients are very high in catalytic poisoning. Maxted's extensive investigations[49,50] on the poisoning of Group VIII metal catalysts showed that during poisoning the molecules of thiols and organic sulphides are oriented with the sulphur atom towards the metal, while the aliphatic hydrocarbon chains are directed outwards. The element of area associated with one molecule of the thiol increases with the length of the hydrocarbon chain of the latter. This suggests that the molecule rotates, describing a cone with the sulphur atom at its vertex. It appears odd that this area is smaller with dithiols, which contain two sulphur atoms, but this is explained by the second atom acting as an anchor, so that rotation ceases. In this case the molecule is oriented parallel to the surface. Maxted combines structural with electronic concepts, remarking that substances containing atoms having unshared pairs of electrons, such as the sulphur atom in sulphides, are especially strong poisons.

Interesting results have been obtained from a study of adsorption at low temperatures, *i.e.* under precatalytic conditions. Vasserberg, the present writer, and Maksimova[273] have used the B.E.T. adsorption method at 25° to determine the area elements occupied by eight alcohols on aluminium oxide prepared in different ways. These areas were found to increase with increase in the number of carbon atoms in the chain of the alcohol and with its complexity. Thus at low temperatures orientation in the form of a Langmuir array, with the CHOH group towards the catalyst, is accompanied by alignment of the alcohol molecules parallel to the surface owing to the operation of van der Waals forces and hydrogen bonds. The proportion of the parallel orientation falls with rise in temperature, as is to be expected, since molecular vibrations are intensified, and the weaker bonds are ruptured. Kiselev *et al.*[274] observed similar planar adsorption of alkanes on graphitised carbon black.

Thus it follows from the experimental data that the extraindicial substituents can in some cases lie on the surface alongside the multiplet. It is reasonable to expect structural conformity in such cases. Van der Waals atomic radii, which are larger than the valence-bond radii, must usually be employed, although the interatomic distances in the molecules remain the same. Here, as also in the case of crystals having a molecular lattice, the Brigleb–Stuart molecular models should be suitable, these being inapplicable to the indicial groups, since chemical forces operate in catalysis.

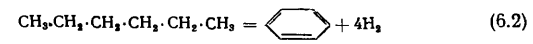
The superposition of extraindicial substituents on the surface was first considered for the opening of five-membered rings during the hydrogenation of hydrocarbons, a reaction discovered by Zelinskii *et al.*[275,276], for example:



(6.1)

Kazanskii *et al.*[277] suggested a duplet–sextet model (Fig. 16) to explain it. The five carbon atoms are arranged on the hexagon formed by platinum atoms in the (111) face, thereby producing a strain in addition to the Baeyer strain. Only two of these carbon atoms undergo reaction, a new bond being formed between them. Cyclohexane would not suffer strain under such conditions. This may explain why the cyclopentane ring is ruptured more easily than the cyclohexane ring, which does not react under such conditions, although the unadsorbed molecules with either six- or five-membered rings, show no Baeyer strain.

Similar considerations can be applied to the aromatisation of paraffins; in the simplest case



(6.2)

(see Section 4). Pitkethly and Steiner[278] suggested a duplet scheme to explain the occurrence of this reaction on chromium oxide. On platinum, however, it is possible that a duplet–sextet model, similar to that illustrated in Fig. 16, is to be preferred: a cyclohexane ring is first formed, and is then dehydrogenated as usual. The intermediate formation of cyclohexane derivatives in the aromatisation of paraffins was demonstrated experimentally by Kazanskii *et al.*[279]

It follows from the experiments of Anderson and Kemball[280] that, in the exchange of deuterium on palladium films, the cyclopentane ring is adsorbed mainly flat against the surface. As the number of D atoms introduced is increased, the percentage exchange first falls, then rises, reaching a maximum at five D atoms, and drops almost to zero at six atoms, after which it begins to increase again. The break in the curve between five and six atoms must be supposed to correspond to the ring turning over. The effect becomes weaker with rise in temperature; it is less marked with cyclohexane than with cyclopentane, and still less with cycloheptane.

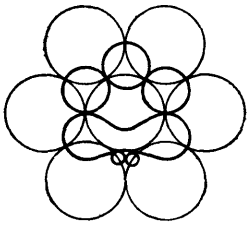
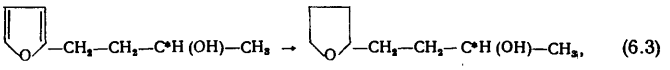


Fig. 16. Duplet–sextet model for the hydrogenolysis of cyclopentane[226].

Extremely interesting work on asymmetric catalysis was begun by Schwab, Rost, and Rudolf. Catalytic asymmetric synthesis was accomplished by Terent'ev and Klabunovskii. The reactions were carried out on metals deposited on right-handed and left-handed quartz. Optically active organic carriers give a still greater effect[281].

Cases are known in which optically active catalysts have different effects on the reaction of the (+)- and (-)-forms of optically active substrates, although the asymmetric carbon atom occurs in the extraindicial substituent, so that its bonds remain unchanged during the reaction. Thus in Ponomarev and Zelenkova's experiments[282] on the hydrogenation of 4-α-furylbutan-2-ol,



(6.3)

on nickel deposited on right-handed quartz, the resulting 4-α-tetrahydrofurylbutan-2-ol possessed an optical activity of $\alpha_D^0 = -0.04$, whereas hydrogenation over nickel on left-handed quartz yielded a different optical activity: $\alpha_D^0 = +0.03$. Since the asymmetric carbon atom is here located in the extraindicial chain, while the bonding energies within the indicial group cannot differ appreciably for the (+)- and (-)-forms, it follows that the extraindicial carbon chain lies on the catalyst surface[196]. Actually, if the chain were not in contact with the latter (as in the model illustrated in Fig. 5, for example), it would be immaterial which way the molecule branched at the asymmetric atom. If, however, the chain lies on the surface, this is no longer immaterial.

According to Klabunovskii and Patrikeev[283], the appearance of optical activity in the reaction products of asymmetric catalysis is due to asymmetric adsorption on the quartz; thus it is the adsorption, not the catalysis, which is asymmetric.

An analogous positioning of extraindicial substituents is indicated also by the fact that, in palladium catalysis obtained by Skitas's method, the presence of an optically active colloid, gum-arabic, results in asymmetric catalysis in the hydrogenation of phenyl- and α-naphthyl-glyoxylic acids[284,285].

7. THE ACTIVE SURFACE

The aim in the present section is not to report all known data on this question but only those which are especially linked with the multiplet theory.

According to this theory, active centres are undeveloped centres of crystallisation. An attempt has recently been made[286] to influence the rate of appearance of such centres, and hence the activity of the catalysts, by exposure to fast electrons (1.5 MeV). In some cases metals actually deposited from the irradiated salt solutions were 4–5 times as active as the usual catalysts (platinum) for the hydrogenation of cyclohexene; the structure of the initial platinum complexes is shown in Fig. 17.

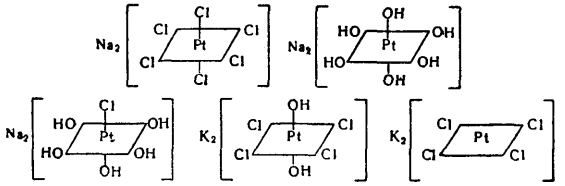


Fig.17. Structure of platinum complexes subjected to the action of fast electrons [286].

In other cases, in contrast, precipitation of the metal during exposure results in less active catalysts (palladium). It is probable that two effects are competing here, acceleration of the formation of crystal nuclei and acceleration of crystallisation, the latter leading to destruction of such nuclei.

Different crystal faces catalyse reactions at different rates. This was first discovered by Gwathmey [287,288] who worked with an optical microscope, and has been shown still more clearly by Roginskii *et al.* [55,289] using an electron microscope (*cf.* also Gomer [290]). During use the smooth, electrolytically polished surfaces of the metal single crystals, cut parallel to definite crystallographic planes, acquire regular rugosities. Thus a smooth palladium surface cut parallel to the (110) plane becomes covered with small pyramids of the octahedral faces. This is a result of catalytic corrosion (see Section 3). A similar complication obviously occurs in work with spherical points in the electron microprojector. Therefore it is impossible to say precisely to which face the maximum velocity of a given reaction corresponds. However, there is no doubt about the fact itself that different faces have different catalytic activities. It is consistent with the multiplet theory.

Ferroni *et al.* [291] established a difference in catalytic activity, for the vapour-phase hydrolysis of diethyl carbonate, between cubic and octahedral crystals of KCl.

The activity can be affected not only by the geometry of the different faces of the crystals which have been formed, but also by the different geometry of molecules trapped during formation of the catalysts and then removed. First Polyakov [292] and then Pauling [293] observed that silica gel, precipitated with acid from sodium silicate solution in the presence of various organic dyes, which were afterwards removed from it, possesses the ability to adsorb the same dyes selectively from fresh solutions thereof. In this way the adsorbent forms a matrix corresponding in shape to the dye molecule. The objection that traces of the dye remain in the silica gel, and act as crystal nuclei during its subsequent adsorption, has been refuted by recent experiments [294].

Patrikeev, Kozarenko, and the present writer [295] transferred such investigations to the field of catalysis. Silica gel which has been precipitated in a solution of dimethyldioxopiperazine and then thoroughly washed catalyses the condensation of alanine esters to the cyclic dimer to a greater extent than does silica gel which has been formed in a similar manner in a solution of alanylglycylglycine, which catalyses condensation mainly to the linear trimer [295]. This occurs probably as a result of the formation of molecular imprints.

Silica gels which adsorb (+)- and (-)-linaloöl selectively can be prepared even in the presence of the right-hand and left-hand forms of *Bacillus mycoides* [296]. Work with optically active clathrate compounds has also been undertaken in our laboratory [297].

Let us now consider the experimental determination of the size and nature of the active centres on the surface [298-302]. It is evident from the above that steric effects arise during hydrogenation. The interfering groups are then located on neighbouring carbon atoms of a C=C bond (in cases of *trans*-superposition) or are close to them. The question arises as to how rigid molecules of complicated shape, which cannot be fitted on a plane and in which the interfering groups are located quite far from the reactive centre, the indicial group, will behave on hydrogenation. With this aim the present writer and Klabunovskii [298-300] investigated the kinetics of the hydrogenation over nickel of derivatives of triptycene

(7.1)

The reaction went under mild conditions (45° and 1 atm), in spite of the possible steric hindrance. Hence it follows that the catalytically active centres must be located not on a smooth surface but on projections, in conformity with Taylor's concept of peaks [22] or Vol'kenshtein's biographic active centres [33]. What is new in our results is that such projections must have small planar faces, on which the indicial groups are arranged [in conformity with the sextet model for the hydrogenation of the benzene ring (Fig.18*a*) or the duplet model for the hydrogenation of the C=O bond (Fig.18*b*)]. At the side of the projections there must be recesses which are sufficiently deep to contain the extra-indicial substituents. The projection in Fig.18 represents the corner of a cube cut off by an octahedral face. Whereas

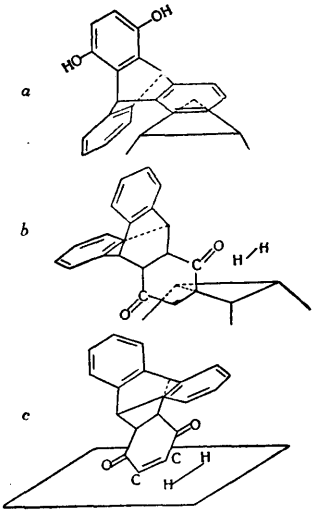
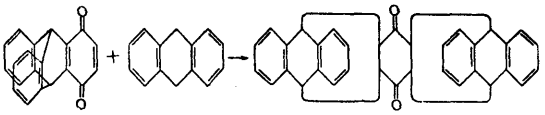


Fig.18. Orientation of molecules of triptycene derivatives on nickel: *a*) hydrogenation of benzene ring; *b*) hydrogenation of carbonyl bond; *c*) hydrogenation of olefinic bond.

reactions (*a*) and (*b*) must take place on projections, reaction (*c*), the hydrogenation of the C=C bond, can occur also on a plane, since the remaining part of the molecule can be oriented away from the catalyst. In the case of Fig.18*a* stereochemical considerations indicate that the minimum depth of the recess is 3.17 Å. Projections are necessary also in the dehydrogenation of secondary alcohols [7] and of 1,1-diphenylethane [7].

Hydrogenation of dianthrylenedihydrobenzoquinone, which was synthesised by the reaction



enabled the same workers [301] to find also the width of the active centres, which must be less than 4.8 Å. The calculations are illustrated by the stereochemical model in Fig.19. The present writer, Klabunovskii, and Antik [302] have investigated also the hydrogenation of dihydroanthrylene-naphthohydroquinone on the same basis. For the chemistry of triptycene see Theilacker *et al.* [303]

The concept of active centres as projections explains (if the random distribution of their heights is taken into account) the appearance of the dispersion parameter h in the kinetic equation for dehydrogenation, which according to work done in our laboratory holds approximately for a hundred pairs of substances on different catalysts [7].

Up to now we have been considering catalysts without additives. The multiplet theory gives two reasons for the promoting action of additives. For the first, see Section 3, paragraph 7. The second cause is entry of the added material into the active centres (for example, the shaded atom in the model illustrated in Fig.5). This cause is operative also in the case of mixed catalysts.

When instead of one phase, such as we have just been examining, two solid phases are present, we must first say something about the action of carriers. In contrast to the second component of a mixed catalyst, carriers do not usually affect the activation energy ϵ. Thus the same value of 18.04 kcal mole^{-1} was found for the dehydrogenation of decalin over platinum on carbon and over platinum on asbestos [304]. Epitaxial relations often exist between catalyst and carrier. Thus in the case of active catalysts for which the structure shown in Fig.20 is possible, the

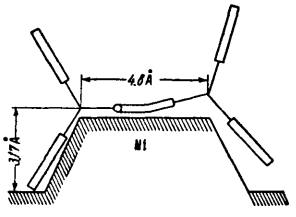


Fig.19. Orientation of the dianthrylene-benzoquinone molecule during hydrogenation on nickel, and limiting dimensions of active centre (side view) [301].

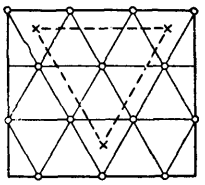


Fig.20. Epitaxial relation between Ni and Al_2O_3.

TABLE 3.

No. of catalyst	1	2	5	6	7	8	Mean
$\varepsilon_{H_2}/\varepsilon_{H_2O}$	(0.32)	0.50	0.61	0.50	0.59	0.57	0.51

ratio of the interatomic distances (M–M)/(O–O) is almost exactly a whole number [305]. For Ni on Al_2O_3, its value is 2.49/1.32 = 1.89; for Cu on Cr_2O_3, it is 2.56/1.32 = 1.94. In the case of the especially active catalyst rhenium on carbon, which we have discovered [7], this ratio is 2.74/1.45 = = 1.89. According to the multiplet theory, one of the functions of the carrier is to preserve the crystal nuclei.

For mixed catalysts consisting of two phases, it was shown in our laboratory that the catalytic activity is localised in space at the interface between the two solid phases. Thus the present writer and Rubinshtein [306,307] measured the activation energies for the dehydrogenation and the dehydration of isopentyl alcohol over catalysts consisting of Ni on Al_2O_3 prepared in different ways. The activation energies of the two processes were found to be interlinked, their ratio remaining constant at approximately 0.5 (see Table 3). But since dehydrogenation takes place on the Ni, while dehydration occurs on the Al_2O_3, the Ni and the Al_2O_3 should also be interconnected spatially: *i.e.* catalysis must occur at the interface between the Ni and the Al_2O_3. A similar result concerning the catalytic action of interfaces was obtained by a different technique for the catalytic reaction of isopropyl alcohol on Al_2O_3 + + ZnO. [308]

Steric factors play a great part also in carbonisation, which has been studied in the present writer's laboratory [309–326]. Alcohols and hydrocarbons, when decomposed on metals, form carbon dendrites. Carbonisation was found to take place by several mechanisms.

8. CLASSIFICATION OF REACTIONS [327,328]

The classification of reactions involving organic catalysis belongs to a different type of structural problem in catalytic chemistry. Reactions between molecules (not with radicals or ions) must first be distinguished according to their multiplet character, whether duplet, triplet, etc. (see above). The bond may be either covalent or semi-polar.

A further step is the systematic variation of atoms and bonds within the indicial group. Part of such a classification[5] is given in Table 4. Since different energies of bonding between the reactant molecules and the catalyst correspond to different catalysts Z, different catalysts correspond to reactions having different indicial groups.

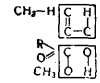
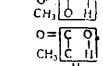
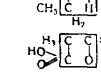
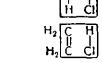
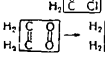
It is also evident from Table 4 that the main classes of reactions in organic catalysis[329] are in fact represented by duplet indicial groups. The resulting classification is similar to the usual classification (after Sabatier[176]), but is distinguished by greater detail. Thus according to Sabatier the dehydrogenation of hydrocarbons and that of alcohols belong to the same class, whereas according to the multiplet classification they belong to different classes, since with alcohols the indicial group contains an oxygen atom, which is replaced by a carbon atom in the case of hydrocarbons; and in fact the catalysts in the two cases are different (see Table 4).

Duplet reactions are very widespread in organic catalysis. Most of the catalytic reactions studied by Zelinskii[198] are duplet reactions[216] (and almost all the remainder are sextet reactions). All the reactions in a survey of Favorskii's work[330] can be represented as duplet reactions (caustic potash is here acting as a catalyst). The paper on catalytic condensation by Adickes and Du Mont in Schwab's multivolume work[331] examines duplet indicial groups, for example condensation by the interaction of a C–H with a C=O bond, which is represented in the multiplet theory by the duplet scheme

(8.1)

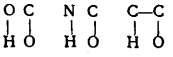
In several duplet reactions the same starting materials can yield the same reaction products by different paths. Such reactions were termed "olistomeric"[332], and the structural conditions for their occurrence were determined on the basis of the multiplet theory. Thus in esterification, bond rupture can theoretically take place in two ways: HO–CO·R + H–OR and H–O·CO·R + HO–R. A tracer method shows that reaction usually takes place by the first mechanism. For "semiduplet" schemes based on such experiments[333], into which duplet indicial groups for reactions in solutions are broken down, see Ref.28.

TABLE 4. Correspondence between groups of reactions and groups of catalysts.

Reaction group	Indicial group	Group of catalysts
Dehydrogenation of hydrocarbons		Cr_2O_3, MoO_2, V_2O_5
Dehydrogenation of alcohols		Cu, MnO_2, ZnO, CdO
Dehydration of alcohols		Al_2O_3, ThO_2, W_2O_5
Hydrogenation of olefines		Pt, Pd, Ni, Fe, Cu
Catalytic cracking (one of the reaction types)		$Al_2O_3 + SiO_2$
Migration of double bond		Cr_2O_3, Pd
Hydrolysis of esters		$SiO_2 \cdot nH_2O$
Decarboxylation		Ni, Cu
Ketonisation of acids		$CaCO_3$, $BaCO_3$, MnO, ThO_2
Chlorination		$BiCl_3$, $SbCl_3$, C
Addition of HCl to olefines		$AlCl_3$, $BaCl_2$
Oxidation of olefines		Os, Cu

Exhaustive variation of the atoms and bonds has enabled a complete set of duplet reactions to be obtained[327] for C, H, N, O, S, and Cl, which is far more detailed than that in Table 4 and comprises about 2000 types. Such a system was obtained by using special mathematical methods. It is not given here in order to economise space, those who are interested being referred to the original paper[327]. The significance of this classification for organic catalysis is analogous to that of the complete set of forms derived from the symmetry groups in crystallography by Fedorov (see, for example, Ref.334), which embraces all possible forms.

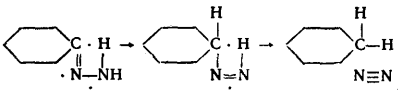
The multiplet classification is of heuristic value, assisting the discovery of types of reactions which are as yet unknown (provided that they are thermodynamically possible). Since the classification was worked out, many squares have been filled, for example, by the discovery of the formation of vinylacetylene from acetylene[335], Yur'ev's reactions[336], etc. Conscious search in the present writer's laboratory led to a series of reactions, predicted by the multiplet classification, being carried out for the first time. Examples are given in various places in the present paper. Here we may note the hydrogenolysis of *N*-bromoacetamide[23] and of t-butyl hypochlorite[23], the dehydrogenation of aliphatic amines to ketimines[84-86], and the hydrolysis of ethyl ether over mixed catalysts[337]. Al_2O_3 catalyses reactions having indicial groups (8.2) in which one atom is successively replaced:



(8.2)

i.e. the hydrolysis of ethyl ether, the preparation of *N*-monoethylaniline from alcohol and aniline, and the dehydration of alcohols to olefines. Promotion of the catalyst has different effects on these reactions, in conformity with the multiplet theory. Thus addition of oxides of Fe, Ni, and Zn accelerates the first reaction and retards the second and third[337-339]. Incidentally, the present writer and Sokolova found that Nb_2O_5 and Ta_2O_5 are good catalysts for the preparation of monoethylaniline[340], and also for the esterification of alcohols by acids[340]; Nb_2O_5 effects the condensation of acetaldehyde to crotonaldehyde[341].

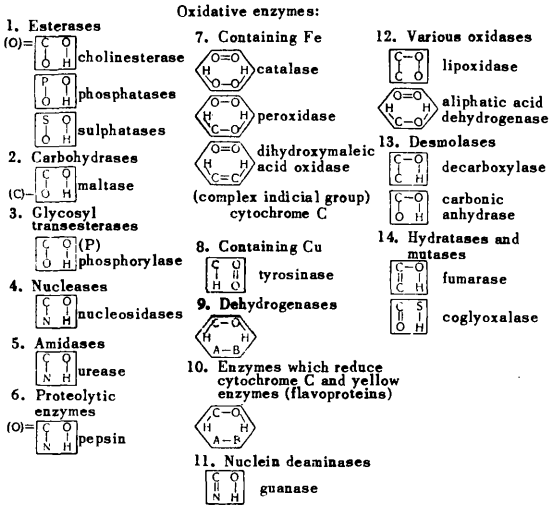
Catalytic reactions which do not fit into duplet schemes sometimes really prove to be consecutive duplet processes. An example of this type which has been studied kinetically is Kishner's reaction. The present writer and Vaskevich[6] showed that cyclohexylidenehydrazine is converted on platinum into cyclohexane (and nitrogen) *via* cyclohexyldiimine, which is short-lived (time of half-decomposition 34 sec at 150° and 1 atm):



(8.3)

Examination of the classification shows that there are still many hundreds of types of reactions awaiting discovery in organic catalysis[327].

TABLE 5. Types of enzymes and their indicial groups.



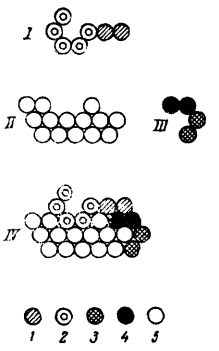


Fig. 21. Formation of intermediate complex in an enzymic reaction: I) substrate; II) protein part of enzyme; III) coenzyme; IV) intermediate complex, 1) atoms of indicial group; 2) atoms of substituents; 3) atoms of coenzyme; 4) atoms of active part of coenzyme; 5) atoms of protein part of enzyme.

This classification is valuable not only for the kinetics and equilibria of heterogeneous catalytic reactions having a duplet mechanism but also for the equilibria of homogeneous catalytic reactions, as well as non-catalytic reactions, since the equilibria do not depend on the reaction mechanism. It is interesting that the four- and six-membered cyclic activated complexes postulated by Syrkin[342] are none other than duplet and triplet indicial groups, so that the multiplet classification should be valid for them too, and is thus applicable to the kinetics of reactions other than the heterogeneous catalytic type.

Recently the multiplet theory has been applied to enzymic reactions[343-345]. Practically all of them are found to belong to the duplet or triplet type (Table 5). Their selectivity is governed by: (1) the nature of the atoms within the indicial group (Table 5); (2) the effects of extraindicial substituents on the energies of the bonds within the indicial group; and (3) the positioning of extraindicial substituents on the surface alongside the active centres (see Fig. 21), which requires a high degree of structural conformity (surface isomorphism). Antimetabolites also show surface isomorphism, but are unreactive. For further details, see Ref. 344. In the study of enzymes, conclusions similar to those of the multiplet theory have been reached by Pauling[346] and the biochemist Dreiding[347] from the Karrer school.

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REACTIONS OF NITRILES WITH HYDROGEN HALIDES AND NUCLEOPHILIC REAGENTS

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I. INTRODUCTION

The ability of nitriles to form addition compounds with nucleophilic and electrophilic reagents derives from the electronic structure of the triple carbon–nitrogen bond[1]. We have recently reviewed the reactions of nitriles with electrophilic reagents[1], and these will be considered only to a limited extent. Because of the reduced electron density at the carbon atom of the cyano-group, nitriles should react very readily with nucleophilic reagents. Compounds such as hydrogen sulphide and hydroxylamine do in fact add to nitriles to form thioamides and amidoximes, but in general nitriles are very stable towards many other nucleophilic reagents (water, alcohols, amines, etc.). The reactivity of nitriles is increased and the range of their reactions with nucleophilic reagents broadened in the presence of acidic or alkaline compounds, the action of which is evidently due to the ready polarisability of the cyano-group; also the presence of acids creates suitable conditions for the appearance of electrophilic activity at the nitrile carbon atom and the formation of new bonds between this atom and atoms of oxygen, sulphur, nitrogen, carbon, etc.

Hydrogen halides are particularly important as acid catalysts for reactions of the cyano-group, and in many cases, especially with hydrogen chloride, they are specific catalysts. The Pinner reaction (preparation of imidate salts), Hoesch reaction (preparation of ketimine salts), Gattermann reaction, Stephen reaction (preparation of aldimine salts), and several other acid-catalysed reactions of nitriles are carried out in the presence of hydrogen halides, and do not occur with other protogenic or Lewis acids in the absence of hydrogen halides. In the literature these reactions are very often discussed without consideration of the nature of the products of the reaction of nitriles with hydrogen halides, which may be formed under the experimental conditions. These products are often formulated as imidoyl halides, although these have never been isolated and there is no proof of their existence in the reaction medium. There have been no attempts in the review literature to generalise the existing data on the reactions of nitriles with hydrogen halides in the absence of other reagents.

This review is intended to fill the existing gaps. We shall consider the structure of the hydrohalogenation products of nitriles and hydrogen cyanide, and describe the reactions of nitriles with hydrogen halides and other reagents: hydroxylic compounds (water, alcohols, and organic acids), aldehydes and ketones, amines and aromatic compounds (the Gattermann and Hoesch reactions). The reduction of nitriles in the presence of hydrogen halides and other matters related to these reactions of nitriles will also be considered.

II. REACTIONS OF NITRILES WITH HYDROGEN HALIDES

A. Nitrile Hydrohalides of Composition RCN.*n*HX

Nitrile hydrochlorination products were first isolated in 1866 by Gautier[2-4], and the hydrohalogenation of nitriles was much studied in the last century[5-10]. Several nitrile hydrohalides were apparently obtained in admixture with other compounds in the bromination of aliphatic nitriles[11,12]. Until 1931 it was thought that one or two hydrogen halide molecules could add to nitriles in the cold, to form imidoyl halides and amino-halides respectively, but, after more careful study of the composition of the very unstable reaction products of nitriles and hydrogen halides, Hantzsch concluded[13] that the monohydrochlorides were not obtained, and that only the saltlike dihydrochlorides exist. By hydrobromination, however, Hantzsch obtained mono- and di-hydrobromides. Hantzsch's experiments on hydrobromination were later repeated by Klages and Grill[14], who showed that Hantzsch's results on nitrile monohydrobromides were in error. In 1957 it was reported[15] that treatment of *N*-acylaminoacetonitriles with hydrogen chloride in the cold produces monohydrochlorides, and these were stated to be the first isolated imidoyl chlorides or nitrilium salts; however, hydrogen chloride can add not only to the cyano-group, but also to the amide group, and this possibility was not considered. Moreover, the hydrochlorides obtained melted above 100°, and it is improbable that imidoyl halides would melt at such high temperatures. Up

to the present, therefore, only nitrile dihydrohalides have been prepared (textbooks [16] and monographs [17] still erroneously refer to the existence of solid monohydrohalogenated nitriles).

The 1 : 2 reaction products of nitriles and hydrogen halides are also obtained by treating carboxylic acid amides with PCl_5; [18] these products have been shown to be identical with those obtained by direct hydrochlorination of nitriles [13]. Kirsanov has studied the reaction of carboxylic acid amides with PCl_5, [19-21] and his data confirm the earlier suggestion [22] that the primary reaction products are trichlorophosphazoacyl compounds:

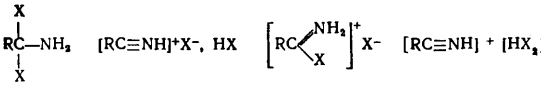
$$RCONH_2 + PCl_5 \rightarrow R\overset{\overset{O}{\|}}{C}-N=PCl_3 + 2\,HCl.$$

These can be obtained in high yields if the hydrogen chloride is removed from the reaction zone. In the presence of the hydrogen chloride they decompose into nitriles and $POCl_3$:

$$R\overset{\overset{O}{\|}}{C}-N=PCl_3 \xrightarrow{HCl} RCN + POCl_3.$$

The resulting nitriles react further with the hydrogen chloride in the normal fashion, *i.e.* to form the 1 : 2 addition products.

The 1 : 2 addition products of nitriles with hydrogen halides have been given various structural formulae. In the older literature they were considered to be amino--halides (A).[23] In 1931 Hantzsch [13] suggested the formula (B), according to which they are hydrochlorides of nitrilium salts, and this formula is met with today [16]. Klages and Grill found [14] that the properties of the nitrile dihydrohalides correspond best to those of imidoyl halide salts [24], *i.e.* halogenoiminium halides (C). Finally, Janz has suggested [25] that the nitrile hydrochlorides may have formula (D):



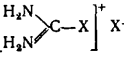
(A) (B) (C) (D)

The nitrile dihydrohalides show a high conductivity in liquid sulphur dioxide [14] and are therefore salts and cannot be amino-halides (A). The nature of the bond between the nitrilium salt and the hydrogen halide molecule in formula (B) is not clear. There can be no suggestion of the formation of a hydrogen bond between the hydrogen halide and the cation, since the nitrilium ion has no free electron pair to act as a base [14]. Formula (B) cannot therefore represent the true structure of the nitrile dihydrohalides. Unlike formula (B), the other nitrilium salt structure (D) is quite possible, since the existence of the dihalide anion HX_2^- has been proved [26-31]. It has been suggested [26] that the stability of the anion HCl_2^-, by analogy with HF_2^-, is due to the formation of a hydrogen bridge between the hydrogen atom in the HCl and the chloride ion ($Cl-H\cdots Cl^-$). There are also no particular objections to formula (C), representing a halogenoimonium structure for the salts RCN.2HX.

The infra-red spectra of acetonitrile dihydrobromide have shown it to be acetobromoimonium bromide [25]; an attempt was also made to obtain the infra-red spectra of solid acetonitrile dihydrochloride, but was unsuccessful because of its instability. The infra-red spectra of very dilute solutions (up to 1.15 M) of hydrogen chloride in acetonitrile revealed no band due to a C–Cl bond (750 cm^{-1}) but there was a band at 1180 cm^{-1} characteristic of the HCl_2^- anion [27]. It was therefore concluded that for the dihydrochloride, unlike the dihydrobromide or dihydriodide, the most probable formula is (D). Janz did not consider this structure as proved, because (a) the structure of nitrile dihydrochlorides may be different in dilute solution than in the solid state, and (b) the measurements were made [25] at room temperature, while even at +6° acetonitrile dihydrochloride dissociates into the nitrile and hydrogen chloride [32].

The existing data are therefore insufficient to ascribe to the dihydrochlorides a structure different from the structure of the other dihydrohalides. In order to establish finally the structure of nitrile dihydrochlorides, their spectra must be investigated under conditions such that their conversion into other nitrile–hydrogen chloride reaction products is excluded.

It is of interest that no difference has been found in the structures of solid cyanamide dihydrochloride and dihydrobromide [33] and both salts have been given the same halogenoformamidinium halide structure:



The dihydrohalides described in the literature, which are in all probability of structure (C), include the dihydrochlorides of acetonitrile [32], bromo- and fluoro-acetonitrile [34], benzonitrile [8], *p*-tolunitrile [13], and *p*-methoxybenzonitrile [35], the dihydrobromides of acetonitrile [25], bromoacetonitrile [34], phenylacetonitrile and benzonitrile [14], and *p*-tolunitrile [13], and the dihydriodides of acetonitrile [25], phenylacetonitrile, *o*-, *m*-, and *p*-tolunitrile, *o*-, *m*-, and *p*-nitrobenzonitrile, succinonitrile, terephthalonitrile, etc. [10].

Of the acetonitrile dihydrohalides, the hydriodide melts at the highest temperature (above 100°); the hydrobromide and hydrochloride melt at 75°–80° and about 20° respectively [25,36]. The thermal stability of the salts (ease of formation) also increases in this order:

$$CH_3CN.2HCl < CH_3CN.2HBr < CH_3CN.2HI.$$

The stability of the halogenoimonium halides is related to the polarisability of the hydrogen halides [36]: the least polarisable hydrogen chloride forms the least stable salts, and the most polarisable hydrogen iodide the most stable salts.

On heating, the halogenoimonium halides are usually decomposed into the nitriles and the hydrogen halides. The vapour pressure of certain bromoimonium bromides has been shown to depend on the temperature [14]. The heat of dissociation into the initial components was calculated; for benzobromoimonium bromide ΔH = 30 kcal per mole.

Nitrile dihydrochlorides enter into exchange reactions with other anions, and form stable salts with complex anions [14]. The following have been described: benzochloroimonium and acetochloroimonium hexachlorostannates, and benzochloroimonium, *p*-nitrobenzochloroimonium, and acetochloroimonium hexachloroantimonates [37].

Certain nitrogen-unsubstituted nitrilium salts with complex anions have been prepared where the corresponding halides are unknown. Benzo- and aceto-nitrilium hexachlorostannates and *p*-nitrobenzo- and aceto-nitrilium hexachloroantimonates have been prepared [37]. The reaction between benzonitrile, hydrogen chloride, and zinc chloride gave benzonitrilium trichlorozincate [38]. Their conductivity in liquid sulphur dioxide confirms their salt structure [37].

According to Klages[37], which complex is formed depends on the reaction temperature. There is no reaction between a nitrile, the complex-forming reagent, and hydrogen chloride at a very low temperature; in the intermediate region nitrilium salts are formed, and at higher temperatures two hydrogen chloride molecules react, with the formation of imonium salts. In some cases there is no intermediate region, *i.e.* nitrilium salts could not be obtained.

On heating, the complex nitrilium salts disproportionate to form the more stable chloroimonium salts.

$$2\,[RC{\equiv}NH]^{+}\,SbCl_6^{-} \rightarrow \left[RC\begin{matrix}NH_2\\Cl\end{matrix}\right]^{+} SbCl_6^{-} + RC{\equiv}N{\cdot}SbCl_5.$$

Study of the fusion diagrams of binary mixtures of hydrogen chloride with acetonitrile, propionitrile, butyronitrile, and benzonitrile has shown that these nitriles can form low-melting non-saltlike molecular compounds of formula RCN.HCl.[39] Thus CH_3CN.HCl melts at -63.2° and C_2H_5CN. .HCl at -97.2°. The molecular compounds RCN.HCl may be formed as a result of reaction between the unshared electron pair of the nitrile nitrogen and a molecule of hydrogen chloride. The above nitriles also form complexes of composition RCN.*n*HCl (where n = 5 or 7) and 2RCN.3HCl, which have even lower melting points than the compounds RCN.HCl. It is suggested[39] that in these compounds the unshared electron pair of the nitrogen and also π electrons act as donors, and the compounds RCN.*n*HCl are apparently therefore examples of the so-called π-complexes.

It must be emphasised that the compounds described by Murray and Schneider[39] are fundamentally different from all the other hydrohalogenation products of nitriles, which are salts. All the described molecular compounds retain the covalent bond between the hydrogen and chlorine in the hydrogen chloride molecule, and are apparently intermediates in the formation of the saltlike nitrile hydrohalides (see below).

B. Some Properties of Solutions of Hydrogen Halides in Nitriles

It has been known for a long time that hydrogen halides ionise comparatively readily in nitriles[40], and the conductance has been the most studied physical property of the solutions[25,37,41-44]. The polarographic behaviour of solutions of hydrogen chloride in acetonitrile has been investigated[45,46], and cryoscopic measurements have been made on dilute solutions of hydrogen chloride in benzonitrile[37].

The conductimetric study of the reaction between hydrogen chloride and acetonitrile[43], benzonitrile, β-chloropropionitrile, $\alpha\beta$-dichloropropionitrile, β-ethoxypropionitrile, and adiponitrile[44] shows that the conductance decreases as the HCl concentration is increased. In some cases the conductance curves pass through a minimum. Plots of λ (equivalent conductance) against $\sqrt{c}$ for solutions of HCl in adiponitrile and β-chloropropionitrile show two intersecting straight lines, *i.e.* within certain concentration limits the conductivity of these dilute solutions is described by Kohlrausch's formula for low concentrations of strong electrolytes. Plots of λ against $1/\sqrt{c}$, which are used for systems with chemical reaction[43], are linear for acetonitrile, adiponitrile, benzonitrile, and β-chloropropionitrile, the last two giving two intersecting lines[44].

The complexity of the conductance–concentration relationship, and in particular the presence of intersecting curves on the diagrams, can be explained by a given nitrile forming with the hydrogen halide, depending on the reaction conditions, not one but several compounds, some which ionise and some which do not[44]. The nitrile solutions may contain, for instance, the molecular compounds RCN.*n*HCl. Conductimetric and cryoscopic study of dilute solutions of HCl in benzonitrile has shown[37] that the compound C_6H_5CN. .HCl is formed. Of the known types of saltlike compounds, the nitrile solutions may contain halogenoimonium halides[14,47], compounds with the HX_2^- anion[25], and possibly also nitrilium salts and salts of composition 2RCN.*n*HX (see below). It must be assumed[44] that in general the nature of the reaction products between nitriles and hydrogen halides changes continuously in the qualitative and quantitative sense as the relative proportions of the reactants are varied.

The formation of compounds between nitriles and hydrogen halides is sometimes quite slow; for example, at 0° in ether (twice the reactant volume) the reaction between adiponitrile and hydrogen chloride in the molar ratio 1 : 2 is practically complete only after 24 h.[47] The conductance of freshly-prepared solutions of hydrogen halides in nitriles increases with time and reaches a maximum[42,44]. The slowness of the reaction enables the conductimetric method to be used to study the reaction mechanism[36,42].

The increase in conductance of solutions of hydrogen halides in nitriles with time means that the ionising compounds are not formed immediately. A similar effect was found with the systems acetonitrile–picric acid[48] and acetonitrile–iodine monohalides[49].

The donor-acceptor properties of the solvent and solute influence the rate of equilibration in the reaction of nitriles with hydrogen halides. It is assumed that the slow increase in conductance is due to the high ionisation potential of the nitrile, so that the latter is slowly protonated[42,48]. The polarisability of solvent and solute must also influence the rate of ionisation to a similar extent; the maximum conductance is reached earlier in the acetonitrile–HI and acetonitrile–HBr systems than in the acetonitrile–HCl system[42], the equilibrium conductances in these systems being in the ratio 60 : 20 : 1.[36]

From the conductivity data, Janz and Danyluk suggested[42] two mechanisms for the reaction between nitriles and hydrogen halides. The primary reaction products are unionised molecular compounds ("outer complexes") which are then converted into saltlike compounds ("inner complexes")[49,50]. Mulliken and Reid associate the slow salt-formation with a considerable energy barrier for this reaction[51].

The first of Janz' and Danyluk's mechanisms[42] for the reaction of nitriles with hydrogen halides comprises the following stages:

$$RCN + HX \rightleftarrows RCN{\cdot}HX \rightleftarrows RCNH^+X^- \rightleftarrows RCNH^+ + X^-_{solv}.$$

In the compound RCN.HX, which is an "outer complex", the hydrogen halide molecule still retains its σ bond, but this is then broken to form the "inner complex", which ionises in solution to form the solvated anion X^-_{solv}; this then reacts with a second hydrogen halide molecule to form the anion HX^-_{2solv}.

The second mechanism[42] involves a nucleophilic attack by hydrogen halide on the "inner complex" to form the halogenoimonium halide, the anion of which is then solvated:

$$[CH_3C{\equiv}NH^+X^-] \rightleftarrows [CH_3\overset{+}{C}{=}NH{\cdot}X^-] \overset{HX}{\rightleftarrows} CH_3\overset{X}{\underset{|}{C}}{=}NH_2^+X^- \rightleftarrows \left[CH_3C\begin{matrix}X\\ \diagdown\\ \diagup\\ NH_2\end{matrix}\right]^+ + X^-_{solv.}$$

The solvated halide ion can obviously again react with a second hydrogen halide molecule to form the anion $HX_{2\,solv}^-$, so that the overall reaction in the solution is

$$CH_3CN + 3\,HX \rightleftarrows \left[CH_3C\begin{matrix}X\\ \diagdown\\ \diagup\\ NH_2\end{matrix}\right]^+ + HX^-_{2\,solv.}$$

The compound $[C_6H_5CCl{=}NHC_6H_5]^+HCl_2^-$ has recently been prepared[52] by reacting *N*-phenylimidoyl chloride with hydrogen chloride.

The second mechanism was essentially that put forward[14] in 1955 as the only possible one for the reaction between nitriles and hydrogen halides. Attention was directed to the exceptional energetic instability of nitrogen-unsubstituted nitrilium salts, and to their strong tendency to add halide ions to yield undissociated imidoyl halides which, being bases, then react further with the hydrogen halide[14]. The addition of hydrogen halides to *N*-substituted imidoyl halides has been described[53,54].

C. Nitrile Hydrohalides of Composition 2RCN.*n*HX

Certain halogenonitriles react with hydrogen halides under normal conditions to give saltlike products which have different chemical properties from the nitrile hydrohalides described above[55-59]. Although these salts were known to give secondary amides with water, the attempt to assign to them a more or less acceptable structure was for long unsuccessful, until Grundmann and coworkers convincingly demonstrated[60] that they are dimer salts of composition 2RCN.HX and have the *N*-alkylideneamidine structure (E) or (F):

$$\underset{(E)}{RC(X){=}N{-}C(R){=}NH} \quad [R\overset{+}{C}{=}N{-}C(R){=}NH \longleftrightarrow \underset{(F)}{RC{\equiv}\overset{+}{N}{-}C(R){=}NH]\,X^-}.$$

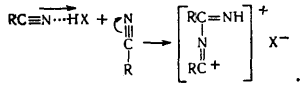
Alkylideneamidine chlorides of this type were prepared[60] from mono-, di-, and tri-chloroacetonitrile and α-dichloropropionitrile; the last reacts similarly with hydrogen bromide.

The *N*-alkylideneamidine structure has been assigned to the reaction product of hydrogen chloride with α-cyanoethyl acetate[61]. It has been reported that unsubstituted acetonitrile forms a dimer salt[32]; the reaction product was characterised as α-chloroethylideneamidine. The treatment of chloro-, fluoro- and bromo-acetonitriles with hydrogen chloride or bromide at about room temperature gives compounds of composition 2RCN.3HCl and $2ClCH_2CN.3HBr$[34,62] having the same chemical properties as the salts 2RCN.HX; the products may therefore be formulated as, for instance,

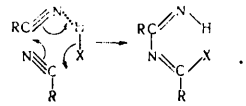
$$[RC(Cl){=}N{-}C(R){=}NH_2]^+HCl_3^-.$$

The reaction products of chloro- and bromo-acetonitrile with hydrogen chloride, which were formulated as imidoyl chloride hydrochlorides[63], are in fact dimer salts[38].

Lazaris and coworkers[34], using the reactions of fluoro- and bromo-acetonitrile with hydrogen chloride, were the first to show that, depending on the reaction conditions, the same nitriles may produce either halogenoimonium halides or dimer salts: the former were obtained between -50° and -5°, and the latter between 0° and 20° and above. In each case unstable outer and inner complexes are apparently first formed; at low temperatures these compounds are stabilised by addition of a hydrogen halide molecule to form the halogenoimonium halide. At a higher temperature the equilibrium in the formation of the unstable complexes is displaced towards the formation of the initial products, producing a higher concentration of the free nitrile. The cyano-group has both nucleophilic and electrophilic properties, and the unstable complexes are therefore stabilised by addition of the nitrile, giving the dimer salts:



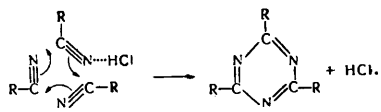
Cyclic electron transfer is also a probable mechanism in the formation of the dimer salts:



D. Preparation of 1,3,5-Triazines

In the presence of hydrogen halides some nitriles, chiefly α-halogenonitriles, polymerise at room temperature and above to produce 1,3,5-triazines[1,64]. Grundmann and coworkers[60] consider that the trimerisation of nitriles is preceded by the formation of the dimer salts (see above), which then react with the nitrile by the diene synthesis to form 1,3,5-triazines. However, this mechanism is inconsistent with their inability to prepare 1,3,5-triazines from the dimer salts and nitriles, and chloroacetonitrile, which forms the dimer salt more easily than any other nitrile, does not trimerise at all; on the other hand, trichloroacetonitrile, which gives the dimer salt with great difficulty[60], polymerises exceptionally readily. Hence the dimerisation of nitriles to dimer salts cannot be an intermediate stage in the production of 1,3,5-triazines, and these must be considered as competing reactions, as the early workers assumed.

The comparative ease of formation of 1,3,5-triazines may be due to cyclic electron transfer:



According to this mechanism, both the free nitrile and its hydrogen halide complex take part in the reaction. The required free nitrile content is met because the triazine synthesis is usually carried out at room temperature and above, when the nitrile hydrochlorides are already partially dissociated. Since the reaction proceeds less easily in the absence of the nitrile hydrohalide, an increase of reaction temperature above a certain limit should reduce the yield of triazine, and this has been confirmed experimentally[65]. The experimentally observed evolution of hydrogen chloride in the formation of 1,3,5-triazines[60] also does not contradict the suggested reaction mechanism.

Dimer salts and triazines are obtained most easily from α-halogenonitriles: electronegative α-substituents produce a comparatively low electron density at the nitrile carbon atom, and hence increase the electrophilic reactivity of the nitriles.

Up to the present, therefore, the reaction of nitriles with hydrogen halides has given three main types of stable compound: the dihydrohalides (apparently halogenoimonium halides), dimer salts (*N*-alkylideneamidines), and 1,3,5-triazines. The reactions commence with the formation of unstable complexes between the reactants, and these are then stabilised by one of the above mechanisms, depending on the properties of the initial components and the reaction conditions.

E. Hydrogen Cyanide Hydrohalides

Hydrogen cyanide reacts with hydrogen chloride to produce two compounds, of composition 2 : 3 and 2 : 1.

The sesquichloride 2HCN.3HCl [66] has been assigned the dichloromethylformamidine hydrochloride structure [67,68]:

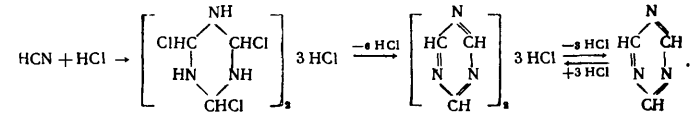
$$Cl_2CHNHCH{=}NH\cdot HCl,$$

or, in more recent work, the following non-saltlike structure [69-74]:

$$Cl_2CHNHCHClNH_2.$$

The sesquichloride readily loses two-thirds of its hydrogen chloride to form the compound 2HCN.HCl, which was earlier considered to be chloromethyleneformamidine ClCH = NCH = NH.[69] Further dehydrochlorination, *e.g.* by means of quinoline, gives the so-called "dimeric hydrocyanic acid",[75] which has been given the iminoformylcarbylamine structure C = NCH = NH.[76]

The structure of these reaction products was considered afresh by Grundmann and coworkers [77-80], who put forward completely new formulae for them. According to Grundmann, the product initially formed is 2,4,6-trichlorohexahydro-1,3,5-triazine hydrochloride, the compound thought to be chloromethyleneformamidine is 1,3,5-triazine sesquichloride, and exhaustive dehydrochlorination produces 1,3,5-triazine, which is unstable:

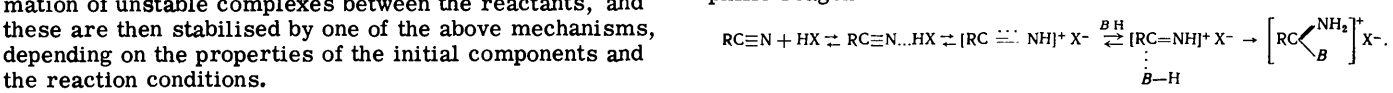


At various times the reactions of the hydrogen cyanide hydrochlorination products with water, alkali, alcohols [66], amines [68], aromatic compounds (in the presence of aluminium chloride) [67,73,74], and other compounds have been studied. The compositions of the molecular compounds formed between aluminium chloride and all three of the HCN–HCl reaction products have also been investigated [80].

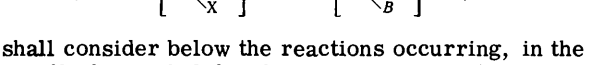
Hydrogen cyanide reacts with hydrogen bromide to give the analogous bromine compounds 2HCN.3HBr and 2HCN. .HBr.[71,81]

III. REACTIONS OF NITRILES WITH HYDROGEN HALIDES AND NUCLEOPHILIC REAGENTS

As stated above, in the absence of acids nitriles do not as a rule react with hydroxylic or other nucleophilic reagents. The addition of a proton to the nitrile nitrogen atom "opens up" the triple bond, and hence considerably increases the ability of the cyano-group to react with electron-donating compounds; it must be assumed, therefore, that the reaction of nitriles with water, alcohols, organic acids, mercaptans, and other nucleophilic reagents is preceded by the formation of nitrile–hydrogen halide addition products. Possible intermediates in these reactions of nitriles are the unstable strongly polarised 1 : 1 nitrile–hydrogen halide complexes described in the previous section; these are then stabilised by addition of the nucleophilic reagent:



Since nitriles also form extremely stable reaction products with hydrogen halides, the halogenoimonium halides, these must also be considered to take part in the reactions between nitriles, hydrogen halides, and nucleophilic reagents:



We shall consider below the reactions occurring, in the presence of hydrogen halides, between nitriles and hydroxylic compounds and amines, and also the Gattermann and Hoesch syntheses. In discussing these reactions, we shall show that in many cases there has been experimental confirmation of two main reaction stages: reaction between the nitrile and the hydrogen halide, and, subsequently, addition of the electron-donating compound. In some cases the experimental results have been sufficient to decide which of the two mechanisms is predominant in the first stage, *i.e.* whether only the unstable complexes are formed, or whether the saltlike nitrile dihydrohalides are also produced. Some of the results do not exclude the possibility, in individual cases, of synchronous reactions, *i.e.* reactions passing through a single transition state. Knowledge of the mechanism of the electrophilic reactions of nitriles has enabled known syntheses to be improved and new ones developed.

This section includes a subsection devoted to the reactions of the nitrile dimer salts with hydroxylic compounds. Since the previously little known amide hydrohalides are often the final products in the reaction of nitriles with hydrogen halides and hydroxylic compounds, a separate subsection is devoted to their properties. Finally, we shall consider the selective reactivity of one of the cyano-groups of adiponitrile, which is particularly evident in the presence of hydrogen chloride.

A. Reactions with Water

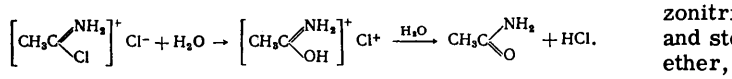
1. Preparation of amides and their hydrohalides. Amides are obtained when nitriles are treated with concentrated hydrochloric acid at room temperature [82-94], or, more rapidly, at 50°–60°. At higher temperatures carboxylic acids are formed [90,95]. Nitriles containing reactive groups are hydrated at room temperature or at 0°.

The hydrolysis of nitriles with hydrochloric acid of various concentrations has been investigated [96]; with concentrated acids hydrolysis stops at the amide stage, while in dilute acids carboxylic acids are obtained. Since the HCl content of concentrated hydrochloric acid at room temperature is at most 36–38%, the amides formed by the hydration of nitriles are sometimes partially or completely

hydrolysed to carboxylic acids even at low temperatures[97]. To suppress hydrolysis of the amides the nitriles must be hydrated under conditions such that there is no large excess of water. In some cases the nitriles have been dissolved in concentrated hydrochloric acid, or mixed with a little water, and the solution cooled to between -5° and 0° and saturated with hydrogen chloride[17,98-101]. Treatment of the reaction products of nitriles and dry hydrogen chloride with water usually gives the initial nitriles[13,17,32], but in certain cases nitrile–hydrogen chloride reaction products have been said to be intermediates in the production of amides from nitriles[92,102,103]. The formation of amides from nitriles and water in the presence of hydrogen chloride is the basis of proposed methods for the dehydration of acids[104] and esters[105].

As early as 1877 Pinner and Klein[8] passed hydrogen chloride into a mixture of equivalent quantities of water and acetonitrile or benzonitrile and obtained compounds which they described as amide hydrochlorides, but the reaction conditions and the yield and properties of the salts were not given. Later it was stated[25,99,103] that amide hydrochlorides are intermediates in the preparation of amides from nitriles, water, and hydrogen chloride, but here also the amide hydrochlorides were not identified. Treatment of adiponitrile with water and hydrogen chloride[106] gave a chlorine-containing product which was wrongly described as an imidoyl chloride hydrate.

According to Zil'berman and Kulikova's results[47,107-112], earlier statements[13,32] that the action of water on nitrile–hydrogen halide reaction products can only produce the initial reactants are only partly correct. With an excess of ice water acetochloroimonium chloride does in fact dissociate to give the initial nitrile, but the addition of small quantities of water to an ether solution of the chloride gives a precipitate of acetamide hydrochloride (acetimidic acid hydrochloride), which on hydrolysis produces the free amide:



Treatment of mixtures of equivalent quantities of nitriles and water with hydrogen chloride has given high yields of amide hydrochlorides derived from aliphatic acid amides[47,110], aliphatic acid diamides[111], and ring-substituted benzamides[35]. In some cases the amide hydrochlorides are very unstable, readily losing hydrogen chloride, and even before hydrolysis are partially converted into the free amides. Some nitrile hydration products (*e.g.* from chloroacetonitrile[110]) contained so little hydrogen chloride that they should be classed as free amides rather than amide hydrochlorides. Hydration of trichloroacetonitrile[110] and αβ-dichloropropionitrile[112] gives the free amides. The considerable negative inductive effect of the chlorine atoms in these amides apparently so weakens the nucleophilic properties of the oxygen atom that it becomes unable to add a proton. Unlike these, however, capronitrile[109], methacrylonitrile, and lactonitrile[112] do apparently form amide hydrochlorides, but they could not be isolated from the reaction mixture. The corresponding amides were obtained immediately on hydrolysis of the reaction mixture.

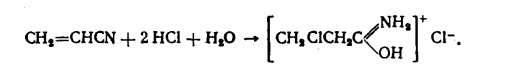
As a rule, the order of addition of the nitrile, hydrogen chloride, and water to the reaction mixture plays substantially no part in the reaction, but in certain specific cases a particular order of addition is essential for obtaining optimum yields of hydrochlorides or free amides. In the preparation of most amides equivalent quantities of nitrile and water are added to an organic solvent, and hydrogen chloride is passed into the solution; after a definite time the precipitate is filtered off. Because of the reactivity of the hydroxy-groups in lactonitrile and acetonecyanohydrin, the corresponding amides can only be prepared by adding the nitrile to a solution of hydrogen chloride in aqueous ether[112]. Adiponitrile was converted quantitatively into δ-cyanovaleramide hydrochloride by passing hydrogen chloride into a solution of adiponitrile in ether for at least four hours and then adding the calculated quantity of water[47]. This procedure was also the most suitable for preparing diamides of dibasic acids[111].

The larger the excess of hydrogen chloride with respect to the nitrile, the more rapidly is the amide hydrochloride formed[110]; evidently excess of hydrogen chloride increases the concentration of primary nitrile–hydrogen chloride reaction products, which then react with the water. An excess of hydrogen chloride is not necessary in the hydration of nitriles of high electrophilic reactivity. In the preparation of lactamide, α-hydroxyisobutyramide hydrochloride[112], and δ-cyanovaleramide hydrochloride the molar ratio of nitrile to hydrogen chloride should be 1 : 2. The formation of most amide hydrochlorides is complete within 24 h, but in some cases (*e.g.* with stearamide, adipamic acid methyl ester[110], *p*-toluamide[35], etc.) the reaction had to be continued for 5–10 days.

Amide hydrochlorides are usually prepared at ~0°,[110] but with some nitriles of low reactivity (*e.g.* stearonitrile, capronitrile, and benzonitrile) room temperature was preferred.

Amide hydrochlorides can be prepared from nitriles, water, and hydrogen chloride in the presence or absence of inert organic solvents, so long as the nitrile dissolves in the reaction mixture. The amide salts are often prepared in ether[110]. Substituted benzamides are prepared in dioxane, which unlike ether partially dissolves substituted benzonitriles[35]. The comparatively slow-reacting capronitrile and stearonitrile have been hydrated in toluene, since ether, dioxane, and similar oxygen-containing compounds were not found to be suitable solvents. The reaction between hydrogen chloride and the ethers apparently displaces the equilibrium of the nitrile–hydrogen chloride reactions towards the initial reactants, and the reduced concentration of intermediate products in the reaction mixture lowers the rate of formation of the amides.

When αβ-unsaturated nitriles (acrylonitrile, methacrylonitrile) are treated with hydrogen chloride and water, they are hydrated and also hydrochlorinated at the double bond[112]:



Some nitriles (β-ethoxypropionitrile, azodiisobutyronitrile[110], *o*-nitrobenzonitrile[35], etc.) have proved impossible to hydrate to amides, presumably because of steric hindrance. *Ortho*-substituted benzonitriles are known[113,114] to be inactive in other reactions also: *e.g.* they do not form imidate hydrochlorides with hydrogen chloride and alcohols. The stability of β-ethoxypropionitrile under normal conditions for the preparation of amide hydrochlorides may be because, as has been suggested[115], β-substituents in the aliphatic series produce the same steric hindrance as is found in *ortho*-substituted aromatic compounds.

The reaction of nitriles with deuterium chloride and deuterium oxide is a convenient method for preparing

ON-deuterated imidic acid hydrochlorides [116]:

$$RCN + DCl + D_2O \rightarrow \left[RC\begin{matrix}ND_2\\OD\end{matrix}\right]^+ Cl^-.$$

Treatment of these salts with heavy water causes deuterium exchange at the α-carbon atom, forming *NC*-deuterated amides with a high deuterium content. Trichloroacetonitrile, which has no α-hydrogen and does not form the imidic acid hydrochloride, reacts with deuterium chloride and deuterium oxide to produce deuterotrichloroacetamide in high yield. Obviously, other isotopic varieties of water will react with nitriles in the same way as D_2O.

2. Mechanism of the reactions of nitriles with hydrogen halides and water. Two reaction mechanisms for the reaction between nitriles, hydrogen halides, and nucleophilic reagents were given at the commencement of Section III: (a) the formation of unstable complexes between nitriles and hydrogen halides, and (b) the formation as intermediates of saltlike nitrile hydrohalides (halogenoimonium halides).

Investigation of the reaction of substituted benzonitriles [35] and aliphatic dinitriles [111] with hydrogen chloride and water has confirmed that the reaction proceeds in stages. The possibility of carrying out the reaction by way of chloroimonium chloride was shown experimentally in the selective hydration of one nitrile group of adiponitrile [47]. To obtain the theoretical yield of δ-cyanovalerimidic acid hydrochloride, the 1:2 nitrile–hydrogen chloride reaction product (δ-cyanovalerochloroimonium chloride) must first be prepared:

$$NC(CH_2)_4CN + 2HCl \rightleftarrows \left[NC(CH_2)_4C\begin{matrix}NH_2\\Cl\end{matrix}\right]^+ Cl^- \xrightarrow{H_2O}$$

$$\rightarrow \left[NC(CH_2)_4C\begin{matrix}NH_2\\OH\end{matrix}\right]^+ Cl^- + HCl.$$

There are cases, *e.g.* in the hydration of chloroacetonitrile [62], when the chloroimonium chloride formation is unnecessary or even impossible. In the treatment of certain reactive nitriles, particularly halogenoacetonitriles, with water and hydrogen chloride, the unstable outer and inner complexes RCN.HCl may be intermediate products. It is also possible that in this case the addition of water and hydrogen chloride takes place in a single transition state.

It must be assumed that in most actual cases of the hydration of nitriles in the presence of hydrogen halides the reaction mechanism is more complex than those given above. The addition of water may proceed simultaneously, for example, by two or three mechanisms.

In each stepwise reaction mechanism there are at least two stages: (1) reaction of the nitrile with hydrogen chloride, and (2) reaction with the nucleophilic hydroxy-compound. To decide which is the rate-determining step, the influence of substituents in benzonitrile on the rate of formation of the corresponding benzimidic acid hydrochlorides has been studied [35]. The activating effect of the substituents on the rate of reaction decreases in the series:

(1) *p*-substituents: $NO_2 > COOH > Br, Cl > CH_3 > H \gg \gg OCH_3$;

(2) $p\text{-}NO_2 > m\text{-}NO_2 \gg o\text{-}NO_2$.

The more electronegative the *p*-substituent, the more readily, as a rule, is the nitrile hydrated in the presence of the hydrogen chloride. Since the inductive effect and the effect of conjugation of electronegative substituents in benzonitrile reduce the electron density at the nitrile carbon atom, the rate-determining step in the reaction of nitriles with hydrogen chloride and hydroxy-compounds is the nucleophilic attack by water. In one case, however, this rule is not obeyed: *p*-tolunitrile has an electropositive substituent but stands above benzonitrile in the above series. The comparative ease with which *p*-tolunitrile is hydrated is apparently due to the activating effect of the *p*-methyl substituent on the first reaction step (reaction of the nitrile with hydrogen chloride). The presence of the electropositive substituent in the tolunitrile molecule causes additional displacement of electrons towards the nitrogen (the dipole moment of *p*-tolunitrile is 4.37 D, against 4.08 D for benzonitrile [117]) and so facilitates its nucleophilic reactions. Thus in the case of *p*-tolunitrile the rate of formation of the imidic acid hydrochloride is determined both by the reaction with the nucleophilic reagent and by the reaction of the nitrile with the hydrogen chloride. The reaction of *p*-tolunitrile with hydrogen chloride in the absence of water [35] supports this conclusion: it readily forms the chloroimonium chloride, while under the same conditions benzonitrile does not. *p*-Methoxybenzonitrile forms the chloroimonium chloride even more readily than *p*-tolunitrile, even in the presence of water, but because of the electropositive methoxy-group, the nucleophilic attack is completely suppressed, and *p*-methoxybenzimidic acid hydrochloride is not produced.

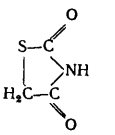
3. Reaction of alkyl thiocyanates with hydrogen chloride and water. Organic thiocyanates often react in the same way as nitriles. Treatment of methyl, ethyl, *n*-propyl, and *n*-butyl thiocyanates with hydrogen chloride and water produces the corresponding *S*-alkyl esters of monothiocarbamic acid in moderate yields [118]:

$$RSCN + H_2O \xrightarrow{HCl} RSC\begin{matrix}O\\NH_2\end{matrix}.$$

The comparatively slow hydration of alkyl thiocyanates is due to the presence in the SCN group of the sulphur atom, which has unshared electron pairs and by conjugation increases the electron density of the thiocyanate carbon atom, so hindering nucleophilic attack on this atom by a water molecule.

Heating methyl thiocyanoacetate with hydrochloric acid produces 2,4-dioxothiazolidine [119]:

$$NCSCH_2COOCH_3 \xrightarrow{HCl,\ H_2O}$$

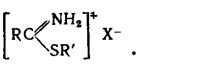


B. Reactions with Alcohols

1. Preparation of imidate hydrohalides. Boiling a mixture of a nitrile, alcohol, and water with strong acids produces esters [120], and these are also obtained by passing hydrogen chloride into hot mixtures of nitriles, alcohols, and water [121]. In an anhydrous medium the reaction between nitriles, alcohol, and hydrogen chloride (the so-called Pinner synthesis [122]) produces imidate hydrochlorides (imino-ether hydrochlorides): [8,123]

$$RCN + R'OH + HCl \rightarrow \left[RC\begin{matrix}NH_2\\OR'\end{matrix}\right]^+ Cl^-$$

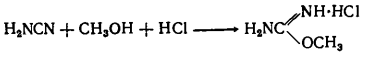
Under the same conditions nitriles, mercaptans, and hydrogen halides produce thioimidate hydrohalides:



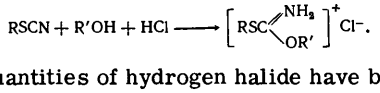
Imidate hydrochlorides, unlike amide hydrochlorides, are well known in organic chemistry. The preparation and chemical properties of imidates have been described in recent detailed reviews [17,122] covering the literature up to 1959, and we shall therefore consider here only matter outside the scope of these reviews and data which have appeared only after the date of submission of Roger and Neilson's review [122].

Although three reactants participate in the formation of imidate hydrohalides, it is usually presented as a single-stage reaction [17,122], but the mechanism of the reaction of nitriles and hydrogen halides with alcohols is close to the mechanism of their reaction with water. The imidate hydrohalides are formed by way of the corresponding halogenoimonium halides [124] and also directly from unstable reaction products of nitriles and hydrogen halides with alcohols. The halogenoimonium halide mechanism is also confirmed by the treatment of acetochloroimonium chloride [32], bromoacetochloroimonium chloride, and bromoacetobromoimonium bromide [34] with alcohols, when the corresponding imidate salts are obtained.

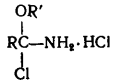
Imidate hydrochlorides are formed not only from nitriles, but also from other compounds containing the cyano-group, when treated with alcohols and hydrogen chloride. Cyanamide, methanol, and hydrogen chloride give methylisourea hydrochloride [125]:



Organic thiocyanates react similarly [126]:



Various quantities of hydrogen halide have been used in the preparation of imidates. In his first study of imidates Pinner [8] gave the following structure for the reaction products of nitriles, alcohols, and hydrogen chloride:



When dried, these split out one molecule of hydrogen chloride, leaving the imidate hydrochloride. On this basis, in his early work [8,127] on the preparation of imidate salts Pinner used the nitrile, alcohol, and hydrogen chloride in the ratio 1:1:2, but later he apparently realised that the imidate group usually combines with only one hydrogen chloride molecule, and in his monograph [123] he gave the optimum reactant ratio as 1:1:1. Up to the present this ratio of 1:1:1 has very frequently been used in the production of imidate salts, or a slight excess (10–25%) of hydrogen chloride is used [128–130]. However, as in the preparation of amide hydrochlorides (see above), an excess of hydrogen chloride accelerates the reaction, and therefore, when free hydrogen chloride does not cause decomposition of the resulting imidate hydrochloride, it is useful to saturate the reaction mixture with hydrogen chloride [131–136]. The use of a large excess of hydrogen halide is particularly effective when nitriles of low electrophilic reactivity are reacted with alcohols. There are particular cases [124] when the reaction product can only be obtained in a pure state by using a reactant ratio of 1:1:2; as will be shown below, this ratio is not due to addition of two hydrogen chloride molecules to the imidate, but is necessary because the intermediate reaction product is sometimes the corresponding chloroimonium chloride.

The compound 6-methoxy-2-naphthimino-ether dihydrochloride was prepared in 1947.[137] The formation of this imidate with two molecules of hydrogen chloride can be explained either by one of the HCl molecules adding to the oxygen of the methoxy-group, or by the imidate salt having the HCl_2^- anion.

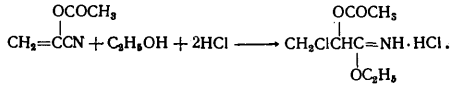
It has recently been suggested that hydrogen bromide or iodide be used to accelerate imidate salt formation and increase the yield of product [138].

Ethyl ethoxycarbonylacetimidate hydrochloride has been prepared from ethyl cyanoacetate and ethanol in the presence of hydrogen chloride formed *in situ* from equimolar quantities of thionyl chloride and water [139].

In addition to the solvents previously used [122], CCl_4 has also been employed as reaction medium for the preparation of imidate hydrohalides [140]. When imidate salts are to be prepared from nitriles which are insoluble in the usual organic solvents, the reaction can be carried out in suspension [133,141]. In the preparation of the imidate salt from β-cyanoethyl *p*-toluenesulphonate a saturated solution of hydrogen chloride in absolute alcohol was shaken at room temperature with the solid nitrile until a homogeneous solution was obtained [142].

In the preparation of the overwhelming majority of imidate salts, the order of addition of the nitrile, alcohol, and hydrogen halide to the reaction mixture is immaterial; usually the nitrile and alcohol are mixed with an inert organic solvent, into which the hydrogen halide is passed at ~0°. In individual cases other procedures have proved convenient. To prevent side reactions in the preparation of the imidic acid hydrochloride derived from ethyl β-chlorolactate acid, hydrogen chloride is passed into the alcohol and then the nitrile is added while continuing the addition of hydrogen chloride [143].

Imidate hydrochlorides are used in the preparation of certain polymerisable acrylates [144]. When hydrogen chloride is passed through a mixture of alcohol and an αβ-unsaturated nitrile, β-chloroimidate hydrochlorides are obtained [142,145], for example [144]:

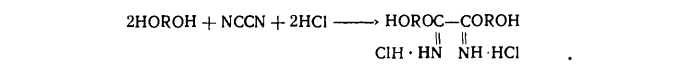


Hydrolysis of the imidate hydrochlorides produces esters of β-chlorocarboxylic acids, which in the presence of dehydrohalogenation agents are converted into esters of αβ-unsaturated acids.

Imidate hydrochlorides derived from dibasic aliphatic acids can be used as additives, *e.g.* for food products and synthetic polymers, to prevent the catalytic action of metals on the organic materials; they inhibit, for example, their autoxidation [146].

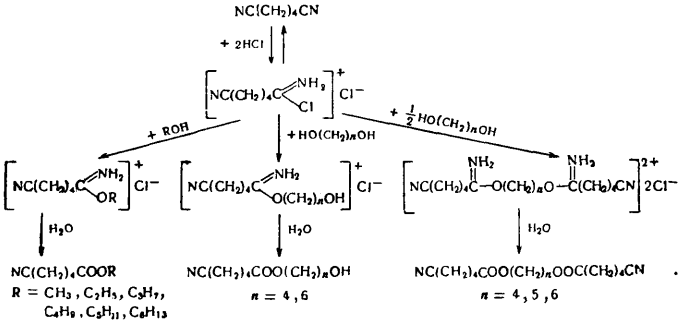
2. New syntheses from dinitriles. A large number of diimidate salts obtained from dinitriles and monohydric alcohols or mononitriles and glycols have been described [122]. Woodburn and coworkers [147] have studied the reaction of cyanogen with hydrogen chloride and certain

glycols; diimidate hydrochlorides were prepared from propane-1,2-diol, propane-1,3-diol, and butane-2,3-diol:

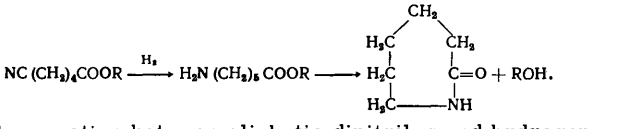


In most other reported reactions between dinitriles, glycols, and hydrogen chloride, however, mixtures of unidentified imidate salts were obtained [148].

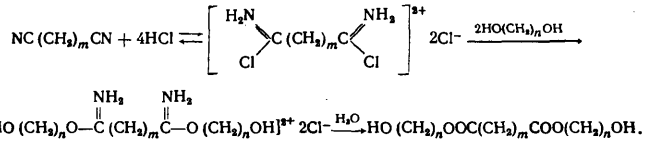
In 1959 Zil'berman and Kulikova showed [124,149] that for successful preparation of individual compounds from certain dinitriles, glycols, and hydrogen chloride, the hydrochlorination of the dinitrile and the reaction of the product with the alcohol must be carried out separately, *i.e.* the dinitrile should first be treated with the calculated amount of hydrogen chloride, and then the alcohol added after a definite time. This procedure gave a number of interesting compounds from adiponitrile, which, because of the selective reactivity of one of its cyano-groups, gave the following series of reactions [124,149-152]:



The yields of alkyl δ-cyanovalerates [124], ω-hydroxyalkyl δ-cyanovalerates, and alkylene (from alkanediols) di(δ-cyanovalerates) [152] were close to theoretical. Earlier procedures for the preparation of alkyl δ-cyanovalerimidates [129,153,154] gave the desired products in low yields and in admixture with a molecular compound formed between the alkyl imidate hydrochloride and adiponitrile [124]. It is important to obtain alkyl δ-cyanovalerates in high yields because they are starting materials for the production of caprolactam [155]:

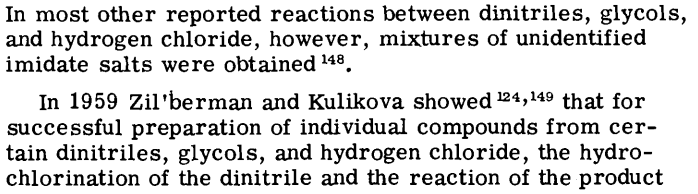


The reaction between aliphatic dinitriles and hydrogen chloride in a molar ratio of at least 1:4 in the cold produces solid products, apparently di(chloroimonium) dichlorides, which precipitate if insufficient solvent is used. These were treated with twice the molar quantity of glycols without separation from the reaction mixture. The resulting diimidate hydrochlorides when treated with an excess of water gave di(ω-hydroxyalkyl) esters of dibasic acids:



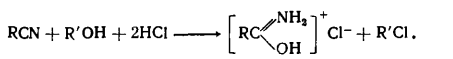
This reaction has been carried out with such glycols as butane-1,4-diol, pentane-1,5-diol, and hexane-1,6-diol. [151,152,156] Di(ω-hydroxyalkyl) esters were not obtained from ethyleneglycol or *p*-xylyleneglycol, since under the reaction conditions the hydroxy-groups of these glycols are partly replaced by chlorine [151,157].

The reaction between dinitriles, hydrogen chloride, and glycols in the ratio $1:n:1$, where $n \geqslant 4$, has been used to prepare polyimidate hydrochlorides, which on hydrolysis give polyesters [151,157-160]:



Polyesters of molecular weight 650-1650 have been obtained from the dinitriles of adipic, azelaic, sebacic, and *p*-phenylenediacetic acids and ethyleneglycol, butane-1,4-diol, diethyleneglycol, and *p*-xylyleneglycol. In addition to nitrile and hydroxy-groups, chlorine was also found as an end-group in some cases. Increasing the reaction temperature from 0 to 20° considerably increased the chlorine content of the polyester and lowered its molecular weight. Excess of glycol or dinitrile also reduces the molecular weight of the final polyester. Unlike the pasty polycondensation products obtained from dibasic acids and glycols, which are slightly coloured, the polyesters obtained from polyimidate hydrochlorides are often white powders, because of the mild conditions under which they are prepared.

3. Preparation of amides and their hydrochlorides. The reaction products obtained from nitriles, hydrogen chloride, and tertiary alcohols remained unidentified for a long time [161,162]. Zil'berman and Sladkov showed [163] that many nitriles react in the cold with hydrogen chloride and tertiary alcohols to yield not imidate ester salts, but imidic acid hydrochlorides (amide hydrochlorides) and tertiary alkyl chlorides:

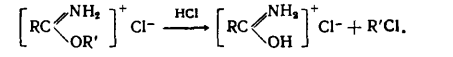


Nitriles with strongly electronegative substituents in the α-position give the free amides and not the amide hydrochlorides.

Several mechanisms are possible for the formation of amides and their hydrochlorides in this reaction [163]; for example, tertiary alcohols react with hydrogen chloride to give tertiary alkyl chlorides and water, and the latter may be expected to react with the nitrile-HCl reaction products to give imidic acid hydrochlorides.

According to a second mechanism, the initial nitrile-hydrogen chloride reaction products, particularly the chloroimonium chlorides, which have a high electrophilic reactivity, dehydrate the tertiary alcohols, the liberated water reacting with the nitrile and HCl in the normal way.

In a third possible mechanism, the nitriles and hydrogen chloride react initially with the tertiary alcohols in the same way as with primary and secondary alcohols, *i.e.* to form imidate hydrochlorides, which then undergo the Pinner rearrangement [8,122,164]:



Normally this last reaction is carried out by heating the imidate salts in the absence of free hydrogen chloride, and the products are then the free amides and not the amide hydrochlorides. The basic literature on this reaction has

been reviewed [122], and we only mention here that this splitting of imidate hydrochlorides has been shown to involve a bimolecular nucleophilic substitution reaction (S_N2) [165,166], although in some cases the reaction follows an S_N1 mechanism [167,168]. With increasing electron-donating properties of the alkyl radical, a carbon atom of which undergoes substitution in such reactions, the rate of reaction first decreases (S_N2 mechanism) and then increases (S_N1 mechanism) [169], and it may therefore be assumed that when the alkyl radical R′ is the strongly electropositive tertiary alkyl group, the splitting will proceed by an S_N1 mechanism. This also explains the ease with which tertiary alkyl imidate hydrochlorides are split, even at the moment of their formation.

Experiments on the hydration of a number of substituted benzonitriles using hydrogen chloride and dimethylethylmethanol aimed at establishing whether the reaction of the nitrile with the hydrogen chloride or the hydration is the rate-determining step gave the same results as in the study of the mechanism of the reaction between nitriles, HCl, and water [35] (see p. 621).

Amides or their hydrochlorides are also sometimes obtained in the reaction of nitriles and hydrogen chloride with primary or secondary alcohols; this was observed, for example, in attempts to prepare primary alkyl imidate hydrochlorides from trichloro-, dichloro-, tribromo-, nitro- and dichloronitro-acetonitrile [162,170-172]. Chloroacetonitrile, which has only one electronegative chlorine atom in the α-position, gives the imidate hydrochloride on reaction with hydrogen chloride and methanol [171]; the use of a secondary alcohol (cyclohexanol) in this reaction gives the imidate or amide hydrochloride, depending on the reaction conditions [163]. α-Phenylaminoacetonitrile gives the amide instead of the imidate [173].

Unlike tertiary alkanols, tertiary alkyl mercaptans react normally with nitriles and HCl, to form the corresponding thioimidate hydrochlorides [161,174].

The scission of imidate salts into amides and alkyl halides may be used preparatively [122]; it has been used for the production of oligomeric amides from adipic acid and hexamethylenediamine [175]:

$$NC(CH_2)_5NHCO(CH_2)_4CONH(CH_2)_5CN \xrightarrow{2C_2H_5OH,2HCl}$$

$$\rightarrow ClH\cdot HNC(OC_2H_5)(CH_2)_5NHCO(CH_2)_4CONH(CH_2)_5C(OC_2H_5)NH\cdot HCl \xrightarrow{-2C_2H_5Cl}$$

$$\rightarrow H_2NOC(CH_2)_5NHCO(CH_2)_4CONH(CH_2)_5CONH_2.$$

C. Reactions with Organic Acids

Treatment of mixtures of nitriles and carboxylic acids with hydrogen halides gives amide hydrochlorides and the acid anhydrides or chlorides [176-180]:

$$RCN + HCl + 2R'COOH \rightarrow \left[RC(NH_2)(OH)\right]^+ Cl^- + (R'CO)_2O,$$

$$RCN + 2HCl + R'COOH \rightarrow \left[RC(NH_2)(OH)\right]^+ Cl^- + R'COCl.$$

A similar reaction is obtained with hydrocyanic acid, hydrogen chloride, and carboxylic acids [181].

An excess of hydrogen halide accelerates the formation of the amide salt [179]. The reaction proceeds in any solvent, polar or non-polar. Under otherwise the same conditions, the basicity of the solvent greatly affects the yield of imidic acid hydrochloride. It must be supposed that the reaction of the HCl with solvents having nucleophilic properties competes with the main reaction and noticeably reduces its rate [180]. However, as in reactions of nitriles and hydrogen chloride with other nucleophilic reagents, the determining factor in the choice of solvent is not its acid-base properties, but the solubility of the reaction components in it.

An excess of the hydrating acid may be used as solvent, and this is particularly useful when the nitrile is poorly soluble in other organic solvents, *e.g.* with *p*-nitrobenzonitrile and *p*-cyanobenzoic acid [180].

Hydration of the cyano-group under the influence of hydrogen bromide and acetic acid or acetic anhydride is evidently the basis of the production of caprolactam from ε-alkoxycapronitriles by way of ε-bromocapramide [182].

Study of the liquid reaction products of acetonitrile, hydrogen chloride, and butyric acid has shown that the acid is converted partly into the anhydride and partly into the acid chloride.

These data and the study of the reaction of a number of substituted benzonitriles with hydrogen chloride and acetic acid [35] show the general relationship between the hydration of nitriles using carboxylic acids and the other reactions described above between nitriles, nucleophilic reagents, and hydrogen halides; we may assume that the initial stages in all these reactions are the same, the reaction products of nitriles and hydrogen halides with acids being converted into the unstable isoimide salts [179]. Since these should possess considerable acylating activity, they react with the acids to form imidic acid hydrochlorides and the acid anhydrides or halides:

$$RC(=\overset{+}{N}H_2Cl^-)(-O-C(H)(OCOR')-O-CR'=O) \rightarrow \left[RC(NH_2)(OH)\right]^+ Cl^- + (R'CO)_2O.$$

N-substituted imidoyl chlorides react with carboxylic acids by an analogous mechanism [183].

The reactive imidoyl derivatives (isoimides) of trichloroacetic acid have been widely used in recent years as reagents for the selective esterification of phosphoric acid derivatives [184-188]. The isoimides are also intermediates in other acylation reactions [189,190].

Nitriles react with thio-acids in the presence of hydrogen chloride by the mechanism [191] given above for carboxylic acids:

$$RCN + R'COSH \rightleftharpoons RC(=NH)(SCR'=O) \xrightleftharpoons{HCl} RCSNH_2 + R'COCl.$$

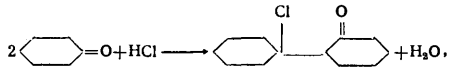
In the presence of hydrogen chloride nitriles react with thio-amides in ether in the cold [192] or in dimethylformamide on heating [193] in the same way as with acids:

$$RCN + R'CSNH_2 \rightleftharpoons RC(=NH)(S-CR'=NH) \rightleftharpoons RC(NH_2)(=S) + R'CN.$$

This reaction has been proposed for the preparation of thio-amides [193].

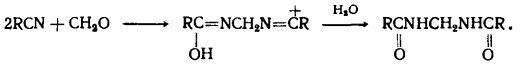
D. Reactions with Carbonyl Compounds

Aldehydes and ketones react with nitriles and hydrogen chloride in the cold to give imidic acid hydrochlorides [194,195] or compounds with a new carbon–nitrogen bond [1]. A necessary condition for the formation of imidic acid hydrochlorides is the ability of the carbonyl compound to undergo autocondensation with the splitting out of water [196]. For example, when a mixture of a nitrile and cyclohexanone is treated with hydrogen chloride, the ketone condenses with itself:



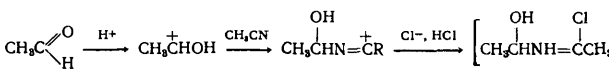
and the liberated water then reacts with the nitrile and hydrogen chloride in the normal way.

In a second process the nitrile and an aldehyde, taken in the molar ratio 2 : 1, react in the presence of hydrogen chloride to form a solvated carbonium ion, which with water gives a bisamide:



The preparation of bisamides from nitriles and aldehydes has been reviewed [1]. In a recent work [196] benzonitrile and hydrogen chloride were reacted with acetaldehyde and benzaldehyde to obtain ethylidene- and benzylidene-bisbenzamide. A bisamide is obtained from *p*-nitrobenzaldehyde, hydrogen cyanide, and hydrogen chloride [72].

The reaction between acetonitrile, acetaldehyde, and hydrogen chloride did not give either a primary amide salt or a bisamide [197]. The salt obtained in the absence of water contains the initial reactants in the ratio 1 : 1 : 2; [196] its chemical properties indicate it to be an *N*-substituted chloroimonium chloride, and the following mechanism has been put forward for its formation:



E. Structure and Chemical Properties of Amide Hydrohalides

Amide hydrohalides were earlier prepared by reacting the corresponding amides with hydrogen halides in inert organic solvents in the cold [198–201]. However, most *N*-unsubstituted amides are insoluble in organic solvents, and this method can therefore only be used to obtain hydrohalides of some of the simplest aliphatic and aromatic amides. Until recently there were almost no published data on the properties of amide hydrohalides, apparently because adequate general methods for their preparation were unavailable. Since, as described above, treatment of nitriles with various hydroxy-compounds can easily yield various amide hydrochlorides, the study of their structure and chemical properties is now of interest.

1. Structure of amide hydrohalides. Carboxylic acid amide salts have one of the following structures:

(G) (H)

The question of which is the actual structure is related to the question of the nucleophilic centre of the amides.

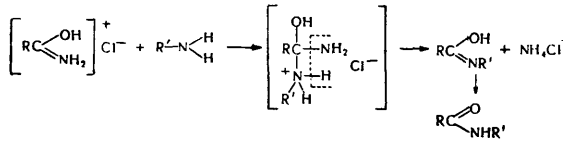
Davidson [202] reviewed a number of reactions between amides and nucleophilic reagents (acids, anhydrides, acid chlorides and amides, and alkyl halides), and concluded that the oxygen atom is the nucleophilic centre of amides. Nuclear magnetic resonance spectra of amides in the pure state and in solution in water, deuterium oxide, and hydrogen and deutero-acids indicate [203–204] that the products are protonated predominantly on the oxygen. Kinetic data on the hydrolysis of amides in concentrated acids [205] and the basicity of amides [206,207] are in accord with the view that it is the amide oxygen and not nitrogen to which the proton attaches. This *N*-protonated imidic acid structure of amide hydrochlorides finds confirmation in the infra-red and nuclear magnetic resonance spectra of the complexes of amides with boron halides and titanium halides [208], the infra-red spectrum of the dimethylacetamide–iodine complex [209], and in other studies [210–213].

In the comparatively old literature [214] amide salts are also given the structural formula (G), and this is still sometimes preferred [215–217]; for example, Spinner [216] attempted to base structure (G) on his infra-red spectroscopic studies. In the spectrum of acetamide hydrochloride he found a band with ν_{max} = 1695 cm^{-1}, which coincides with $\nu_{C=O}$ for acetamide, and he therefore concluded that the proton is attached to the amide nitrogen. However, it has been demonstrated [218] that the presence of this band is due to free amide impurity, and not to the amide hydrochloride.

Comparison of the frequencies observed with acetic, δ-cyanovaleric, adipic, and benzoic acid amide hydrochlorides indicates that the *N*-protonated imidic acid group has the following characteristic frequencies [218]: (*a*) three bands in the 3500–3000 cm^{-1} region, of which the one of shortest wavelength corresponds to ν_{O-H} (this band is not always resolved and is often observed as a shoulder); $\nu_{as}NH_2$ is at 3250 cm^{-1} and νNH_2 at 3160–3200 cm^{-1}; (*b*) a single band in the 1600–1700 cm^{-1} region, the 1650–1660 cm^{-1} frequency corresponding to vibrations of the C=N group.

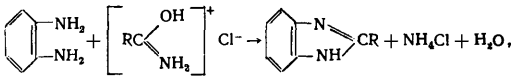
2. Reactions of amide hydrochlorides. Acid amides are weak acylating agents. Fatty acid amides do not react with aniline even at 100°: only on boiling are anilides produced in small amounts [219]. Formylation of amines with formamide proceeds slightly more readily [220], but in practice, because of their comparatively low reactivity in the absence of catalysts, amides are rarely used for acylation [221]. The aminolysis of amides is considerably accelerated in the presence of acid catalysts [222–224]. Good yields of *N*-substituted amides have been obtained in the reaction of amides with amine hydrohalides [225–227]. Jaunin has suggested [223] that the function of the acid catalysts is to add a proton to the amide oxygen to form an imidic acid structure, and this increases the electrophilic reactivity of the carbon atom.

In accordance with these results, the reaction between amines and amide hydrochlorides, which already have the imidic acid hydrochloride structure, would be expected to give a very smooth acylation reaction by the mechanism

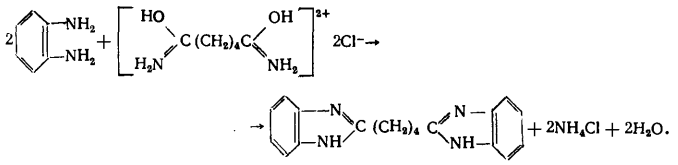


When aniline[228,229] or other aromatic amine[230] was heated with acetimidic acid hydrochloride, δ-cyanovalerimidic acid hydrochloride, and benzimidic acid hydrochloride at 160°–170°, the *N*-acylated amines were sometimes obtained in high yield. Aliphatic amines are acylated with considerably more difficulty than aromatic amines. In the benzoylation of hexamethylenediamine with benzimidic acid hydrochloride, the diamine hydrochloride had to be used in place of the free amine[230].

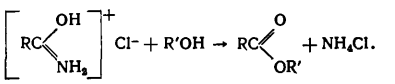
Heating imidic acid hydrochlorides with *o*-phenylenediamine at 140°–190° produces benzoimidazoles in high yields:



where R = CH_3, $(CH_2)_4CN$, C_6H_5;

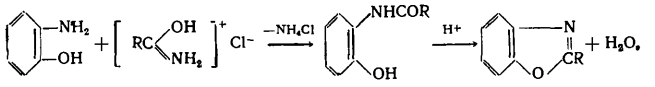


These imidic acid hydrochlorides react at 100°–170° with alcohols (n-butanol, ethylene glycol) and phenols (phenol, *o*- and *m*-cresol, resorcinol monomethyl ether, *p*-nitrophenol) to form the corresponding esters[231]:



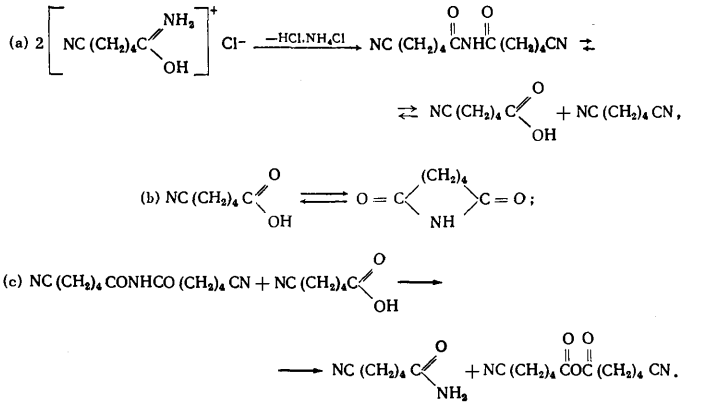
The aliphatic alcohol esters were obtained in 61–75% yields, and the phenol esters in somewhat lower yields. In some cases, *e.g.* in the preparation of ethylene and *p*-phenylene di(δ-cyanovalerates) (from ethylene glycol and hydroquinone), acylation with the imidic acid hydrochloride is more convenient than earlier methods for the preparation of esters.

Two products were obtained by heating *o*-aminophenol with imidic acid hydrochlorides[230], the *o*-hydroxyanilides or the 2-substituted benzoxazoles; the former were the main product if the reaction were carried out under reflux, and the latter if the water of reaction were removed as it formed. Heating the *o*-hydroxyanilides with catalytic amounts of acids converted them into the benzoxazoles; the former are apparently intermediates in the preparation of benzoxazoles from *o*-aminophenol and imidic acid hydrochlorides:



where R = CH_3, $(CH_2)_4CN$ or C_6H_5. In the single-stage production of benzoxazoles (without intermediate separation of the *o*-hydroxyanilides from the reaction mixture) the unreacted imidic acid hydrochloride or the ammonium chloride may act as the acid catalyst. The presence of the acid catalyst should promote lactimisation of the amide group of the *o*-hydroxyanilide; this increases the reactivity of the amide group and the intramolecular interaction of the functional groups thus becomes possible.

Thermal decomposition of imidic acid hydrochlorides gives the acid, acid halide, nitrile, and a secondary amide[199,200]. The mechanism of the decomposition was investigated by studying the pyrolysis products (180°) from δ-cyanovalerimidic acid hydrochloride[232]; hydrogen chloride, ammonium chloride, di(δ-cyanovaleramide), δ-cyanovaleric acid, adiponitrile, adipamide, δ-cyanovaleramide and, apparently, δ-cyanovaleric anhydride were found. The following mechanism based on these results was suggested:



The pyrolysis of other imidic acid hydrochlorides shows the same features. This reaction may be used for the preparation of secondary amides[232]. The reaction between formamide hydrochloride and *m*-nitrobenzaldehyde gives *m*-nitrobenzylidenebisformamide[72].

The thermal decomposition of amide hydrochlorides thus gives products which are formed from the free amides only at considerably higher temperatures[224,233,234]. This difference in the behaviour of amides and their hydrochlorides is apparently due to the latter existing in the more reactive imidic acid form.

F. Selective Reactivity of One Cyano-Group in Adiponitrile

Several instances of the selective reactivity of one of the two cyano-groups of adiponitrile with hydrogen chloride and nucleophilic reagents (water, primary alcohols, and diprimary glycols) have been described above. Aliphatic dinitriles with a hydrocarbon chain shorter or longer than adiponitrile do not exhibit this selective reactivity of one cyano-group[111]. The different reactivities of the cyano-groups in adiponitrile and such compounds as, for example, δ-cyanovalerimidic acid hydrochloride and alkyl δ-cyanovalerimidate hydrochlorides are apparently due to the particular molecular configuration of adipic acid derivatives with the formation of cyclic systems[111,235].

One cyano-group of αα′α′-tetrachloroadiponitrile could not be selectively hydrated in the presence of hydrogen chloride; the mutual repulsion between the chlorine atoms and the nitrile nitrogen apparently hinders the formation of cyclic systems during the hydrochlorination and hydration. However, treatment of β-methyladiponitrile with HCl and water in the ratio 1 : 2 : 1 with subsequent hydrolysis gave a mixture of nitrile-amides in high yield. The introduction of the β-methyl substituent into adiponitrile apparently restricts its internal rotation, so that "convoluted" configurations are more easily formed and the reacting groups approach each other more closely[235].

With adiponitrile itself, the selective reactions of one cyano-group with hydrogen chloride take place under rigorously defined conditions. The interaction between the solvent, dinitrile, and hydrogen chloride has a large influence on the reactivity of adiponitrile. In the reaction

between adiponitrile, hydrogen chloride, and water (in the ratio 1:2:1) at 0° selective reactivity is found in isopropyl, ethyl or butyl ether as solvent, but not in solvents which are more basic (tetrahydrofuran, tetrahydropyran or dioxane) or less basic (benzyl ether, β-chloroethyl ether, carbon tetrachloride, toluene, benzene, dichloroethane, or chloroform) than the above ethers [235]. At room temperature there is no selective reaction of one cyano-group of adiponitrile with hydrogen chloride and water, even in ether [235].

There is no selective reaction of one cyano-group of adiponitrile with hydrogen chloride and such nucleophilic reagents as acetic acid [179] and alkanethiols [235], apparently because of the high reactivity of the hydrogen atom of mercapto- and carboxy-groups, which readily interact with the cyano-group and so destroy the unstable intramolecular ring of the reacting molecule; this straightens out, and both adiponitrile cyano-groups become energetically equivalent.

A non-equivalent reactivity of the two cyano-groups of adiponitrile is also sometimes found in the absence of hydrogen chloride. The formation of the unsymmetrical amidoxime has been described [236]:

$$NC(CH_2)_4CN + NH_2OH \longrightarrow NC(CH_2)_4C\begin{matrix}NOH\\NH_2\end{matrix}.$$

Hydrogenation of adiponitrile can produce ε-aminocapronitrile in high yield [237-240]:

$$NC(CH_2)_4CN + 2H_2 \longrightarrow NC(CH_2)_5NH_2.$$

G. Reactions with Amines

The most general method for the preparation of amidines from nitriles is based on the reaction between imidate hydrohalides and amines [241]. Many attempts have been made to obtain amidines directly from nitriles without the intermediate stage of imidate salt formation, but the direct addition of amines only proceeds readily with nitriles having two or three α-halogen atoms, *e.g.* trichloroacetonitrile and trifluoroacetonitrile [242-248]:

$$CF_3CN + NH_3 \longrightarrow CF_3C\begin{matrix}NH\\NH_2\end{matrix}.$$

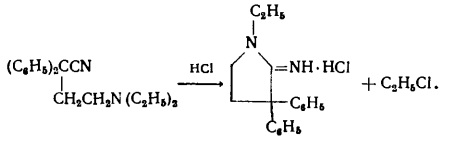
The amination of α-halogeno-nitriles is accelerated in the presence of hydrogen halides (in practice, amine hydrohalides) [242]. Primary and secondary aliphatic amines add to hydrogen cyanide to form unstable formamidines, which with water are converted into *N*-substituted formamides [249,250].

When nitriles free of electronegative substituents react with ammonia or amines in the presence of the base hydrohalide, amidines are generally not formed or are formed in only moderate yields. The rather sparse literature on these reactions has been given in a review on the chemistry of amidines [241].

Amidine hydrohalides are usually prepared from nitriles and amine hydrohalides at 170°–200° or above [241,251,252]. The thermally unstable nitrile–hydrogen halide compounds cannot participate in the reaction under these conditions, and compounds of the halogenoimonium halide type easily lose hydrogen halide in the presence of amines. The activating effect of hydrogen halides in the preparation of amidines from nitriles may be explained by a mechanism similar to those already given (see p. 619).

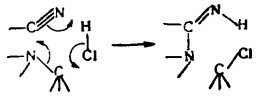
One case has been described in which a chloroimonium chloride reacts with an amine in the cold [32]: at -16° acetonitrile dihydrochloride and dimethylaniline yield α-tri(dimethylaminophenyl)ethane.

The amidine group is formed by intramolecular condensation when various γ-, δ-, and ε-amino-nitriles are heated with hydrogen chloride or hydrochloric acid [253-257]; for example, at 275° αα-diphenyl-γ-diethylaminobutyronitrile gives 1-ethyl-2-imino-3,3-diphenylpyrrolidine hydrochloride:



Certain 2-iminopyridine and 2-iminohexamethyleneimine hydrochlorides have been prepared analogously. Hydrolysis of 2-iminopolymethyleneimines sometimes yields the corresponding lactams.

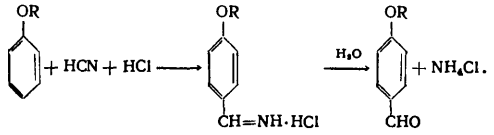
Since the 2-iminohexamethyleneimines are obtained at high temperatures, it is difficult to see how the unstable hydrochlorides of the initial nitriles can be intermediates [257]. A more probable interpretation of the intramolecular reaction between the functional groups is cyclic electron transfer:



H. The Gattermann Reaction

The Gattermann and Hoesch (Houben–Hoesch) reactions differ from the reactions between nitriles, hydrogen halides, and nucleophilic reagents described above, in that new carbon–carbon bonds are formed.

In the Gattermann reaction [258] an aromatic compound reacts in an inert solvent in the cold with hydrogen chloride and hydrocyanic acid to yield an aldimine hydrochloride, which on hydrolysis is converted to the aldehyde:



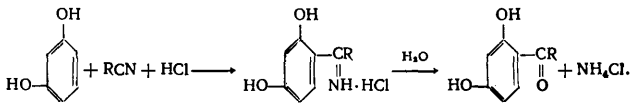
According to Gattermann, hydrogen cyanide and hydrogen chloride react under the above conditions to produce formimidoyl chloride HC(:NH)Cl, but as in the case of hydrochlorination products of nitriles, hydrogen cyanide monohydrochloride does not apparently exist (see p. 619).

Hinkel and coworkers [259] suggested that in the Gattermann synthesis the hydrogen cyanide and hydrogen chloride react as chloromethyleneformamidine (2HCN.HCl), so that the reaction product is not an aldimine hydrochloride, but an arylmethyleneformamidine hydrochloride RCH=NCH=NH.HCl. Later [70] Hinkel showed that this view of the intermediates in the Gattermann reaction is incorrect, and he put forward [260] a new mechanism, according to which the aromatic compound reacts with the sesquichloride 2HCN.3HCl; however, this also is not supported by the experimental data on the Gattermann synthesis of aldehydes, and contradicts more recent views on the structure of hydrogen cyanide hydrochlorides [78].

Hydrogen cyanide dihydrochloride (a compound of the chloroimonium chloride type) is unknown, or at least is not formed in the Gattermann reaction, and the only remaining possibility is that stable hydrogen cyanide hydrochlorides are not intermediates when the reaction is carried out in the normal manner (by passing hydrogen chloride into a mixture of the aromatic compound, hydrogen cyanide, and $ZnCl_2$ or $AlCl_3$ as catalyst). The reaction apparently involves the formation of unstable complexes between hydrogen chloride, hydrogen cyanide, and the catalyst, with a reduced electron density at the cyano-carbon atom. Analogous mechanisms for reactions of nitriles are given above. The Gattermann synthesis has been reviewed [261,262].

J. The Hoesch Reaction

The first studies describing the synthesis of ketones by the Hoersch reaction were developments of the Gattermann reaction. The Hoesch ketone synthesis [263] is based on the reaction, in a solvent, between a nitrile, hydrogen chloride, and a phenol (usually a polyhydric phenol) to form a ketimine hydrochloride, followed by hydrolysis:



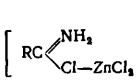
The suggestion [264] that the primary reaction products are imidate hydrochlorides which then rearrange to ketimine hydrochlorides has not been confirmed [265]. Most workers consider that under the conditions of the Hoesch synthesis the nitrile and hydrogen chloride react to form the imidoyl chloride, which then condenses with the phenol [264,266,267]. Zil'berman and Rybakova have put forward [268] new mechanisms for the formation of ketimine hydrochlorides in the Hoesch synthesis, similar to those described above for the reaction of nitriles with hydrogen chloride and hydroxy--compounds.

The utility of the Hoesch synthesis is considerably increased when it is carried out in accordance with these mechanisms [268]. Unlike the usual procedures [266] for preparing ketones by the Hoesch reaction, the reaction between the nitrile and hydrogen chloride and the subsequent electrophilic attack on the phenol are carried out separately. In many cases it has also been found preferable to carry out the reaction not at room temperature, but at 0° (decreasing the temperature increases the stability of the saltlike nitrile hydrohalides [14]). The use of the new procedure has shown that, contrary to published opinion [266], ketimine hydrochlorides can be obtained from aromatic nitriles in yields as high as those obtained with aliphatic nitriles [268]. Diketones have been obtained in high yields from resorcinol and various dinitriles (adiponitrile, pimelonitrile, sebaconitrile, *p*-xylylene dicyanide, etc.) [269], although it had previously been considered [266] that the Hoesch synthesis is of little value for the production of diketones.

Of the more interesting studies of the Hoesch synthesis appearing after Spoerri and Du Bois' review [266], mention may be made of the condensation of resorcinol or its derivatives with trichloroacetonitrile and hydrolysis of the reaction products to the corresponding benzoic acid derivatives [270].

Under the conditions of the Hoesch synthesis, cyanopyridines react with pyrroles and indoles to yield the corresponding ketimines and hence the corresponding ketones [271]. Dihydroisoquinolines have been obtained by condensation of the chlorination products of various amides with isosafrole and methylisoeugenol; the suggested mechanism for this reaction is close to that of the Hoesch synthesis [272].

The most frequently used catalyst in the Hoesch synthesis is zinc chloride [266]; in individual cases ferric chloride [273] or aluminium chloride [274,275] is a more suitable catalyst. The catalytic action of zinc chloride has recently been investigated in more detail [38]. It might have been expected that the catalytic action of zinc chloride on the Hoesch synthesis is manifested through the complexes $RCN.ZnCl_2$ and $(RCN)_2.ZnCl_2$ or the nitrilium salt $[RCNH]^+ZnCl_3^-$, but stable complexes of such structures were tested and found not to react with resorcinol in many cases, particularly at low temperature. It has been suggested that in the presence of zinc chloride the Hoesch synthesis involves the formation of unstable complexes with a covalently-bonded $ZnCl_3$ group, *e.g.*:

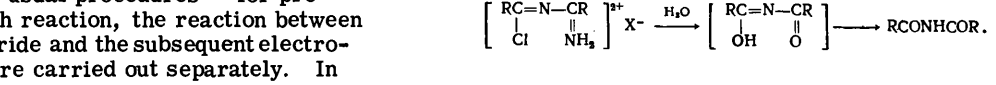


The part played by the zinc chloride in the production of ketimine hydrochlorides from nitriles which under the conditions of the Hoesch synthesis react with hydrogen chloride to form salts of the *N*-alkylideneamidine type [38], is interesting; it was found that in the reaction between resorcinol, hydrogen chloride, and chloroacetonitrile the catalyst acts primarily to prevent dimerisation of the nitrile.

In the presence of $SnCl_4$ and $TiCl_4$, which readily form stable complexes with nitriles, ketimine hydrochlorides are produced only in very low yields [38].

K. Reaction of Dimeric Nitrile Salts (2RCN.*n*HX) with Hydroxy-Compounds

1. Reaction with water. The structures of most of the known dimer salts of composition 2RCN.*n*HX, where *n* is 1 or 3, have been proved by reaction with water:

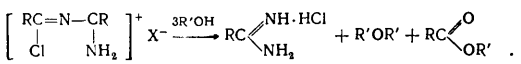


This method for the production of secondary amides was known [59,63] even before Grundmann and coworkers suggested [60] this formula for the dimer salts. The reaction is usually carried out by dissolving the dimer salt in water at room temperature or at 0°. A modified procedure has been used to prepare hexachlorodiacetamide without further hydrolysis of the product at the moment of its formation: a suspension of the trichloroacetonitrile dimer salt in chloroform was shaken with an excess of finely ground ice [60].

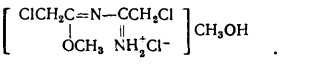
Hydrolysis of the dimer salts derived from chloroacetonitrile and hydrogen bromide yields $\alpha\alpha'$-dichlorodiacetamide having some of the chlorine atoms replaced by bromine. A similar exchange also took place in the reaction of bromoacetonitrile dimer salt with hydrogen chloride [94].

The $\alpha\alpha'$-dichlorodiacetamide obtained from chloroacetonitrile, deuterium chloride, and deuterium oxide contained 1.5 atoms of deuterium. The infra-red spectrum of the deuterated dichlorodiacetamide indicated the presence of N–H, N–D, C–H, and C–D bonds [116].

2. Reaction with alcohols (amidine hydrochloride synthesis). Treatment of dimer salts of composition $2RCN.nHX$ derived from fluoro-, chloro-, and bromo-acetonitrile with primary and secondary alcohols at room temperature causes unsymmetrical scission, with the formation of halogenoacetamidine hydrochlorides, ethers, and esters [34,62,276]:



Methanol reacts anomalously; instead of the chloroacetamidine salt, it gives a compound of empirical formula $2ClCH_2CN.2CH_3OH.HCl$, which with water gave chloroacetamidine hydrochloride. The primary reaction product probably has the constitution

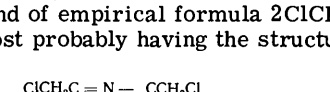


The reaction of the dimer salts with other alcohols apparently also involves a first step in which a labile chlorine atom is replaced by an alkoxy-group, but the resulting intermediates are unstable and cannot therefore be isolated.

The fact that alcoholysis of the dimer salt produces (in addition to the amidine hydrochloride) a mixture of ester and ether, and not an ortho-ester, merits attention. Certain imidate salts also react with alcohols to yield a mixture of ester and ether instead of an ortho-ester [277].

Cyclohexanol reacts with the di(chloroacetonitrile) salt to form a molecular compound of chloroacetamidine hydrochloride with cyclohexanol [34].

3. Reaction with acetic acid. Treatment of the di(chloroacetonitrile) salt with acetic acid in the cold produces a compound of empirical formula $2ClCH_2CN.CH_3COOH.HCl$, most probably having the structure



With water it yields *sym*-dichlorodiacetamide [34].

IV. REDUCTION OF NITRILES IN THE PRESENCE OF HYDROGEN CHLORIDE

According to the data available, the reduction of nitriles in the presence of hydrogen chloride may produce three types of compound: (*i*) aldimines, which on hydrolysis yield aldehydes; (*ii*) acyclic trimerisation products, which give bisamides with water; and (*iii*) amines.

A. Preparation of Aldehydes by the Stephen Method

Nitriles can be reduced in the presence of hydrogen chloride by the Stephen method [278] with stannous chloride; stannous bromide also gives good results. Chromous chloride, vanadium trichloride, and titanium trichloride could not be used as reducing agents in this reaction [279]. The reaction is usually carried out in ether, dioxane, chloroform, ethyl acetate, or other solvent at about room temperature. Aromatic nitriles, as a rule, give good yields of aldimines and hence of aldehydes. Adehydes cannot always be obtained from aliphatic nitriles [280].

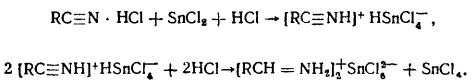
The Stephen reaction has been reviewed [281,282]. After the appearance of these reviews, it was shown that a reaction competing with the reduction of the nitrile to the aldimine is the conversion of the nitrile to the imidate, which takes place under the action of the alcohol formed as a result of scission of the ethyl ether by the hydrogen chloride. At elevated temperatures this process may completely suppress the reduction of the nitrile [283].

The effect of steric hindrance in the reduction of substituted benzonitriles has been investigated [284].

The order in which the various reactants enter into the reaction has not been studied. It must be assumed that, as in other reactions of nitriles in the presence of hydrogen halides, outer and inner complexes of nitriles with hydrogen halides and chloroimonium chlorides are formed in the Stephen synthesis of aldehydes also; Stephen's last study [285] supports this assumption.

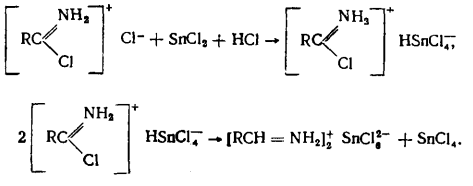
Although earlier the reaction was usually carried out [281] by adding the nitrile to the solution of stannous chloride and hydrogen chloride, according to a modified procedure [285] a solution of the nitrile in the inert solvent is saturated with hydrogen chloride at 0°, and then a solution of stannous chloride and hydrogen chloride in the same solvent is added. The modified Stephen method gives higher yields of aldehydes, presumably because of preliminary reaction between the nitrile and hydrogen chloride at the low temperature.

The mechanism of the Stephen reaction with the intermediate formation of nitrilium salts [282] may be represented as follows:



The aldimine hexachlorostannates very often separate from the reaction mixture as easily crystallising precipitates [281].

If the intermediates are chloroimonium chlorides, the probable mechanism is

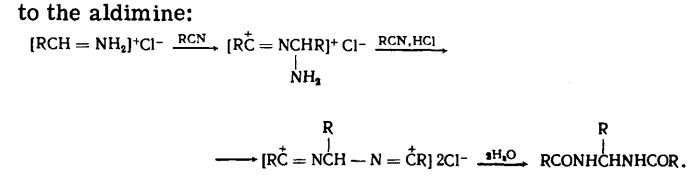


B. Preparation of Bisamides in the Reduction of Nitriles by the Stephen Method

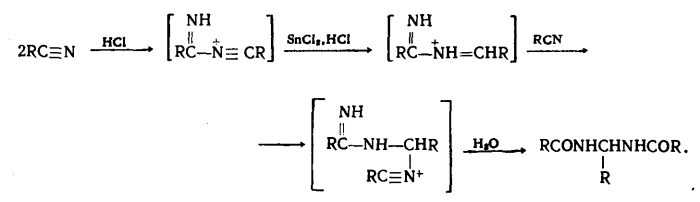
Stephen showed [278] that aliphatic nitriles are reduced to aldimines as readily as aromatic nitriles; however, more recent workers have found [286] that the reduction of lauric acid nitrile by stannous chloride followed by hydrolysis produces not the aldehyde [287], but the *NN'*-alkylidenebisacylamide RCONHCH(R)NHCOR.

Two mechanisms have been suggested for the formation of bisamides in the reduction of nitriles. The intermediate which is hydrolysed to the bisamide may be

formed[286] by the stepwise addition of two nitrile molecules to the aldimine:



According to Meerwein[282], there is first formed a product from two nitrile molecules, similar to the dimer salts of α-halogenoacetonitriles (see p. 618), which is then reduced. The reduction product reacts with a third nitrile molecule to form a salt, which is hydrolysed to the bis-amide:



C. Preparation of Amines

In certain extremely rare cases the reduction of nitriles by the Stephen method does not stop at the aldimine stage, but proceeds further to form primary amines[288]. An analogous effect is observed in the stannous chloride reduction of various heterocyclic *N*-phenylimidoyl chlorides, where the reaction products were not the aldimines expected by Sonn and Müller[289], but secondary amines[290].

Hydrogen chloride also promotes the catalytic hydrogenation of nitriles[291-295]; for example, mandelonitrile is reduced on a palladium catalyst to phenylacetonitrile in the absence of hydrogen chloride and to phenylethylamine in its presence. The influence of hydrogen chloride on the catalytic reduction of nitriles is apparently due to the formation of reactive complexes between the nitriles and HCl.[294]

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CHEMICAL ADVANCES IN SYNTHESIS AND REACTIONS OF DIARYLUREAS

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I. INTRODUCTION

Urea (carbamide) and its derivatives have found wide application in the aniline dye industry and in the production of macromolecular compounds — plastics, synthetic resins, and rubber. They are of great importance also in the production of mineral fertilisers and feeding stuffs, and also in the preparation of chemical poisons for use in agriculture as insecticides, fungicides, and weed-killers.

Urea and its substituted derivatives are widely used in the synthesis of medicinal preparations, such as the complex aromatic urea derivative Germanin, which is more effective than any other trypanocidal preparations known hitherto.

Diphenylurea and its substituted derivatives are acquiring increasing importance every year. They form the starting materials for the synthesis of various chemical products.

Until recently, however, many questions of theoretical and practical significance concerning synthesis and reactions in the diarylurea series remained unanswered. The number of new compounds synthesised remained very inadequate, while known diarylureas and their derivatives were little studied.

With the evolution of chemical science and technology, it became necessary to investigate more thoroughly the reaction between aromatic amines and carbonyl chloride with the aim of obtaining diarylureas having various substituents both in the aromatic ring and attached to the nitrogen, and also to establish how the chemical, physicochemical, and other properties of the synthetic compounds varied with the nature and number of such substituents.

The synthesis of new compounds required a study of the chemistry of phosgenation processes, investigation both of the main reaction and of side-reactions, and study of the kinetics and mechanism of the reaction of carbonyl chloride with aromatic amines as a function of the reaction conditions.

Research workers have also been interested in the synthesis of diarylureas by the reaction of aromatic amines with aryl isocyanates. This method makes it possible to synthesise both symmetrical and unsymmetrical diarylureas as well as monoaryl- and arylalkyl-ureas.

Investigators have also studied the reaction of urea and diarylureas with aromatic amines at high temperatures, and this has led to the development of new methods for preparing diarylureas using urea as an acylating agent. Research on these lines led to the discovery of the reaction of transamidation, on the basis of which original methods have been worked out for preparing aromatic amines without the use of the acylating agents carbonyl chloride and urea.

In the course of the investigations it also became necessary to study and work out direct methods for synthesising substituted diarylureas by nitration, chlorination, and sulphonation of the initial diphenylurea. These reactions have been little studied until recently, while in individual cases the evidence was contradictory.

During recent years due attention has been paid to problems of the synthesis of aryl-, arylalkyl-, and diaryl--ureas, the study of their hydrolytic properties, and also the investigation of the various changes accompanying the interaction of diarylureas with aromatic amines.

The present paper discusses chemical progress in synthesis and in reactions in the diarylurea series.

II. SYNTHESIS OF DIARYLUREAS BY PHOSGENATION OF AROMATIC AMINES

The compound which has been studied most thoroughly in the diarylurea series is diphenylurea (carbanilide). It was first prepared by Hofmann [1] by passing carbonyl chloride into a saturated aqueous solution of aniline:

$$2C_6H_5NH_2 + COCl_2 \longrightarrow C_6H_5NHCONHC_6H_5 + 2HCl.$$

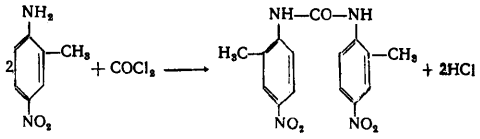
When distilled over phosphorus pentoxide, diphenylurea is partly decomposed into aniline and phenyl isocyanate:

$$C_6H_5NHCONHC_6H_5 \xrightarrow{P_2O_5} C_6H_5NH_2 + C_6H_5NCO.$$

Aromatic amines react readily with carbonyl chloride to form symmetrical diarylureas. This is a general reaction with primary and secondary amines.

A method has been described [2] for obtaining diphenylurea from aniline and carbonyl chloride in the presence of sodium carbonate in aqueous medium. Methods have also been worked out for obtaining diphenylurea by the phosgenation of aniline in aqueous medium, with the use of chalk, caustic alkali, or sodium bicarbonate to remove the hydrogen chloride formed [3].

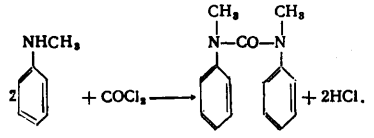
A large number of substituted diarylureas have now been prepared. Thus heating 2-methyl-4-nitroaniline with carbonyl chloride in toluene solution yields bis-2-methyl-4-nitrophenylurea [4]:



This method can be used with certain modifications to obtain the isomeric bismethylnitrophenylureas and bis-dimethylnitrophenylureas, as well as bis-4-nitrophenylurea [5,6].

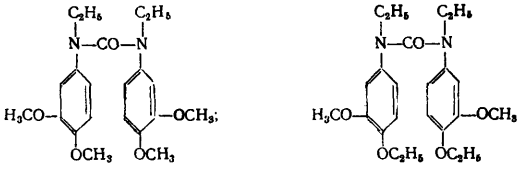
Phosgenation of the corresponding substituted anilines in an inert solvent in the presence of dimethylaniline yields bis-3-chloro-6-methoxy-4-nitrophenylurea and bis-2,5--dimethoxy-4-nitrophenylurea [7,8].

These methods can be recommended also for the preparation of other symmetrical halogeno, nitro, alkyl, and alkoxy derivatives of diarylureas. For example, symmetrical *NN'*-dimethyldiphenylurea (Centralite) is formed by the phosgenation of methylaniline:



Lastovskii[9] obtained the three isomeric (*o*-, *m*-, and *p*-) bisnitrophenylureas by phosgenation of the nitroanilines in nitrobenzene at 140°–150°.

Substituted diarylureas[10] have been synthesised by the phosgenation of methoxy- and ethoxy-anilines. For example, phosgenation of 3,4-$(CH_3O)_2C_6H_3NHC_2H_5$ and 3,4-$CH_3O.(C_2H_5O)C_6H_3NHC_2H_5$ yielded the respective diarylureas



A patent[11] describes the production of substituted diarylureas by the phosgenation of 4-nitro-, 4-acylamino-, and 4-sulphamoyl-2,5-dialkoxyanilines. All these compounds are intermediates in the synthesis of polyazo-dyes for colouring cellulose.

The synthesis of 1,3-bis-(4-dodecanoylsulphamoylnaphth-1-yl)urea by phosgenation of the amine $1,4\text{-}H_2NC_{10}H_6SO_2.NHCO[CH_2]_{10}CH_3$ has been described. The resulting urea derivative is used as a virus-inhibitor[12].

Considerable interest attaches to the synthesis of halogenated diarylureas. The chlorinated derivatives are very stable, and are obtained from the corresponding chlorinated anilines, methods for preparing which are well known. By varying these methods slightly to introduce chlorine into the ring in a specified position, the required chlorinated anilines were prepared. The latter were phosgenated in an organic solvent to yield di-, tetra-, and hexa-chlorodiphenylureas, and also the isomeric (*o*-, *m*-, and *p*-) bischlorophenylureas[13].

Phosgenation of 2,4-dichloroaniline in nitrobenzene at 100°, and in aqueous dichloroethane at 65°, yielded bis-2,4-dichlorophenylurea[14]. The isomeric bis-2,6-dichlorophenylurea was synthesised in a similar manner[15].

The three isomeric bistrichlorophenylureas (2,4,6-, 3,4,5-, and 2,4,5-) have been synthesised by reaction of the corresponding trichloroanilines with carbonyl chloride in dichloroethane or in nitrobenzene[13].

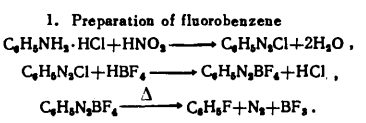
Phosgenation of tetrachloroaniline in nitrobenzene at 130° yields bis-2,3,5,6-tetrachlorophenylurea[14].

Apart from the above chlorinated diarylureas, the synthesis of bis-2,4,6-tribromophenylurea by the phosgenation of 2,4,6-tribromoaniline in nitrobenzene at 130° has been described[14].

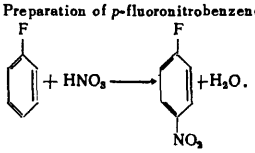
The synthesis of tetra- and hexa-fluorodiarylureas is of great interest, since the fluorine–carbon bond is more stable than those between carbon and the other halogens. Therefore the tetra- and hexa-fluorodiphenylureas possess the greatest chemical stability compared with the other halogenated diphenylureas.

The present author and his collaborators[20] have described multistage methods for preparing bis-2,4-difluoro- and bis-2,4,5-trifluoro-phenylureas. The synthesis of the latter compound, for example, comprises ten stages:

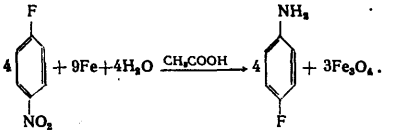
1. Preparation of fluorobenzene



2. Preparation of *p*-fluoronitrobenzene

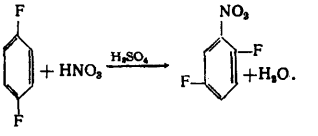


3. Preparation of *p*-fluoroaniline



4. Preparation of *p*-difluorobenzene
(by the method described in stage 1)

5. Preparation of 2,5-difluoronitrobenzene



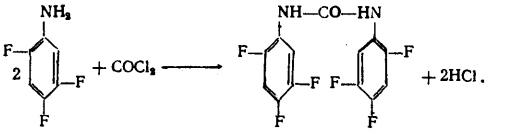
6. Preparation of 2,5-difluoroaniline
(by the method described in stage 3)

7. Preparation of 1,2,4-trifluorobenzene
(by the method described in stage 1)

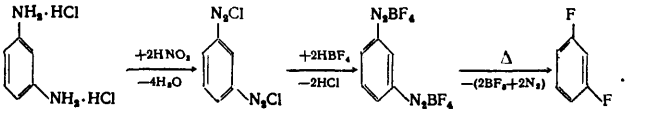
8. Preparation of 2,4,5-trifluoronitrobenzene
(by the method described in stage 5)

9. Preparation of 2,4,5-trifluoroaniline
(by the method described in stage 3)

10. 10. Preparation of bis-2,4,5-trifluorophenylurea



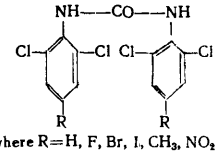
Bis-2,4-difluorophenylurea was synthesised in a similar manner but by a shorter reaction pathway, the starting material being *m*-phenylenediamine, which was converted into *m*-difluorobenzene. In this case we used Schiemann's method[18] to replace both amino-groups simultaneously by fluorine atoms[17]:



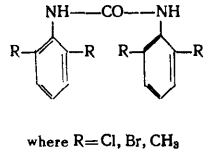
It is of interest to synthesise diarylureas containing both a halogeno and a polar group such as nitro in the ring; bis-2,6-dichloro-4- and bis-2,4-difluoro-6-nitrophenylurea have been prepared. Characteristically, reaction of dihalogenonitroanilines with carbonyl chloride does not lead to formation of the corresponding diarylureas either in aqueous dichloroethane in the presence of anhydrous sodium carbonate and an emulsifier or in nitrobenzene at

135°.[16] We were able to obtain bis-2,6-dichloro-4-nitrophenylurea only by phosgenation of 2,6-dichloro-4-nitroaniline in toluene solution in a sealed tube at 150°. Later an 80% yield of this compound was obtained by nitration of bis-2,6-dichlorophenylurea[15]. Bis-2,4-difluoro-6-nitrophenylurea is obtained in very low yield[16] by phosgenation of 2,4-difluoro-6-nitroaniline in trichlorobenzene in a sealed tube at 85°–90°, the initial difluoronitroaniline being obtained by nitration of 2,4-difluoroacetanilide with nitrosylsulphuric acid[19]. Thus derivatives of aniline containing both a halogeno- and a nitro-group in the ring react with carbonyl chloride much less readily than did those containing only halogens.

The syntheses have recently been described[15] of the substituted diarylureas represented by the formulae



where R=H, F, Br, I, CH_3, NO_2



where R=Cl, Br, CH_3

Apart from these compounds, bis-2,4-dichloro-6-fluorophenylurea has also been synthesised.

All these diarylureas are obtained comparatively easily by phosgenation of the corresponding anilines in an inert organic solvent with heating.

It has been found[15] that a carboxylic or a sulphonic acid group in position 4 has a still greater effect than the nitro-group in hindering the reaction of 2,6-dichloroanilines with carbonyl chloride. Thus substituted diarylureas could not be obtained by phosgenation of 4-amino-3,5-dichlorobenzoic or 4-amino-3,5-dichlorobenzenesulphonic acid. Such compounds can be synthesised by phosgenation of 2,6-dichloroaniline with subsequent introduction of the appropriate groups into the 4-positions of the bis-2,6-dichlorophenylurea.

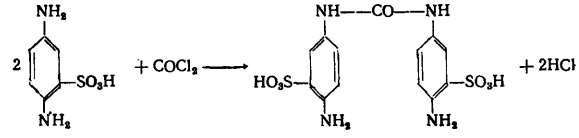
The phosgenation has been studied[3,20] of other aromatic amines as well, both in aqueous alkaline medium and in inert organic solvents. Almost quantitative yields of the corresponding diarylureas were obtained by phosgenation of aniline and *o*-anisidine in aqueous alkaline medium. However, the yield of bis-4-nitrophenylurea in the phosgenation of *p*-nitroaniline is very low (8.5%).

The high yields of diarylureas obtained in the phosgenation of aniline and *o*-anisidine are due to the ability of these amines to form emulsions with water, which ensure good contact between the amine and the carbonyl chloride.

On the other hand, the rate of phosgenation depends on the nature of the amine itself, increasing with increase in its basicity. The yields of diarylureas were in all cases considerably lower in the phosgenation of nitroanilines, whether in aqueous alkaline medium or in organic solvents, than in that of amines possessing more strongly basic properties (aniline, *o*-anisidine, *p*-anisidine, *o*-toluidine). Phosgenation of 2-methyl-4-nitroaniline in nitrobenzene gave a 79.6% yield of bis-2-methyl-4-nitrophenylurea.

The literature contains examples[21] of the phosgenation of aromatic amines containing various substituents in the ring. With *p*-aminobenzonitrile in 50% aqueous dioxane in the presence of anhydrous sodium carbonate at ordinary temperatures, for example, a 77% yield of bis-4-cyanophenylurea (m.p. 305°) was obtained.

Cases are known of the phosgenation of aromatic compounds containing substituents other than the amino-group which are able to react with carbonyl chloride. The presence of a second amino-group in the ring makes possible the formation of a large number of different substances, including polymers. The patent literature[22] refers to the possibility of obtaining diacyl derivatives of bis-4-aminophenylurea by phosgenation of substituted *N*-acylphenylene-1,4-diamines. In the phosgenation of 2,5-diaminobenzenesulphonic acid, it is the amino-group not *ortho* to the sulphonic acid group which reacts with the carbonyl chloride, resulting in the formation of bis-4-aminophenylurea-3,3′-disulphonic acid:[23]



Similarly, bis-4-amino-3,5-dichlorophenylurea is obtained from 2,6-dichlorophenylene-1,4-diamine[24].

Phosgenation of *p*-phenylenediamine in chloroform or in water in the presence of sodium acetate yields a polymer, a *p*-phenyleneurea derivative[25]. A similar phenomenon is observed in the phosgenation of *m*-phenylenediamine[26,27].

With aromatic *o*-diamines, carbonyl chloride forms heterocyclic urea derivatives[28–30]. Phosgenation of aromatic amines of the naphthalene series yields the corresponding diarylurea derivatives[31].

The patent literature[32–36] describes the preparation of urea derivatives by phosgenation of 1-aminonaphthalene-4-sulphonic acid, and also of urea derivatives based on 4-amino-5-hydroxynaphthalene-1,7-disulphonic acid and on *p*-nitrophenylcarbamoyl chloride.

Aminonaphthols having the amino- and hydroxy-groups *ortho* or *peri* relative to one another react with carbonyl chloride, in the presence of acceptors for hydrogen chloride, only at the amino-groups, the hydroxy-groups remaining unaffected[36].

Phosgenation of 6- and 8-amino-4-hydroxynaphthalene-2-sulphonic acids gave the corresponding urea derivatives.

Phosgenation in aqueous alkaline solution of metanilic and sulphanilic acids, with subsequent neutralisation of the reaction medium, yielded diphenylurea-3,3′-(and -4,4′-)disulphonic acids.

Thus it is possible to obtain various symmetrical diarylureas and their derivatives by phosgenation of aromatic amines.

III. CONDITIONS FOR AND MECHANISM OF THE PHOSGENATION OF AROMATIC AMINES

Symmetrical diarylureas and their substituted derivatives are synthesised by reaction of the corresponding aromatic amines with carbonyl chloride according to the equation

$$2RNH_2+COCl_2 \rightarrow RNHCONHR+2HCl.$$

Aromatic amines can be phosgenated either in an inert organic solvent or in aqueous medium[20]. In the former

case the reaction systems comprise a gas (carbonyl chloride) and a homogeneous liquid mixture (the amine dissolved in the organic solvent); in the latter case the reaction systems comprise a gas (carbonyl chloride) and a two-phase liquid system — an aqueous emulsion or suspension of the amine.

Sometimes the carbonyl chloride is passed through a suspension in the liquid of two solids, the amine and an inorganic base, the latter being used to combine with the hydrogen chloride.

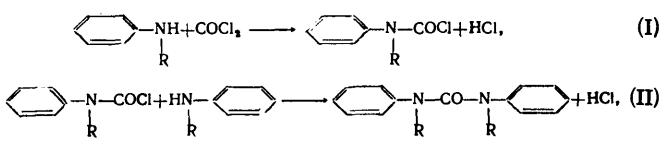
In the phosgenation of amines in aqueous medium, various bases (sodium carbonate, calcium carbonate, sodium acetate, magnesium oxide, zinc oxide, etc.) are employed to combine with the hydrogen chloride. If the reaction is carried out in organic solvents, organic bases, for example dimethylaniline and other amines, are most often employed as acceptors for the hydrogen chloride.

Processes involving phosgenation usually take place at a great rate, but in isolated cases such reactions may be relatively slow. The velocity of phosgenation has been found[20] to be affected by the temperature, the phase constitution of the reactant systems, and the removal of the resulting hydrogen chloride. Until recently inadequate attention has been paid in the literature to problems associated with the mechanism of the interaction of amines with carbonyl chloride. This applies especially to aniline derivatives containing alkyl and chloro-groups in the ring.

Several workers[37,38] have suggested that reaction between carbonyl chloride and amines takes place in stages. Addition of two molecules of the amine to the carbonyl chloride takes place first of all. Lastovskii[39], who holds this view, considers that dimethylaniline forms with carbonyl chloride the addition product $2[C_6H_5N(CH_3)_2].COCl_2$. He established that, when this product is heated, dimethyldiphenylurea and methyl chloride are formed:

$$2[C_6H_5N(CH_3)_2]\cdot COCl_2 \xrightarrow{\Delta} C_6H_5{-}N(CH_3){-}CO{-}N(CH_3){-}C_6H_5 + 2CH_3Cl.$$

This view is consistent with results obtained by Wahl[40], who studied the interaction of carbonyl chloride with dimethylaniline, diethylaniline, and dibutylaniline. Michler and Zimmermann[26,27] investigated the reaction of carbonyl chloride with secondary aromatic amines, and established that it takes place in two stages. A diarylcarbamoyl or an alkylarylcarbamoyl chloride is first formed, and this then reacts with the secondary amine to form the tetrasubstituted urea:



(I)

(II)

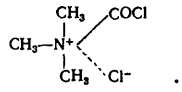
where R = alkyl or aryl.

Lastovskii concluded[39] from a study of the reaction between carbonyl chloride and secondary alkylarylamines in aqueous alkaline medium that at 10°–35° the alkylarylcarbamoyl chloride is formed, whereas at 100° it is mainly the dialkyldiarylurea which is obtained.

It is known[41,42] that reaction of dimethylaniline and diethylaniline with carbonyl chloride at 15°–50° leads to the formation of the *p*-dialkylaminobenzoyl chloride. At 100°–120° this condenses with dimethylaniline to form bis-4-dimethylaminobenzophenone (Michler's ketone).

Shilov and Dement'ev[43] observed that at 15°–20° dimethylaniline absorbs carbonyl chloride extremely readily, in amount considerably exceeding the theoretical amount for the formation of the ketone. Formation of *p*-dimethylaminobenzoyl chloride, however, occurs extraordinarily slowly. This fact points to the formation of addition compounds between carbonyl chloride and the tertiary amine, but these workers were unable to isolate such products. At higher temperatures (~200°) reaction between the starting materials leads to the formation of the dialkyldiarylurea.

Rudenko *et al.*[44] isolated an addition compound of carbonyl chloride and trimethylamine, to which they ascribed the structure



Such compounds are extremely unstable and have been little studied.

Until recently the mechanism of the reactions between carbonyl chloride and anilines which have been alkylated or halogenated in the ring remained obscure. This process is known to be extremely complicated, the first stage probably involving addition to the chloride of either one or two molecules of the aromatic amine, depending on the basic strength of the latter.

The carbonyl chloride molecule, being the complete acid chloride of carbonic acid, possesses highly electrophilic properties, which are due to the presence of the electronegative chlorine and oxygen atoms in its molecule. Therefore in the phosgenation an aromatic amine, possessing nucleophilic properties, reacts with the electrophilic molecule of carbonyl chloride, forming a new donor–acceptor C–N bond.

Since the partial positive charge on the carbon atom in the carbonyl chloride molecule is constant, it can be concluded that the rate of phosgenation of amines under the same conditions will depend on the nucleophilic properties of the aromatic amine.

The basic properties of aromatic amines are known to depend on the number and nature of the ring substituents. If the benzene ring of the amine contains electronegative substituents (atoms or groups), the amine will be feebly basic, *i.e.* it will have weak nucleophilic properties. As such properties become less marked, such aromatic amines react with carbonyl chloride with considerable difficulty. In order to obtain reasonable yields of the diarylureas, phosgenation must then be carried out in organic solvents at elevated temperatures, and sometimes under pressure as well. Aromatic amines possessing strongly basic properties react readily with carbonyl chloride, and the yields of the diarylureas are almost quantitative.

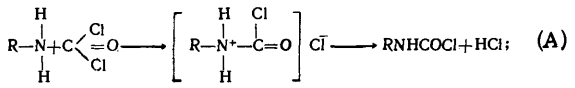
All the above points have been fully confirmed in the present author's investigations[45]. Thus aniline, the toluidines, *o*-anisidine, and other aromatic amines having strong nucleophilic properties react easily with carbonyl chloride in aqueous medium to form diarylureas in high yields. And conversely, aromatic amines having weak

nucleophilic properties, such as those containing halogeno-, nitro-, etc., substituents, have considerably greater difficulty in reacting with carbonyl chloride, and require more severe conditions.

The results obtained for the phosgenation of aromatic amines as a function of their nucleophilic properties are given in Table 1.[45]

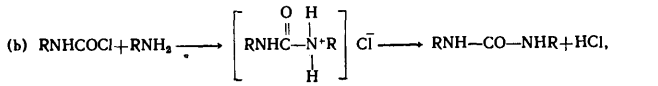
Nevertheless, the rate of phosgenation of arylamines also depends on the structure of the amines, on their solubility in water and in inert organic solvents, and on the nature of the solvent in which reaction is taking place[20]. Phosgenation of 2,4,6-trichloroaniline goes better in 1,2,4--trichlorobenzene than in chlorobenzene under otherwise identical conditions[14], the optimum temperatures for the reaction in the two solvents being 120° and 110° respectively.

In an investigation of the mechanism of the reaction between 2,4,5-trichloroaniline and carbonyl chloride[46], 2,4,5--trichlorophenylcarbamoyl chloride and 2,4,5-trichlorophenyl isocyanate were identified as intermediate products. From a theoretical consideration of the data obtained, it can be concluded that the mechanism of the phosgenation of the trichloroaniline under conditions involving the formation of the bistrichlorophenylurea is as follows[47]:



(A)

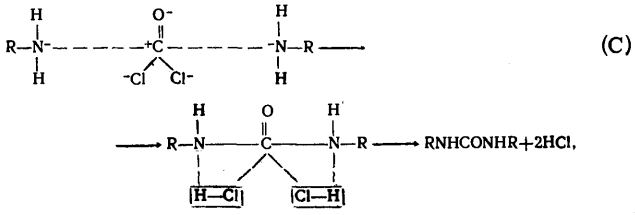
(B)



where R = $C_6H_2Cl_3$.

The first stage involves the addition of a molecule of the aromatic amine to the carbonyl chloride with formation of a transition complex of the quaternary ammonium base type, which is extremely unstable, decomposing with elimination of hydrogen chloride to form trichlorophenylcarbamoyl chloride. The second stage involves two main reactions taking place simultaneously. On the one hand, the trichlorophenylcarbamoyl chloride under the influence of heat splits off hydrogen chloride to form the trichlorophenyl isocyanate, which adds on trichloroaniline at its double bond, being thus converted into the bistrichlorophenylurea. In the other simultaneous reaction, the trichlorophenylcarbamoyl chloride reacts directly with the trichloroaniline, the reaction involving an onium type of transition complex as in the first stage of the process. The complex decomposes with elimination of hydrogen chloride and formation of the bistrichlorophenylurea. The symmetrical diarylurea produced in the reaction is weakly basic, does not form onium compounds with mineral or organic acids, and is stable.

In view of the highly electrophilic properties of carbonyl chloride, it can also be supposed that the latter can simultaneously add on two molecules of an aromatic amine with subsequent elimination of two molecules of hydrogen chloride and formation of the diarylurea, the mechanism of the process being as follows[47]:



(C)

where R = $C_6H_2Cl_3$.

Similar considerations have been put forward also in papers by other workers[37-39]. In the present author's view the above mechanism (C) is most likely with aromatic amines having highly nucleophilic properties.

The reaction of aromatic amines with carbonyl chloride is extremely complicated, the main process being accompanied by side-reactions. Phosgenation of aromatic amines involves the evolution of hydrogen chloride, which combines rapidly with the amine to form a salt. The resulting hydrochloride of the amine undergoes decomposition when heated to its dissociation temperature, as a result of which the free base is formed, which can react with carbonyl chloride to give the carbamoyl chloride[48-50]:

$$RNH_2 \cdot HCl + COCl_2 \longrightarrow RNHCOCl + 2HCl.$$

The carbamoyl chloride, on being heated or recrystallised from hot carbon tetrachloride, readily loses hydrogen chloride, being converted into the aryl isocyanate. This reaction is reversible: when dry hydrogen chloride is passed into the isocyanate, the carbamoyl chloride is formed[51-61].

$$RNCO \underset{-HCl}{\overset{+HCl}{\rightleftharpoons}} RNHCOCl.$$

Arylcarbamoyl chlorides even at low temperatures react with primary aromatic amines to form diarylureas:

$$RNHCOCl + RNH_2 \longrightarrow RNHCONHR + HCl.$$

This reaction takes place readily also with secondary amines[26,27].

Aryl isocyanates react readily with aromatic amines to form diarylureas:

$$RNCO + RNH_2 \longrightarrow RNHCONHR.$$

Depending on the conditions of phosgenation, the aryl isocyanates can easily undergo further changes. If water is present in the reaction medium, the isocyanate reacts with it to form the diarylurea[62]:

$$2RNCO + H_2O \longrightarrow RNHCONHR.$$

The process is slow, pyridine having a catalytic effect and accelerating the reaction[59].

TABLE 1.

Amine	Conditions of phosgenation, °C	Yield of diarylurea, %	Amine	Conditions of phosgenation, °C	Yield of diarylurea, %
$C_6H_5NH_2$	A, 20	99.4	2-CH_3-4-$NO_2C_6H_3NH_2$	B, 40	79.6
2-$CH_3OC_6H_4NH_2$	A, 25	98.8	2-$ClC_6H_4NH_2$	A, 30	87.6
4-$CH_3OC_6H_4NH_2$	B, 40	94.1	3-$ClC_6H_4NH_2$	A, 30	85.3
2-$CH_3C_6H_4NH_2$	B, 40	95.2	4-$ClC_6H_4NH_2$	A, 30	92.5
2-$NO_2C_6H_4NH_2$	C, 100	80.8	2,4-$Cl_2C_6H_3NH_2$	B, 120	90.5
3-$NO_2C_6H_4NH_2$	B, 40	79.5	2,4,6-$Cl_3C_6H_2NH_2$	B, 130	86.3
4-$NO_2C_6H_4NH_2$	B, 40	91.5			

Note. A = aqueous alkaline medium; B = nitrobenzene as solvent; C = toluene as solvent.

The diarylureas, in their turn, are also able to react further with the carbonyl chloride. They do not react at ordinary temperatures, but a rise in temperature leads to the formation of the arylcarbamoyl chlorides[63,64]:

$$RNHCONHR+COCl_2 \longrightarrow 2RNHCOCl\ .$$

The arylcarbamoyl chloride on being heated decomposes with elimination of hydrogen chloride and formation of the aryl isocyanate[65]:

$$RNHCOCl \longrightarrow RNCO+HCl.$$

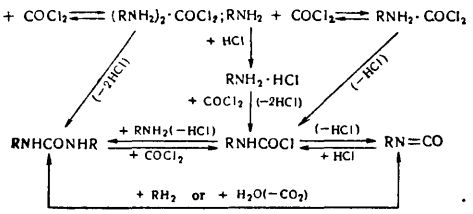
When an arylcarbamoyl chloride is heated in ethyl acetate with a large amount of hydrogen chloride, the latter reacts with the carbamoyl chloride, the resulting aniline and carbonyl chloride interacting to give the diarylurea[46]:

$$RNHCOCl+HCl \longrightarrow RNH_2+COCl_2,$$

$$2RNH_2+COCl_2 \longrightarrow RNHCONHR+2HCl.$$

The formation of a bistrichlorophenylurea is associated with the presence of a large amount of hydrogen chloride in the reaction mixture. At elevated temperatures the hydrogen chloride reacts with the carbamoyl chloride to form trichloroaniline and carbonyl chloride, which interact to yield the bistrichlorophenylurea. The possibility of the latter reactions occurring is confirmed by the decomposition of pure trichlorophenylcarbamoyl chloride to the isocyanate when it is heated in ethyl acetate in the presence of hydrogen chloride, bistrichlorophenylurea and trichloroaniline being isolated.

Thus it can be concluded from the above that the phosgenation of aromatic amines begins with the formation of addition compounds of the amines and carbonyl chloride, after which extremely complicated changes, depending on the conditions, take place. These reactions can be represented by the following scheme[20]:



It can be seen that the formation of addition compounds containing either one or two molecules of the aromatic amine combined with the carbonyl chloride molecule can take place simultaneously.

IV. SYNTHESIS OF DIARYLUREAS AND ARYLALKYLUREAS BY THE REACTION OF AMINES WITH ARYL ISOCYANATES

Aryl isocyanates are extremely reactive, their properties and preparation having been widely described in the literature[66]. They are formed by the reaction of aromatic amines with carbonyl chloride[67]:

$$RNH_2+COCl_2 \longrightarrow RNCO+2HCl.$$

The patent literature[68] gives methods for obtaining isocyanates by vapour-phase phosgenation of amines. Organic polyisocyanates are also formed from primary polyamines by the action of an excess of carbonyl chloride at 60°.[69]

An American patent[70] describes a continuous process for preparing aromatic isocyanates by the addition of carbonyl chloride to a solution of a primary diamine in a chlorinated aromatic solvent (boiling at 130°–300°).

A noteworthy process for obtaining aromatic isocyanates is the vapour-phase reaction of symmetrical diphenylurea with hydrogen chloride at 350°–370°.[71] Aniline hydrochloride is formed as well as phenyl isocyanate.

4,4'-Biphenylylene diisocyanate is obtained by the reaction of benzidine hydrochloride and carbonyl chloride in the presence of an inert organic liquid at 120°–140°.[72]

The preparation of some new polyhalogenated phenyl isocyanates is of great interest. Thus, for example, a process has been described for obtaining chlorophenyl isocyanates[73] by treating with carbonyl chloride a solution of 2,5-dichloroaniline hydrochloride in chlorobenzene, and then gradually heating the reaction mixture to boiling. 2,5-Dichlorophenyl isocyanate, 2,4,6-trichlorophenyl isocyanate, and also a mixture of various ring-chlorinated diarylureas are formed as a result of the reaction.

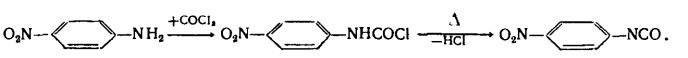
A process has been worked out for synthesising the isomeric 2,4,5-, 3,4,5-, and 2,4,6-trichlorophenyl isocyanates by heating in dichloroethane or in ethyl acetate the corresponding trichlorophenylcarbamoyl chlorides, which in turn are obtained from the corresponding anilines and carbonyl chloride[46].

In the preparation of trichlorophenyl isocyanates in ethyl acetate, the main reaction, resulting in formation of the isocyanate, is accompanied by the formation of up to 50% of the bistrichlorophenylurea. If, however, the solvent (ethyl acetate) is distilled from the reaction mixture in a vacuum at 30°, the yield of trichlorophenyl isocyanate reaches 75%, while the amount of bistrichlorophenylurea is considerably diminished.

Processes for obtaining organic di- and poly-isocyanates have been described in the patent literature[74-76]. There is an interesting method for the formation of chlorosulphonylaryl isocyanates — by the reaction of unsubstituted aromatic sulphonic acids or their salts with carbonyl chloride in an inert solvent at 150°, among the products obtained being *o*- and *p*-chlorosulphonylphenyl isocyanates, 4-chlorosulphonyl-1,3-phenylene diisocyanate, 4-chlorosulphonylnaphth-1-yl isocyanate, 3-chlorosulphonyl-6-methylphenyl isocyanate, etc.

Recently methods have been described in the literature for obtaining other aryl isocyanates. Most of them are based on the interaction of arylamines with carbonyl chloride, and differ little from those described above.

The arylcarbamoyl chlorides, obtained, like the aryl isocyanates, by the interaction of aromatic amines with carbonyl chloride[48,77], are also of definite value for the synthesis of diarylureas. Under the action of heat or of a dehydrochlorinating agent, however, they are converted into aryl isocyanates. For example, *p*-nitrophenyl isocyanate is readily formed by the reaction of *p*-nitroaniline with one equivalent of carbonyl chloride in an organic solvent, or when the resulting *p*-nitrophenylcarbamoyl chloride is distilled until hydrogen chloride is completely removed:



Thus published data indicate the relative ease with which aryl isocyanates can be synthesised, and their high reactivity, which enables them to be used extensively for the preparation of diarylureas.

The action of water on a solution of *p*-nitrophenyl isocyanate in acetone yields bis-4-nitrophenylurea [78].

Diarylureas are readily formed by the reaction of aryl isocyanates and arylcarbamoyl chlorides with aromatic amines, which makes it possible to synthesise both symmetrical and unsymmetrical diarylureas [79-81]:

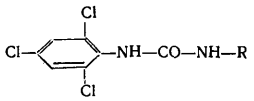
$$RNCO+RNH_2 \longrightarrow RNHCONHR,$$
$$RNCO+R'NH_2 \longrightarrow RNHCONHR'.$$

In most cases the reaction between aryl isocyanates and aromatic amines is carried out in an inert organic solvent, when practically all the amine undergoes reaction, and the yield of diarylureas are close to theoretical. Thus the reaction of phenyl isocyanate with *p*-toluidine gives 4-methyldiphenylurea:

$$C_6H_5NCO+CH_3C_6H_4NH_2 \longrightarrow CH_3C_6H_4NHCONHC_6H_5.$$

Methods have been described for obtaining nitro-derivatives of diarylureas from phenyl isocyanates and nitroanilines [82].

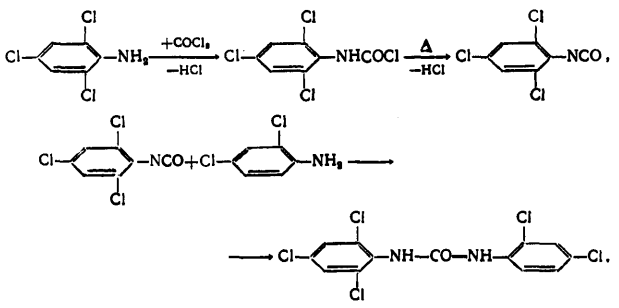
Unsymmetrical chlorinated diarylureas can be obtained [83] by the reaction of trichlorophenyl isocyanates with various halogenated anilines in inert organic solvents, the reaction products having the general formula



Among the compounds synthesised were 2,4,6,2′,6′- and 2,4,6,2′,5′-pentachloro- and 2,4,6,4′-tetrachloro-diphenylurea, etc. All these compounds were obtained by the reaction of 2,4,6-trichlorophenyl isocyanate with the appropriate chlorinated anilines in dry dichloroethane at 20°. Formation and separation of the final compounds takes place at different rates. The position and the number of chlorine atoms in the amine molecules will obviously have a considerable influence on the rate of their reaction with 2,4,6-trichlorophenyl isocyanate. The most reactive amine proved to be *p*-chloroaniline.

All the unsymmetrical substituted ureas obtained were colourless, odourless, amorphous powders, insoluble in water and sparingly soluble in organic solvents, melting in a sealed capillary quite sharply and without decomposition.

2,4,6,2′,4′-Pentachlorodiphenylurea was obtained according to the equations [83]



(I)

(II)

The following unsymmetrically chlorinated symmetrical diphenylureas have been obtained in a similar way: 2,4,6-, 2,4,6,4′-, 2,4,6,2′,4′-, 2,4,6,2′,5′-, 2,4,6,2′,4′,5′-, and 2,4,6,2′,3′,5′,6′-.

During synthesis of the trichlorophenyl isocyanates it was found [46] that, when 2,4,5-trichlorophenylcarbamoyl chloride is heated in ethyl acetate solution in the absence of hydrogen chloride, ethyl trichlorophenylcarbamate is formed.

$$RNHCOCl+C_2H_5O_2CCH_3 \longrightarrow RNHCO_2C_2H_5+CH_3COCl,$$

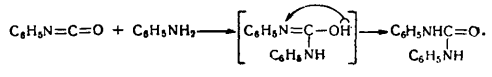
where R = $C_6H_2Cl_3$.

It was mentioned above that diarylureas are readily obtained by the reaction of arylcarbamoyl chlorides with aromatic amines, which makes it possible to synthesise also symmetrical and unsymmetrical diarylureas. In order to obtain high yields of diarylureas, the reaction is carried out in an excess of the base, which is an acceptor for hydrogen chloride. Several different unsymmetrical aryl-, arylalkyl-, and diaryl-ureas have been described [84,85]. These are formed by the reaction of aromatic amines with dialkylcarbamoyl chlorides, and also by the reaction of aryl isocyanates or arylcarbamoyl chlorides with aromatic and aliphatic amines.

Phenyl isocyanate reacts with ammonia forming phenylurea, and with aniline to yield diphenylurea:

$$C_6H_5NCO+NH_3 \longrightarrow C_6H_5NHCONH_2,$$
$$C_6H_5NCO+C_6H_5NH_2 \longrightarrow C_6H_5NHCONHC_6H_5.$$

In the latter case the aniline probably adds on at the carbonyl group with subsequent formation of the diphenylurea:



Phenyldimethylurea is obtained by the reaction of aniline with dimethylcarbamoyl chloride in an organic solvent (benzene or ether) [86].

Reaction between *p*-chloroaniline and dimethylcarbamoyl chloride in the presence of pyridine in dioxane at room temperature yields *N*-4-chlorophenyl-*N′N′*-dimethylurea [87]. This compound is also obtained by the reaction of *p*-chlorophenyl isocyanate with dimethylamine:

$$C_6H_4ClNCO+NH(CH_3)_2 \longrightarrow C_6H_4ClNHCON(CH_3)_2.$$

With diethylamine in dioxane at 20°–30°, *p*-chlorophenyl isocyanate yields *N*-4-chlorophenyl-*N′N′*-diethylurea [88]:

$$C_6H_4ClNCO+NH(C_2H_5)_2 \longrightarrow C_6H_4ClNHCON(C_2H_5)_2.$$

Methods have recently been described [89] for preparing aryldialkylureas without using the toxic carbonyl chloride as starting material. For example, heating an alcoholic solution of *p*-chlorophenyl isothiocyanate with dimethylamine yields *N*-4-chlorophenyl-*N′N′*-dimethylthiourea, which on oxidation with alkaline hydrogen peroxide is converted into 4-chlorophenyldimethylurea:

$$C_6H_4ClNCS+NH(CH_3)_2 \longrightarrow C_6H_4ClNHCSN(CH_3)_2,$$
$$C_6H_4ClNHCSN(CH_3)_2 \xrightarrow[-(H_2O+S)]{+H_2O_2} C_6H_4ClNHCON(CH_3)_2.$$

Syntheses have been described[90] for urea derivatives by the condensation of aminophenols with halogenophenyl isocyanates or of halogenophenols with isocyanates, azides, and esters of carbamic acid, *N*-3,4-dichlorophenyl-*N'*-4'--chloro-2'-hydroxyphenylthiourea, *N*-4-chlorophenyl-*N'*--3',4'-dichloro-6'-hydroxyphenylurea, as well as other urea derivatives being obtained. These compounds possess good bactericidal properties, and are used in the preparation of bactericidal soaps.

Condensation of ethylenedicarbamoyl chlorides $ClCONRCH_2CH_2NRCOCl$ with amines yields the biologically active urea derivatives $R'CONRCH_2CH_2NRCOR'$, where R = = C_6H_5, $C_6H_5CH_2$, etc., and R' = morpholino, piperidino, etc.[91]

The above methods have been used to obtain various aryldimethyl- and aryldiethyl-ureas containing fluorine, chlorine, bromine, or iodine in the aromatic ring, and also aryldialkylureas containing both halogeno and methyl or methoxy-groups in the ring[84].

Aryldialkylureas containing different alkyl radicals have been prepared[84].

Aryldialkylureas are of great value for the synthesis of various preparations. Several of them have found practical application as weed-killers, among them being *N*-phenyl--*N'N'*-dimethylurea (Phenuron), *N*-4-chlorophenyl-*N'N'*--dimethylurea (Monouron), *N*-3,4-dichlorophenyl-*N'N'*-dimethylurea (Diuron), and a new preparation of this group, *N*-3,4-dichlorophenyl-*N'*-n-butyl-*N'*-methylurea (Neburon)[85].

Aryldialkylureas in which the aryl is a naphthyl or a biphenylyl radical[85], for example *N*-2-naphthyl-*N'N'*-dimethylurea, have been prepared and recommended as weed-killers. However, compounds of this type are considerably inferior in such activity to the corresponding phenyl derivatives of urea[92].

Much attention has been paid to the synthesis of arylureas containing alkenyl instead of alkyl groups attached to nitrogen, for example *N*-3,4-dichlorophenyl-*N'*-allyl-*N'*--methylurea and other compounds. Preparations of this group possess high herbicidal activity[93].

Various urea derivatives containing a heterocyclic substituent have been synthesised, such as the *N*-methyl-, *N*-butyl-, *NN*-dimethyl-, *N,N,N'*-trimethyl-, and *N*-isopropyl-*N*-methyl-*N'*-benzothiazol-2-ylureas and other compounds of similar structure, obtained by the reaction of 2-aminobenzothiazole with alkyl isocyanates or *NN*-dialkylcarbamoyl chlorides[94].

Derivatives of urea, such as for example *N*-acylarylalkylureas, are formed by the reaction of amides and isocyanates or of anilides and carbamoyl chlorides. In the former case the reaction is carried out by heating in an organic solvent, toluene or dioxane. In the second case a toluene solution of the sodium salt of the anilide is first prepared from the latter and sodium methoxide, and is then made to react with the carbamoyl chloride[95,96].

A process has been described[97] for obtaining an unsymmetrical chlorinated phenylalkylurea containing a hydroxy--group, $3,4\text{-}Cl_2C_6H_3NHCONH[CH_2]_3OH$. This compound was prepared by the reaction of the corresponding dichlorophenyl isocyanate with 3-aminopropan-1-ol in ethyl ether. The compound $3,4\text{-}Cl_2C_6H_3NHCONHCH_2CH(OH)CH_3$ is obtained in a similar manner. Compounds of this type are effective antiseptics at contents of up to 5% in soaps.

Arylalkylurea derivatives containing other groups have also been obtained. Thus, for example, *N*-4-acetamidobenzenesulphonyl-*N'*-butylurea is formed by heating *N*-butylcarbamoyl chloride with *N*-acetylsulphanilamide in anhydrous pyridine at 120°–125° and then treating the mixture with aqueous sodium carbonate solution[98]. The synthesis has been described[99] of diarylureas of general formula $ArNRCONR'[CH_2]_nNR''R'''$ from the diamines $R'NH[CH_2]_n$. .$NR''R'''$ and carbamoyl chlorides ArNRCOCl or the isocyanates ArNCO. In this case Ar is an aryl, and R an alkyl, group. The resulting compounds of this type possess therapeutic properties.

Several arylurea derivatives have a sweet taste, among them being *NN'*-dimethyldiphenylurea and *p*-ethoxyphenylurea $p\text{-}C_2H_5OC_6H_4NHCONH_2$. The latter compound is sometimes used as a sugar substitute under the name "Dulcin".

V. SYNTHESIS OF DIALKYLUREAS AND DIARYLUREAS BY THE REACTION OF AMINES WITH UREA

Symmetrical dimethylurea was first obtained by Wurtz[100] by the action of water on methyl isocyanate:

$$2CH_3NCO+H_2O \longrightarrow CH_3NHCONHCH_3+CO_2.$$

He gives a method[101] for obtaining monoalkylureas by evaporating a solution of an amine hydrosulphate to dryness with potassium cyanate:

$$RNH_2\cdot H_2SO_4+KCNO \longrightarrow RNHCONH_2+KHSO_4.$$

Methylurea can be obtained by a process based on the Hofmann rearrangement of halogenoamides, by the action of bromine and caustic soda on acetamide and subsequent treatment with nitric acid[102]:

$$CH_3CONH_2 \xrightarrow[-(HBr+H_2O)]{+NaOH+Br_2} CH_3{-}\underset{\underset{Br-N}{\|}}{C}{-}ONa \xrightarrow[-(NaNO_3+HBr)]{+HNO_3} CH_3NCO \rightarrow$$

$$\xrightarrow{+CH_3CONH_2} CH_3NHCONHCOCH_3 \xrightarrow[-CH_3COOH]{+H_2O} CH_3NHCONH_2.$$

Symmetrical dialkylureas, like the diarylureas, are readily obtained by the phosgenation of aliphatic amines. Marckwald[103] prepared symmetrical dimethylurea by treating an aqueous solution of methylamine with carbonyl chloride in benzene solution in the presence of alkali. Dimethyl-, diethyl-, and difuryl-urea were obtained by this method. According to this worker, the yield is quantitative:

$$2RNH_2+COCl_2+2NaOH \longrightarrow RNHCONHR+2NaCl+H_2O\ .$$

Degner and von Pechmann[104] prepared mono- and di--methylurea *via* methyl isocyanate, the latter being formed from equimolar quantities of nitrourea and diazomethane. Methyl isocyanate in ethereal solution is converted by dry ammonia or alkali-metal carbonates into mono- and di--methylurea:

$$O{=}C\begin{matrix}NH_2\\NHNO_2\end{matrix} \longrightarrow O{=}C{=}NH+NH_2NO_2, \quad (a)$$

$$HNCO+CH_2N_2 \longrightarrow CH_3NCO+N_2, \quad (b)$$

$$CH_3NCO+NH_3 \longrightarrow CH_3NHCONH_2, \quad (c)$$

$$2CH_3NCO+H_2O \longrightarrow CH_3NHCONHCH_3+CO_2. \quad (d)$$

Boehmer [105] confirmed Wurtz's results, and obtained symmetrical dialkylureas by the action of water on aliphatic isocyanates:

$$2RNCO+H_2O \longrightarrow RNHCONHR.$$

Perret [106] gives a method for obtaining alkylated and arylated ureas from dicyanodiamidine (carbamidinourea) by the action of alkylamines and arylamines:

$$NH_2-C(=NH)-NH-C(=O)-NH_2+2RNH_2 \longrightarrow RNHCONHR+H_2NC(=NH)NH_2+NH_3.$$

This method gives a quantitative yield of benzylurea, but only a 10% yield of methylurea.

Davis *et al.* [107,108] obtained symmetrical dimethylurea by heating equimolar quantities of urea and the amine hydrochloride to 160°–170°. Minute amounts of methylurea are also formed:

$$2NH_2CONH_2+3CH_3NH_2\cdot HCl \longrightarrow CH_3NHCONHCH_3+CH_3NHCONH_2+3NH_4Cl.$$

Similarly, mono- and di-phenylurea are formed when a solution of aniline hydrochloride is boiled with urea:

$$2NH_2CONH_2+3C_6H_5NH_2\cdot HCl \longrightarrow C_6H_5NHCONHC_6H_5+C_6H_5NHCONH_2+3NH_4Cl.$$

Heating diethylurea with aniline to 170° yields symmetrical diphenylurea and ethylamine:

$$C_2H_5NHCONHC_2H_5+2C_6H_5NH_2 \longrightarrow C_6H_5NHCONHC_6H_5+2C_2H_5NH_2.$$

Methyl-, ethyl-, butyl-, and other alkyl-ureas are obtained [109] by the reaction of equimolar quantities of the primary amines and nitrourea in aqueous medium. This is a general method and is used for the synthesis of alkylureas.

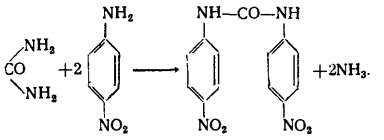
Davis and his coworkers showed that when urea reacts with amine hydrochlorides, either on fusion of the dry reactants or in boiling aqueous solution, whether a monosubstituted or a disubstituted urea is formed depends primarily on the concentration of the amine or its salt and also on the reaction conditions. In several cases only one of these two urea derivatives is formed. Thus when benzylamine is heated with urea in water (under reflux), only the monobenzylurea is formed (95.8%), even with a large excess of benzylamine. Attempts to bring urea into reaction with methylaniline (in water) or with dibutylamine hydrochloride (by melting together), however, were unsuccessful.

According to the patent literature [110], arylalkylureas are obtained by heating urea with an aromatic amine to 100°–200° in an alcohol of high boiling point, for example, cyclohexanol or phenol, ammonia being evolved. A dialkylamine is added to the hot mixture, and the solvent is distilled off, the aryldialkylurea being obtained in the residue. This reaction obviously takes place according to the following mechanism:

$$H_2NCONH_2+ClC_6H_4NH_2 \longrightarrow ClC_6H_4NCO+2NH_3,$$
$$ClC_6H_4NCO+NH(CH_3)_2 \longrightarrow ClC_6H_4NHCON(CH_3)_2.$$

Higher yields are obtained if the process is carried out in two stages. The arylamine (in excess) is then heated with urea with stirring at 140°–180° for 1½ h, after which the mixture is cooled and washed with acetic acid. In the second stage a mixture of the resulting symmetrical diarylurea and the dialkylamine (in excess) is passed through a tube heated to 400°, when the aryldialkylurea is obtained [111].

Great interest attaches to methods for obtaining substituted diarylureas by the reaction of urea with aromatic amines. Thus, for example, when urea is fused with *p*-nitroaniline at 190°, bis-4-nitrophenylurea is formed [112]:



This reaction takes place also in boiling isopentyl alcohol [113].

A series of substituted diarylureas have been obtained by the reaction of the corresponding arylamines with urea in various organic solvents. For example, bis-4-hydroxyphenylurea has been obtained by heating urea in isopentyl alcohol with *p*-aminophenol (molecular proportions 2 : 1) at 132° for 8 h. [3]

A very interesting method has been described in the patent literature [114–116] for obtaining bis-2,4,6-trichlorophenylurea from 2,4,6-trichloroaniline or its hydrochloride and urea in glacial acetic acid in the presence of sulphuric acid or hydrogen chloride.

The reaction is carried out by boiling with a (2–8)-fold excess of urea at 125°–132°. The bistrichlorophenylurea can be obtained continuously by first heating the reaction mixture of trichloroaniline (or its hydrochloride), urea, and acetic acid to 125°–132°, and then feeding it continuously into the reaction vessel at a rate of 25 ml min^{-1}. At the same time sulphuric acid is introduced in amount sufficient to give a pH of 1.5–1.8. With these concentrations and velocities of the reactants, which are optimum, the time of reaction is 2–3 h. The final product is obtained in yields up to 84.5%. The use of trichloroaniline hydrochloride halves the consumption of sulphuric acid compared with the use of trichloroaniline.

The preparation of substituted dibenzylureas has been described [117]. When a mixture of urea and 4-ethoxy-3-methoxybenzylamine is boiled in water for 4 h, *NN'*-bis-4-ethoxy-3-methoxybenzylurea is formed. *NN'*-Bis-3,4-dimethoxybenzylurea is obtained similarly. Corresponding symmetrical dialkyldiarylureas have also been synthesised, examples being *NN'*-diethyl-bis-4-ethoxy-3-methoxybenzylurea and *NN'*-diethyl-bis-3,4-dimethoxybenzylurea.

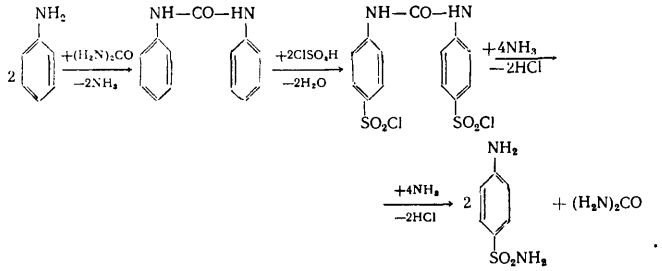
Heating urea with *N*-acetyl-*p*-phenylenediamine at **150°** yields bis-4-aminophenylurea [118]. Urea reacts with *p*-phenylenediamine and its substituted derivatives in inert diluents at high temperatures [119,120], bis-4-aminophenylurea and bis-4-amino-3-methylphenylurea being obtained in this way. Diaminodimethyldiphenylurea is formed in a similar manner.

Bis-4-aminophenylurea is also obtained by heating urea and *p*-phenylenediamine in water to 103° and then distilling the reaction mixture [121,122].

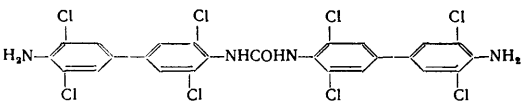
When urea is heated with an aqueous solution of the hydrochloride of 1-aminonaphth-2-ol at 200°, *NN'*-bis-2-hydroxynaphth-1-ylurea is formed. The product reacts with dimethyl sulphate to yield *NN'*-bis-2-methoxynaphth-1-ylurea [123].

In the synthesis of sulphanilamide from aniline, urea is used as an acylating agent [124,125]. Thus when diphenylurea

4,4′-disulphonyl chloride is heated with ammonia, sulphanilamide and urea are formed[126]:



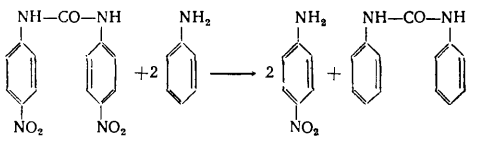
The reaction of urea with tetrachlorobenzidine has been studied[3], a mixture of the reactants being heated in isopentyl alcohol for 5 h. At 340° the product charred without melting. The structure of the resulting compound can be represented as a cyclic diamide[26,27] or as a bistetrachlorobenzidinourea of diamine type[127]:



The reaction of diphenylurea and its derivatives with aromatic amines has been extensively investigated during recent years. When, for example, *N*-phenyl-*N*′-*p*-tolylurea is heated with *p*-toluidine, bis-*p*-tolylurea and aniline are formed.

Bis-4-sulphamoylphenylurea reacts with aniline to form sulphanilamide and diphenylurea[129].

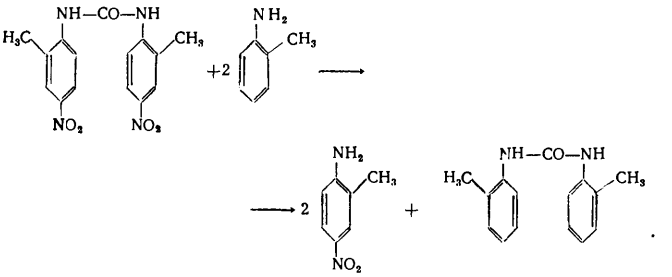
The present author has made a detailed investigation[130] of the reaction of bis-4-nitrophenylurea with aniline;



With optimum proportions of 3.2 moles of aniline per mole of the diphenylurea and heating at 180° for 15 min, the yield of *p*-nitroaniline approaches theoretical (99.4%). In ethylene glycol, at temperatures up to 190°–195°, the yield of *p*-nitroaniline reaches 99.8%. In the absence of ethylene glycol at the same temperature, the yield is considerably lower, and appreciable charring occurs.

The author has also studied the reaction of other nitrodiphenylureas with aniline[30,130]. For example, reaction of bis-3-nitrophenylurea with aniline at 180° for 15 min results in the formation of *m*-nitroaniline and diphenylurea.

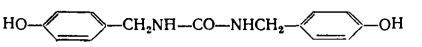
When bis-2-methyl-4-nitrophenylurea is heated with aniline at 180° for 1 h, 2-methyl-4-nitroaniline and diphenylurea are obtained. Similar reactions take place when bis-2-methoxy-4-nitrophenylurea and bis-2-chloro-4-nitrophenylurea are treated with aniline. Aniline can be replaced by other aromatic amines in the above reactions. Thus heating bis-2-methyl-4-nitrophenylurea with *o*-toluidine to 200° yields 2-methyl-4-nitroaniline and bis-*o*-tolylurea[130]:



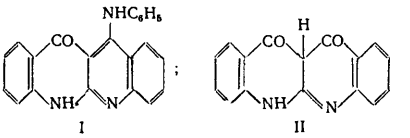
A paper by Gerchuk *et al.*[131] describes the reaction of *p*-dipropylaminoaniline with diphenylurea, the products being bis-4-dipropylaminophenylurea and aniline. When 2-aminopyridine is heated with diphenylurea, *NN*′-dipyrid-2-ylurea and aniline are obtained[131].

A process has been patented[132] for obtaining diarylureas by treating primary arylamines with carbonyl sulphide in the presence of an alkaline catalyst in an enclosed reaction vessel at 120° under pressure for 4 h. For example, $C_6H_5NH_2$, $N(C_2H_5)_3$, and COS yield bis-2-ethylphenylurea. Similarly, the corresponding aryl- and alkyl-amines and carbonyl sulphide give bis-2-methyl-, bis-4-chloro-, bis-4-methoxy-, bis-4-hydroxy-phenylurea, etc.

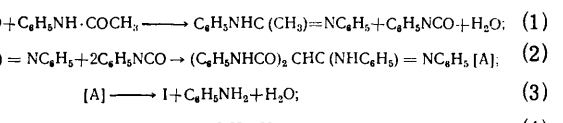
Interesting reactions of urea and its derivatives with other compounds have been described. Thus condensation of phenol and urea with formaldehyde yields the symmetrical bis-4-hydroxybenzylurea[133]:



When diphenylurea is heated with acetanilide at 250°–280° for 3 h, the mixture then treated with warm ethanol (to dissolve 2,4-dianilinoquinoline), and the residue extracted with benzene, the following substances are obtained[134]:



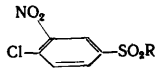
Compound I melts at 323°, and crystallises from 50% acetic acid. The other compound (II) is produced from the former by heating with KOH and ethyl alcohol at 200° under pressure. This compound melts at 400°, and forms solid acetates in concentrated acetic acid. The reaction mechanism proposed by the discoverers is:



Urea is sometimes used in chemical processes because it readily gives off ammonia. When it is heated with 2,4-dinitrophenol, for example, 2,4-dinitroaniline is formed, and with dinitronaphth-1-ol the product is dinitronaphth-1-ylamine[135].

Substituted aromatic compounds have been prepared[136] by the reaction of urea with halogenopolynitrobenzenes.

Aromatic compounds containing one halogen atom and one or two nitro-groups *ortho* or *para* to the halogen in the benzene nucleus were shown to react with urea forming amino-compounds. When compounds of the type



(where R can be CH_3, $NHCH_3$, C_6H_5, or $CH_2C_6H_5$) are fused with urea, amines are formed in lower yield (69% instead of 83%) than in the reaction of urea with 2-chloro-*N*-methyl--5-nitrobenzenesulphonamide.

The base-catalysed reaction of *S*-phenyl thiocarbamate $NH_2COSC_6H_5$ or of an *N*-monosubstituted derivative with ammonia or a primary or secondary amine, amide, or hydrazine results in the formation of substituted ureas such as *N*-phenyl-*N'*-pyrid-1-yl-, *N*-phenyl-*N'N'*-dimethyl-, and *N*-phenyl-*N'*-n-butyl-urea, symmetrical diphenylurea, etc. [137]

A review [138] has described the reactions of compounds, formed at 100°–300°, containing isocyanate, urea, and urethane groups. These reactions are very valuable for the preparation of polyureas and polyurethanes having improved thermal stability, and also for studying the changes in properties undergone by these substances at elevated temperatures. All these problems require special consideration.

VI. CONDITIONS FOR AND MECHANISM OF THE REACTION OF DIARYLUREAS WITH AROMATIC AMINES

The interaction of urea and its derivatives with aromatic amines has been frequently studied. Reactions of this type were first investigated in the case of urea and aniline. Thus Baeyer [139] obtained diphenylurea by heating 1 part of urea with 3 parts of aniline to 150°–170°. Fleischer [140] obtained monophenylurea on heating urea with one mole of aniline. Claus [141] demonstrated the reversibility of this process:

$$C_6H_5NHCONHC_6H_5+2NH_3 \rightleftarrows H_2NCONH_2+2C_6H_5NH_2.$$

When diphenylurea is fused with alkalis, aniline is split off, and triphenylguanidine is formed [142].

In the presence of glacial acetic acid as catalyst, reaction between urea and aniline results in the formation of diphenylurea [143].

Davis and his collaborators have published a series of papers [107-109,144,145] on the reaction of amines with urea and its derivatives, in which they showed that urea on being heated undergoes an intramolecular rearrangement leading to the formation of ammonium cyanate:

$$NH_2{-}\underset{\underset{O}{\|}}{C}{-}NH_2 \rightleftarrows HNCO+NH_3 \rightleftarrows NH_4NCO \ .$$

Similar changes were observed by Werner [146], who obtained ammonia and isocyanic acid on heating dry urea.

The above rearrangement of urea explains the formation of alkyl- and aryl-urea:

$$RNH_2+HNCO \rightleftarrows RNHCONH_2 \rightleftarrows RNCO+NH_3 \ ,$$

$$RNH_2+RNCO \rightleftarrows RNHCONHR \ .$$

On the basis of the existence of a reversible equilibrium between urea, ammonia, and isocyanic acid, Davis and his coworkers consider that, on being heated with aniline (or other primary amine) at 160°, urea dissociates into ammonia and isocyanic acid, the former escaping from the reaction zone, while the acid combines with the aniline to form phenylurea, which at 160° can undergo the following rearrangement

$$HNCO+C_6H_5NH_2 \rightleftarrows C_6H_5NHCONH_2 \rightleftarrows C_6H_5NCO+NH_3 \ .$$

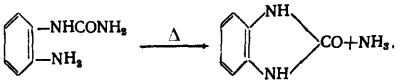
The phenyl isocyanate which is formed reacts with the aniline, resulting in the production of diphenylurea:

$$C_6H_5NCO+C_6H_5NH_2 \rightleftarrows C_6H_5NHCONHC_6H_5 \ .$$

This process can be represented by the following general scheme:

$$H_2NCONH_2+C_6H_5NH_2 \xrightarrow[-NH_3]{} H_2NCONHC_6H_5 \xrightarrow[-NH_3]{} C_6H_5NCO \xrightarrow{+C_6H_5NH_2} C_6H_5NHCONHC_6H_5.$$

Interesting changes are observed when arylureas are heated above their melting points. Thus unsymmetrical arylureas containing an amino-group *ortho* to a urea nitrogen are converted, on being heated, into the corresponding *NN'-o*-phenyleneureas. For example, prolonged heating at 150°–180° converts 2-aminophenylurea into *NN'-o*--phenyleneurea [147]:



Substituted ureas in which different substituents are attached to the nitrogen atoms undergo a series of changes at high temperatures, associated with the formation of new compounds and decomposition products [148,149]. When 4-nitrophenylurea is heated above its melting point, bis-4-nitrophenylurea is obtained.

Heating *N*-ethyl-*N'*-naphthylurea above its melting point results in formation of the symmetrical *NN'*-dinaphthyl- and *NN'*-diethyl-ureas [150,151].

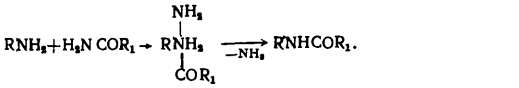
Bognar *et al.* [152] also mention that monoarylureas are converted at their melting points into diarylureas. The rate and the extent of conversion depend mainly on the reaction conditions and also on the position and nature of the ring substituents.

When ethoxy-derivatives of diarylureas (p-$C_2H_5OC_6H_4$·NHCONHC$_6$H$_4$OC$_2$H$_5$-p) are heated [153] with urea dissolved in an aliphatic alcohol, dissociation occurs into the aryl isocyanate (p-$C_2H_5OC_6H_4NCO$) and the aromatic amine (p-$C_2H_5OC_6H_4NH_2$).

In confirmation of this, the same workers [153] obtained an unsymmetrical substituted diarylurea (p-$C_2H_5OC_6H_4NH$··CONHC$_6$H$_5$) by the reaction of bis-4-ethoxyphenylurea and phenyl isocyanate. These results showed that, in the reaction between aromatic amines and diarylureas, the process begins with dissociation of the latter into aromatic amines and aryl isocyanates.

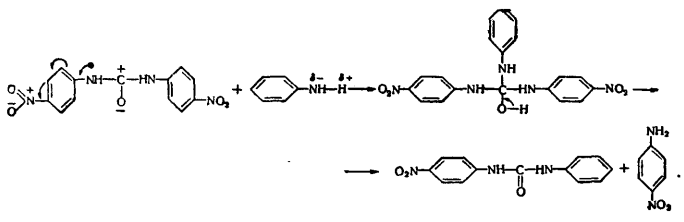
Until recently there was no generally accepted view concerning the mechanism of the reaction between diarylureas and aromatic amines. Porai-Koshits [154,155] proposed a mechanism for this reaction after having investigated the analogous reaction between phthalamic acids and aromatic

amines. According to him, the process involves the intermediate addition of the amide to the aniline:

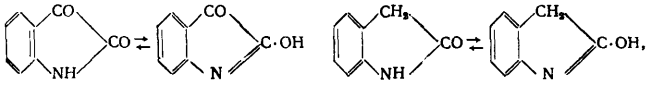


Formation of an intermediate product involving addition of an amino-group to the amino-nitrogen and the formation of a hydrazine group is not very probable. A nitrogen atom could hardly be linked by five covalent bonds with other atoms, when it would be surrounded by ten electrons instead of an octet.

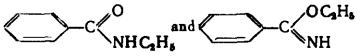
At relatively low temperatures, when dissociation of the substituted diarylurea into aromatic amine and aryl isocyanate has not yet occurred, another reaction mechanism seems more probable, in which aniline is added to a tautomeric form of bis-4-nitrophenylurea or, more precisely, to the polarised molecules[3,130]:



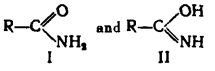
The most significant feature of such changes is the addition of an amino-group not to nitrogen but at the double bond in the tautomeric form of the carbamide. The existence of such tautomeric forms in carboxyamides is a general property of acid amides. We may point to the tautomerism of isatin and oxindole[150,156]:



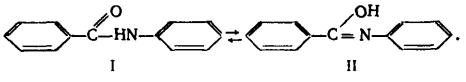
and that of acid amides, for example benzamide, with which the existence of *O*- and *N*-ethyl derivatives of the two tautomeric forms has been demonstrated[157,158]:



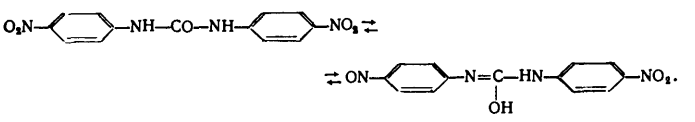
Hantzsch[159] found, in an investigation of the tautomerism of carboxyamides, that the actual amide form (I) should be assigned to amides in the solid state, whereas in alkaline solution they react in the tautomeric imidic acid form (II):



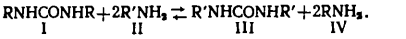
Like acid amides, anilides also react in two forms, as the anilide (I) and the *N*-phenylimidic acid (II):



As Orlov[160] showed, the anilide and the toluidide of formic acid exist in two forms, one of which is readily soluble, while the other is insoluble, in aqueous caustic potash. It is therefore quite likely that bis-4-nitrophenylurea will react with aniline in the tautomeric imidic form, as was established for similar compounds by Gershzon[161]:

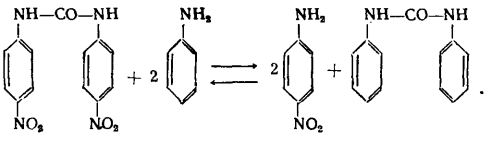


Gerchuk *et al.*[162] established that the reactions between diarylureas and primary aromatic amines are fundamentally reversible, and lead to the formation of symmetrical diarylureas:



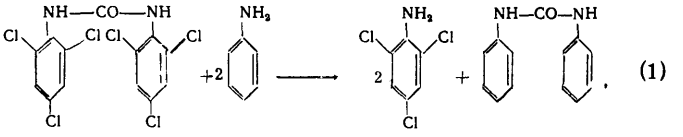
These workers conclude that the more marked the basic properties of the amine II, the higher is the yield of the substituted urea III. Hence in the reaction of primary amines with the substituted urea I, the equilibrium is shifted towards the formation of the amine IV having the feebler basic properties. Since *p*-nitroaniline is a weaker base than aniline, they conclude that practically no reaction takes place between the former and diphenylurea. However, this last statement requires correction, as will be shown below.

It was mentioned above[130] that the reaction between bis-4-nitrophenylurea and aniline is almost complete at 180°, with the formation of *p*-nitroaniline and diphenylurea. The possibility of the occurrence of the reverse reaction was investigated. For this purpose, diphenylurea was fused with an excess [(10–15)-fold compared with the theoretical amount] of *p*-nitroaniline. The reaction was carried out both in nitrobenzene and in the absence of solvent at 190°–195° for 2–3 h. It proved possible to isolate bis-4-nitrophenylurea from the reaction mass. Thus investigation of this reaction showed that it is reversible and takes place as follows:

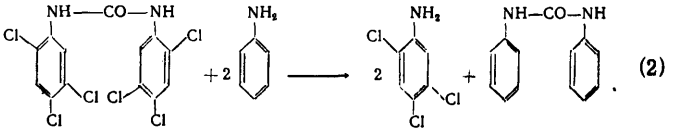


The reverse process occurs with considerably greater difficulty than the forward reaction, and requires a large excess of *p*-nitroaniline.

The present author and Potashnik[163] investigated the reaction of two isomeric bistrichlorophenylureas with aniline:



(1)



(2)

Several intermediate compounds were isolated, such as trichloroaniline and the unsymmetrical 2,4,6-trichlorodiphenyl urea. On the basis of published information and the experimental results, the mechanism of the reaction between bistrichlorophenylureas and aniline at high temperatures can be represented by the scheme [163]:

$$C_6H_2Cl_3NH\cdot CO\cdot NHC_6H_2Cl_3 \rightleftharpoons C_6H_2Cl_3NH_2 + C_6H_2Cl_3NCO, \quad (I)$$

$$C_6H_2Cl_3NCO + C_6H_5NH_2 \longrightarrow C_6H_2Cl_3NH\cdot CO\cdot NHC_6H_5, \quad (II)$$

$$C_6H_2Cl_3NH\cdot CO\cdot NHC_6H_5 \longrightarrow C_6H_2Cl_3NH_2 + C_6H_5NCO, \quad (III)$$

$$C_6H_5NCO + C_6H_5NH_2 \longrightarrow C_6H_5NH\cdot CO\cdot NHC_6H_5. \quad (IV)$$

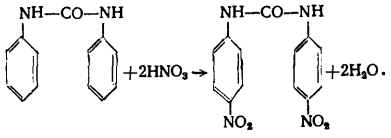
It has been shown experimentally that trichlorophenyl isocyanate is formed when bistrichlorophenylureas is heated [163]. The latter was heated in decalin, and the 2,4,6-trichlorophenyl isocyanate formed under these conditions gave with 2,4-dichloroaniline the 2,4,6,2',4'-pentachlorodiphenylurea, which was isolated in pure form.

Investigation of the reaction of urea and its derivatives with aromatic amines has shown that all derivatives of urea undergo this reaction. The reaction of diarylureas with aromatic amines at high temperatures is a complicated process, involving thermal decomposition of the diarylureas in addition to transamidation, accompanied by oxidation, resinification, and degradation of the breakdown products.

VII. SYNTHESIS OF SUBSTITUTED DIARYLUREAS BY NITRATION, CHLORINATION, AND SULPHONATION OF DIPHENYLUREA

Apart from the methods described above, other pathways exist for the synthesis of substituted diarylureas, namely nitration, chlorination, or sulphonation of diphenylurea. For a long time there was no accepted view as to the orientation or the number of nitro-groups entering the diphenylurea.

Comparatively recently a detailed study has been made [3,164] of the nitration of diphenylurea with nitric acid:

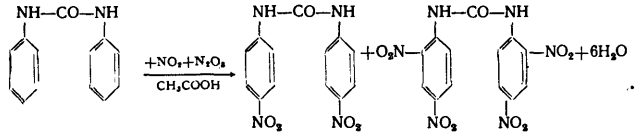


Nitration of diphenylurea was carried out in concentrated sulphuric acid, glacial acetic acid, various organic solvents, in aqueous medium, and also in aqueous medium containing various antioxidants and dispersing agents. It was established that, in most cases of nitration with nitric acid, the nitro-group enters the *para*-position with respect to the acylated amino-group, and only to an insignificant extent the *ortho*-position. In no case was the formation of bis-3-nitrophenylurea observed.

At about the same time more reliable information appeared in the literature [165,166] to the effect that bis-4-nitrophenylurea is formed when diphenylurea is nitrated with nitric acid in glacial acetic acid. These papers, too, indicate that the nitro-group enters the *para*-position with respect to the acylated amino-group.

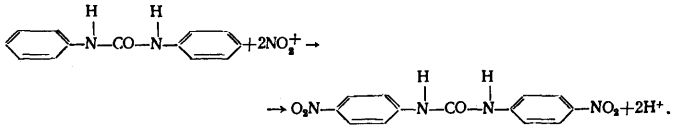
Curtius's view [167] that bis-3-nitrophenylurea is formed in the nitration of diphenylurea with nitric acid was not confirmed. Nitration with concentrated nitric acid, containing oxides of nitrogen, also yielded bis-4-nitrophenylurea, but more highly nitrated products, 2,4,2',4'-tetranitro- and 2,4,6,2',4',6'-hexanitro-diphenylurea, were formed as well.

The action of oxides of nitrogen on diphenylurea in acetic acid solution results in the formation of dinitro- and tetranitro-diphenylurea derivatives [112]:



Nitration of diphenylurea in aqueous suspension with dilute nitric acid at high temperatures (90°–100°) yields almost exclusively bis-4-nitrophenylurea [168]. Under these conditions, too, the group which directs the nitro-groups to the *para*-positions of the aromatic rings in diphenylurea is the carbamido-group. Thus in the nitration of diphenylurea with nitric acid, the nitro-group enters mainly the *para*-position with respect to the acylated amino-group, and only to a slight extent the *ortho*-position, as in the numerous other cases of the nitration of acylated derivatives of aniline (formanilide, acetanilide, oxanilide, etc.).

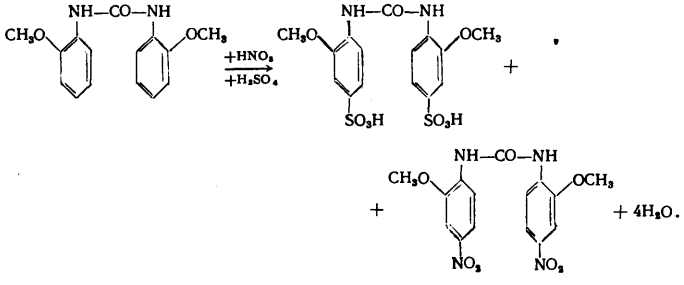
The nitrating agent is known to be the nitronium cation [169-172]:



Conditions were determined [3,164] for the nitration of diphenylurea with nitric acid, on the basis [173] that too acid a medium has a detrimental effect on nitration and proton transfer to the acceptor, while too low an acidity diminishes the concentration of NO_2^+ and thereby affects the process adversely. The optimum concentration of nitric acid was found to be 20–30%. With lower concentrations the yield of nitro-compounds was always reduced, since the NO_2^+ concentration is then diminished. With higher concentrations of nitric acid, the concentration of proton-acceptors (bases) is decreased, which hinders proton transfer to the acceptor, so that the yield of nitro-compounds is lower than under the optimum conditions.

The effect of temperature on the yield of the final products of the nitration of diphenylurea with 20% and 30% nitric acid for 5 h was also investigated. The optimum temperature for nitration under these conditions was 90°.

When bis-2-methoxyphenylurea is treated with nitric acid in concentrated sulphuric acid, sulphonation takes place, and only minute amounts of nitro-derivatives are formed [174,175]:



When bis-2-methoxyphenylurea is nitrated in acetic acid, bis-2-methoxy-4-nitrophenylurea is formed, together with other nitro-derivatives [176].

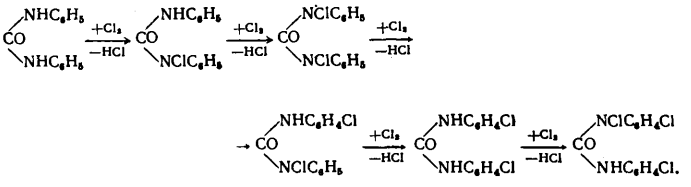
It was shown later [177] that bis-2-methoxy-4-nitrophenylurea is readily formed by the nitration of bis-2-methoxyphenylurea with weak nitric acid in aqueous medium at high temperatures. The bis-2-methoxy-4-nitrophenylurea is prepared by nitrating the initial diarylurea in aqueous suspension with 15% nitric acid at 80° for 3 h, the yield of the final product reaching 93%. The isomeric bis-2-methoxy--6-nitrophenylurea is formed only in extremely minute amounts, while the corresponding 5-nitro-isomer is not formed at all under these conditions.

Bis-2-methyl-4-nitrophenylurea was synthesised in a similar manner [3]. Nitration of the initial bis-2-methoxyphenylurea and bis-*o*-tolylurea in organic solvents (chlorobenzene, etc.) does not improve the results, the yield of the final products in no case exceeding 80%.

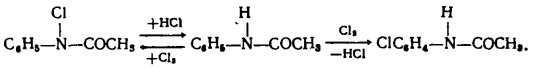
Nitrosation of the initial diarylureas yields various nitroso-derivatives. Thus Lastovskii [178], for example, synthesised *N*-nitrosodiarylureas, and studied the conditions for the nitrosation of monoarylureas and symmetrical diarylureas. He demonstrated the influence of substituents in the aromatic ring on the formation of the mono-*N*-nitrosodiphenylurea.

At the beginning of this century it was shown by the work of Chattaway and his collaborators [179-184] that chlorinated mono- and di-phenylureas can be obtained by treating the initial compounds with elementary chlorine, for example with the urea derivatives dissolved in glacial acetic acid in the presence of sodium acetate.

This method was used to synthesise the unsymmetrical 4-chloro-, 2,4-dichloro-, and 2,4,6-trichloro-phenylureas, and also the symmetrical bis-4-chlorophenyl-, bis-2,4--dichlorophenyl-, and bis-2,4,6-trichlorophenyl-ureas. The symmetrical bis-2,4,6-trichlorophenyl-*NN'*-dichlorourea was prepared by chlorination of diphenylurea. The above workers started from diphenylurea (without ring substituents), which they chlorinated with elementary chlorine in dilute acetic acid in the presence of sodium acetate. The resulting *N*-chloro-derivatives were then heated in glacial acetic acid, when the chlorine atoms migrated into the aromatic rings:



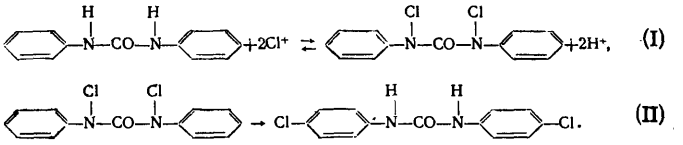
Such reactions are characteristic also of *N*-chloroacetanilides, in which the chloramide rearrangement takes place under the influence of hydrochloric acid [185,186]:



This arrangement makes it possible to obtain successively compounds containing one, two, or three chlorine atoms in the ring. The quantitative conversion of *N*-chloroacetanilide into a mixture of *o*- and *p*-chloroacetanilides is due to the irreversibility of the ring chlorination. The method described above for obtaining octachlorodiphenylurea is only of theoretical interest, and is of no practical value, since the yield of the final product is negligible.

Recently the present author and his coworkers [187] have developed methods for preparing chlorinated diphenylureas, and in particular bis-2,4,6-trichlorophenylurea, based on the chlorination of diphenylurea with elementary chlorine both in aqueous medium and in various organic solvents. In all cases a reasonable yield of the final product is obtained. In isolated cases the reaction does not go to completion, the hexachlorodiphenylurea sometimes containing up to 20–22% of the tetrachloro-derivative.

The reaction itself was also investigated [187]. The chlorine cation, formed in acid medium by the dissociation of hypochlorous acid, is known to be the chlorinating agent. The highly electrophilic Cl^+ cations attack the benzene rings of the diarylurea, first replacing the hydrogen atoms attached to nitrogen, and then migrating from the nitrogen into the ring in conformity with the rules of orientation:



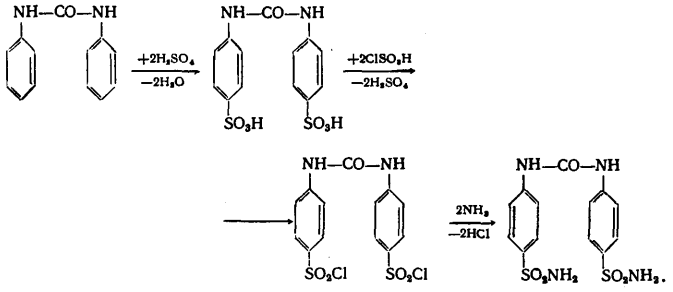
The *para*-hydrogen atoms are replaced first, and only then the hydrogen atoms in the *ortho*-positions of the phenyl radicals in diphenylurea. Introduction of the last two chlorine atoms into the *ortho*-positions of bis-2,4-dichlorophenylurea or of one chlorine atom into the *ortho*-position of 2,4,6,2',4'-pentachlorodiphenylurea is therefore difficult. In order to obtain reasonable yields of the final product, bis-2,4,6-trichlorophenylurea, chlorination must be carried out at a high temperature for a long time. These difficulties can probably be explained by steric factors and the inductive effect, due to the presence of the electronegative chlorine atoms in the aromatic rings of the diphenylurea.

Chlorination of diphenylurea in acetic acid leads to the formation [187] not only of impurities of a low degree of chlorination but also of heptachlorocyclohexenone (up to 10%), while in aqueous medium tetrachloro-*p*-benzoquinone (chloranil) is formed. These results must obviously be due to the simultaneous occurrence of a more extensive chlorination of the diphenylurea with subsequent breakdown of the diarylurea molecule and further reactions of the decomposition products.

The formation of brominated diarylureas has been described [188,189]. Di-, tetra-, and hexa-brominated diphenylureas have been prepared by dissolving diphenylurea in hot glacial acetic acid containing sodium acetate, and then saturating the solution for a prolonged period with bromine.

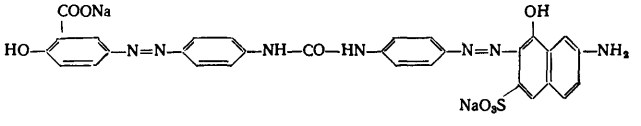
Published information on the sulphonation of diarylureas is extremely limited. In a study of the hydrolysis of diphenylurea in sulphuric acid, it has been established [3,190] that cleavage of the molecule is accompanied by the formation of diphenylurea-4,4'-disulphonic acid.

Later a report appeared[166] stating that heating diphenylurea with fuming sulphuric acid at 140° yields the 4,4'-disulphonic acid, which can be subsequently converted into various diarylurea derivatives:



The 4,4'-disulphonyl chloride can be prepared[191] by treating diphenylurea with an excess of chlorosulphonic acid at 50°–70°, removing the sulphonated mass from the apparatus, and cooling it to 20°–25°. A later investigation[192] showed that the diphenylurea first undergoes sulphonation, and the resulting disulphonic acid is converted into the corresponding disulphonyl chloride.

Many other substituted diarylureas of various types have been described. Those obtained by reduction of the corresponding nitro-derivatives are noteworthy, particularly bis-4-aminophenylurea, obtained[193] by reducing bis-4-nitrophenylurea with iron in acid medium. This compound is very valuable for the synthesis of azo-dyes. Thus, for example, it has been diazotised and coupled with *m*-phenylenediamine, *p*-nitroaniline, salicylic and sulphanilic acids, 4-amino-5-hydroxynaphthalene-2,7-disulphonic acid, phenol, and 6(and 7)-amino-4-hydroxynaphthalene-2-sulphonic acids to yield brownish dyes. The direct brown dye obtained by coupling bis-4-aminophenylurea with 6-amino-4-hydroxynaphthalene-2-sulphonic acid and salicylic acid showed good results on being tested.

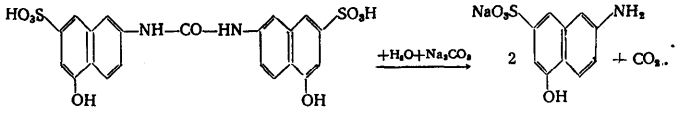


The new dye showed better fastness than the direct brown formed by coupling benzidine with gamma-acid and salicylic acid[193] [2-hydroxynaphthalene-6,8-disulphonic acid (Ed. of Translation)].

VIII. HYDROLYSIS AND OTHER REACTIONS OF DIARYLUREAS

Diarylureas are hydrolysed only under relatively severe conditions. For example, diphenylurea is split into aniline and carbon dioxide on being heated with concentrated hydrochloric acid in a sealed tube[194,196]. Breakdown products of diphenylurea are formed also on prolonged boiling with acetic anhydride in the presence of sodium acetate[196]. Cleavage of diphenylurea is quite complete in glacial acetic acid or in boiling aqueous pyridine[197]. Claus[141] obtained aniline and urea on heating diphenylurea in alcoholic ammonia in a sealed tube to 140°–150°. According to the patent literature[198], hydrolysis of diphenylurea and its nitro-derivatives also occurs when they are heated in aqueous ammonia under pressure.

Heating diphenylurea in 80–90% sulphuric acid at 170°–180° leads to the formation of aniline and sulphanilic acid[199]. In this case ring sulphonation takes place at the same time as hydrolysis of the diphenylurea. The hydrolysis products of diphenylurea are stable in alkaline medium. For example, 5,5'-dihydroxydinaphth-2-ylurea-7,7'-disulphonic acid is hydrolysed on being heated in sodium carbonate solution, and is converted into a salt of J-acid, the degree of hydrolysis depending on the temperature and the duration of heating[200]:



Bis-*o*-tolylurea, which is little affected by treatment with acid or alkali at normal pressures, is almost completely hydrolysed in acid medium under high pressures[195]. Also, bisnitrotolylurea and bischloronitrophenylurea are readily hydrolysed in concentrated acetic acid or in aqueous pyridine on heating[197].

A detailed investigation[3,190,201] of the hydrolysis of diphenylurea and bis-4-nitrophenylurea showed that the hydrolysis of these diarylureas is greatly affected by the medium, the temperature, and the duration of heating.

Hydrolysis of diphenylurea in hydrochloric acid is observed only when the mixture is heated in a sealed glass tube above 100°. The degree of hydrolysis increases with rise in temperature, and also in the concentration of hydrochloric acid. Whereas at 105° the yield of aniline is 55.9% after 2 h, at 150° it reaches 99%.

A similar situation is found in the hydrolysis of diphenylurea and bis-4-nitrophenylurea in sulphuric acid. The yield of aromatic amines increases as the concentration of sulphuric acid is increased. The optimum acid concentration is 75%, further increase leading to a diminution in the yield of amines.

In alkaline medium the hydrolysis of diphenylurea takes place as in acid media, but at temperatures above 100°. When the compound is heated with 10% caustic soda solution to 150°, the yield of aniline is 98.8%. Increasing the caustic soda concentration to 20% diminishes the yield of aniline, and a tarry black product appears.

Heating diphenylurea in 4.5% aqueous ammonia in a sealed glass tube at 150° for 4 h gives an almost theoretical (99.25%) yield of aniline. The peculiar ease of hydrolysis of diphenylurea in the presence of ammonia is probably due to the ammonia reacting directly with the diphenylurea to form aniline and urea, the latter being decomposed by water to yield ammonia and carbon dioxide:

$$C_6H_5NHCONHC_6H_5+2NH_3 \rightarrow 2C_6H_5NH_2+H_2NCONH_2,$$

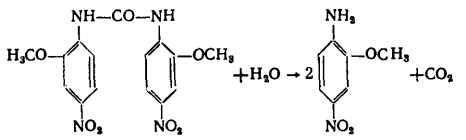
$$H_2NCONH_2+H_2O \rightarrow 2NH_3+CO_2.$$

The resulting ammonia then reacts afresh with the diphenylurea, and so on. With bis-4-nitrophenylurea, the best hydrolysing agent is aqueous ammonia, which even in minute concentrations effects almost quantitative hydrolysis of the starting material.

Alkaline hydrolysis takes place more readily than does acid hydrolysis. Complete hydrolysis of diphenylurea requires the use of concentrated hydrochloric acid (36.37%),

whereas the same degree of hydrolysis requires only 10% alkali.

An investigation has been reported[177] of the hydrolysis of bis-2-methoxy-4-nitrophenylurea with aqueous ammonia:



Hydrolysis was carried out at 150° under pressure. In 1% aqueous ammonia it went smoothly, giving a yield of 2-methoxy-4-nitroaniline exceeding 90% of theoretical. It was also found that bis-2-methoxy-4-nitrophenylurea is comparatively readily hydrolysed under pressure at high temperatures in aqueous medium even without the addition of ammonia. However, when the diarylurea is heated in aqueous medium (without ammonia) to 150° and above under pressure, resinification of the product occurs, indicating that the main reaction (hydrolysis) is accompanied by side-reactions involving oxidation.

Hydrolysis in aqueous ammonia under pressure at 150° has been studied also[3] in the case of bis-3-nitrophenylurea, bis-*o*-tolylurea, bis-2-methyl-4-nitrophenylurea, and bis-4-aminophenylurea. In all cases high yields of the final products were obtained.

Under identical conditions, bis-4-nitrophenylurea is somewhat more difficult to hydrolyse than is diphenylurea itself. The presence of two electrophilic nitro-groups in the molecule increases the stability of the molecule as a whole, so that more severe conditions are required for reaction.

The present author made a detailed study[202] of the hydrolysis of bis-2,4,6- and bis-2,4,5-trichlorophenylureas. These compounds are more stable to hydrolysis and undergo cleavage only under severe conditions. This hydrolytic stability is considerably influenced by the medium (acid or alkaline), elevated temperatures, and the duration of the process. These compounds undergo hydrolysis relatively easily in aqueous ammonia. A comparative estimate of the rate of hydrolysis of bis-4-nitrophenylurea and bis-2,4,6-trichlorophenylurea (containing considerable amounts of tetra- and penta-chloro-derivatives) showed the chlorinated diarylureas to be more resistant to hydrolysis. The results are illustrated by the curves in Fig. 1.

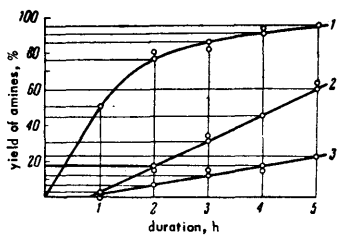
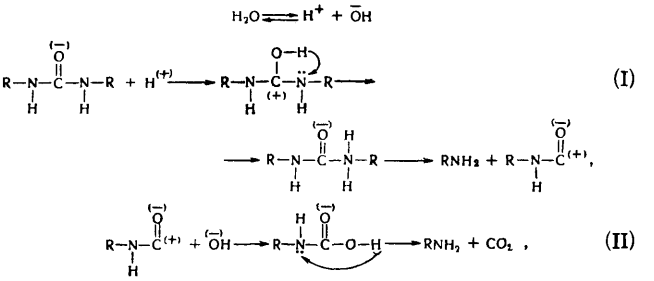


Fig. 1. Yield of amines in the hydrolysis of substituted ureas: 1) *p*-nitroaniline; 2) 2,4,6-trichloroaniline; 3) 2,4-dichloroaniline.

It was found that, of the two bistrichlorophenylureas, the 2,4,5-isomer is more difficult to hydrolyse in sulphuric acid than is the 2,4,6-compound. In 90% sulphuric acid at room temperature, the former remains unchanged for 24 h, whereas under the same conditions the bis-2,4,6-trichlorophenylurea slowly breaks down into trichloroaniline and carbon dioxide. This difference in behaviour between the two isomers can obviously be explained by the presence in each ring of the 2,4,6-isomer of two *ortho*-chlorine atoms, which strengthen the inductive effect, and tend to weaken the amide bond.

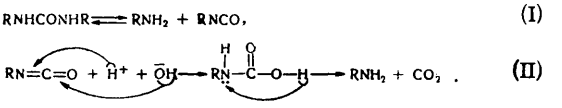
Hydrolysis of diarylureas takes place by an ionic mechanism[202]:



(I)

(II)

where R = C_6H_5, $C_6H_2Cl_3$, $C_6H_3Cl_2$, $C_6H_4NO_2$, etc. At higher temperatures under pressure, however, it is likely that hydrolysis can take place also by a different mechanism[202]:



(I)

(II)

According to this mechanism, the diarylurea, under the influence of temperature and pressure, dissociates into an aromatic amine and an aryl isocyanate, and the latter, being extremely reactive, reacts rapidly with a dissociated water molecule, forming a transition compound, which owing to its instability is decarboxylated with formation of a second molecule of the aromatic amine.

In spite of the great stability of the diarylureas to hydrolysis, they are able to undergo several chemical reactions, which have also been investigated recently. However, the differences in chemical properties among individual diarylureas are not substantial, and are exhibited only under severe conditions. An attempt was made to examine the reasons for the differences in chemical properties between several diarylureas as a function of their structure[203].

In order to study the influence of the number and nature of the substituents in the benzene rings on the stretching vibration of the carbonyl group, the infra-red spectra of a series of diarylureas were determined. The results in Table 2 show that the frequencies of the stretching vibrations of the carbonyl groups are fundamentally the same in all the diarylureas examined. They are practically unaffected by introducing different numbers and different types of substituents into the aromatic rings. In this case the inductive effect, for example of chlorine atoms present in the aromatic rings of a diarylurea, is unable to affect the vibration frequency of the carbonyl group.

This phenomenon is probably due to the ability of the carbonyl group to form a hydrogen bond of the type >C=O...H–N<.[204,205] It must be assumed that the hydrogen

TABLE 2.

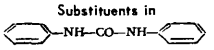
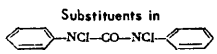
Substituents in 	ν_{max}, cm^{-1}
Unsubstituted diphenylurea	1640
2,4,2′,4′-Tetrachloro-	1640
2,4,6,2′,4′,6′-Hexachloro-	1640
2,3,5,6,2′,3′,5′,6′-Octachloro-	1640
2,4,6,2′,4′-Pentachloro-	1643
2,4,6,4′-Tetrachloro-	1645
2,4,5,2′,4′,5′-Hexafluoro-	1646 and 1683

TABLE 3.

Substituents in 	ν_{max}, cm^{-1}
2,4,2′,4′-Tetrachloro-	1709
2,6,2′,6′-Tetrachloro-	1714
2,4,6,2′,4′,6′-Hexachloro-	1721
2,4,5,2′,4′,5′-Hexachloro-	1723
2,3,5,6,2′,3′,5′,6′-Octachloro-	1735
2,4,5,2′,4′,5′-Hexafluoro-	1727
2,4,6,2′,4′-Pentachloro-	1730

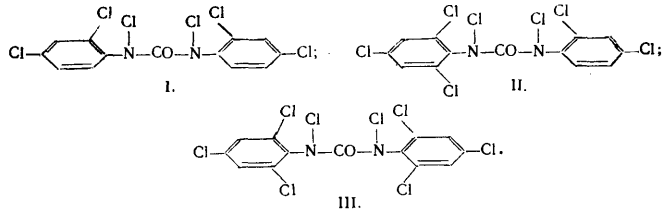
bond exerts a stronger influence than does the inductive effect transmitted through the aromatic ring. This results in the effect of the hydrogen bond on the C=O frequency predominating over that due to the substituents. On the basis of these ideas it is possible to explain the constancy of the C=O frequencies in the case of ring-chlorinated diarylureas and unsubstituted diphenylurea.

In this way the peculiarities in the chemical properties of diarylureas can obviously be explained by the presence of hydrogen bonds between the carbonyl oxygen and the hydrogen atoms attached to the nitrogen atoms. This explains the slight diminution in the basic properties of the diarylureas — the suppression of the reactivity of the carbonyl double bond and thereby an increase in chemical stability.

Replacement by chlorine of the hydrogen atoms attached to nitrogen in a diarylurea produces a marked change in the physical state of the compounds. The infra-red absorption spectra of various *N*-chlorinated diarylureas were therefore examined[203], and the frequencies of the carbonyl stretching vibrations in these compounds determined.

It is evident from the results (Table 3) that in this case the situation is completely different. Whereas the carbonyl stretching frequencies in the original diarylureas were fundamentally constant at 1640 cm^{-1}, in the *N*-chlorinated derivatives the frequencies varied, their minimum value being 1709 cm^{-1}. Furthermore, the C=O stretching frequencies increase with increase in the number of halogen atoms in the aryl radicals of the *N*-chlorinated diarylureas. Obviously, this fact also indicates the presence of hydrogen bonds in the original diarylureas. The observed vibrational frequencies of the carbonyl group in the *N*-chlorinated diarylureas are consistent with modern views on the inductive effect of substituents on such frequencies[205,206].

The increase in the frequency of the stretching vibration of the carbonyl group in *N*-chlorinated diarylureas with increasing number of substituents in their benzene rings, is consistent with the variation in the dipole moments. The latter were determined for several *N*-chlorodiarylureas, the values obtained being 3.29 D for *NN′*, 2,4,2′,4′-hexachlorodiphenylurea (I), 3.45 D for *NN′*, 2,4,6,2′,4′-heptachlorodiphenylurea (II), and 3.88 D for *NN′*, 2,4,6,2′,4′,6′-octachlorodiphenylurea (III).[203]



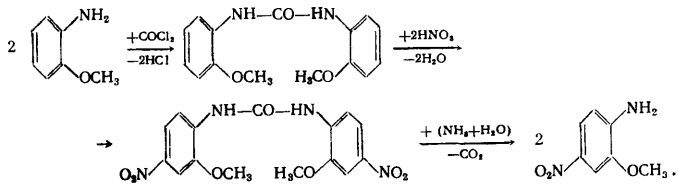
I. II.

III.

The results indicate that the dipole moments of *N*-chlorinated diarylureas increase with increasing number of chlorine atoms in the aromatic radicals.

IX. SYNTHESIS OF AROMATIC AMINES *VIA* DIARYLUREAS AND BY OTHER NEW METHODS

The results obtained for the nitration, chlorination, and hydrolysis of the diarylureas, and also the work on their interaction with aniline and other reactions, have been of definite practical value. They have formed the basis of new processes for preparing *p*-nitro-*o*-anisidine, *p*-nitroaniline, trichloroanilines, and other aromatic amines, as well as some benzene derivatives. Thus, for example, a new method[177] has been developed for obtaining *p*-nitro-*o*-anisidine (Azoamin Pink O, C.I. Azoic Diazo Component 5) *via* the diarylurea and its dinitro-derivative:



In this process carbonyl chloride is used as an acylating agent, which with *o*-anisidine readily yields bis-2-methoxyphenylurea. Nitration of this product with nitric acid forms bis-2-methoxy-4-nitrophenylurea, hydrolysis of which under appropriate conditions gives up to 93% yields of *p*-nitro-*o*-anisidine. Azoamin Pink O is an important intermediate in the production of azo-dyes.

It has been suggested[3,164] that *p*-nitroaniline could be produced in a similar manner *via* bis-4-nitrophenylurea.

Nitration of diphenylurea is effected with dilute nitric acid, when bis-4-nitrophenylurea is formed almost exclusively[168]. Hydrolysis of the latter with aqueous ammonia under pressure yields *p*-nitroaniline[201].

A noteworthy new process[130] for obtaining *p*-nitroaniline from aniline and nitric acid without an acylating agent involves a closed cycle based on displacement of one amine by another (transamidation), which can be represented diagrammatically as in Fig. 2. In this process the diphenylurea also undergoes nitration with dilute nitric acid[168]. The final products, *p*-nitroaniline and diphenylurea, are formed by the reaction of the resulting bis-4-nitrophenylurea with

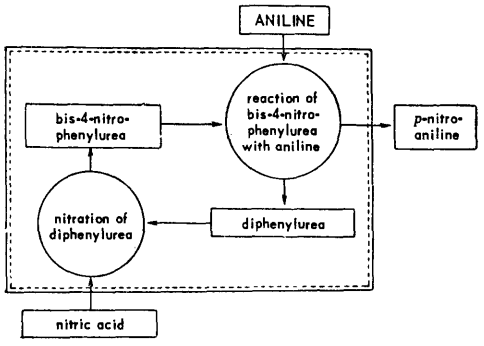
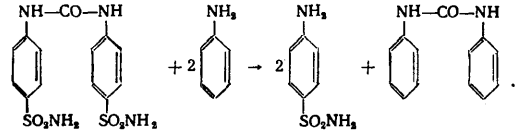


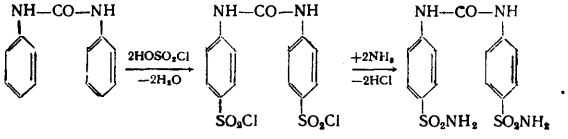
Fig. 2.

the aniline. After separation of the *p*-nitroaniline, the diphenylurea again undergoes nitration, and so on.

Gerchuk and Livshits[207,208] suggested a method based on transamidation for producing sulphanilamide (Prontosil Album) from diphenylurea 4,4'-disulphonamide. When the latter is heated with aniline, reaction takes place with the formation of sulphanilamide and diphenylurea:

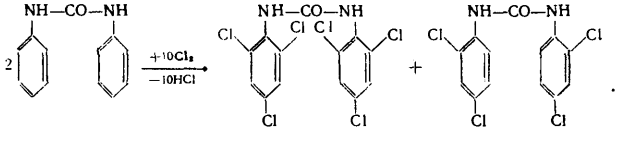


After separation of the sulphanilamide, the resulting diphenylurea is successively chlorosulphonated with an excess of chlorosulphonic acid and amidated with ammonia:



The resulting diphenylurea 4,4'-disulphonamide again reacts with aniline, and so on.

In the course of research on the chlorination and the hydrolysis of diarylureas, the present author and his collaborators[187,202] developed a process for the simultaneous production of 2,4,6-trichloroaniline and 2,4-dichloroaniline *via* chlorinated diarylureas. For this purpose, diphenylurea is chlorinated with elementary chlorine in aqueous medium at 70° for 40 h:



The resulting mixture of bis-2,4,6-trichlorophenylurea and bis-2,4-dichlorophenylurea is hydrolysed.

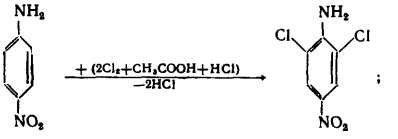
This process is very simple and practicable, in contrast to those described in the literature for preparing chlorinated anilines[209].

A very interesting new method for preparing 2,4,6-trichloroaniline from aniline and chlorine[163] can be applied as a closed cycle (see Fig. 3). Diphenylurea is chlorinated with elementary chlorine in acetic acid. The resulting bis-2,4,6-trichlorophenylurea is heated with aniline, and displacement of one amine by the other results in the formation of 2,4,6-trichloroaniline and diphenylurea. The latter, after separation of the trichloroaniline, is again subjected to chlorination, and so on.

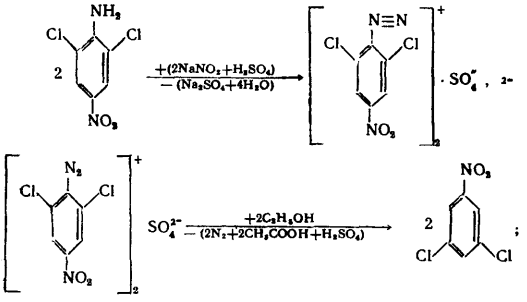
Since small amounts of bis-2,4-dichlorophenylurea are formed in the chlorination of diphenylurea, 2,4-dichloroaniline will, of course, be formed in the transamidation. The latter is readily removed by treating the mixture of chloroanilines with 5% hydrochloric acid[202]. Better results are obtained by separating the chloroanilines by partition chromatography[210].

The present author and Rozanova[13] have also developed a process for preparing chemically pure 2,4,6-trichloroaniline by introducing chlorine into a specified position in the aromatic ring:

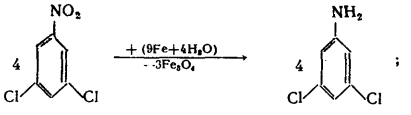
1. Preparation of 2,6-dichloro-4-nitroaniline



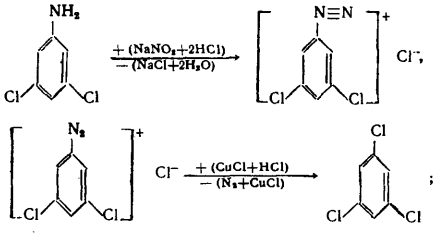
2. Preparation of 3,5-dichloronitrobenzene



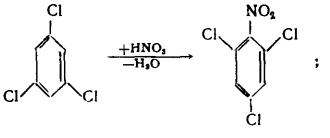
3. Preparation of 3,5-dichloroaniline



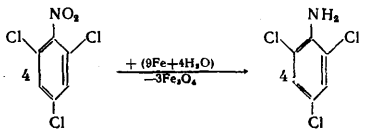
4. Preparation of 1,3,5-trichlorobenzene



5. Preparation of 2,4,6-trichloronitrobenzene



6. Preparation of 2,4,6-trichloroaniline



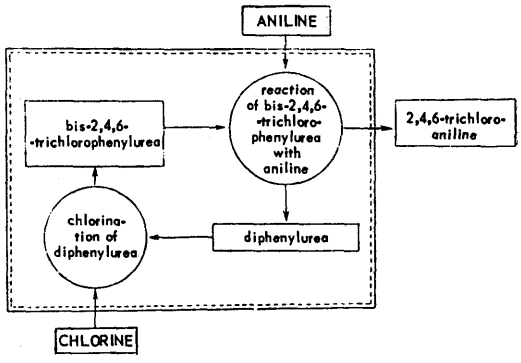
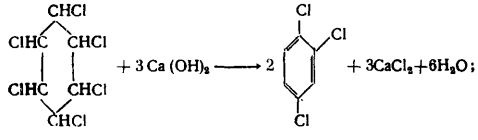


Fig. 3.

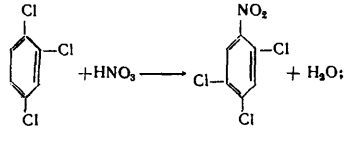
The preparation of the 3,5-dichloronitrobenzene involves diazotisation of the 2,6-dichloro-4-nitroaniline followed by reaction of the diazonium salt with alcohol[211]. Conversion of the 3,5-dichloroaniline into 1,3,5-trichlorobenzene is effected by replacement of the amino-group in the former with chlorine by Sandmeyer's method[212].

Chemically pure 2,4,6-trichloroaniline was used in the synthesis of bis-2,4,6-trichlorophenylurea of a high degree of purity for physicochemical investigations and for other purposes.

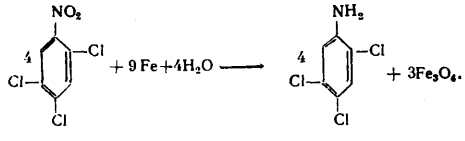
The results obtained in work on the starting materials for the synthesis of diarylureas enabled a method to be developed for preparing 2,4,5-trichloroaniline from non-toxic hexachlorocyclohexane isomers[213]:



Preparation of 2,4,5-trichloronitrobenzene

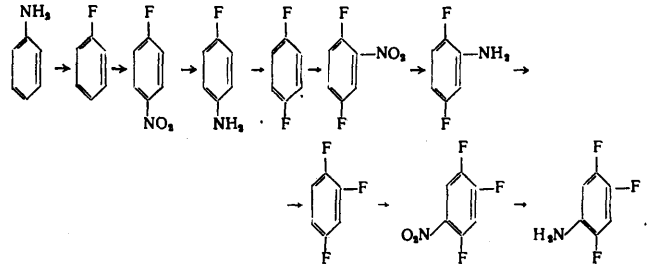


Preparation of 2,4,5-trichloroaniline



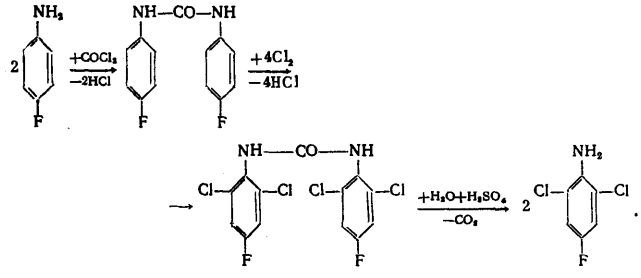
2,4,5-Trichloroaniline is of practical value for the synthesis of bis-2,4,5-trichlorophenylurea and for other preparations.

In the course of the synthesis of diarylureas, methods were worked out[17] for obtaining fluorinated nitrobenzenes and anilines:



Fluorobenzene is prepared from aniline by Schiemann's method[18], which is also used to introduce subsequent fluorine atoms into the ring. Nitration of the fluorinated benzenes is carried out with either fuming nitric acid or with a nitrating mixture. The nitro-compounds are reduced to the corresponding fluorinated anilines by means of iron filings in the presence of acetic acid and emulsifier OP-7.

The present author and his collaborators[13,15,16] have elaborated methods for obtaining various chlorinated, brominated, and iodinated nitrobenzenes and anilines. For example, 2,6-dichloro-4-fluoroaniline is obtained as follows[15]:



Similarly, 2,4-dichloro-6-fluoroaniline has been obtained starting from *o*-fluoroaniline. 4-Bromo-2,6-dichloroaniline is readily obtained in good yield by bromination of 2,6-dichloroaniline in acetic acid. Iodination of 2,6-dichloroaniline with iodine monochloride in acetic acid yields 2,6-dichloro-4-iodoaniline.

All these compounds are of great value for the production of lightfast dyes, and for various technological materials, including polymers.

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Thus we see that considerable progress has been made during recent years in synthesis and reactions of diarylureas. A large number of previously undescribed substituted diarylureas have been synthesised as a result of the research that has been done. These comprise primarily ring-halogenated derivatives containing fluorine, chlorine, and the other halogens. In several cases other ring substituents are also present.

Chlorinated and fluorinated diarylureas are widely used in the synthesis of various medicinal preparations, while

their *N*-chloro-derivatives serve as degasifying, disinfecting, and disinfesting agents. *N*-Substituted dialkyldiphenylureas are employed as stabilisers for smokeless powders, etc.

Investigations of the diarylurea series have involved the synthesis of several new starting materials, in particular fluorinated and chlorinated benzenes, aromatic amines, aryl isocyanates, and other compounds, which are of great practical interest and may serve as intermediates for the production of stable, lightfast organic dyes, for weed-killers, insecticides, and fungicides, and also for the preparation of various new polymeric materials possessing superior physical and mechanical properties.

Several theoretical studies have been undertaken. The influence of substituents, of their nature and number, on the properties of diarylureas, in particular on the reactivity, has been elucidated. For the first time a detailed study has been made of the mechanism of the reaction between aromatic amines and carbonyl chloride, the possible steps involved have been given, and some intermediate compounds have been isolated. The reactivity of aromatic amines towards carbonyl chloride has been studied, and its fundamental causes have been established. All these results are of practical value for the development of industrial methods for the preparation substituted diarylureas.

The reactions studied are of great interest. During the course of these investigations various new chlorinated aryl isocyanates have been synthesised, enabling processes to be worked out for obtaining unsymmetrical diarylureas, which had not previously been described in the literature, and are also of practical interest.

Theoretical studies have been made of the transamidation of diarylurea derivatives. This reaction was investigated in detail in the case of the interaction of bisnitro- and trichloro-phenylureas with aromatic amines. The reversibility of the reaction between bis-4-nitrophenylureas and aniline has been demonstrated. New methods have been worked out, based on the reaction between aromatic amines and urea, for obtaining substituted diarylureas, bistrichlorophenylurea, and others, without using carbonyl chloride.

Noteworthy work has been done on the preparation of substituted diarylureas by direct nitration or chlorination of the original diphenylurea. These researches have led to a detailed study of the nitration and chlorination processes. On the basis of these reactions, a new method has been worked out for obtaining bis-4-nitrophenylurea by nitrating diphenylurea with nitric acid. Processes have also been developed for preparing bistrichlorophenylurea by chlorinating diphenylurea with elementary chlorine. All these methods are of great practical value.

The hydrolytic properties of diarylureas and their substituted derivatives have been studied. It has been found that these compounds possess great stability to hydrolysis, undergoing cleavage only under severe conditions. A mechanism has been proposed for the hydrolysis of diarylureas. Several of their other chemical properties have been studied.

The studies on the nitration, chlorination, and hydrolysis of diphenylurea and its derivatives, as well as research on the reaction of diarylureas with aniline, have led to new methods for preparing *p*-nitroaniline, trichloroaniline, and other aromatic amines.

The advances which have been made in synthesis and reactions of diarylureas are of undoubted theoretical interest and of great practical value.

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THE CHEMISTRY OF AQUEOUS SOLUTIONS OF ZIRCONIUM SALTS (DOES THE ZIRCONYL ION EXIST?)

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1. INTRODUCTION

The considerable progress made in the chemistry of zirconium in aqueous solutions in the past 10–15 years urgently demands reconsideration of some of the ideas which have prevailed in the science of zirconium for a whole century, since the time of Berzelius, Hermann, Endemann, and other 19th century chemists. This relates primarily to the assertion, which appears in all modern textbooks, that the majority of zirconium salts are derivatives of the "zirconyl", "dizirconyl", and similar radicals.

The question of the existence of the zirconyl ion is one of the fundamental and at the same time one of the most complex problems in the chemistry of zirconium. It is usually assumed that "zirconyl chloride", "zirconyl nitrate", and other basic products of the hydrolysis of the Zr^{4+} ion, containing one or two equivalents of acid per zirconium atom, are compounds whose individual nature is sufficiently well-defined and whose analytical formula has been reliably established. Nevertheless there is no direct proof for the "zirconyl" structure of these compounds.

Modern reviews of the chemistry of zirconium usually do not discuss the history of the development of the "zirconyl theory" and the "zirconyl structure" of zirconium salts is regarded as an obvious property of the element. In the present paper an attempt has been made to systematise the published data on the chemistry of zirconium in aqueous solutions. It is shown, from an examination of the properties of aqueous and acidic solutions of, for the most part, the chlorides and nitrates, that there is no justification for the zirconyl theory.

2. HISTORICAL REVIEW

When dissolved in water, zirconium tetrachloride, like most other normal zirconium salts, is readily converted to the "oxychloride", which can be isolated from solution either by concentrating solutions of the chloride or by treating these with concentrated hydrochloric acid. The fact that hydrochloric acid solutions of zirconium always give a compound containing about two chlorine atoms per atom of zirconium attracted the attention of research workers at an early date. This phenomenon was first observed by Berzelius[1], who did not, however, consider it possible to ascribe any definite formula to the basic chloride which he isolated; the Zr : Cl ratio in this compound was not always constant and often varied within the range 1 : 1.6 – 1 : 1.9.

Berzelius' observation — that a characteristic feature of this compound was its ready loss not only of water but also of hydrogen chloride, even at comparatively low temperatures†, so that, as he suggested, a compound of indefinite composition is formed — did not, however, prevent Hermann[2] from announcing, in 1844, the existence of zirconyl chloride.

In his first studies Hermann made no definite attempt to relate the characteristic properties of this salt to its composition, but he nevertheless put forward two ways for writing the formula of this compound: $ZrOCl_2.9H_2O$ or $Zr(OH)_2Cl_2.8H_2O$‡. In subsequent papers[3,4] Hermann finally brought into use the zirconyl formula for basic zirconium chloride, based entirely on its property of separating from acidic solutions in the form of a precipitate containing about two chlorine atoms per zirconium atom.

By analogy with zirconyl chloride, Endemann[9] attributed to the monochloride which he isolated the formula $Zr_2O_3Cl_2.xH_2O$. Subsequently workers such as Paÿkyll[10], Bailey[11], Venable[12], Ruer, Chauvenet, and others unreservedly postulated the zirconyl structure for the basic chlorides and extended it not only to chlorides of any composition but also to other basic and complex zirconium compounds.

Ruer and Chauvenet strengthened the zirconyl theory of the structure of basic zirconium compounds. In a study of the electromigration of the metal in solutions of the chlorides[6,13,14] and sulphates[14,15], Ruer found that in the latter case the zirconium migrates chiefly to the anode, whereas in the presence of hydrochloric acid, cathodic migration is observed. Ruer attributed this marked difference in the properties of the chloride and sulphate solutions of zirconium to the presence, in the sulphate solutions, of a complex ion with the zirconyl structure $[ZrO(SO_4)_2]^{2-}$. Moreover, the characteristic properties of the sulphate solutions with respect to precipitation by oxalic acid, together with the exceptional stability to heat of the monohydrate of normal zirconium sulphate, were taken by Ruer as further confirmation of the zirconyl structure of the sulphate complex. Even at the present time, Blumenthal[16–18] puts forward these hypotheses of Ruer as a decisive argument in support of the zirconyl structure for the sulphates and other compounds of zirconium.

Ruer also considered that the ions of the metal present in chloride solutions also have the zirconyl structure. Two types of ion, the zirconyl and dizirconyl ions, were said to exist.

Chauvenet[19] carried out conductimetric titration of aqueous solutions of some normal zirconium salts and found that the titration curves were not straight lines, like those usually obtained in acid–base titrations, but had an appreciable curvature. The tangents drawn at the end of the curve intersect at a point corresponding to the addition of approximately two equivalents of alkali. Chauvenet considered that these experiments provided convincing proof of the existence of the zirconyl ion.

The development of the chemistry of zirconium up to this period was reviewed by Venable[12]. On the basis of the ideas of the "zirconyl theory", he put forward the following scheme for the hydrolysis of zirconium tetrachloride:

$$ZrCl_4+H_2O \rightarrow ZrOCl_2+2HCl,$$
$$2ZrOCl_2+H_2O \rightarrow ZrO(OH)_2.ZrOCl_2+2HCl.$$

If more than two molecules of zirconyl chloride are hydrolysed, the formation of a more complex product, for example Rodd's salt $Zr_5O_8Cl_4.xH_2O$,[20] is possible.

General schemes for the hydrolysis of the chlorides, nitrates, and other compounds of zirconium were subsequently considered by many workers, but these differ little

† The liberation of free hydrogen chloride when aqueous solutions of zirconium dichloride were evaporated or during thermal dehydration of the salt $ZrOCl_2.xH_2O$ ($x \leq 10$) was subsequently shown by a number of workers[2–8].

‡ Komissarova *et al.*[8] gives a complete compilation of the hydrated forms of zirconium dichloride.

from those given above, particularly Blumenthal's schemes, and are therefore not discussed here.

Better justified views on the nature of aqueous solutions of zirconium salts were put forward by Britton[21], who repeated Chauvenet's experiments and found that the statement regarding the existence of the zirconyl ion was inaccurate. According to Britton, the mean composition of zirconium chloride in solution changes continuously during the electrometric titration; this is due to the fact that the basic chlorides do not contain zirconyl groups and the quantity of hydroxy-groups attached to the zirconium increases continuously with increase in pH. Normal zirconium tetrachloride, on dissolution in water to give a 0.1 M solution, is hydrolysed to the extent of 58%, while the basic chloride with a Zr : Cl ratio of 1 : 1.737 in 0.01 M solution is hydrolysed to the extent of 54%. One of the intermediate products of the hydrolysis is a chloride with empirical composition $[Zr(OH)_{3.5}Cl_{0.5}]$. As emphasised by Britton, the formation of this chloride is responsible for the inflection on the curve taken by Chauvenet as obvious proof of the existence of the zirconyl ion. On the basis of these data and the results of conductimetric titration of aqueous solutions of normal zirconium sulphate, Britton categorically rejected the existence of the zirconyl ion. Britton confirmed Chauvenet's observation regarding the formation, under certain conditions, of a highly hydrolysed sulphate with a $Zr : SO_4^{2-}$ ratio of 1 : 0.5. He was the first to focus attention on the colloidal nature of solutions of zirconium salts.

Unfortunately, Britton's work did not become widely known, but the correctness of his views can now be supported by a large quantity of experimental data, some of which will be examined below.

The zirconyl theory was opposed not only by Britton, but also by Kulka[22], who considered that the composition of zirconium dichloride can be expressed by a formula which does not include the zirconyl oxygen atom, and later by Schmid[23], who predicted, on the basis of structural theories, that the zirconyl ion should not exist. Schmid was the first to prepare zirconium trichloride, whose composition is close to the empirical formula $ZrOCl_2.HCl.xH_2O$ or $Zr(OH)Cl_3.xH_2O$. The existence of zirconium trichloride cannot be explained by the zirconyl theory.

Recently, Larsen[24] pointed out that 0.05 M zirconium dichloride solution has a pH of ~1. These observations are difficult to reconcile with the results of cryoscopic measurements[25,26] and electrical conductivity measurements, if it assumed, as is usually done, that the solution contains only the zirconyl ion.

3. PROPERTIES OF AQUEOUS SOLUTIONS OF ZIRCONIUM SALTS

Hydrolysis. The tetrachloride, tetranitrate, and other normal salts of zirconium cannot be recrystallised, even from strongly acidic solutions, without some hydrolysis. Dissolution in water is accompanied by extensive hydrolysis of these compounds, so that aqueous solutions of normal zirconium salts are strongly acidic. Similar properties are exhibited by solutions of basic zirconium chlorides.

Ruer[6,13] measured the electrical conductivity of 0.25 M zirconium dichloride solution at 18° and found that hydrolysis increases with time and is much more extensive at higher temperatures. Venable and Jackson[27] repeated Ruer's experiments and demonstrated the dependence of hydrolysis on the concentration of the original solution. They showed that hydrolysis increases with dilution. Similar results were obtained by Jander and Jahr[28].

According to Adolf and Pauli[29], the change in the degree of hydrolysis of zirconyl chloride with time in the concentration range 0.0022–0.125 M is irregular, and when equilibrium is reached, in ~10 days, the degree of hydrolysis amounts to 35–50%. Küntzel and Rosenbusch[30] and Tananaev and Guzeeva[31] give for similar conditions the values 48.3% and 30% respectively. Simple recalculation of the data[31] by Britton's method[21] shows, however, that the degree of hydrolysis changes with dilution from 27% in 0.25 M solution to 40% in 0.01 M solution[32]. Solovkin[32] has compiled the pH values for solutions of the dichloride of different concentrations and has pointed out that the measurements of the pH of solutions of the same concentrations by different workers often do not agree, due to the characteristic properties of zirconium salt solutions, and in particular to the slow rate of attainment of equilibrium, which may take several weeks[33], months[34], or years[35] in the case of the sulphate solutions.

Green[36] and Sandell[37] consider that the colorimetric determination of zirconium with alizarin S is possible only in 0.1–0.2 M HCl, since extensive hydrolysis takes place at lower hydrochloric acid concentrations. Mayer and Bradshaw[38] found, however, that hydrolysis of zirconium is suppressed only in 1.5 M HCl. In a study of the reaction of zirconium with alizarin S, the authors established that when solutions with an acidity less than 0.5 M with respect to HCl were allowed to stand, irreversible hydrolysis occurred, but that in 1.0–1.5 M HCl solutions of zirconium underwent no significant hydrolysis over a period of 266 h. Intensive hydrolysis of a 5×10^{-4} M solution of the dichloride was observed by Gübely and Jacoby[39]. According to their data, the reaction with alizarin S takes place only in the presence of hydrochloric acid, and the order of addition of the reagents to the aqueous dichloride solution is of considerable importance. If the alizarin S is added first, followed by HCl, the results of the determination vary considerably and are difficult to reproduce. The reversal of hydrolysis is slow. The reverse order of addition of the reagents, which also ensures that the zirconium is kept in HCl solution, makes it possible to obtain reproducible results.

Many other examples of the influence of hydrolysis on the analytical chemistry of zirconium are given by Elinson and Petrov[40].

Larsen and Gammill[41] established that zirconium solutions containing a small quantity of free hydrochloric acid contain an extensively hydrolysed ion whose mean composition can be represented by the formula $[Zr(OH)_{3.4}]_n^{0.6n+}$. This corresponds closely to Britton's data[21]. With macro-concentrations of zirconium (0.04 M), hydrolysis is observed even in 4 M HNO_3.[42] With tracer quantities of ^{95}Zr, however, according to Paramonova and Voevodskii's data[50], hydrolysis takes place only at an acidity less than 1 M with respect to HNO_3. Intensive hydrolysis of zirconium salts in aqueous and weakly-acidic solutions has been reported by a number of authors[43–48] and in some earlier papers[12,18,49]. The nature of the acid has a significant influence on the hydrolysis of zirconium. As shown by Jander and Jahr[28] and Larsen[24], hydrolysis in perchloric acid solutions is much less than that in hydrochloric or nitric acids.

Polymerisation. Sol formation in aqueous and acidic solutions of zirconium has often been observed, and this phenomenon considerably complicates the chemical behaviour of zirconium. Sol formation is directly related to hydrolysis and explains many features of the chemistry of zirconium in aqueous solutions.

When caustic alkali or ammonia is added to solutions of zirconium chlorides or nitrates, hydrolysis proceeds to completion with the precipitation of zirconium hydroxide, which has an extremely high adsorbent power[51]. Zirconium hydroxide does not form hydrates of definite composition[52-55]. The product precipitated on boiling is less soluble than that precipitated in the cold.

Boiling, or even slight heating, leads to more extensive hydrolysis. The most basic products are those obtained at high temperatures. Although zirconium can be precipitated from nitric acid solutions hydrolytically, *i.e.* merely by boiling the dilute solutions, no precipitates have been obtained hydrolytically from solutions of the chlorides. For example, Bashilov[56] reported that zirconium can be precipitated hydrolytically from hydrochloric acid solutions only if the hydrochloric acid content of the solution does not exceed several mg per litre.

Repeated evaporation of aqueous solutions of the chlorides leads to volatilisation of hydrochloric acid, and it is possible to prepare solutions in which the Zr : Cl ratio = 1 : 0.35.[7] The solutions are stable at a 5 M zirconium concentration for 6 months. Ruer[6,57,58] by repeated evaporation of a dilute aqueous solution of zirconium dichloride, obtained gelatinous precipitates of composition $(ZrO)_5(OH)_8Cl_2.xH_2O$ and $Zr_{10}O_{19}Cl_2.xH_2O$, which he believes to be derivatives of "metazirconic acid" $ZrO(OH)_2$, which is generally precipitated from boiling solutions. These compounds ("metazirconyl chlorides") are particularly stable and can be converted to zirconyl chloride only by prolonged boiling with concentrated hydrochloric acid for 30 h.

Zirconium hydroxide, particularly that prepared from boiling solutions, is readily peptised by water[59] or by solutions of zirconium nitrate or sulphate; in the latter case the peptisation product is not converted to basic nitrates or sulphates and retains the properties of a sol for prolonged periods[60,61]. The hydro-sols are stable in moderately-concentrated acid solutions[62].

Zirconium hydroxide sol has been prepared directly by precipitating with alkali and by dialysis of aqueous and acidic solutions at room temperature or above[63]. A complete review has been given by Blumenthal[18]. The sol has high adsorptive power and may have either positive or negative charges, due to adsorption of an excess of cations or anions[51,64]. The sols isolated by different methods may have zirconium : anion weight ratios of 20 : 1,[65] 7 : 1,[66] 8.1–17 : 1,[67] 40 : 1,[57] 6.6–16.2 : 1,[68] etc. The sol is sensitive to the action of electrolytes and in some cases can be precipitated quantitatively by the addition of dilute solutions of salts such as KCl, KBr, etc[45,69-72]. Increase in temperature increases the quantity of the sol, and the sol is converted to a gel[62]. Coagulation is more extensive when zirconyl chloride or zirconyl nitrate solutions are diluted[45]. Ruer[57] pointed out that addition of $AgNO_3$ to an aqueous solution of a sol prepared by dialysis of zirconium chloride does not give a precipitate of silver chloride. A precipitate can be obtained only after the sol has been boiled for a prolonged period with concentrated acid.

After aging and boiling the sol is hydrolysed with the liberation of free HCl[67]. In this case the duration of boiling has a considerable influence. The pH of the solutions remains unchanged after boiling, indicating that the process is irreversible. The pH was measured 6 h and 6 months after boiling.

According to Robinson and Ayres' data[62], the viscosity of the sol decreases with increase in temperature, and the percentage coagulation of the sol increases. Heating leads to a continuous decrease in the pH of the solutions and a decrease in the degree of hydration of the sol. Thomas and Owens[67] have shown that the decrease in pH of the solutions when the sol is aged or boiled is due to a structural rearrangement.

The nature of the polymers (colloids) obtained at low acidities or present in dilute aqueous solutions of zirconium salts differs considerably from that of the polymers observed in strongly acidic media[24]. In the latter case the reaction readily becomes reversible. Even at high hydrogen ion concentrations, however, solutions containing zirconium, when allowed to stand for a prolonged period, contain polymers whose formation is not readily reversible and which have the same properties as the polymers obtained at low acidities. For example, they are difficult to convert to compounds extractable by various organic solvents. Larsen[24] has related the difference between these two forms to their particle size.

Lister and McDonald[42] used ^{95}Zr to study spontaneous diffusion in a 0.1 M solution of zirconium in nitric acid and established that in the HNO_3 concentration range 0.02–6 M the molecular weight of the polymers decreases by a factor of approximately 6. From ion-exchange data, these authors conclude that in 6 M HNO_3 the size of the zirconium ions is not greater than 4–6 Å. The zirconium cations contain nitrate ions in addition to OH^-.

The state of zirconium in neutral and acidic aqueous solutions. The properties of freshly prepared solutions of normal and basic zirconium salts differ sharply from those of the aged or boiled solutions. The former give no precipitate when sulphuric acid or soluble sulphates are added, whereas the latter form persistent precipitates. From the freshly prepared solutions, alkali metal tartrates and oxalates precipitate zirconium salts which are readily soluble in an excess of precipitant, whereas in the case of the aged or boiled solutions the precipitates do not redissolve. The hydroxide precipitated from the boiled solution has a different composition after drying at 100° and dissolves (is peptised) in aqueous zirconium chloride solution, whereas zirconium hydroxide obtained from the freshly prepared solution is insoluble in this solvent.

It is possible to distinguish arbitrarily three states of zirconium in neutral and weakly acidic aqueous solutions of its salts, depending on the temperature and time (for macroconcentrations). Solutions freshly prepared in the cold show many reactions characteristic of the relatively weakly hydrolysed and polymerised ionised zirconium, which is present predominantly, as will be shown below, in the cationic form (nitrates, halides, perchlorates). Solutions which have been allowed to stand for a short time, or solutions which have been extensively diluted, are characterised by a greater degree of hydrolysis and polymerisation, and this leads to the separation of such strongly basic products as Rodd's salt. Aqueous solutions of Rodd's salt differ from freshly prepared solutions in that they give precipitates when sulphate ions are added.

Boiling for a short period with hydrochloric acid converts it almost completely to basic zirconium chloride, indicating that the hydrolysis and polymerisation processes taking place during its formation are reversible. In solutions which have been allowed to stand for a prolonged period, or which have been boiled, irreversible rearrangement of the colloidal zirconium structure takes place, leading to the appearance of such stable compounds as Ruer's salt. The processes taking place in this case will be examined below. The unhydrolysed monomer can exist only in strongly acidic media.

The conversion of zirconium from one state to another is accompanied by the following phenomena: a change in the pH of the solution, with time, a change in viscosity, an increase in the degree of hydrolysis and polymerisation, conversion of the sol to a gel, the formation of non-extractable forms, etc.

The very marked influence of the conditions of preparation and storage of solutions of zirconium salts on their properties necessitates special methods for the preparation of solutions of monomolecular zirconium, particularly in work with radioactive isotopes.

Ayres[73] has shown by an ion-exchange method that 0.1 M zirconium nitrate solution is colloidal and has no clearly defined ionic character. In 1.5 M HNO_3, however, the cationic character of zirconium is retained for one month[75]. Contrary to the data of Benedict and Schumb[75], it has been reported, on the basis of a study of the adsorption of zirconium on cation-exchange resins[71,72,74], that solutions of tracer quantities of zirconium in 1 M HNO_3 and HCl are partly colloidal. In accordance with this, Schubert and coworkers[71,72,74] and Steinberg[76] recommend that zirconium be kept in 10 M HCl. They consider that only under these conditions does zirconium remain in the form of a monomeric cation. The storage of zirconium in concentrated acids to prevent hydrolysis and polymerisation is recommended by a number of authors[38,39,77].

Starik[78], however, suggests that the data of Schubert and coworkers can be explained by the formation, in moderately acidic media, of neutral molecules of the type $[Zr(OH)_x(NO_3)_{4-x}]^0$ whose existence has been established for the case of macroquantities of zirconium[42].

The cationic nature of zirconium in dilute hydrochloric, perchloric, and nitric acids, which have a weak complexing action on zirconium, is now generally accepted. The cathodic migration of zirconium in hydrochloric acid solutions was first observed by Becquerel[79], who electrolysed zirconium and ferric chlorides and isolated a film of zirconium crystals on the cathode. Ruer[6] studied the electromigration of zirconium in 0.5 M HCl and found 0.028 g of the metal on the cathode but only 0.0005 g on the anode. The existence of a singly-charged zirconium cation in weakly acidic solutions has been demonstrated by Hildebrand[80], Britton[21], and the Kurbatovs[45]. Laubengayer and Eaton[43] tried to reduce zirconium in hydrochloric acid solutions to the tri- and di-valent states. According to their data, aqueous solutions of the chlorides are complex in character, and in weakly acidic solutions the chief form of zirconium is a cation with Zr : Cl = 1. The cationic nature of zirconium in the range of at least moderate concentrations of acids and the presence of cationic forms in aqueous solutions of the normal sulphate have been shown by ion exchange[81,82], electrolysis[83-86], and other methods[46,87]. The existence of the hydrated cation $[ZrO(H_2O)_4]^{2+}$ has been reported by Hevesy and Wagner[88].

Repeated assertions in the literature that anionic forms of zirconium exist in aqueous solutions of the chlorides and nitrates, or in weakly acidic (HCl, HNO_3) solutions, have not subsequently been confirmed experimentally. Adolf and Pauli[29] tried to establish the composition of the equilibrium solutions of basic zirconium chloride. According to their data, measurements of the pH of the solutions and study of electromigration indicate the presence of ions of two types: the cations $[2Zr(OH)_4.ZrOCl_2.ZrO]^{2+}$, $[Zr(OH)_4.ZrO]^{2+}$, $[2Zr(OH)_4.ZrO]^{2+}$, etc., and the anions $[Zr(OH)_2Cl_4]^{2-}$, $[Zr(OH)_4Cl_2]^{2-}$, etc. An interesting feature is that in these formulae the authors introduce hydroxyls as well as zirconyl groups; none of the anionic forms assume the zirconyl structure.

Sidgwick[64] and Weiser[51] consider, however that Adolf and Pauli's conclusions[29] regarding the existence of anionic forms of zirconium under the conditions described are contradictory to other data, particularly the data of Ruer[6,13,14] and Britton[21], and that the source of their errors is sol formation and the extremely high adsorptive power of the sols.

In this respect Blumenthal's work is significant. In 1949 Blumenthal[16] detected the existence of the $[ZrO_2Cl_2]^{2-}$ ion during the conductimetric measurement of the pH of boiling aqueous solutions of zirconium chloride, and assumed that the zirconyl chloride is present almost entirely in the form of this complex. Nevertheless, no indications of the formation of such an acido-complex were found in subsequent papers[17,18].

The existence of negatively charged zirconium ions is possible only in strongly acidic media or in the presence of powerful complex-forming reagents. The anionic nature of zirconium, particularly in concentrated hydrochloric acid and nitric acid solutions, has been shown by ion exchange[89], extraction[32], and preparative methods[34]. In the presence of complex-forming reagents such as HF,[90,91] salicylate, citrate, tartrate, H_3PO_4,[92] and H_2SO_4,[93] zirconium for the most part forms negatively charged complexes.

Considerable anodic migration of zirconium in perchloric acid solutions at $HClO_4$ concentrations greater than 1 M was established by Lister and McDonald[42]. These authors noted that, in sulphuric acid solutions, zirconium migrates chiefly to the anode, but that in 0.5 *N* H_2SO_4 anodic migration takes place to a much smaller extent than was observed by Ruer[13] and decreases in the H_2SO_4 concentration range 1.5–3 *N*. Lister and McDonald pointed out that the rate of hydrolysis and polymerisation processes in zirconium salt solution is low, so that equilibrium in systems such as the perchloric, hydrochloric, nitric, and sulphuric acid solutions is established slowly over a period of many days or weeks, depending on the nature of the anion of the acid. For concentrations of the order of 0.1 M the authors give the following possible formulae for the state of zirconium in solution.

1. In perchloric acid solutions, with increase in acidity, colloidal $Zr(OH)_4$ is first converted to highly polymerised, positively charged ions and then to the dizirconyl ion $Zr_3O_3^{2+}$, which in turn is converted to the monomer $Zr(OH)_2^{2+}$ and to acido-complexes whose nature has not been established.

2. In nitric and hydrochloric acid solutions Lister and McDonald[42] identified a large number of ionic and molecular forms of zirconium containing nitrate or chloride ions: $Zr_3O_5^{2+}$ (or $Zr_4O_7^{2+}$) $\xrightarrow{HNO_3}$ $Zr_2O(OH)_4^{2+}$ $\xrightarrow{HNO_3}$ $\xrightarrow{HNO_3}$ $Zr(OH)_3^+$ $\xrightarrow{HNO_3}$ (at low zirconium concentrations) $Zr(OH)_2(NO_3)^+$ $\xrightarrow{HNO_3}$ $Zr(OH)_2(NO_3)_2$ and $Zr(NO_3)_2^{2+}$ $\xrightarrow{HNO_3}$ $\xrightarrow{HNO_3}$ $Zr(OH)_2(NO_3)_4^{2-}$ or $Zr(NO_3)_6^{2-}$.

3. In sulphuric acid solutions, in the H_2SO_4 concentration range $< 0.5\ N$, zirconium exists in both cationic and anionic forms, but in the H_2SO_4 concentration range $> 1.5\ N$ only neutral and negatively charged forms are assumed to be present. Similar results have been obtained by other workers[94,95].

On the basis of their studies, Lister and McDonald concluded that the Zr^{4+} ion does not exist, but Larsen and Wang[96] pointed out that this conclusion is erroneous. Subsequently, the Zr^{4+} ion was identified by a number of workers by extraction, ion exchange, and other methods (see below).

Contrary to the data of Lister and McDonald[42], Nabivanets[97] in a study of the electromigration of zirconium ions at a zirconium concentration 0.05 M, observed no significant migration of zirconium to the anode in perchloric acid solutions. He found that Lister and McDonald's error in the design of their experiment lay in the use of zirconium nitrate as starting material; this could lead to the formation in solution of mixed nitratoperchlorato anionic species. Nabivanets[97] established that in perchloric, hydrochloric, and nitric acids at $[H^+] \leq 0.5$ M, zirconium is present only in cationic forms. Increase in the perchloric acid concentration above 1 M leads to the appearance of anionic complexes, but the cationic species still predominate; the quantity of neutral complexes increases with increase in the $HClO_4$ concentration. The formation of anionic and neutral complexes is observed in hydrochloric and nitric acid solutions at $[H^+] > 0.5$ M. The quantities of cationic and anionic species become equal at HCl and HNO_3 concentrations 8–9 M and ≥ 4 M respectively.

Lister and McDonald's data[42], obtained for macroconcentrations, cannot be extended to solutions containing tracer quantities of zirconium. In the first place, at microconcentrations, no polymerisation takes place over a wide range of hydrogen ion concentrations[78], which simplifies considerably the identification of the ionic state of zirconium in solutions of perchloric, hydrochloric, and nitric acids.

The state of tracer quantities of zirconium in solution was studied by ion exchange and electrophoresis by Belyavskaya and Mu Ping-Wên[98], who found that hydrochloric acid solutions contain the $Zr(OH)_3^+$ ion at an HCl concentration $\sim 0.1\ N$, the $Zr(OH)_2^{2+}$ ion in the range 0.5–1.5 N HCl, and the $Zr(OH)^{3+}$ ion in 2 N HCl. In the case of nitric acid solutions in the HNO_3 concentration range 0.03–2 N these authors assume that positively charged zirconium ions predominate, and that neutral species are also formed. In sulphuric acid solutions, they observed considerable cationic absorption at an H_2SO_4 concentration 0.076 N, but in $\sim 4\ N$ solution the cationic absorption decreases sharply to zero and anionic absorption becomes fairly high. More acidic solutions apparently contain only negatively charged ions and neutral molecules. These assumptions were confirmed by electrophoretic data.

In agreement with Belyavskaya and Mu Ping-Wên, Yatsimirskii and Raizman[99] assume that the $Zr(OH)_3^+$ ion predominates at pH 1 in dilute solutions of the dichloride.

Starik[78] made a detailed examination of the state of radiozirconium ^{95}Zr in solutions. Comparison of the data of Starik[78] and coworkers with published data obtained in the study of the state of zirconium by different methods showed that in aqueous solutions at a concentration $\sim 10^{-11}$ M, depending on the conditions, zirconium may exist as simple and complex ions, neutral molecules, adsorption colloids (pseudocolloids) (pH 1.6–4), and true colloids (pH 4–12) of zirconium hydroxide.

4. COMPLEX FORMATION BY ZIRCONIUM IN AQUEOUS AND ACIDIC SOLUTIONS OF ITS SALTS

Complex formation with OH^- ions and polymerisation. Zirconium is a typical transition element with valence-electron configuration $4d^25s^2$, and its properties in aqueous solutions are determined by the electrostatic characteristics of the Zr^{4+} ion. The high charge, small radius, and comparatively low ionisation potential make it possible to classify Zr^{4+} among the electrostatic complex-forming ions[100].

In an examination of complex ions in solution it is necessary to take into consideration the fact that water molecules may also act as ligands, forming complex aquo-ions. In the formation of aquo-complexes a decisive part is played by ion–dipole interaction. For the formation of a stable complex with ionic bonding, it is necessary not only that the central ion have a high charge and small radius, but also that the ligand be able to satisfy conditions for ion–dipole interaction to a sufficient extent. Water has a considerable dipole moment and high electron affinity, and forms stable aquo-ions with Zr^{4+} characterised by ionic bonding[100].

The first task in the study of aquo-complexes should be the determination of the pH range in which they exist in the presence of anions which are not complex-forming agents.

Qualitative predictions of the hydrolytic behaviour of hydrated ions can be made on the basis of energetic characteristics. If the type of bonding is the same, in all cases the relative tendency of quadruply-charged ions to undergo hydrolysis should increase in the order

$$Th^{4+} < U^{4+} < Np^{4+} < Pu^{4+} \simeq Ce^{4+} < Hf^{4+} < Zr^{4+},$$

i.e. in the order of increasing ionic potential, f. The Zr^{4+} ion, which has the highest ionic potential ($f = 5$, $z = 4$, $r = 0.8$)[100,101] in this series, shows a clearly defined tendency to undergo complex formation with hydroxide ions. Theoretical calculations show that the equilibrium constant for the reaction

$$M(H_2O)_x^{4+} + H_2O \rightleftharpoons M(OH)(H_2O)_{x-1}^{3+} + H_3O^+,$$

should vary[101] from approximately 2×10^{-4} for Th^{4+} to 2.5×10^{-1} for Zr^{4+}, so that hydrolysed hydrated ions, particularly the Zr^{4+} ion, should be stable in solutions of dilute acid.

Recent experimental studies not only give qualitative data on the state of zirconium in solution over a wide range of hydrogen ion concentrations, but also make possible a quantitative characterisation of the hydrolytic and polymerisation processes.

Using different physicochemical methods, Starik and Skul'skii[102] studied the state of ^{95}Zr ($\sim 10^{-9}$ M) in nitric acid solutions. According to their data, zirconium exists in the following forms, depending on the pH of the medium: the monomers Zr^{4+} and $Zr(OH)^{3+}$ at pH < 0; the monomers $Zr(OH)^{3+}$, $Zr(OH)_2^{2+}$, $Zr(OH)_3^+$, and $Zr(OH)_4$ at pH 0–1; the monomer $Zr(OH)_4$ and polymers $[Zr(OH)_x^{4-x}]_n$ at pH 1.5–4; polymers $[Zr(OH)_4]_n$, colloidal, at pH 4–12; zirconates at pH > 12. Similar results were obtained for hydrochloric acid solutions in the hydrogen ion concentration range 0.1–2 M.[97]

Connick and coworkers[103,104] studied the hydrolysis and polymerisation of zirconium perchlorate at 25° by extracting ^{95}Zr with thenoyltrifluoroacetone and found that, at tracer concentrations in 2 M $HClO_4$, zirconium exists chiefly in the form of the monomer Zr^{4+}. In the range 0.2–2 M $HClO_4$ the mean composition of zirconium ions corresponds to the formula $Zr(OH)^{3+}$, and at $HClO_4$ concentrations less than 0.2 M to the formula $Zr(OH)_2^{2+}$. The equilibrium constant for the reaction[24]

$$Zr(OH)^{3+} + H_2O \rightleftharpoons Zr(OH)_2^{2+} + H^+,$$

is 0.187. Increase in the zirconium concentration leads to the formation of polymers. The concentration threshold for polymerisation is $\sim 2 \times 10^{-3}$ M in 2 M $HClO_4$ and decreases to 2×10^{-4} M at $[H^+] = 1$ M.

According to Paramonova and Sergeev's data[105], hydrolysis in solutions containing tracer quantities of zirconium begins at $HClO_4$ concentrations less than 1–1.2 M. Larsen and Wang[96] report that, at concentrations of the order of 10^{-4} M in 2 M $HClO_4$, zirconium exists chiefly as the Zr^{4+} ion[96].

Solovkin[32] used Connick and McVey's experimental data[103] to calculate the equilibrium constants for the successive reactions involved in the hydrolysis of the Zr^{4+} ion in $HClO_4 + LiClO_4$ solutions at an ionic strength of 2:

$$Zr^{4+} + H_2O \rightleftharpoons Zr(OH)^{3+} + H^+; \quad K_1 = 0.6 \pm 0.05,$$

$$Zr(OH)^{3+} + H_2O \rightleftharpoons Zr(OH)_2^{2+} + H^+; \quad K_2 = 0.24 \pm 0.03,$$

$$Zr(OH)_2^{2+} + H_2O \rightleftharpoons Zr(OH)_3^+ + H^+; \quad K_3 = 0.09 \pm 0.01,$$

$$Zr(OH)_3^+ + H_2O \rightleftharpoons Zr(OH)_4 + H^+; \quad K_4 = 0.068 \pm 0.006.$$

The values of the first and second constants agree satisfactorily with other published data[24,101].

Peshkova *et al.*[106] give the following values for the hydrolysis constants of the Zr^{4+} ion at tracer concentrations at an ionic strength of 1, maintained by $HClO_4 + NaClO_4$: $K_1 = 2 \times 10$; $K_2 = 0.87$; $K_3 = 0.45$; and $K_4 = 0.23$.

The constant for the hydrolysis of the Zr^{4+} ion according to the equation

$$Zr^{4+} + H_2O \rightleftharpoons ZrO^{2+} + 2H^+,$$

was estimated approximately ($K \simeq 2$)[107] on the basis of a study of the solubility of zirconium mandelate in $HClO_4$ solution. Pyatnitskii and Pilipyuk[107] postulated the existence of the ZrO^{2+} ion.

Quantitative data characterising the polymerisation process, which, according to Schultz and Larsen[108], takes place according to the equation

$$Zr_n(OH)_{nx}^{n(4-x)+} \rightleftharpoons nZr(OH)_x^{(4-x)+},$$

and the most probable forms of the polymers in dilute perchloric and hydrochloric acids have been given by Zielen and Connick[109] and Kraus and Johnson[110,111]. The latter[110] studied 0.05 M solutions of zirconium in the systems 1 M MCl + 1 M HCl, where M = Li, Na, and Cs, by means of an ultracentrifuge and detected only one form of zirconium, with an apparent degree of polymerisation equal to 3 and charge < 3. In solutions of 0.1 M HCl + + 1.9 M NaCl the degree of polymerisation varied in the range 4–5.4. Similar observations were made for $HClO_4$ + + $NaClO_4$ solutions but in this case the charge on the polymers was higher.

Later[111] it was found that in 1 M HCl or $HClO_4$ the most stable species are trimers and tetramers, with a charge of ~ 1 per monomeric unit in the case of the solutions in HCl. Decrease in temperature from 25° to 5° leads to a considerable decrease in the degree of polymerisation of zirconium in 0.08 M HCl. Aging or heating increases the degree of polymerisation. In 5 M HCl the degree of polymerisation is < 2.

These results were confirmed by Zielen and Connick[109], who established that in 1 M and 2 M $HClO_4$ at 25°, in the zirconium concentration range $0.02–10^{-4}$ M, the chief forms are the trimer $Zr_3(OH)_4^{8+}$ and the tetramer $Zr_4(OH)_8^{8+}$. These authors[109], in agreement with Johnson and Kraus' data[111], found no evidence of the existence of dimers (the dizirconyl ion). This contradicts the results of Lister and McDonald[42] and imposes some limitations on their conclusions. The formation constants at 25° for the trimer and tetramer

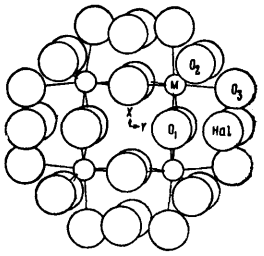
$$nZr^{4+} + xH_2O \rightleftharpoons Zr_n(OH)_x^{(4n-x)+} + xH^+,$$

at an ionic strength of 2 and hydrogen ion concentrations 1 M and 2 M were found to be $(2.4 \pm 0.3) \times 10^5$ and $(2.5 \pm \pm 0.4) \times 10^5$ for the trimer and $(2.0 \pm 0.2) \times 10^8$ and $(1.5 \pm \pm 0.2) \times 10^8$ for the tetramer, respectively.

This work[102–104,109–111] provides an experimental basis for a critical examination of existing views on the chemistry of zirconium in aqueous medium, particularly with regard to the statements that zirconyl and dizirconyl ions are the chief forms in which zirconium exists in aqueous solution. The incorrectness of these views is proved not only by the work cited, but also by X-ray diffraction studies of crystalline basic zirconium chloride and bromide[112] and their aqueous solutions[113], and by data on the dehydration of the basic chloride, whose composition, according to various workers[114], is represented by the empirical formula $ZrOCl_2 . 9(10)H_2O$.

There is no need to deal in detail with Clearfield and Vaughan's demonstration[112] that the structure of basic zirconium chloride is described by a formula including the tetramer $[Zr_4(OH)_8 . 16H_2O]^{8+}$, although this is of considerable interest from the viewpoint of the structural and preparative chemistry of zirconium. For an understanding of the phenomena taking place in aqueous solutions of zirconium salts, an X-ray diffraction study[113] of aqueous solutions of basic zirconium chloride and bromide is more important.

Aqueous solutions (2 M) of these salts were studied. The experimental data clearly indicate the existence, under these conditions, of $[Zr_4(OH)_8(H_2O)_{16}]X_8$, where $X = Cl^-$ or Br^-. The dichloride is more stable than the dibromide. Similar observations were made for hafnium halides. On the basis of these results, a structural formula is suggested (see Figure) for the "oxyhalides" of zirconium and hafnium in solution (for the latter, in the salt concentration range 0.5–2 M).



Structure of zirconyl chloride and hafnyl chloride in aqueous solutions[113]. [Here M = metal, O = oxygen, and Hal = halogen atom. Muha and Vaughan[113] comment that this structure for the hafnyl halides gives good agreement with X-ray scattering data but the agreement is not as good for zirconyl halide solutions and there may be more highly polymerised species in the latter (Ed. of Translation).]

An extremely unusual feature is that the chloride ions in the structure of the tetramer are not directly bound to the zirconium ion.

In the light of this work, the ideas of Larsen[24] and Connick and McVey[108] regarding the continuous polymerisation of zirconium in aqueous solutions§ in the range of concentrations of zirconium and hydrogen ions studied[109-111,113] are incorrect. It follows from the above that, depending on the metal concentration and acidity of the aqueous solution, zirconium may exist either in the form of monomers of general formula $Zr(OH)_x^{4-x}$, where $x = 0, 1, 2, 3$, and 4 (at a zirconium concentration of the order of 10^{-9} M and pH < 1.0) or in the form of the trimer and tetramer (at high acidities up to a zirconium concentration 2 M). The existence of an extended concentration plateau corresponding to polymer formation was noted by Lister and McDonald[42], but these authors did not determine the composition of the polymers and merely drew attention to their small dimensions. The average charges on the trimer and tetramer depend on the acidity, zirconium concentration, and nature of the anion of the acid. In perchloric acid solutions (1 M and 2 M) the average charges on one monomeric unit are 2.66 and 2.0 respectively (the degree of hydrolysis and polymerisation increases), but in 1 M HCl the charge is approximately equal to unity, and this is apparently due both to an increase in the degree of hydrolysis and to complex formation by the Zr^{4+} and Cl^- ions. In aqueous 2 M solutions of basic zirconium halides, the zirconium is present in the form of a neutral hydrated complex (tetramer). The trimer and tetramer (together with the monomer) are evidently the most stable forms of zirconium in aqueous solutions. Ions and molecules with a higher degree of polymerisation are observed only in the range of low hydrogen ion concentrations, or, what is essentially the same thing, in dilute solutions of zirconium salts. The latter feature, although it appears to contradict the ideas regarding the increase in the degree of polymerisation with increase in the zirconium concentration, is fairly simply explained: dilution of solutions of, for example, zirconium dichloride, leads to a decrease in the total concentration of hydrogen ions (despite the increase in the degree of hydrolysis), and this facilitates polymerisation (the concentration threshold of polymerisation is displaced towards much lower concentrations in the range of high pH values). This can be seen particularly clearly from a paper by Solovkin[7], who showed that, whereas 5 M solutions of the chloride with a Zr : Cl ratio = 1 : 0.35 are transparent and stable over a fairly prolonged period, the 0.5 M solutions show a marked opalescence and a tendency to deposit a gel. The retarding influence of hydrogen ion on polymerisation was observed by Britton[21]. The question of whether the polymerisation process under these conditions is stepwise or continuous has not been clarified.

The foregoing relates to solutions which have not been heated or aged. As already noted, heating or aging changes the properties of aqueous solutions of zirconium salts, and this has a significant influence on much of the work with zirconium.

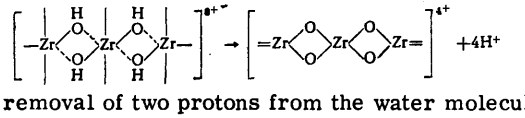
A theoretical explanation of the processes taking place when zirconium salt solutions are aged or heated has been given by Thomas[116,117], who found that zirconium salts in solution are condensed systems in which the metal atoms are joined by hydroxyl and (or) oxygen bridges to form polyatomic ions or molecules. The first stage in the condensation involves hydrolysis and the formation of hydroxyl bridges, accompanied by the liberation of the appropriate number of protons (olation). Here it is assumed that the formation of hydroxyl bridges involves the water molecules present in the first coordination sphere of the hydrated ion, for example according to the reaction (for the formation of the trimer)

$$3[Zr(H_2O)_x]^{4+} + 4H_2O \rightleftharpoons [Zr_3(H_2O)_{3x-4}(OH)_4]^{8+} + 4H_3O^+.$$

Increase in temperature or the duration of the aging process leads to further dissociation with the liberation of protons (oxolation):

$$[Zr_3(H_2O)_{3x-4}(OH)_4]^{8+} + 4H_2O \rightleftharpoons [Zr_3O_4(H_2O)_{3x-4}]^{4+} + 4H_3O^+.$$

When the hydrogen ion concentration in the solution is low, the rates of the olation and oxolation reactions increase. The first of the reactions is reversible (although the reactivity of the coordinated OH^- ions decreases in the olation process), whereas the second is difficult to reverse, particularly in the case of the zirconium oxide hydrosols. The condensed ions or molecules often contain the anions of the acid present in the solution. If the coordination sphere of the hydroxo- or oxo-compounds contains a sufficient number of anions, the complex acquires a negative charge (when an excess of soluble salts is added). The structural formulae of the condensed ions can be represented as follows:



The removal of two protons from the water molecule at the zirconium explains the appearance, under suitable

§ It has recently been found by dialysis[115] that the degree of polymerisation of zirconium in 2 M, 1 M, and 0.1 M solutions of $HClO_4$ increases continuously with change in the metal concentration from 1×10^{-3} M to 1×10^{-1} M, but these results, according to the authors are approximate, since the degree of hydration of the simple and, particularly, the polymeric forms of zirconium is unknown. Moreover, the retarding action of the membrane may be different for particles whose dimensions differ considerably.

conditions, of small but extremely stable species in strongly acidic media (probably the trimer or tetramer with oxygen bridges), whose formation cannot easily be reversed[24]. At high pH values further hydrolysis of the polymers takes place by the above mechanism, leading finally to an increase in the degree of polymerisation and dehydration (the mechanism of dehydration of basic zirconium chloride has been examined by Castor and Basolo[114]). The formation of Rodd's salt is apparently the first step in this direction. The properties of Rodd's salt show that the bond between the zirconium atoms in this case is formed chiefly by hydroxyl-bridges.

The theory devoloped by Thomas explains many of the properties of boiled or aged solutions of zirconium salts, described in detail above. In particular, it explains the formation and exceptional stability of Ruer's metazirconyl chloride and metazirconic acid, and also the chief properties of boiled or aged solutions, compared with freshly prepared solutions or solutions which have been allowed to stand for a short period.

Complex formation with other inorganic and organic ligands. It has been established[118] that the tendency to form complexes with zirconium, shown by the ligands normally used in chemistry, decreases in the following order: $OH^- > F^- > PO_4^{3-} > > C_2O_4^{2-} > SO_4^{2-} > NO_3^- > Cl^-$. It has also been noted[72] that HF has a much more powerful complexing action on zirconium than H_3PO_4 and, more particularly, H_2SO_4. The formation of complexes by zirconium with HF[31,38,71,115,119] and H_2SO_4[38,39,50,120-126] has been described.

Thomas and Owens[67] studied the influence of the addition of neutral potassium salts of various organic and inorganic acids on the pH of a zirconium hydrosol and showed that the ligands which they studied can be arranged in the following order: citrate > oxalate > malate > > tartrate > glycolate > succinate ~ malonate ~ maleate ~ ~ propionate ~ acetate ~ fumarate > formate > sulphate > chloride ~ nitrate.

Complex formation by zirconium with sulphuric, hydrofluoric, oxalic, malonic, succinic, glutaric, fumaric, maleic, orthophosphoric, orthoboric, metasilicic, acetic, and trifluoroacetic acids, and with hydrogen peroxide, was studied by Connick and McVey[103], who established that of these the most powerful complex-forming reagents are HF, $H_2C_2O_4$, and H_2SO_4. Acetic, orthoboric, succinic, and malonic acids have almost no complexing action on zirconium.

Connick and coworkers[103,104] made a detailed study of complex formation by zirconium with sulphate and fluoride ions in 2 M $HClO_4$ and showed that the complexes formed by zirconium with F^- ions are more stable than those formed with HSO_4^- ions. They obtained the following values for the successive reactions involved in the formation of complexes with F^- and HSO_4^- ions:

$$Zr^{4+} + HF \rightleftharpoons ZrF^{3+} + H^+; \quad K_1 = 63 \times 10^5,$$
$$ZrF^{3+} + HF \rightleftharpoons ZrF_2^{2+} + H^+; \quad K_2 = 2.1 \times 10^4,$$
$$ZrF_2^{2+} + HF \rightleftharpoons ZrF_3^{+} + H^+; \quad K_3 = 6.7 \times 10^2,$$
$$Zr^{4+} + HSO_4^- \rightleftharpoons ZrSO_4^{2+} + H^+; \quad K_1 = 4.6 \times 10^2,$$
$$ZrSO_4^{2+} + HSO_4^- \rightleftharpoons Zr(SO_4)_2 + H^+; \quad K_2 = 53,$$
$$Zr(SO_4)_2 + HSO_4^- \rightleftharpoons Zr(SO_4)_3^{2-} + H^+; \quad K_3 = 1.$$

As can be seen from these equations, the authors did not assume the zirconyl structure for the complexes which they identified.

Complex formation by zirconium with sulphate ions was studied by Marov[127] by an ion-exchange method at an ionic strength of 2.33; he obtained for the equilibrium constants of the reaction

$$Zr^{4+} + i\ HSO_4^- \rightleftharpoons Zr(SO_4)_i^{4-2i} + iH^+ \quad (i \leqslant 3),$$

the values $K_1 = 466$, $K_2 = 3.48 \times 10^3$, and $K_3 = 3.92 \times 10^5$.

Nitrate and chloride ions have a weak complexing action on zirconium. The above data show that the tendency to form complex ions with Zr^{4+} is much less for Cl^- and NO_3^- ions than for sulphate and fluoride ions and many organic acids. According to Adamskii *et al.*[128], increase in the nitric acid concentration leads first to a decrease and then to an increase in the activity coefficients of zirconium. The nature of the change in the activity coefficients indicates that processes leading to an increase in the effective zirconium concentration (particularly as a result of extensive hydration) have a greater influence than ion association. All the quantitative calculations on complex formation in nitric and hydrochloric acid solutions refer to tracer quantities, *i.e.* to conditions under which polymerisation does not take place.

Connick and McVey[103] studied the extraction of zirconium nitrate and chloride by thenoyltrifluoroacetone at an ionic strength of 2 and found that the equilibrium constant K_1 for the reaction

$$Zr^{4+} + A^- \rightleftharpoons ZrA^{3+},$$

where A = Cl or NO_3, is equal to 2 in both cases. They pointed out that the values may be high, due to the presence of impurities. Later McKay[129] studied complex formation by Zr^{4+} with thenoyltrifluoroacetone in aqueous solution and obtained $K_1 = 0.59$ and $K_2 = 0.090$ (at an ionic strength of 4).

The values $K_1 = 2.2$, $K_2 = 1.3$ ($K_2 = 1.7$ is given by Paramonova and Sergeev[105]), $K_3 = 0.55$, and $K_4 = 0.15$ were obtained by Solovkin[32] from data on the extraction of ^{95}Zr by tri-n-butyl phosphate in $HNO_3 + HClO_4$ mixtures at a total hydrogen ion concentration 4 M. It was shown that the curve giving the dependence of the logarithm of the zirconium partition coefficient on the nitrate ion concentration in the hydrogen ion concentration range 3–4 M can be explained if it is assumed that under these conditions negatively charged $Zr(NO_3)_5^-$ and $Zr(NO_3)_6^{2-}$ ions, with formation constants $K_5 \simeq 0.03$ and $K_6 \simeq 0.02$, are formed. The existence of these complexes in the HNO_3 concentration range above 2.5 M was pointed out by Trofimov and Stepanova[130].

Marov[127], using an ion-exchange method, found for the stability constants of the nitrato-complexes of the Zr^{4+} ion the values $K_1 = 0.92$, $K_2 = 0.46$, at an ionic strength of 2, and $K_1 = 0.88$, $K_2 = 0.14$, at an ionic strength of 4.

Solovkin[32] used the data of Levitt and Freund[131], obtained at an ionic strength of 6.54, to calculate the constants for complex formation by the Zr^{4+} ion with chloride ions and obtained $K_1 = 8.4$, $K_2 = 21$, $K_3 = 32$, and $K_4 = 15$. He did not consider the possibility of the formation of acido-complexes under these conditions, although Alimarin *et al.*[132] and earlier workers (see above) proved the existence of negatively charged zirconium complexes by ion exchange, electrophoresis, and other methods. According

to Marov's data[127], the stability constants of the chloro--complexes of the Zr^{4+} ion are $K_1 = 0.95$, $K_2 = 0.12$, $K_3 = 0.07$, and $K_4 = 0.08$ at an ionic strength of 2, and $K_1 = 1.1$, $K_2 = 0.21$, and $K_3 = 0.05$ at an ionic strength of 4.

There are no quantitative data on complex formation by zirconium, at macroconcentrations with hydrochloric and nitric acids. Qualitative observations show that the formation of polynuclear ions and hydrosols containing the anions of the acid present in the solution are exceptionally widespread in the case of zirconium.

Perchloric acid is often used to maintain a constant ionic strength in the study of complex formation by zirconium in solution by various physicochemical methods, and it is usually assumed that the perchlorate ion does not react with Zr^{4+} ions. Lister and McDonald[42], Nabivanets[97], and others have shown, however, that zirconium forms acido-complexes with perchlorate ions even at fairly moderate $HClO_4$ concentrations. On the other hand, data on the extraction of zirconium from perchloric acid by tri-n-butyl phosphate show that reaction between zirconium and $HClO_4$ is also possible at low acidities[133,134]. In particular, Siekierski[134] pointed out that the tendency of the Zr^{4+} ion to form complexes with the ClO_4^- ion is greater than that of the rare-earth elements. Quantitative data on complex formation in perchloric acid solutions have been given by Rama Murthy and Patel[135], who studied the adsorption spectra of zirconium perchlorate and found that the instability constant of zirconyl perchlorate is 1.856×10^{-3}. The adsorption maximum for zirconium in perchloric acid solution was found to be close to 205 mμ, with $\log \epsilon = 1.05 \times 10^2$.

With oxalic acid and soluble oxalates, zirconium forms soluble complexes[76,76a], which do not contain zirconyl groups[136]: $Zr(C_2O_4)^{2+}$, $Zr(C_2O_4)_4^{4-}$, $Zr(C_2O_4)_5^{6-}$ (these complexes have been briefly described by Grinberg and Astapovich[137]). Complex formation with quinic, maleic, and sulphosalicylic acids[138] has been studied; it has been shown that complexes are formed with 2-nitroso-1-naphthol[139], chloranilic[140], citric[141,142], tartaric, malic, trihydroxyglutaric[127,142], ascorbic[40], diethylenetriaminepentaacetic[142a,143], and nitrilotriacetic acids and other polydentate ligands, and with ammonium carbonate[132]. Extremely stable complexes are formed in the reaction with ethylenediaminetetraacetic acid[144,145]. Many data on the use of complex-forming reagents in the analytical chemistry of zirconium have been given by Elinson and Petrov[40]. Grdenic[146] has shown by X-ray diffraction that the characteristic coordination number for zirconium complexes is 8.

The data given here on the ability of zirconium to form complexes with inorganic and organic ligands are not exhaustive, and the number of complexes which have been studied is fairly high. The chemistry of zirconium, including that in aqueous medium, is essentially the chemistry of complex ions and molecules. This is due to the high electrostatic field of the Zr^{4+} ion. The question of the chemistry of zirconium complexes, however, has not yet been specially dealt with in the literature.

5. PREPARATIVE CHEMISTRY OF ZIRCONIUM COMPOUNDS AND ITS RELATION TO THE CHEMICAL STATE OF ZIRCONIUM IN SOLUTIONS

Venable[12] has divided zirconium compounds into three main classes: the first consists of normal tetravalent zirconium salts, which are very few in number, the second consists of the zirconates, and the third and largest group consists of the so-called zirconyl salts and other basic products of hydrolysis of the normal salts. It would be no great exaggeration to say that if we exclude complexes isolated under conditions preventing hydrolysis, the chemistry of zirconium is the chemistry of complex hydrolysis products, which is undoubtedly related to its chemistry in aqueous solutions.

The complexity of the state of zirconium compounds in aqueous and acidic solutions and the variety of forms produced, depending on the concentration of metal and hydrogen ions, the presence of complex ligands, or change in temperature, method of solution preparation, order of addition of reagents to the solution, etc., all leave their mark on the preparative chemistry of zirconium. Descriptions have been given of a number of zirconium compounds which are surprising in their unusual composition, for example the ferrocyanides[147], or variety, or both, for example the sulphates[12,18]. In the chemistry of zirconium, many examples are known of non-reproducibility of individual experiments, and contradictory results have been obtained in experiments carried out under similar conditions. Many basic zirconium compounds, to which a definite composition has been attributed, are isolated in the solid state only when the conditions of acidity, temperature, time, etc., are strictly observed. All this makes it necessary to proceed with caution when dealing with the identification, as individual compounds, of the majority of basic products of hydrolysis of the normal salts, described in the literature, particularly for the sulphates, fluorides, etc.

Recent data on the composition of the iodates[7,93,148] and ferrocyanides[149] emphasise convincingly the decisive part played by the ionic state of zirconium in aqueous solutions in the precipitation of sparingly soluble salts, whose mechanism of formation involves chiefly interaction of the ions of the precipitant with all forms of the zirconyl ion present in the solution, and this for the most part leads to the formation of precipitates of indefinite composition, which depends on the concentration of hydrogen ions (*i.e.* on the degree of hydrolysis of the Zr^{4+} ion), the metal concentration (*i.e.* on the degree of polymerisation of the zirconium), the temperature, and the "age" of the solutions (*i.e.* on the structure of the zirconium ions). A characteristic feature of zirconium is thus the formation of precipitates of indefinite composition. This is shown not only in the case of sparingly soluble salts, but also, for example, by the readily soluble nitrates[59] and chlorides (Endemann[9], in particular, isolated compounds of the following empirical compositions: $Zr_3O_4Cl_4.xH_2O$ and $8ZrO_2.7HCl.xH_2O$, and Britton[21] obtained a basic chloride with a Zr : Cl ratio = = 1 : 1.73 by evaporating an aqueous $ZrCl_4$ solution).

In the case of the iodates and ferrocyanides there is no preferential formation of salts containing two equivalents of precipitant per zirconium atom. Moreover, it is found that aqueous solutions of zirconium dichloride or dinitrate, at concentrations < 0.01 M, generally give precipitates containing ~ 1.3 equivalents of precipitant per zirconium atom[148,150], and this suggests the existence, under these conditions, of polymers, possibly the trimer or tetramer, which are hydrolysed to a much greater extent than the trimer or tetramer identified by Zielen and Connick. Under the conditions of maximum hydrolysis[7] the usual products are precipitates with extremely varied values of the Zr : Cl ratio (in the range < 1). From acid solutions, potassium iodate gives precipitates in which the $Zr : IO_3$ ratio is close to 1 : 3 when a large excess of precipitant is present, and

precipitates containing 1–3 iodate groups per zirconium atom when the iodate concentrations are not too high. At a constant concentration of precipitant the number of hydroxyls in the precipitate is greater the lower the hydrogen ion concentration. With suitable control of the excess amount of precipitant, it is possible to obtain a solid phase of so-called definite composition. Precipitates of indefinite composition have been obtained by the reaction of zirconium with H_3AsO_4,[48] 8-hydroxyquinoline[47], etc. Zirconium hydroxyquinolinates of definite composition can be isolated only by precipitation from a medium containing a powerful complex-forming reagent, for example an oxalic acid medium[136].

An extremely interesting feature is that the existence of the trimer is confirmed by the data of Schmid[23], who attributed to the compound which he isolated the empirical formula $ZrOCl_2.HCl.xH_2O$ and in actual fact usually obtained a precipitate with Zr : Cl ratio $\simeq 1 : 2.7$. The formation of these precipitates at high acidity (concentrated hydrochloric acid saturated with gaseous HCl) and at high concentrations of metal in the solution can be explained only if it is assumed that the trimer is present¶.

In the absence of HCl the chief form of zirconium is the tetramer, and this explains the separation, in the solid phase, of compounds containing approximately two equivalents of precipitant per zirconium atom. Since the tetramer forms less soluble salts than the trimer (the solubility of zirconium salts usually decreases with increase in the basic character), the precipitates correspond to the composition of zirconyl chloride, if they do not undergo hydrolysis during washing with water or drying. Indeed, the fact that the tetramer predominates in acidic solutions of zirconium chloride explains the identification of the zirconyl ion. If alcohol or acetone, which decrease considerably the solubility of the chloride, are added to the solutions, precipitates of indefinite composition, like the iodate and ferrocyanide precipitates, are formed if the hydrogen ion concentration is sufficiently low. Similar results may be obtained at higher hydrochloric acid concentrations (in the presence of large quantities of acetone). In this case the precipitates contain more than two chlorine atoms per zirconium atom.

One of the reasons for the formation of precipitates of indefinite composition, particularly the double potassium zirconium iodates[148] or sulphates[153] is the slow rate of attainment of equilibrium in systems containing the liquid and solid phases. As a result of this, analysis of non-equilibrium precipitates, which are mixtures of indefinite composition, usually leads to the identification of a wide variety of compounds of unusual formulae. Moreover, since zirconium salts are readily hydrolysed when washed with water or weakly acidic wash liquid, it is easy to obtain low results for the concentration of precipitant ion present. The question of the influence of the acidity of the wash liquid on the composition of precipitates has been examined in detail for the case of the iodates[148].

It can thus be stated that the iodates and ferrocyanides are not exceptions to the general rule, and merely emphasise the main feature of the chemical behaviour of zirconium. The low solubility of these compounds, even in strongly acidic media, makes it possible to reveal more clearly the regular features of the chemical properties of zirconium. These are apparently common to all the known classes of compound, although they are not taken into account in the discussion of the results of preparative work on zirconium, as can be clearly seen for the case of the sulphates.

¶ The existence of the tetramer is also proved by data on the thermal analysis of zirconium and hafnium fluorides[151] and the existence of the trimer by data on the influence of excess precipitant on the composition of zirconium phosphates[152].

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Zirconium is an element with complex chemical properties, but despite some contradictory data the following general remarks may be made regarding the state of the element in aqueous and acidic solutions.

In the case of microconcentrations (10^{-9}–10^{-11} M ^{95}Zr) in solutions of hydrochloric, nitric, and perchloric acids considerable hydrolysis of the Zr^{4+} ion is observed at hydrogen ion concentrations less than ~ 2 M. Hydrolysis takes place in stages with the formation of hydroxo-cations of general formula $[Zr(OH)_x]^{4-x} (x \leqslant 3)$, the monomolecular hydroxide $Zr(OH)_4$, and mixed complex cations and neutral molecules of the type $[Zr(OH)_xA_i]^{4-(x+i)}$, where $(x+i) \leqslant 4$ and A = Cl, NO_3, and, apparently, ClO_4. In the hydrogen ion concentration range > 2 M, hydrolysis of zirconium is almost suppressed. Under these conditions, the products formed include not only complex cations and neutral molecules ZrA_i^{4-i} $(i \leqslant 4)$, but also negatively charged ions, the quantity of which increases in the $[H^+]$ range > 5–6 M. The analytical formulae of the acido-complexes of zirconium in solutions of strong acids have not been established, but preparative data indicate that, in the presence of weak complex-forming reagents such as HCl, HNO_3, and $HClO_4$, the formation of ions of only one type, $[ZrA_6]^{2-}$ is most probable. From the high value of the ionic potential of Zr^{4+}, it is obvious that the quadruply-charged zirconium ion and its complex ions are hydrated to a considerable extent in aqueous solutions. There are no quantitative data characterising the hydration. Colloidal zirconium (radiozirconium) has been detected at high pH values: adsorption colloids (pseudocolloids) in the pH range 1.6–4 and true colloids of zirconium hydroxide in the pH range 4–12.

In solutions containing macroquantities the chemical behaviour of zirconium is complicated by a number of reactions whose nature has been reliably established only recently. In aqueous solutions of normal or basic zirconium salts, hydrolysis increases with time and becomes much more intense with increase in temperature or on going from more concentrated to less concentrated solutions. In contrast to this, at constant hydrogen ion concentration in acidic solutions the degree of hydrolysis increases with increase in the zirconium concentration: for macroconcentrations 0.04–0.1 M, hydrolysed species are detected even in 4 M nitric acid.

These and other facts can be explained if allowance is made for the possibility of a number of hydrolytic reactions and olation and oxolation reactions.

The aquo-complexes and hydroxoaquo-complexes of zirconium, at suitable metal concentrations, react to form polymers. The first stage in this process, the removal of a proton from a water molecule of the aquo-complex (hydrolysis), is completed with the formation of OH bridging groups, each of which reacts with two zirconium atoms (unlike the bridging or olating groups, coordinated OH groups are joined to only one metal atom). The olation reaction takes place fairly slowly. It is favoured by increase in the metal concentration and temperature and, more particularly, by increase in the concentration of

alkali. Dilution (without significant decrease in the hydrogen ion concentration) or cooling of solutions of the bridged hydroxo-compounds reverses the process very slowly, *i.e.* the olation process decreases the reactivity of the coordinated OH groups. Dilution leading to a decrease in the hydrogen ion concentration, particularly at high pH values, facilitates the olation reaction. The hydroxo-groups readily form aquo-groups under the influence of hydrogen ions. The bridging hydroxo-groups react with hydrogen ions or are replaced by anions less readily, but nevertheless they do react slowly, so that the polymers of low molecular weight formed in quite strongly acidic media can be converted fairly rapidly, under suitable conditions, to simple hydroxoaquo-complexes or to aquo-complexes. The property of more or less ready reversibility is shown by zirconium salt solutions which have been allowed to stand in the cold for a short period, by very dilute solutions, or aged solutions which have been allowed to stand in the cold in acidic media.

The bridging hydroxo-groups give up a proton and are converted to oxo-groups rapidly on heating but extremely slowly in the cold. The compounds formed as a result of the oxolation reactions are extremely stable. The reversal of the oxolation process is extremely slow. In general, compounds with hydroxo-bridges are depolymerised more readily than oxo-compounds, since the protons react more readily with bridging hydroxo-groups than with oxo-groups. The extent to which oxolation proceeds is greatest in dilute solutions of zirconium salts at high pH values with heating, or in concentrated solutions.

In perchloric acid solutions containing 1–2 M $HClO_4$ and $\sim 10^{-4}$–0.02 M zirconium at 25° the olation process takes place in stages and is completed with the formation of the trimer $[Zr_3(OH)_4]^{8+}$ and the tetramer $[Zr_4(OH)_8]^{8+}$. There is no published proof of the existence of the dimer (the dizirconyl ion).

In hydrochloric and nitric acid solutions the compounds containing hydroxo-bridges are present in equilibrium with the ions in the solution, so that in systems containing even relatively weak complex-forming reagents, the charges on the trimer and tetramer are lower than those in perchloric acid solutions. The tetramer is the chief form in which zirconium exists in aqueous solutions of its dichloride at a salt concentration 2 M (and possibly at lower concentrations). In the absence of strong complex-forming reagents the trimer and tetramer containing hydroxo–bridges are converted to the oxo-forms, the conversion being rapid with heating and gradual in the cold. Anions which can enter the coordination sphere and replace hydroxo-groups prevent the formation of hydroxo-bridges, so that in solutions of powerful complex-forming reagents, zirconium appears to be present only in the monomolecular form, for example in oxalic acid media. The extent of the replacement of hydroxo-bridges by anions is determined by the relative concentrations of the reagents, the relative tendency of the anion to enter the coordination sphere, and the duration of aging of the solutions.

In weakly acidic media the olation and oxolation processes are not terminated with the formation of the trimer and tetramer, and proceed without interruption with the final formation of polymers of high molecular weight. In hydrochloric and nitric acid solutions, or when neutral salts with the same anion are added, a change in the charge of the complex ions may take place as the anion penetrates into the coordination sphere of the complex, or as the result of the adsorption of an excess of anions or cations by the large surface of the highly polymerised aggregate. Reversal in the sign of the charge is widely encountered in the case of zirconium oxide hydrosols, and is responsible for the "identification" of a number of non-existent zirconium compounds.

The olation and oxolation processes can take place not only in solution but also in the solid phase. Zirconium hydroxide freshly precipitated in the cold appears to be a complex of relatively low molecular weight, in which the ratio of the number of bridging hydroxo-groups to the number of oxo-groups may be fairly high. This hydroxide dissolves readily in acids. When the hydroxide is precipitated in the cold and allowed to stand for a prolonged period, or when the hydroxide is precipitated from hot solutions, the bridging hydroxo-groups are converted to oxo-groups. The oxides, in which the bridging hydroxo--groups are completely converted to the oxo-form, are quite inert.

The processes taking place in the solutions have a definite influence on the preparative chemistry of zirconium compounds. Published data show convincingly the decisive part played by the ionic state of zirconium in aqueous solutions in the precipitation of sparingly soluble salts, the mechanism of whose formation involves chiefly the reaction of the ions of the precipitant with all the ionic zirconium species present in the solution, and this leads for the most part to the formation of precipitates of indefinite composition, which varies according to the degree of hydrolysis and polymerisation of the zirconium ions and also their structure. Moreover, since washing of the precipitates with a hydrolysing wash liquid leads to replacement of the anions by hydroxo-groups, low results can easily be obtained for the quantity of precipitant anion present. A further reason for the formation of precipitates of indefinite composition is the slow rate of attainment of equilibrium in systems containing liquid and solid phases. The formation of precipitates of indefinite composition is observed not only in the case of sparingly soluble salts, but also in the case of the readily soluble chlorides and nitrates.

The above features of the chemical behaviour of zirconium explain the "identification" of a large number of zirconium compounds of unusual composition, particularly in the case of the sulphates, and the reliability of the analytical formulae for these compounds requires careful confirmation.

SUPPLEMENT

Work reported since the present review was written supplements the data in the main sections.

Zaitsev and Bochkarev[154], using a method involving the displacement of OH^- by fluoride ions, concluded that the zirconyl ion does not exist in aqueous solutions of zirconium salts. They consider that the zirconyl ion, ZrO^{2+} [together with $Zr(OH)_2^{2+}$], can exist only in solids.

Kharitonov and Buslaev[155] and Kharitonov and Rozanov[156] showed, from a study of the infra-red spectra of crystalline salts, that the Zr=O bond is not present in the following compounds: $ZrOCl_2.8H_2O$, $Zr_4F_{10}(OH)_6.3H_2O$, $ZrF_4.3H_2O$, $ZrF_4.H_2O$ (obtained by dehydrating $ZrF_4.3H_2O$), and $Zr_4F_{14}O$. According to their data, the following compounds contain the Zr=O bond: $Zr_4F_{10}O_3$, $ZrF_4.H_2O$ (obtained by dehydrating $HZrF_5.4H_2O$), $ZrOF_2$, $KZrOF_3.2H_2O$,

and $ZrO(NCS)_2.MNCS.2H_2O$ (where M = NH_4, K, Rb, Cs, or pyridine).

Singh and Banerjee [157] studied the precipitation of basic zirconium salts and hydroxide from solutions of the sulphate, chloride, and nitrate. Their data for the most part confirm Britton's conclusions[21]. Conductimetric and potentiometric (pH) titration of aqueous solutions of the salts with barium and sodium hydroxides gave basic salts of the following empirical compositions $Zr(OH)_{3.72}(SO_4)_{0.14}$, $Zr(OH)_{3.92}Cl_{0.08}$, and $Zr(OH)_{3.94}(NO_3)_{0.06}$.

The relationship between the chemistry of aqueous solutions of zirconium salts and the preparative chemistry of the element has been pointed out in a number of papers. Ionova and Tananaev[158] noted the influence of hydrogen ion concentration on the composition of zirconium ferrocyanides and confirmed that normal zirconium ferrocyanide can be precipitated only from acid media. Karlysheva and Sheka[159] isolated zirconium cupferronates of variable composition, depending on the concentration of acid in the zirconium salt solutions, the method of preparation, and the time for which the solutions were kept.

Babko and Gridchina[160] studied the influence of the state of zirconium in different media on the rate and extent of the reaction of zirconium with xylenol orange.

New data on the values of the successive instability constants of fluoro-complexes of zirconium have been given by Buslaev[161].

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CHARACTERISTIC CHEMICAL PROPERTIES OF ORGANIC COMPOUNDS CONTAINING POSITIVE HALOGEN

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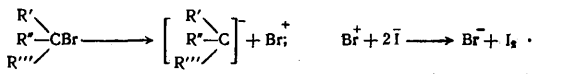
1. INTRODUCTION

Reviews of the chemistry of compounds containing positive halogen are very few [1-3], or are concerned mainly with the use of such compounds for preparative purposes [4]: substantial parts of them are devoted to preparative problems and also to the consideration of inorganic compounds of similar type. Consequently these reviews are usually confined to discussion of only a narrow range of reactions of organic compounds containing positive halogen.

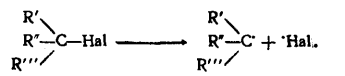
Our aim in compiling the present survey was to examine and compare, from a broader point of view, the characteristic reactions of different classes of organic compounds containing positive halogen, and to describe present views of their chemical behaviour.

We have not attempted to given an exhaustive survey of the literature on these questions, for such a task would be beyond the scope of a journal review, and have chosen mainly aliphatic compounds for consideration. Such a choice, it seems to us, enables all the characteristic features of the chemistry of positive halogen to be followed with quite striking examples.

Compounds containing positive halogen are characterisedi experimentally by the ability to displace iodine from potassium iodide or hydriodic acid. The view is generally held that this reaction involves heterolytic cleavage of the carbon–halogen bond with formation of halogen cations rather than the corresponding anions



However, there also exists a different view of the mechanism of this reaction. Thus Waters [5] considers that rupture of a carbon–halogen bond in compounds containing positive halogen takes place homolytically with formation of free radicals



Ordinary alkyl halides do not oxidise potassium iodide. Even carbon tetrabromide does not displace iodine from this salt, but if a bromine atom is replaced by a nitro-group, the resulting tribromonitromethane is now able to effect such a reaction. An ester group has a similar activating influence, although it is considerably weaker than that of the nitro-group. The presence of only one such group is insufficient to make the bromine labile (tribromoacetic ester does not react with potassium iodide), and only the presence of at least two ester groups (bromomalonic and dibromomalonic esters) makes the halogen sufficiently labile [6]. A bromine atom acquires a well defined positive character also if it is adjacent to an ester and a carbonyl group or to two carbonyl groups. Thus the halogen in cyclic compounds containing a $-COCBr_2CO-$ group (dibromoindanedione, dibromobarbituric acid) is highly active. Positive properties are less well defined in compounds containing one carbonyl group (α-halogeno-ketones). Reactions characteristic of positive halogen can

also be given by compounds in which the halogen is adjacent to a multiple bond, especially those containing the grouping $-C:C\cdot CBr_2\cdot C:C-$.

Apart from the many compounds in which positive halogen is linked to a carbon atom, several compounds are known in which it is combined with a nitrogen atom, among them being *N*-halogenated acid amides, *N*-halogenoamines, and *N*-halogenoarenesulphonamides.

Finally, alkyl hypohalites, compounds of type RCOOHal, and several others provide examples of substances in which a positive halogen atom is combined with oxygen.

Thus compounds containing positive halogen belong to the most varied types, but fundamentally they are united by a common property: the organic radicals which confer a positive character on the halogen are invariably groups which strongly attract electrons. This structural peculiarity definitely diminishes the tendency to cleavage with formation of a halide anion which is normal in a covalent halogen compound.

2. PROPERTIES COMMON ALSO TO ALKYL HALIDES

Before describing the characteristic properties of compounds containing positive halogen, let us consider a few similarities between these compounds and ordinary alkyl halides. Coleman and his coworkers showed that chloroamines of various structures react with a Grignard reagent according to the scheme [7,8]

$$NH_2Cl + RMgX \longrightarrow RNH_2 + MgXCl.$$

The yield of amine is higher in the case of RMgCl and lower on reaction with RMgI, and it increases when R is a secondary or a tertiary hydrocarbon radical. If the chloroamine is replaced by alkylchloroamines of the type $RNCl_2$, R_2NCl, and RNHCl, the corresponding secondary and tertiary amines can be obtained by this reaction [9]. The reaction is interesting, since it is not always a simple task to obtain individual amines by other methods.

Like alkyl halides, several substances containing positive halogen react with formation of a new carbon–carbon bond under the influence of alkaline reagents or the sodium derivatives of some organic compounds. Bischoff and his collaborators studied this reaction with chloro- and bromo-malonic esters, and showed that sodiomalonic ester reacts quite readily with chloromalonic ester to form an ethanetetracarboxylic ester [10]

$$(C_2H_5OOC)_2CHNa + ClHC(COOC_2H_5)_2 \longrightarrow (C_2H_5OOC)_2CHCH(COOC_2H_5)_2 + NaCl.$$

If chloromalonic or bromomalonic ester is treated with an alkaline reagent (sodium ethoxide or methoxide, potassium carbonate), an ethylenetetracarboxylic ester is formed [11–14]

$$2CHBr(COOR)_2 \xrightarrow{K_2CO_3} 2HBr + (ROOC)_2C=C(COOR)_2.$$

Bischoff [15] made a detailed study of the reaction of various bromomalonic esters with the sodium derivative of nitrophenol, and obtained various nitrophenoxymalonic esters

$$NO_2C_6H_4ONa + BrCX(COOR')(COOR'') \longrightarrow NaBr + NO_2C_6H_4OCX(COOR')(COOR'').$$

A similar reaction takes place also with *N*-bromoamines, although the yields are low. Farenhorst and Koogman [16] showed that t-butyl-*N*-bromoamine reacts with silver oxide according to the equation

$$2(CH_3)_3CNHBr + Ag_2O \longrightarrow 2AgBr + H_2O + (CH_3)_3C-N=N-C(CH_3)_3.$$

A peculiar "dimerisation" of bromomalonic ester has been described by Arbuzov and Abramov [17], who established that on reaction with derivatives of phosphorous acid this compound yields an ethanetetracarboxylic ester

$$2(C_2H_5O)_2PONa + 2BrCH(COOC_2H_5)_2 \longrightarrow 2NaBr + (C_2H_5OOC)_2CHCH(COOC_2H_5)_2 + [(C_2H_5O)_2PO]_2.$$

This reaction does not occur with chloromalonic ester.

Several further cases can be mentioned in which compounds containing positive halogen react in a similar manner to alkyl halides. Thus sodium azide reacts with bromomethylmalonic ester to form the ester of azidomethylmalonic acid [18]. The reaction of potassium xanthate and alkali-metal salts of brominated malonic acids was studied by Bülmann and Madsen [19], who showed that the reaction is represented by

$$C_2H_5OCSSK + RBrC(COOH)_2 \longrightarrow C_2H_5OCSSCR(COOH)_2 + KBr.$$

Scheiber and Haun [20] found that *N*-bromosuccinimide and *N*-bromophthalimide are able to exchange their halogen for an organic radical when treated with compounds containing an active hydrogen atom:

$$\begin{matrix}-CO\\ \\ -CO\end{matrix}\!\!>\!NBr + Na^+(CHX_2)^- \longrightarrow \begin{matrix}-CO\\ \\ -CO\end{matrix}\!\!>\!N-CHX_2 + NaBr,$$

where X = $COOC_2H_5$, $COCH_3$, COC_6H_5, CN.

From these examples it is evident that compounds containing positive halogen can in several cases react like ordinary alkyl halides. However, the behaviour of positive halogen is in general markedly different from that of halogen in alkyl halides being characterised by a series of special reactions, as will be shown subsequently in this review.

3. HYDROLYSIS

Compounds containing positive halogen behave differently from alkyl halides on hydrolysis: the reaction involves replacement of the halogen by hydrogen or other positive group. Birckenbach and his coworkers [21] have done some interesting work on the hydrolysis of such compounds. They consider that the radicals of strong acids, such as $(CN)_3C-$ and $(CH_3CO)_3C-$, are similar to a free halogen, and belong to the group of pseudohalogens. The chemical properties of the corresponding halogenated derivatives show them to be typical compounds containing positive halogen. When potassium cyanide reacts with a halogenated triacetylmethane, for example, the halogen is replaced by the positive potassium ion. Hydrolysis of a triacetylhalogenomethane results in formation of the hypohalous acid and of triacetylmethane itself.

Haszeldine and coworkers [22] made a detailed investigation of the nature of the carbon–iodine bond in trifluoroiodomethane. This work merits thorough examination as one of the few rigorous studies which show clearly that, depending on the conditions, the same halogenated derivative can yield either free radicals or the halogen cation.

The carbon–iodine bond in trifluoroiodomethane is known to undergo homolytic fission with the formation of a free trifluoromethyl radical, which yields an organometallic derivative and also initiates the polymerisation of alkenes. In solvents of high dielectric constant, however,

trifluoroiodomethane behaves as a compound containing positive halogen, and on treatment with caustic potash gives fluoroform and the hypoiodite:

$$CF_3I + KOH \longrightarrow CHF_3 + KOI.$$

The reaction velocity increases with increase in the dielectric constant of the solvent. In ether, for example, reaction is slow, while in alcohol and acetone it is rapid and complete. It is assumed that the reaction involves attack on the trifluoroiodomethane by the hydroxyl ion with subsequent reaction of the trifluoromethyl anion with the solvent, or by decomposition of CF_3K, formed as an intermediate product, by water:

$$OH^- + ICF_3 \longrightarrow CF_3^- + HOI \xrightarrow{KOH} KOI + H_2O.$$

The positive character of iodine in trifluoroiodomethane is supported also by the fact that it did not prove possible to obtain the usual nucleophilic substitution products with such reagents as moist silver oxide, potassium phthalimide, and metal cyanides and nitrates, which are known to react readily with methyl iodide. The iodine atom in pentafluoroiodoethane, which on hydrolysis yields pentafluoroethane[23], is similar in character.

It was concluded from a radiochemical investigation of the mechanism of the hydrolysis of trifluoroiodomethane in a solvent of high dielectric constant that the fluorinated iodides (trifluoroiodomethane and pentafluoroiodoethane) do not ionise appreciably; they do not liberate iodine from potassium iodide. But ions are formed in a solvent of high dielectric constant and at elevated temperatures, as is confirmed by exchange between trifluoroiodomethane and sodium iodide containing radioactive iodine:

$$CF_3I + Na^{131}I \longrightarrow CF_3{}^{131}I + NaI.$$

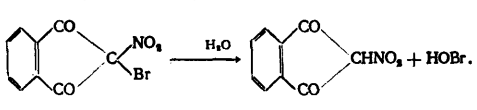
The reaction takes place by the unimolecular ionic mechanism (1) with electron transfer (2) and recombination (3)

$$CF_3I \rightleftarrows CF_3^- + I^+, \quad (1)$$

$$I^+ + (^{131}I)^- \rightleftarrows I_2 \rightleftarrows I^- + (^{131}I)^+, \quad (2)$$

$$CF_3^- + (^{131}I)^+ \rightleftarrows CF_3{}^{131}I. \quad (3)$$

Bromoindane-1,3-dione is hydrolysed, on being boiled with water, to indane-1,3-dione and hypobromous acid. Bromonitroindane-1,3-dione is hydrolysed still more readily, at room temperature, yielding nitroindanedione and hypobromous acid[24,25]:



Halogen is readily eliminated from nitro-compounds containing a halogen atom and more than one nitro-group, or a nitro-group and more than one halogen atom, attached to the same carbon atom. In neutral or acid medium the positive halogen in such compounds is replaced by hydrogen, and in alkaline medium by a metal[26-29]; the iodine derivatives are hydrolysed more readily than the corresponding bromine derivatives, and still more readily than the chlorine derivatives[26,30].

Conrad studied the reactions of halogenomalonic acids and esters on treatment with alkaline reagents and showed that the presence of only two carboxyl groups is insufficient to make the halogen labile. Thus chlorine is not eliminated when chloromalonic acid is treated with potassium hydroxide. Dichloromalonic ester on treatment with alcoholic ammonia yields dichloromalonamide. Hence the chlorine remains untouched by the ammonia. In the case of bromochloromalonic ester, however, the bromine atom reacts as well as the ester groups[31,32], and bromonitromalonic ester reacts still more readily with alkaline reagents: with ammonia, potassium hydroxide, or dimethylamine, it undergoes a reaction typical of positive halogen, the latter being replaced by the cation of the alkaline reagent[33]. Bromonitroacetic ester is incapable of such a change[34].

With α-bromoketones[35,36] and halogenated β-keto-esters[37] cases are known in which positive bromine is replaced by a hydrogen atom or an amino-group.

N-Halogenated compounds hydrolyse still more readily than do *C*-halogenated derivatives. The labile halogen in such compounds is replaced by hydrogen by the action of water, hydrobromic or hydrocyanic acid, or hydrogen peroxide[38-42].

$$CH_3CONHBr + H_2O \longrightarrow CH_3CONH_2 + BrOH,$$

$$CH_3CONHBr + HCN \longrightarrow CH_3CONH_2 + BrCN.$$

It is quite evident from the above work that hydrolysis is a very characteristic reaction of compounds containing positive halogen: when such compounds are hydrolysed, the halogen is replaced by hydrogen, in contrast to ordinary halogenated compounds, in which it is replaced by hydroxyl†.

4. OXIDISING PROPERTIES

As noted above, the ability to oxidise potassium iodide or hydriodic acid serves as a criterion of the positive character of halogen in a given compound[5,45,46]. This reaction, which goes rapidly in the cold, can serve for the quantitative determination of compounds containing positive halogen. This method is used to estimate, for example, α-halogenonitro-compounds (chlorides, bromides, and iodides) containing two, three, or more nitro-groups in the molecule[47-49].

The oxidation of hydrazine by substances containing positive halogen (which is characteristic of compounds of this class) was studied in detail by Macbeth and his collaborators[45,50,51]. Compounds in which the halogen is electronegative in character, for example acid halides, sulphonyl chlorides, picryl chloride, yield hydrazides on reaction with hydrazine. Those containing positive halogen, however, readily oxidise the hydrazine with the evolution of nitrogen. This reaction not only demonstrates the lability of positive halogen but also provides a method for determining it quantitatively.

With *NN*-dichlorosulphonamides, *N*-chloroacetanilide, *N*-bromoacetamide, and series of bromomalonic esters and α-halogenonitro-compounds, this reaction is represented by the following equations:

$$RSO_2NCl_2 + NH_2NH_2 \longrightarrow RSO_2NH_2 + N_2 + 2HCl,$$

$$2C_6H_5NClCOCH_3 + NH_2NH_2 \longrightarrow 2C_6H_5NHCOCH_3 + N_2 + 2HCl,$$

$$2CH_3CONHBr + NH_2NH_2 \longrightarrow 2CH_3CONH_2 + N_2 + 2HBr,$$

$$2CRBr(COOC_2H_5)_2 + NH_2NH_2 \longrightarrow 2CRH(COOC_2H_5)_2 + N_2 + 2HBr,$$

$$2(NO_2)_3CBr + NH_2NH_2 + 4KOH \longrightarrow 2(NO)_2C{=}NO_2K + 2KBr + N_2 + 4H_2O.$$

Hirst and Macbeth[45] note that hydrazine reacts more readily with *N*- than with *C*-halogenated compounds, and hence conclude that halogen linked with nitrogen is the more labile.

† Only a few cases are described in the literature of the replacement of positive halogen by a hydroxy-group (for example the alkaline hydrolysis of bromo- and chloro-malonic esters[43,44]).

Compounds containing positive halogen are able to oxidise also (in solution) potassium cyanide, sodium sulphide, hydrogen bromide and especially hydrogen iodide, and also several other inorganic compounds. Thus the oxidation of hydrogen bromide with the separation of free bromine is a general property of α-bromoketones [35,36,52], the ease with which this reaction occurs depending on the mobility of the positive bromine in the ketone. The simplest α-bromoketones (for example bromoacetophenone) react only in the presence of an acceptor for the bromine. Compounds in which the positive bromine is activated by two carbonyl groups (for example bromo-derivatives of methone‡, dibenzoylbromomethane, etc.) react considerably more readily, as do also di- and tri-bromoketones (dibromoacetophenone, etc.). Bromoacetoacetic ester [52,53] and brominated malonic acids [54] are active oxidants of hydrogen bromide and iodide [54].

Compounds containing positive bromine or iodine react in a characteristic manner with hydrogen chloride, the bromine or iodine atom being replaced by chlorine. In this way *N*-chloroacetamide is formed from *N*-bromoacetamide [55], chlorobarbituric acid from bromobarbituric acid [56], and chlorotrinitromethane from iodotrinitromethane [6].

Organic compounds are more difficult than inorganic compounds to oxidise with positive halogen.

The oxidising properties of *N*-halogenated compounds towards organic substances were noted by Selivanov as long ago as 1892. [39] He showed that chlorosuccinimide in the presence of water oxidises primary and secondary, but not tertiary, alcohols.

Chattaway and Orton [40] observed, together with other characteristic properties of *N*-bromoacylamides, their oxidising ability. Thus acetaldehyde was detected among the reaction products with ethanol. These workers suggested that the acetaldehyde is formed according to the equations:

$$RCON(R')Br + C_2H_5OH \longrightarrow RCONHR' + CH_3CH_2OBr,$$

$$CH_3CH_2OBr \longrightarrow CH_3CHO + HBr.$$

Somewhat later Tscherniac [42] showed convincingly that the oxidising action of *N*-halogenated imides is a property of these compounds themselves, and not of the hypohalous acid formed by their interaction with water. The opposite, incorrect, view of the mechanism of this reaction was held by Selivanov [39].

A thorough study of the oxidising properties of *N*-bromosuccinimide was made by Blair *et al.* [57] with some substituted aromatic alcohols as examples. The fact that ultra-violet irradiation of the reaction mixture increases the yields of the final products suggests that the oxidation takes place by a free-radical mechanism.

The dehydrogenation of primary and secondary alcohols by *N*-chlorosuccinimide was later studied by Grob and Schmidt [58], who obtained good yields of the corresponding aldehydes and ketones in this way; the lower aliphatic alcohols are the most easily oxidised, the reaction taking place rapidly and under mild conditions. Similar work was carried out simultaneously by Hebbelynck and Martin [59], who in particular confirmed the observations of other workers on the comparative oxidising power of chloro- and bromo-derivatives§: the oxidising action of positive chlorine is more strongly marked than that of positive bromine. Hebbelynck and Martin showed that primary and secondary aromatic alcohols are oxidised on being heated with *N*-chlorosuccinimide, the reaction usually being carried out in anhydrous medium. It is interesting that the reactions take place even in the dark, in contrast to Blair's experiments, in which oxidation with *N*-bromosuccinimide was effected under ultra-violet irradiation [57].

Lecomte and Dufour [60] used *N*-bromoacetamide to oxidise aromatic alcohols, and found that primary and secondary alcohols in which the hydroxy-group is attached to a carbon atom directly linked to the aromatic nucleus are oxidised quantitatively to the corresponding aldehydes and ketones. When the hydroxyl group is more remote from the aromatic ring, the yield of aldehydes and ketones drops sharply.

Many other investigators have studied the oxidising action on organic compounds of substances containing positive halogen. Thus Dale [61], by dehydrogenating squalene with *N*-bromosuccinimide, obtained a mixture of carotenoid pigments. Schönberg *et al.* [62] showed that the action of *N*-bromosuccinimide on α-amino-acids yields aldehydes containing one carbon atom fewer than in the original acid.

N-Bromosuccinimide is used for the dehydrogenation of more complicated cyclic systems to give aromatic compounds as reaction products [63-66]. The selective oxidising action of this compound is utilised in steroid chemistry [67-71].

It is interesting that the chain oxidation of tetralin is catalysed by compounds containing positive halogen, both *N*- and *C*-derivatives, which act as sources of free radicals [5].

These results show that oxidising properties are very characteristic of compounds containing positive halogen, and can be exploited for preparative purposes.

5. HALOGENATING PROPERTIES

The halogenating action of compounds containing positive halogen has been studied most fully. The most important application of this reaction is the halogenation of alkenes in the allyl position¶. Substances containing positive halogen are also used for the addition of halogens to a double bond, in the halogenation of aromatic and heterocyclic compounds (in the ring), and also for the halogenation of amines (on the nitrogen). We shall examine the literature in this field in the same sequence.

The halogenating properties of positive halogen were first studied early in this century by Wohl [75,76], who used *N*-bromoacetamide. However, the bromination of unsaturated compounds with this agent gave low yields and was accompanied by side reactions.

It is not so long ago that Ziegler *et al.* [77] succeeded in working out a preparative method for the halogenation of unsaturated compounds in the allyl position. They found that *N*-bromosuccinimide possessed the best brominating properties: hydrogen in a methyl and especially in a

‡ 5,5-Dimethyl-1,3-cyclohexanedione (Ed. of Translation).

§ For a brief review of work on this question see Hebbelynck [1].

¶ A great deal of factual information on this question can be found in the reviews of Djerassi [72] and of Machinskaya and Barkhash [73] (see also Waters [74]).

methylene group can be replaced by bromine; a tertiary carbon atom is not brominated, and it is impossible to brominate a methyl or a methylene group directly linked to a system of conjugated double bonds. On the other hand, dienes containing two isolated double bonds are readily brominated in the allyl position. Apart from *N*-bromosuccinimide, Ziegler studied the halogenating properties of *N*-bromophthalimide and various *N*-halogenated sulphonamides and imides, and showed that, in contrast to *N*-bromosuccinimide, these compounds do not possess a selective halogenating action; in these cases more than one reaction takes place at the same time. The ability of alkenes to be halogenated in the allyl position is linked with the fact that the hydrogen atoms in the β and β' positions in a $-CH_2-CH=CH-CH_2-$ chain are more reactive than those in the α and α' positions. If a β-methylene group is linked to an alkyl substituent, the substitution becomes easier with increasing chain length of the substituent, which is consistent with the inductive effect of alkyl groups [78].

It can now be regarded as proved that the halogenation of unsaturated compounds in the allyl position by means of compounds containing positive halogen has a radical mechanism.

Thus Waters [79] remarks that compounds containing positive halogen are preferentially decomposed with the formation of free radicals. This has been confirmed by several later investigations.

Schmid and Karrer [80], investigating the effect of catalysts on bromination in the allyl position, found that bromination with *N*-bromosuccinimide is greatly accelerated by the addition of 5–10% of freshly prepared benzoyl peroxide to the reaction mixture. Use of a catalyst not only speeds up the process but also enables several substances to be brominated which, according to Ziegler [77], do not react under normal conditions with *N*-bromosuccinimide. For example, the former workers [80] succeeded in substituting bromine for hydrogen attached to a tertiary carbon atom and in a methyl group adjacent to two conjugated bonds.

The use of peroxides enables halogenation to be carried out smoothly in several other cases as well. Thus the bromination of hexa-1,5-diene with *N*-bromosuccinimide is greatly accelerated in the presence of benzoyl peroxide, with the formation of mono- and di-bromo-derivatives [81]

$$CH_2=CHCH_2CH_2CH=CH_2 \xrightarrow{NBS} CH_2=CHCHBrCH_2CH=CH_2 \xrightarrow{NBS}$$
$$\longrightarrow CH_2=CHCHBrCHBrCH=CH_2.$$

Methylenecyclobutane is also brominated in the allyl position by *N*-bromosuccinimide in the presence of benzoyl peroxide [82]. Bromination of cyclohexa-1,4-diene yields either 3-bromo- or 3,6-dibromo-cyclohexadiene depending on the reaction conditions [83].

The fact that ultra-violet irradiation accelerates bromination in the allyl position is further evidence of the radical character of this reaction [84].

Tertiary aliphatic azo-compounds, which are typical initiators of radical reactions, also catalyse bromination with *N*-bromosuccinimide. In the presence of these catalysts a 75% yield of 3-bromocyclohexene can be obtained from cyclohexene (no reaction takes place in the absence of catalyst) [85].

The mechanism of substitution with halogen was studied by Bloomfield [86], who also held the view that allyl bromination takes place by a radical mechanism represented by the following scheme:

$$(C_4H_4O_2)NBr \longrightarrow (C_4H_4O_2)N^{\cdot} + Br^{\cdot},$$
$$-CH_2CH=CH- + (C_4H_4O_2)N^{\cdot} \longrightarrow -\dot{C}H-CH=CH- + (C_4H_4O_2)NH,$$
$$-\dot{C}HCH=CH- + Br^{\cdot} \longrightarrow -CHBrCH=CH- \text{ chain termination},$$
$$-\dot{C}HCH=CH- + (C_4H_4O_2)NBr \longrightarrow -CHBrCH=CH- + (C_4H_4O_2)N^{\cdot}.$$

This mechanism is to some extent confirmed by results obtained by Ford and Waters [85] showing that the succinimido-radical $\begin{matrix}CH_2-CO\\ \\ CH_2-CO\end{matrix}\!\!>\!N^{\cdot}$ is strongly dehydrogenating, and readily removes an active hydrogen atom from the α-methyl-end-group of an unsaturated compound.

Several of the *N*-chloro-derivatives, for example *N*–*p*-dichloroacetanilide and *N*-chloro-*p*-nitroacetanilide, are able to chlorinate unsaturated compounds in the allyl position [77]. *NN*-Dichlorosulphonamides such as Chloramines B and T, which are well known disinfectants and decontaminants, are unsuitable for allyl chlorination.

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The first information on the addition of halogen to a double bond by means of compounds containing positive halogen was obtained by Wohl [75,76], who isolated dibromides as well as allyl bromination products from the reaction of unsaturated compounds with *N*-bromoacetamide. Later Buckles [87] made a detailed investigation of halogenation at a double bond with this reagent, and found that in all cases the reaction is accelerated by heating or by ultra-violet irradiation. From this he concluded that the halogenation of unsaturated compounds with *N*-bromoacetamide takes place by a radical mechanism:

$$AcNHBr + h\nu \longrightarrow AcNH^{\cdot} + Br^{\cdot},$$
$$>C=C< + Br^{\cdot} \longrightarrow >CBr-\dot{C}<,$$
$$>CBr-\dot{C}< + AcNHBr \longrightarrow >CBr-\underset{|}{C}Br + AcNH^{\cdot},$$
$$Br^{\cdot} + AcNHBr \longrightarrow Br_2 + AcNH^{\cdot},$$
$$Br_2 + h\nu \longrightarrow 2Br^{\cdot},$$
$$Br_2 + >CBr-\dot{C}< \longrightarrow >CBr-\underset{|}{C}Br + Br^{\cdot}.$$

The action of *N*-bromosuccinimide on $\alpha\beta$-unsaturated β-phenyl-ketones in the presence of a peroxide also results in the formation predominantly of dibromides [88]. In the bromination of the triple bond in ethyl tetrolate† under Ziegler's reaction conditions, the sole product isolated in a pure form was the 2,3-dibromocrotonic ester, formed by addition of bromine at the triple bond [89].

It is interesting that, if the halogenation of alkenes by *N*-bromoacetamide is carried out in the presence of hydrobromic acid or molecular bromine, the reaction takes place by an ionic mechanism [87]

$$AcNHBr + HBr \rightleftarrows AcNH_2Br^{+} + Br^{-},$$
$$AcNH_2Br^{+} + Br^{-} \longrightarrow AcNH_2 + Br_2.$$

Thus under these conditions the double bond is brominated in effect by free bromine.

Braude and Waight [90] found that, in the presence of tetraethylammonium bromide or other similar salts which catalyse ionic reactions, *N*-bromosuccinimide reacts with cyclohexene to form 1,2-dibromocyclohexane. Reaction

† Ethyl 2-butynoate (Ed. of Translation).

takes place in a similar way with allylbenzene; it is not accelerated by benzoyl peroxide. These workers conclude that the mechanism of the addition consists in heterolytic cleavage of the N–Br bond, which is the primary and rate-determining stage. Under different conditions (in the absence of catalysts for ionic reactions), *N*-bromosuccinimide brominates cyclohexene mainly in the allyl position[82,91]. These examples again show that *N*-bromosuccinimide can react by different mechanisms depending on the conditions (see also Djerassi[72] and Ford[92] on this question).

Bromination with *N*-bromosuccinimide requires a source of hydrogen for recombination with the succinimido-group. In the case of bromination at the allyl position, the compound undergoing bromination itself acts as such a source, but in the case of bromination at the double bond an additional hydrogen-donor is required, and the solvent can fill this role.

Buckles *et al.*[93] have recently concluded from a comparative study that *N*-bromoacetamide brominates predominantly at the double bond, whereas *N*-bromosuccinimide brominates in the allyl position. In an attempt to explain the difference in behaviour of these brominating agents, these workers also suggest, on the basis of the radical reaction scheme proposed by Bloomfield[86], that hydrogen-donors must take part in the addition.

The direction of bromination, at the allyl position or at the double bond, depends not only on the nature of the brominating agent but also on the structure of the unsaturated compound.

Corey[94] showed that, in the reaction between *N*-bromosuccinimide and four unsaturated compounds — methyl crotonate, crotononitrile, methyl vinylacetate, and vinylacetonitrile — the first two, which contain a system of conjugated bonds, are brominated in the allyl position, while the last two compounds, containing a system of isolated bonds, add on bromine mainly at the double bond.

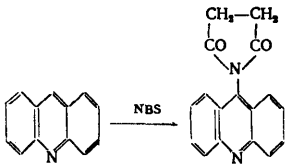
The bromination of vinylacetonitrile with *N*-bromosuccinimide has been investigated also by Baily and Bello[95]. In the presence of a peroxide, both 4-bromocrotononitrile and 3,4-dibromobutyronitrile are formed at the same time. If the peroxide is replaced by *p*-t-butylcatechol, an inhibitor of radical reactions, the yield of the bromine addition product is increased. Hence it can be concluded that *N*-bromosuccinimide can react both by an ionic and by a free-radical mechanism.

The halogenation of aromatic and of heterocyclic compounds with *N*-chloro- and *N*-bromo-acetamides was first studied by Wohl[75,76] and by Steinkopf[96], who showed that mono- and poly-halogenated derivatives can be obtained in this way.

However, the use of these two compounds as halogenating agents did not expand to any considerable extent, since it gave no advantage over other well-known methods for halogenating aromatic and heterocyclic systems.

In 1944 Buu-Hoi[97] demonstrated that *N*-bromosuccinimide is an excellent reagent for the halogenation of such systems. He showed that increase in the mobility of hydrogen in an aromatic compound facilitates its bromination. For example, benzene is brominated neither by *N*-bromoacetamide nor by *N*-bromosuccinimide; naphthalene is brominated by the latter reagent, yielding 1-bromonaphthalene; phenanthrene reacts still more readily; and anthracene reacts vigorously with *N*-bromosuccinimide to form 9-bromoanthracene.

The bromination of heterocyclic compounds also gives high yields of monobromo-derivatives: thiophen gives 2-bromothiophen, 1-benzoylindole yields 1-benzoyl-3-bromoindole, and indene forms 1-bromoindene; although anthracene is brominated vigorously by *N*-bromosuccinimide, acridine is not brominated, but forms a substitution product[98]:



Parke *et al.*[99] studied the mechanism of the bromination of toluene with *N*-bromoacetamide and some of its derivatives containing different numbers of halogen atoms attached to the α-carbon atom: $CH_3CONHBr$, $CCl_3CONHBr$, $CHCl_2CONHBr$, $CH_2ClCONHBr$, and $CF_3CONHBr$. They found that these compounds are able to brominate toluene both in the ring and in the side-chain, the reaction taking place by an ionic mechanism in the former case, and by a free-radical mechanism in the latter.

The experimental data in the accompanying Table show that *N*-bromo-derivatives containing electronegative substituents attached to the α-carbon atom tend to effect bromination predominantly by an ionic mechanism. In other words, the bromine in these compounds is obviously more readily split off as a cation. The differences in brominating power of the compounds in the Table no doubt depend on the strength of the positive character of the bromine which they contain.

Other similar results have been obtained, and are summarised in the review by Pierce and McBee[100]. The use of perfluorinated *N*-bromoimides strengthens the positive character of the bromine and its brominating power. Toluene can be readily brominated in the nucleus by means of perfluorinated *N*-bromosuccinimide[101].

The anhydrous chlorides of aluminium, iron, and zinc have been investigated[102] as catalysts for the bromination of benzene with *N*-bromosuccinimide. In the presence of these catalysts, 40–70% yields of bromobenzene and bromotoluene can be obtained from benzene and toluene respectively; benzene cannot be brominated with *N*-bromosuccinimide in the absence of a catalyst. In the presence of these catalysts bromination probably takes place by an ionic mechanism. These results can be appropriately compared with those of Derbyshire and Waters[103] on the bromination of aromatic compounds with elementary bromine in the presence of the same catalysts. These

TABLE.

Brominating agent	Proportion of reaction products, %	
	Br—C_6H_4—CH_3	$C_6H_5CH_2Br$
$CH_3CONHBr$	0	100
$CCl_3CONHBr$	17	83
$CHCl_2CONHBr$	62	38
$CClH_2CONHBr$	82	18
$CF_3CONHBr$	88	12

workers consider that the active brominating agent is the bromine cation, which is formed as follows:

$$Br_2 + FeBr_3 \longrightarrow (Br^+)(FeBr_4^-).$$

There is undoubtedly a close connection between the (nuclear) bromination of aromatic systems with the elementary halogen and with compounds containing the positive halogen: in both cases the halogen cation is the brominating agent.

Orazi and his coworkers [104-112] have made a detailed investigation of the halogenating properties of 3-mono- and 1,3-di-halogenated derivatives of 5,5-dimethylhydantoin, which contain positive halogen. With these compounds he obtained high yields of halogenated aromatic compounds which already contained various substituents. Halogenation with halogenated 5,5-dimethylhydantoins is carried out under roughly the same conditions as with *N*-bromosuccinimide. In both cases halogenation is accelerated by addition of peroxide compounds and by illumination.

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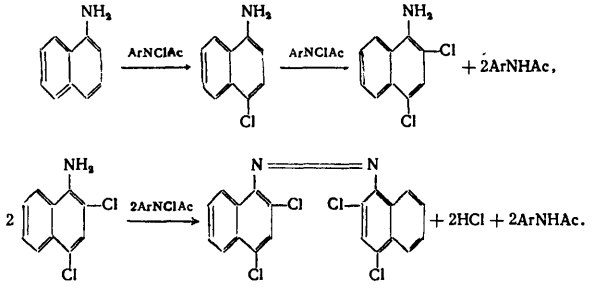
Insufficient work has been done on the halogenation of amines with positive halogen, existing data indicating that this reaction cannot yet serve as a reliable method for introducing halogen into the amino-group. Datta [113] studied the chlorination of benzylamine with dichlorourea, and obtained a mixture of the mono- and di-chloroamines. He found that chlorination takes place slowly, with considerable resin formation and gas evolution. Likhosherstov [114] attempted to introduce chlorine into the amino-group of aniline and other aromatic amines by means of dichlorourea, but obtained only resinous products. Danilov and Koz'mina [115] studied the possibility of using *N*-chloroacylanilines to chlorinate the amino-group in aromatic, aliphatic, and mixed amines. It was found that interaction of the reactants in anhydrous medium resulted first in chlorination of the benzene ring containing the amino-group, and with excess of the chlorinating agent the nuclear-chlorinated amine is oxidised to an azo-compound:



With primary and secondary aliphatic amines the chloroacylamines undergo double decomposition with the formation of *N*-chloroamines:

$$ArNClAc + RNH_2 \longrightarrow RNHCl + ArNHAc,$$

$$2ArNClAc + RNH_2 \longrightarrow RNCl_2 + 2ArNHAc,$$

$$2ArNClAc + R_2NH \longrightarrow R_2NCl + ArNHAc.$$

Reaction of chloroacylamines with tertiary aliphatic and mixed aliphatic–aromatic amines involves the elimination of one alkyl group, its oxidation to an aldehyde, and chlorination of the resulting dialkylamine.

Waters and coworkers [46] studied the chlorinating action of *N*-chloro-2,4,6-trichlorobenzanilide on aliphatic amines of the type $NR(CH_2CH_2Cl)_2$, and found that halogenation of the radical R takes place first of all, for example:

$$NCH_3(CH_2CH_2Cl)_2 \longrightarrow NCH_2Cl(CH_2CH_2Cl)_2.$$

Treatment of this base with water entails dealkylation:

$$NCH_2Cl(CH_2CH_2Cl)_2 + H_2O \longrightarrow HCl + CH_2O + NH(CH_2CH_2Cl)_2.$$

Dealkylation of amines in this way might have provided a new method for the controlled cleavage of cyclic amines such as nicotine and other alkaloids. However, later work showed [116] that this process is exceptional in character, and cannot be of practical value. Thus when cyclic amines (*N*-methylpiperidine, 1,2,3,4-tetrahydro-1,6,8-trimethylquinoline, nicotine, and ergotoxine) are treated with *N*-chloro-2,4,6-trichlorobenzanilide, the ring is chlorinated in all possible positions.

Summarising the literature on the halogenation of organic compounds with compounds containing positive halogen, we conclude that *N*-halogenated agents have become widely used in the practice of synthetic organic chemistry, and have made it possible to obtain several halogeno-derivatives which cannot be readily prepared in other ways.

In contrast, compounds having positive halogen linked to carbon find no great application as halogenating agents, although halogenation by means of them is in principle possible (for example, see Henderson and Macbeth [117], also Gabriel [118]).

The mechanism of the characteristic reactions of compounds containing positive halogen has been studied in the greatest detail in work on halogenation with *N*-halogenated amides and it can be concluded that compounds containing positive halogen can react either by an ionic or by a free-radical mechanism depending on the reaction conditions. This emphasises yet again the very labile and peculiar character of the halogen in these compounds.

6. ADDITION TO MULTIPLE BONDS

The addition of compounds containing positive halogen to multiple bonds has been investigated mainly in connection with halogenation by *N*-halogenated compounds. Apart from general cognitive purposes, work on these lines has been pursued with the aim of developing a method for synthesising halogenated multifunctional compounds.

Földi showed [119] that *N*-bromo-*N*-methylbenzenesulphonamide readily adds to the double bond of 1-phenylpropene giving a 90% yield of addition product:

He was unable to extend this reaction to purely aliphatic unsaturated compounds, since under his conditions the corresponding bromination products were mainly formed.

Later Kharasch and Priestley [120] effected the addition of *N*-bromosulphonamides to propene, isobutene, vinyl chloride, and styrene. They were also able to add on *NN*-dibrominated aromatic sulphonamides to styrene, anethole, and isosafrole. The nature of the radicals, R, R′, and R″ (see equation below) was found to be of secondary importance. Thus phenyl-, *p*-tolyl-, and benzyl-sulphonyl derivatives of methyl-, benzyl-, and phenethyl-amine and other compounds of this type could be used in this reaction equally successfully. Determination of the positions of the nitrogen and bromine atoms in the addition

products is of undoubted theoretical interest, since it can serve as an indirect proof of the ionic or radical mechanism of the process. It was found that *N*-bromosulphonamides add to alkenes with the formation of products in which the bromine atom occupies the same position as in the "normal" addition of hydrogen bromide to these alkenes:

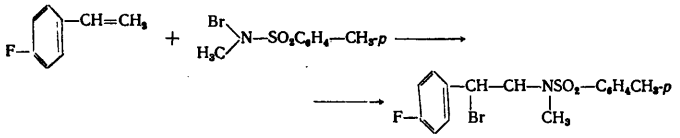
$$RCH=CH_2 + BrNR''SO_2R' \longrightarrow RCHBrCH_2NR''SO_2R'.$$

NN-Dibromosulphonamides add to alkenes to yield products in which the bromine occupies the same position as in the "anomalous" addition of hydrogen bromide (the brominated alkene is formed at the same time):

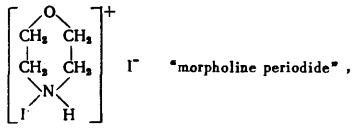
$$2RCH=CH_2 + Br_2NSO_2R' \longrightarrow RCH(NHSO_2R')CH_2Br.$$

There are indications that *N*-chlorinated aromatic sulphonamides, for example, *N*-chlorobenzenesulphonamide [121] and *N*-chlorosaccharin [77], are also able to add to unsaturated compounds.

Fosdick *et al.* [122], in the search for methods of synthesising hypotensive amines containing fluorine and chlorine in the aromatic ring, used the addition of *N*-bromo-*N*-methyl-*p*-toluenesulphonamide to halogenated styrenes and hydroxystyrenes, and obtained the desired products in good yields:



Investigation of the mechanism of the bromination of unsaturated compounds with *N*-bromosuccinimide led Southwick and coworkers to study the reaction of iodamines with $\alpha\beta$-unsaturated ketones [123]. They showed that complexes of iodine with amines, for example, the so-called morpholine periodide:



"morpholine periodide",

react rapidly with *trans*-1,2-dibenzoylethylene, *trans*-3-benzoylacrylic acid, cinnamaldehyde, and β-nitrostyrene at room temperature. In the case of nitrostyrene, a good yield of the addition product of *N*-iodomorpholine was isolated [123-125]:

$$C_6H_5CH=CH-NO_2 \xrightarrow{OC_4H_8NH\cdot I_2} C_6H_5CH(NC_4H_8O)CHINO_2.$$

It is interesting that in this case the orientation of addition is opposite to that observed by Fosdick [122]: the halogen adds at the β-position with respect to the benzene ring.

These workers were also able to add *N*-bromomorpholine to *trans*-benzylideneacetophenone [125]:

$$C_6H_5CH=CHCOC_6H_5 + BrN\langle(CH_2CH_2)_2\rangle O \longrightarrow C_6H_5CH(NC_4H_8O)CHBrCOC_6H_5.$$

Addition to multiple bonds of substances containing positive halogen was observed in the work of Parke *et al.* [99] quoted previously. They noted that *N*-bromotrifluoroacetamide and *N*-bromotrichloroacetamide give up to 40% of addition products with cyclohexene.

Baily and Bello [95] observed the addition of *N*-bromosuccinimide as a secondary process in the bromination of vinylacetonitrile. Since the reaction occurs in the presence of benzoyl peroxide, they assume that addition of *N*-bromosuccinimide to a double bond occurs by a free-radical mechanism.

When *NN*-dibromo-amides react with organic acids and unsaturated compounds, only small amounts of addition products of the bromoamides and the alkenes are formed [126].

Probst investigated the reaction of *N*-bromoacetamide with styrene, cinnamic acid and its methyl and ethyl esters, *trans*-stilbene, and benzylideneacetophenone, and showed that the corresponding dibromide is the only product in every case [127]. The reaction of styrene with several other *N*-brominated compounds, such as *N*-bromobenzamide, *N*-bromophthalimide, *N*-bromosuccinimide, etc., was studied, but none was found to give an addition product with styrene.

Comparison of the reactivities of various compounds containing positive halogen shows that addition is characteristic mainly of *N*-halogenated derivatives, especially *N*-halogenated sulphonamides.

Judging from the available literature, addition to unsaturated compounds is not characteristic of the *C*-halogenated derivatives. Thus Baskakov and Mel'nikov [128] found not long ago that, of the many α-halogenonitroalkanes which they investigated, only bromopicrin reacts at an appreciable rate with unsaturated compounds. The reaction is carried out in the presence of benzoyl peroxide or under ultra-violet irradiation.

The addition of substances containing positive halogen to multiple bonds was investigated in some details also in the reaction of alkyl hypohalites with several unsaturated compounds. Thus Conant and Jackson [129] effected the reaction of bromine with cinnamic acid and benzylidineacetophenone in aqueous methanol and obtained the corresponding bromomethoxy-derivatives. In a later series of papers [130-132] Jackson showed that the reaction involves the intermediate formation of the alkyl hypohalite. For example, the reaction of chlorine with unsaturated compounds in the presence of ethanol occurs as follows:

$$CH_3CH_2OH + Cl_2 \longrightarrow CH_3CH_2OCl + HCl,$$

$$C_6H_5CH=CHCOOH + CH_3CH_2OCl \longrightarrow C_6H_5CH(OC_2H_5)CHClCOOH.$$

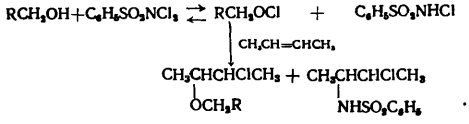
The reaction is carried out at room temperature or by boiling in alcohol. With the bromo-derivatives, dibromides are formed as side-products, but with chlorine only addition products of the alkyl hypochlorite are formed [130].

Methyl hypochlorite adds readily to the triple bond in phenylacetylene [132]

$$C_6H_5C\equiv CH + 2CH_3OH + Cl_2 \longrightarrow C_6H_5C(OCH_3)_2CHCl_2.$$

The possibility of synthesising β-chloroethers by the addition of alkyl hypochlorites to unsaturated compounds has been studied also by Likhosherstov and his coworkers [121,126,133-137]. The source of the hypochlorites was the corresponding alcohol, interacting with free chlorine in the course of the reaction. Diols and also phenols can be used as well as aliphatic alcohols in this reaction. Addition of the elements of an alkyl hypohalite to multiple bonds by interaction with unsaturated compounds in alcoholic media is characteristic of a great variety of compounds containing positive halogen.

Thus several *N*-halogenated amines and amides can be used to provide the chlorine, and they, as well as the alkyl hypohalite, add to the double bond [121,136]:



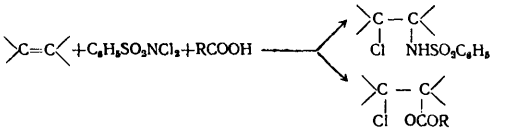
The course of the reaction depends on the properties of alcohol and halogenated amine or amide; a large excess of alcohol results in almost exclusive formation of a β-halogenoether.

In assessing the value of such reactions for preparative purposes, the results of Buckles *et al.*[138] must be borne in mind. Although they showed in several cases the possibility of the addition of bromine plus a radical from a hydroxylated solvent, this reaction is in their opinion of no value as a method of preparation, since it is extremely difficult to purify the desired products from dibromides.

If the halogen is positive in character, *C*-halogenated derivatives can be used, as well as the *N*-halogenated derivatives, to add the elements of an alkyl hypobromite. Methyl and allyl hypobromites, for example, undergo additions to the most varied unsaturated compounds by reaction of the latter with bromonitromalonic ester, bromopicrin [NO_2CBr_3 (Ed. of Translation)] and other α-halogenonitro-compounds in methanol or allyl alcohol respectively[6,139].

If acids are used instead of alcohols as solvents, acyl hypohalites can be added to unsaturated compounds.

Thus Likhosherstov and his coworkers studied the reaction of halogenated sulphonamides with acids in the presence of alkenes and showed that two reactions take place, forming β-chloroethers (and free amides) or β-chlorosulphonamides[137]:



A similar addition of acyl hypochlorites and hypobromites to a double bond was described by Böckemüller and Hoffmann[140].

C-Halogenated compounds can also be successfully used as sources of positive halogen in the addition of acyl hypohalites[141].

It is impossible to discuss the addition of substances containing positive halogen to multiple bonds without mentioning the Meerwein reaction[142], which consists in the halogenoarylation of unsaturated compounds by means of arenediazonium chlorides, these behaving in some reactions like *N*-chloroamines, capable of free-radical reactions[143]. There is no need to consider the Meerwein reaction in any great detail here, since separate reviews have been devoted to it, in particular that published not long ago by Dombrovskii[144]. We may merely note that, even in the case of such an apparently well studied reaction, no uniform view is held concerning the mechanism of addition: up to the present, three mechanisms have been suggested for this reaction — the ionic[142], radical[143,145], and finally the ionic–radical[144] mechanism.

Summarising the literature on the chemistry of compounds containing positive halogen, we readily see that, although these compounds have attracted attention only comparatively recently, convincing evidence has been given of their very specific properties, and the possibility of utilising these properties to solve synthetic problems is already apparent. Nevertheless, although quite wide synthetic possibilities have been demonstrated for compounds containing positive halogen, the problem of controlling these reactions and studying their mechanism cannot be regarded as completely solved.

This problem has proved extremely complicated primarily because compounds containing positive halogen include *N*-, *C*-, and *O*-halogenated derivatives, which differ greatly in reactivity, and can, of course, interact with different organic compounds by different mechanisms and under different conditions.

These specific chemical properties of compounds containing positive halogen are caused by the peculiar state of the N–Hal or C–Hal bond in these compounds. Under the influence of electron-acceptor substituents, which are invariably present in molecules of such compounds, these bonds are polarised so that the halogen atom carries no appreciable negative charge, in contrast to ordinary organic halogen compounds, for example. In limiting cases, when the effect of electron-acceptor substituents is sufficiently great, the halogen atom carries a positive charge. Such a situation occurs, for example, in *N*-iodosuccinimide[146], bromo- and iodo-trinitromethane[147], and iodoacetylene[148].

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A NEW FIELD IN THE STEREOCHEMISTRY OF SUGARS: THE STUDY OF THEIR CONFORMATIONS

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I. INTRODUCTION

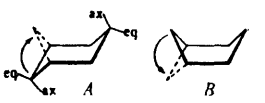
The last decade has been noteworthy for the introduction and vigorous development of a new field in the chemistry of carbohydrates — the study of their conformations[1-4]. It is no exaggeration to say that the new era in carbohydrate chemistry, this new development in the stereochemistry of sugars, is as significant as the period which followed the discovery of the cyclic forms of carbohydrates and the tautomerism between their open-chain and cyclic forms.

Despite this, data on the conformations of carbohydrates, which are relevant to chemists and biochemists, are little used in the USSR. The present knowledge of the conformations of carbohydrates is too broad to be encompassed within a single article, and therefore the object of this review is simply to set out the main theories and consider various examples which illustrate the practical value of this new field.

Conformations are the equilibrium forms of molecules which are taken up by aliphatic compounds because of the free rotation of groups around simple single bonds, or, in the case of cyclic compounds, because of rotation and change of the mutual positions of the individual parts of the molecule; in either case no bonds are broken in the mutual transitions between conformations, which distinguishes this from isomerisation.

In the case of cyclohexane, which may be considered as a model for a pyranose (the most common form of sugars), in addition to unstable transitional forms, the amount of which is usually negligible, two stable forms can exist: the chair form and the boat (or tub) form (Scheme 1). Of these the chair form is the more stable, since it contains the smaller number of mutually "screening" hydrogen atoms; it has 5.6 kcal less energy than the boat form, and under normal conditions it is the conformation taken up almost exclusively (99%) by cyclohexane.

The transition of one of these forms into the other can be considered as a rotation of part of the molecule, as shown by the arrows in Scheme 1, and is associated with a loss or gain of energy. Using the terms introduced into the conformational chemistry of sugars from the chemistry of



Scheme 1. The most stable conformations: ***A*** **chair form,** ***B*** **boat form; ax = axial atoms or groups; eq = equatorial atoms or groups.**

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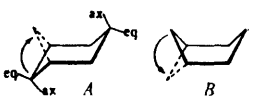
The last decade has been noteworthy for the introduction and vigorous development of a new field in the chemistry of carbohydrates — the study of their conformations[1-4]. It is no exaggeration to say that the new era in carbohydrate chemistry, this new development in the stereochemistry of sugars, is as significant as the period which followed the discovery of the cyclic forms of carbohydrates and the tautomerism between their open-chain and cyclic forms.

Despite this, data on the conformations of carbohydrates, which are relevant to chemists and biochemists, are little used in the USSR. The present knowledge of the conformations of carbohydrates is too broad to be encompassed within a single article, and therefore the object of this review is simply to set out the main theories and consider various examples which illustrate the practical value of this new field.

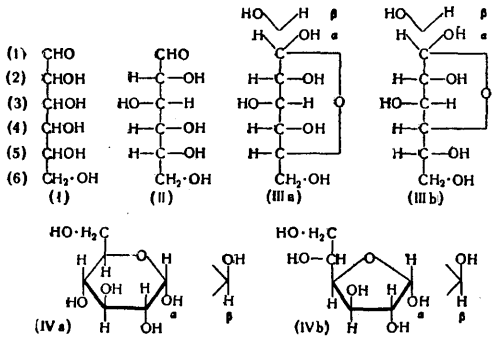
Conformations are the equilibrium forms of molecules which are taken up by aliphatic compounds because of the free rotation of groups around simple single bonds, or, in the case of cyclic compounds, because of rotation and change of the mutual positions of the individual parts of the molecule; in either case no bonds are broken in the mutual transitions between conformations, which distinguishes this from isomerisation.

In the case of cyclohexane, which may be considered as a model for a pyranose (the most common form of sugars), in addition to unstable transitional forms, the amount of which is usually negligible, two stable forms can exist: the chair form and the boat (or tub) form (Scheme 1). Of these the chair form is the more stable, since it contains the smaller number of mutually "screening" hydrogen atoms; it has 5.6 kcal less energy than the boat form, and under normal conditions it is the conformation taken up almost exclusively (99%) by cyclohexane.

The transition of one of these forms into the other can be considered as a rotation of part of the molecule, as shown by the arrows in Scheme 1, and is associated with a loss or gain of energy. Using the terms introduced into the conformational chemistry of sugars from the chemistry of



Scheme 1. The most stable conformations: ***A*** **chair form,** ***B*** **boat form; ax = axial atoms or groups; eq = equatorial atoms or groups.**



Scheme 2. Evolution of ideas on the structure of glucose (1870–1925).

alicyclic compounds, in the chair form of cyclohexane some of the hydrogen atoms are in positions almost in the plane of the molecule: these are called equatorial atoms. The other hydrogen atoms are in positions almost perpendicular to the plane of the molecule: these are called axial positions (Scheme 1).

Having considered the conversions of the conformational forms in the simplest case, cyclohexane, we shall now consider carbohydrates.

The evolution of our conceptions of the structure of monosaccharides (hexoses) is illustrated in Scheme 2.

After formula (I), suggested by Baeyer and Fittig (1870–1871), which only represents the presence of five alcohol groups and one aldehyde group in the molecule and is based mainly on Fischer's work (1890–1891), the configurational formula (II) was proposed (see my historical review[5]). Colley (1870) and Tollens (1883) first suggested cyclic formulae, which were then adapted into the formulae for α- and β-glucopyranose (IIIa) and glucofuranose (IIIb). In 1925 Haworth introduced the cyclic formulae which were the first attempt to reflect the geometry of the molecule as a six-membered ring, IVa and IVb. Such formulae have now been used for 25 years, but during the nineteen fifties they were replaced by conformational formulae which reproduce the form of the molecule more accurately and rationalise many facts which could not be previously explained.

We shall consider below the conformations of pyranoses, furanoses, and open-chain forms, and also oligo- and poly--saccharides.

II. THE CONFORMATIONS OF MONOSACCHARIDES

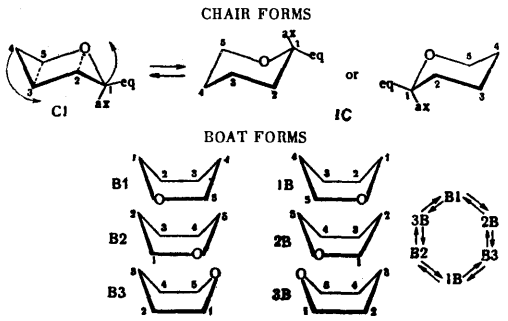
A. The Conformations of Six-Membered Monosaccharide Rings

Haworth's formulae are not completely satisfactory because a planar six-membered ring would be very strained and would not exist under normal conditions. Reeves[6,7] and others have shown that like cyclohexane, the pyranoses exist mainly in two forms which are less strained, the chair form and the boat form. These are very similar to the conformations of cyclohexanes, but with slightly less distortion in the ring and greater lability.

The cyclohexanes have two relatively stable conformations, but the pyranoses, because of the heteroatom and the asymmetric carbon atoms, have eight such conformations; two chair and six boat forms (Scheme 3). These are designated C, from the English word "chair", and B, from the English "boat", respectively. Three of the boat conformations (1, 2, and 3), as Scheme 3 shows, have the oxygen atom in different ring positions. In Scheme 3, the left-hand conformations are the mirror images of the right--hand series; this is indicated by the nomenclature C1 and 1C, B1 and 1B, etc. Although other systems exist[8,9], we shall use the nomenclature suggested by Reeves†.

The mutual conversions of the pyranose ring conformations may be represented as in the following example (Scheme 3): starting with the C1 form, rotation of the part of the molecule containing C_1 upwards and of the part containing C_4 downwards gives the 1C conformation (if this is imagined as turned through 180° it is seen that this conformation is the mirror image of the C1 conformation). It is very important to note that in such a conversion groups which are equatorial in the C1 conformation become axial in the 1C conformation, and *vice versa*. Rotation of the part of the molecule in the C1 conformation containing C_1 upwards but keeping all the other portions of the molecule as before gives the B1 conformation, and so on. The mutual conversions of the boat conformations are shown in the lower right in Scheme 3. For each pyranose, including α- and β-, there is the possibility of the indicated eight relatively stable conformations, without considering any transitional distorted forms.

In practice, however, the picture is somewhat simpler, since the various forms differ in stability. In the various



Scheme 3. Conformations of the pyranose ring. Below right: the possible conversions of conformation.

† It has been proposed[10] to indicate the positions of the hydroxyl groups, particularly the hemiacetal hydroxyl groups, by adding to the symbol for the basic chair or boat conformation (C, B1, B_2, B_3) the letter *A* or *E*, indicating the axial or equatorial position of the hemiacetal hydroxyl. The conformation is described in more detail by indicating the axial or equatorial position of each hydroxyl group, starting from the hemiacetal hydroxyl and then dealing with the others following the numeration of the carbon atoms. Thus the normal conformation of α-D-galactose is given by C(*aeeae*), the symbols *a* and *e* indicating the axial and equatorial positions of the hydroxyl groups starting from the first[11].

conformational conversions large groups normally tend to occupy equatorial positions; this effect, already known in the chemistry of alicyclic compounds from the work of Hassel and coworkers[12], is particularly important in the conformational analysis of sugars.

Reeves, one of the founders of this new chapter in the stereochemistry of sugars, has established[7] three main factors contributing to the instability of pyranose ring conformations:

(1) the presence of axial groups other than hydrogen atoms (for free sugars, the presence of axial hydroxyl groups);

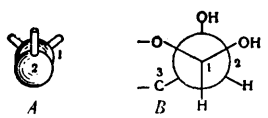
(2) the presence of the so-called Δ2 effect, *i.e.* the presence of an axial hydroxyl group at C_2, the C–O bond of which bisects the angle made by the two C–O bonds at C_1. The spatial distribution of the C–O bonds at C_1 and C_2 is shown in Scheme 4. This distribution, which produces an unfavourable dipole reaction in this conformation, is particularly effective in causing instability;

(3) the presence of an axial 5-hydroxymethyl group on the same side of the ring as other large axial substituents (the Hassel–Ottar effect)[12,13]. Reeves considered that these instability factors are additive, and evaluated the first as one unit for each large axial group, the Δ2 effect as 2.5 units, and the Hassel–Ottar effect as 0.5 unit. By considering these instability factors for each of the eight more stable conformations of a series of sugars and glycosides, Reeves could predict[7] which conformations would be most stable and would therefore predominate, and which would be least stable and would be practically non-existent.

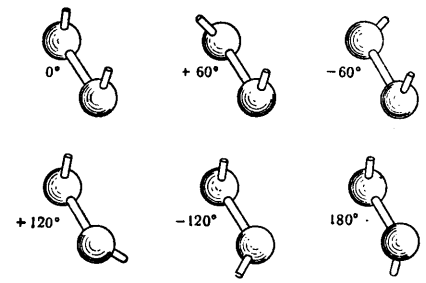
These predictions were confirmed with surprising accuracy in experiments made by Reeves himself and then by several others. We cannot refer to all the experimental data in detail, but shall mention some of them.

Reeves confirmed his predictions by studying the cuprammonium complexes of various substituted and unsubstituted glycosides. With dipolar groupings, *i.e.* two alcoholic hydroxyl groups, the cuprammonium ion forms a complex with a five-membered ring, containing two C atoms, two O atoms, and the cuprammonium ion. The following conditions are necessary for the formation of the complex: (*i*) the hydroxyl groups must be vicinal (with a few exceptions), and (*ii*) since neighbouring hydroxyl groups can be spatially directed on different sides, the distance between the centres of the oxygen atoms should not exceed a definite value, ~2.86 Å.

Scheme 5 shows the possible relative positions of bonds directed from neighbouring carbon atoms to the oxygen



Scheme 4. The Δ2 effect: the C–O bond at the second carbon atom bisects the angle formed by the C–O bonds on the first carbon atom. *A*) Model seen from the side of the second carbon atom; *B*) diagram seen from the side of the first carbon atom.



Scheme 5. The possible positions of bonds directed from neighbouring carbon atoms to the oxygen atoms of dipolar groups in all possible pyranose conformations.

atoms of the dipolar groupings in all possible conformations of pyranoses. If these directions are projected on to a plane perpendicular to the C–C bond, the angle between them will differ in each case, but will be practically constant in the stable conformations. By convention this angle is negative if it is measured in a clockwise direction as seen from the nearer group, and positive if measured in an anticlockwise direction. Complex-formation is possible only with projected angles of 0° and ±60°; only then is the distance between the two oxygen atoms less than the limiting value of 2.86 Å. With angles of ±120° and 180° the distance between the oxygen atoms is 3.45 and 3.71 Å respectively, and complex-formation does not take place.

Complex-formation can be detected most simply by spectrophotometry, or by the change in the plane of the optical rotation; the latter is of particular interest. There can be no change in the rotation, even in the presence of the complexing agent, if the projected angle between the C–O bonds of neighbouring atoms is 0°, since the resulting five-membered ring will be symmetrical. If the projected angle is ±60°, the five-membered ring in the resulting complex will be twisted and asymmetric and, depending on whether the projected angle is +60° or -60°, the resulting rotation will be dextro or laevo. For example, in glycopyranosides the 2-, 3-, and 4-hydroxyl groups are free, and Reeves selected substituted glycosides such that only 2,3-complexes or 3,4-complexes could be formed, and showed that the former, *i.e.* the 2,3-complexes, are laevorotatory, and the latter dextrorotatory. Thus by determining whether or not complex-formation takes place with a change in the rotation of the cuprammonium complexes or not, in various pyranosides and their substitution products, it was possible to evaluate the actual angles made by projection of neighbouring atoms in different parts of the molecule, and hence to find which conformation or conformations are typical for the given glycosides or their derivatives.

The Table gives very abbreviated data on the conformations found in the study of cuprammonium complexes, and the data predicted by evaluation of the instability factors. The correspondence is seen to be very good, except for the gulopyranosides, which exist in fact in only one conformation.

Many methods now exist for the determination of conformations. In addition to the study of cuprammonium complexes and the influence of alkalis on the rotation of sugars[14], other methods also find wide application. Chemical methods

TABLE.

Methylglycopyranoside	Type of complex	Conformation based on	
		complex-formation	calculation of instability factor
α-D-mannopyranoside	dextrorotatory	C1	C1
β-D-mannopyranoside	dextrorotatory	C1	C1
α-L-rhamnopyranoside	laevorotatory	1C	1C
α-D-altropyranoside	dextro-laevo--rotatory	C1, 1C	C1, 1C
β-D-altropyranoside	dextro-laevo--rotatory	C1, 1C	C1, 1C
α-D-gulopyranoside	dextrorotatory	1C	C1, 1C
α-D-idopyranoside	compensation	1C	1C
β-D-xylopyranoside	compensation	C1	C1
β-D-ribopyranoside	compensation	C1	C1
α-D-lyxopyranoside	dextro-laevo--rotatory	C1, 1C	C1, 1C

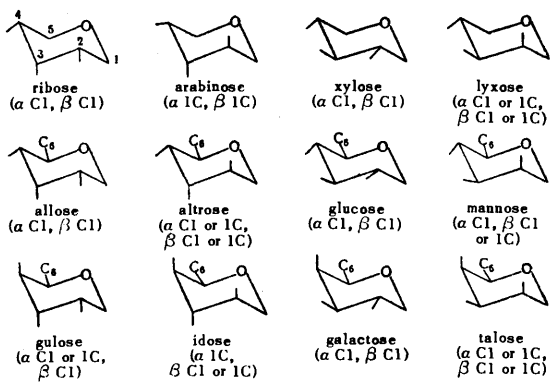
include the oxidation of free sugars with bromine by the Isbell–Pigman method[15]: an equatorial glycoside hydroxyl is much more readily oxidised. Physical methods include infra-red spectroscopy[16,17], which can distinguish between an equatorial and axial hydrogen at C_1 in aldopyranoses: the equatorial C_1–H bond shows a peak at 844 cm^{-1}, and the axial C_1–H bond a peak at 891 cm^{-1}. X-Ray structural analysis is used for crystalline sugars, *e.g.* α-D-glucose[18], α-L-rhamnose[19], and β-D-arabinose[20].

In recent years Lemieux and coworkers[21,22] have used proton magnetic resonance for studying conformations. Other methods have also been used, for instance the study of refraction (*e.g.* of methylglycosides[23]). In almost all cases these methods have confirmed Reeves' results obtained with the cuprammonium complexes.

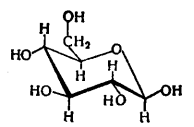
Correlating the results obtained with all the methods indicated, it can be said that the predominant conformation of α- and β-pyranoses and pyranosides is the chair form, usually C1; and of L-arabinosides, L-galactosides and certain others, the 1C form. Scheme 6 shows some of the more important penta- and hexa-pyranoses in the C1 conformation. With unstable C1 and 1C conformations of similar energies, both forms are present simultaneously (*e.g.* with lyxose, altrose, talose, and some others).

The most stable conformation is the C1 conformation of β-glucose (Scheme 7), which has no instability factors: all the hydroxyl groups and the hydroxymethyl group are equatorial. Glucose derivatives are also as a rule more stable than derivatives of other sugars[24]. Certain cases where α-glucose derivatives are most stable than β-glucose derivatives, which were inexplicable from the point of view of conformations (such as the greater stability of α-methylglucopyranoside[25], pentaacetyl-α-D-glucopyranose[26], and acetohalogeno-α-D-glucopyranose[27]), have found explanation from the electronic viewpoint[28].

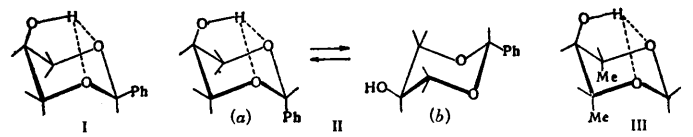
In speaking of the predominance of the chair form in glycosides and especially free pyranoses, it must not, of course, be forgotten that these forms are not infinitely stable; the possibility of their conversion into other (in particular, intermediate) forms cannot be excluded, especially under reaction conditions. Moreover, the solvent may exert a definite action. Water molecules in particular generally hinder the formation of intramolecular hydrogen bonds which might stabilise conformations which are sometimes rather unfavourable. In this connection we recall the model experiments of Stacey and coworkers[29] which showed that in dry CCl_4 *cis*-1,3-*O*-benzylideneglycerol is completely in the form in which there is solely hydrogen bonding with the hydrogen of the C_2 hydroxyl group of the glycerol (Scheme 8, I), while with the *trans*-form an equilibrium mixture exists (Scheme 8, II). In the former, the equatorial phenyl group favours hydrogen bonding. In the case of 1,5-didesoxy-2,4-*O*-methyleneribitol only the unfavourable conformation with two axial methyl groups shows hydrogen bonding (Scheme 8, III).



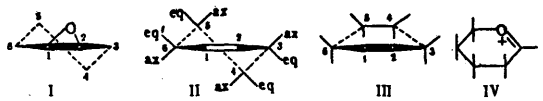
Scheme 6. The C1 conformations of some important pyranoses (pentoses and hexoses). These schematic conformational formulae show only the rings and the bonds leading to the hydroxyl groups and (in the case of the hexoses) the sixth carbon atom.



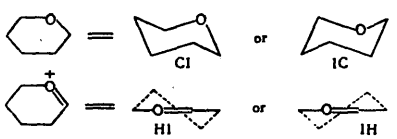
Scheme 7. The normal C1 conformation of glucose and glucosides.



Scheme 8. The role of hydrogen bonding in the formation of conformations: I) *cis*-1,3-*O*-benzylideneglycerol; II) *trans*-1,3-*O*-benzylideneglycerol in two equilibrium conformations with *a*) axial and *b*) equatorial phenyl; III) 1,5-didesoxy-2,4-*O*-methyleneribitol.



Scheme 9. Models of intermediate conformations: I) cyclohexane oxide in the half-chair form; II) cyclohexene, in the half-chair form; III) the half-boat form; IV) the unsaturated oxonium ion.



Scheme 10. The pyranose ring in the chair forms C1 and 1C, and the unsaturated oxonium ion produced from a pyranose, in the half-chair forms H1 and 1H.

In 1957 Reeves and coworkers directed attention to the significance of boat forms[14]. Although the chair form possesses the lower energy, in certain circumstances the energy difference may be very small, when the boat conformation allows all large substituents to be equatorial. The boat forms produced may be distorted and not geometrically exact. Such conformations can arise in the action of alkalis on glycosides; in particular they must be formed in polysaccharides (see below)

Half-chair forms. Intermediate forms, mainly the half-chair form, have recently begun to attract great attention. Alicyclic models of such forms are cyclohexane oxide [1,2-epoxycyclohexane (Ed. of Translation)][30] and cyclohexene[31]. Electron diffraction has shown that the 1, 2, 3, and 6 atoms in these compounds lie in one plane, with the 4 and 5 atoms below and above this plane (Scheme 9, I and II). Molecules may also exist in the half-boat form (Scheme 9, III), but all data indicate that these conformations are less stable than the half-chair form.

Half-chair conformations apparently arise in a number of chemical and biochemical reactions of sugars, and in particular the unsaturated sugar oxonium ion (Scheme 9, IV) which is formed in a number of reactions, apparently has this conformation, the reason being, as with cyclohexene, the presence of the double bond. This ion is formed as an intermediate in the hydrolysis of glycosides (see Section V.4.). The half-chair form is designated H; the mirror-image conformations are called 1H and H1 (Scheme 10).

B. The Conformation of Five-Membered Monosaccharide Rings

According to infra-red spectroscopy the rings of cyclopentane and tetrahydrofuran are not exactly planar, but the actual distortion is so small as to be negligible. Barker and Stephens have said[32] that the infra-red spectra of α- and β-furanosides are identical‡; the two anomers cannot

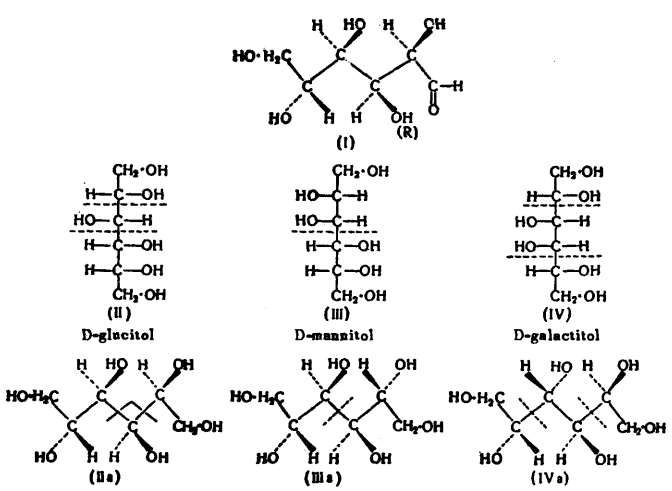
‡ The reader is advised to refer to the original on this point (Ed. of Translation).

Scheme 11. The furanose ring of fructo- and ribo-furanose. The atom C is 0.5 Å outside the plane of the remainder of the ring.

be distinguished by this method, since both have the same angle of projection of the C_1–H bond on to the ring. The X-ray structural analysis of sucrose[33] and crystalline cytidine[34] showed that four of the furanose ring atoms in the fructofuranosyl and ribofuranosyl portions respectively are coplanar, while the fifth projects from this plane by 0.5 Å, and is in each case the C_4 atom, indicated by the letter C in Scheme 11. Apparently the slight bending of the molecule on the A–B axis facilitates the approach of substituents on atoms A, C, and B towards the plane of the ring. In solution the furanose ring may be quite appreciably folded, as is shown by periodate oxidation, which, irrespective of the configuration, causes rupture of the C_2–C_3 bond. Since oxidation by periodate ion proceeds by way of an intermediate complex with a diol[35], the bending for *trans*-diols must be considerable. It is interesting that periodate oxidation does not occur when bending is impossible because of fixation of the system by means of a bridge (*e.g.* in 1,6-anhydroglucofuranose).

C. The Conformation of Acyclic Forms of Monosaccharides

According to modern ideas, the carbon chain in acyclic forms of saccharides is a zig-zag, with the large substituents in zig-zag formation; thus glucose must have the conformation shown in Scheme 12 (I) which is quite unlike the Fischer formula. The following facts demonstrate this.



Scheme 12. The conformational formula of glucose (I), and the Fischer and conformational formulae of the hexitols glucitol (II) and (IIa), mannitol (III) and (IIIa), and galactitol (IV) and (IVa).

In 1957 Schwarz[36], when oxidising hexitols with periodate, found that it is predominantly the *trans*-diol bonds which are ruptured, as shown by the dotted line in Scheme 12 (II) and (III); normally, however, periodate oxidises predominantly *cis*-diol systems. This unusual oxidation of hexitols is easily explained by considering the conformational formulae, which more nearly represent the actual structure. With gluticol, Scheme 12 (IIa), for example, it is seen that the hydroxyl groups at C_2, C_3, and C_4 are in fact in *cis*-positions, and they only appear to be *trans* because of the conventional manner of writing the Fischer formulae, which are projections of molecules with the carbon chain in the form of an arc with the convex side directed towards the observer.

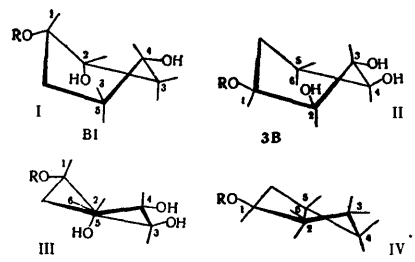
Even more convincing proof of the zig-zag conformation of acyclic forms was given by Hough and Bragg[37], who showed that large substituents R on C_3 hinder reactions by obstructing the approach of reagents to the 1-position, Scheme 12 (I), because of the zig-zag form of the molecule. Finally, Littleton[38] found an almost planar zig-zag carbon chain by X-ray structural analysis of a crystalline gluconate.

III. THE CONFORMATIONS OF OLIGOSACCHARIDES

The conformations of oligosaccharides have been comparatively little studied. As an example of such studies we adduce Bentley's work[39,40] on the conformations of cellobiose and maltose.

In cellobiose both residues have the C1 conformation (Scheme 13). The reducing residue is seen to have this conformation because of its rapid oxidation by bromine water (as in the oxidation of glucose), demonstrating the equatorial position of the hemiacetal hydroxyl. The requirement that both glucose residues should be equatorial has caused certain other suggested possible conformations for the non-reducing residue to be rejected. The X-ray structural study of crystalline cellobiose had already shown that both glucose residues are in the C1 conformation[41]. The same conformations have been found in cellulose[42].

The reducing glucose residue of maltose, like that of cellobiose, has the C1 conformation, as is demonstrated particularly by its rapid oxidation with bromine. With the α-1,4-glycoside linkage the non-reducing residue cannot have the C1 conformation, since the α-hemiacetal hydroxyl is axial, while the hydroxyl group at C_4 is equatorial. Results obtained in the study of the rate of hydrolysis of maltose, the rate of the periodate oxidation of α-methylmaltoside in comparison with the oxidation of certain other glycosides, the behaviour of cuprammonium complexes



Scheme 14. Possible conformations of the non-reducing residue in maltose (III and IV); they are intermediate between the boat conformations B1 and 3B (I and II).

and the action of alkalis, have shown[39,40] that the non-reducing glucose residue in maltose has a distorted conformation intermediate between B1 and 3B; all the properties of maltose confirm this conformation (Scheme 14).

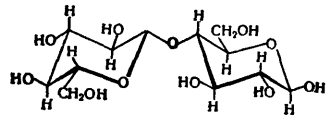
Cellobiose and maltose thus differ not only in having different glycosidic linkages (α and β), but also in the conformation of the non-reducing glucose residue.

IV. THE CONFORMATIONS OF POLYSACCHARIDES

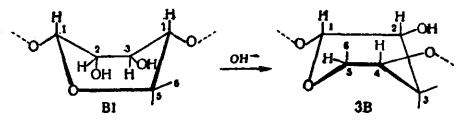
This field is the most complex and the least studied. In discussing the conformations of polysaccharides, two matters arise: (1) the conformation of the monosaccharide residues in the molecule, and (2) the shape of the whole molecule, which depends on the relative orientations of the monosaccharide residues, which can rotate around the glycoside linkages joining them.

The C1 conformation of the glucose residues in cellulose has been demonstrated[42].

The C1 conformation of the glucose residues of starch amylose is improbable, because the α-hemiacetal hydroxyl is axial and the OH at C_4 is equatorial. From study of the cuprammonium complexes and the action of alkalis, Reeves[43] concluded that the glucose residues of amylose exist not in one, but in two conformations, the boat forms B1 and 3B. Alkalis (which are known to change the properties of amylose) change the B1 conformation into the 3B conformation, *i.e.* all the glucose residues in "alkali amylose" are in the 3B conformation (Scheme 15). This change occurs because when the axial hydroxyl groups on the ring dissociate in alkaline medium they take up equatorial positions. These views may be open to some alteration in the light of Bentley's work, referred to above, on



Scheme 13. The conformational formula of cellobiose. Both glucose residues are in the C1 conformation.



Scheme 15. The B1 and 3B conformations of glucose residues in amylose. Alkali converts the B1 conformation into the 3B conformation.

the conformations of the hexose residues in maltose[40], but it is perfectly clear that there will still remain the hitherto unsuspected difference between cellulose and amylose, that the former contains the C1 conformation and the latter at least two conformations, boat forms or distorted forms close to boat forms.

The method of drying, the action of alkalis, and similar factors often greatly affect the properties of polysaccharides. The reason for these changes is probably to be sought in changes of the conformations of the monosaccharide residues, and much work remains to be done in the discovery of the actual causes and their mechanisms.

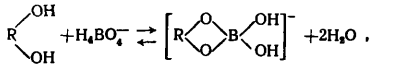
As regards the conformations of polysaccharide molecules as a whole, Everett and Foster recently[44] studied the conformations of amylose in solution, and from the viscosity of a number of amylose sub-fractions in various solvents (KCl and KOH solutions) they concluded that the molecules of these polysaccharides are bent chains but not spirals; the latter, which are more stable structures than rods, exist in a number of amylose complexes (with iodine, alcohols, etc.).

V. SOME PARTICULAR ASPECTS OF THE STUDY OF THE CONFORMATIONS OF CARBOHYDRATES

There are probably no reactions in carbohydrate chemistry for which conformational ideas are without any value, and a very large number of examples could be given where their value is particularly great. We shall refer to some of these.

1. Mutarotation. A good explanation has been given for the conversion of one tautomeric form of monosaccharide into several others, with one predominating, *e.g.* β-D-glucose in a glucose solution: the β-form of glucose has no axial hydroxyl groups while the hemiacetal hydroxyl of the α-form is axial, and this determines the predominance of the β-form. The anomers which are conformationally most stable predominate in the solutions of all sugars.

2. Reaction with borate and electrophoresis. The borate anion forms a complex with a diol of appropriate construction[45,46]:

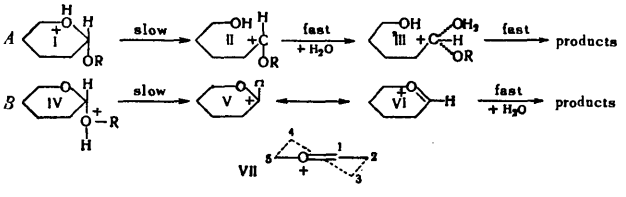


and because of the charge taken up by the sugar the complex will migrate on electrophoresis. The rate of migration of sugar depends on the position of equilibrium, and this depends on the stereochemistry of the dieol. Favourably disposed hydroxyl groups form stable complexes which have a high rate of migration. By studying the rates of migration of various substituted glucoses, Foster showed[47] that at pH 10 glucose can form three types of compound with borate: in the 2,4- and 4,6-positions of the open-chain form of glucose. Scheme 12 (I), and the 1,2-position (*cis*-diol) of the α-form of glucopyranose and glucofuranose. Other points of reaction are possible (*e.g.* 2,3-) but these have no substantial significance. Methylxylopyranoside does not migrate in borate solution, while methylarabinopyranoside migrates rapidly, because of the formation of a complex at the 3,4-diol position. These and a number of other facts[48] are in good agreement with conformational ideas, which can explain and to some extent predict the behaviour of various carbohydrates on electrophoresis.

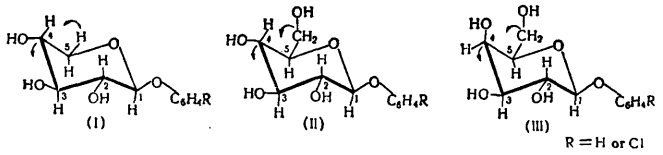
3. Chromatographic behaviour. There are indications[49] that an equatorial hydroxyl group in sugars is more strongly hydrated. It would be expected that a sugar with a small number of axial hydroxyl groups would be more soluble in water and would move more slowly in the corresponding systems. The R_f values of most free sugars can be calculated[2] from the formula $R_f = K + a(n + \alpha)$, where K and a are constants for a given series (*e.g.* the hexoses), n is the number of axial hydroxyl groups in the molecule, and α is the fraction of the anomeric sugar which in the given equilibrium solution contains the first hydroxyl group in the axial position (*e.g.* for glucose α-glucose has the hemiacetal hydroxyl in the axial position, and in solution it makes up ~0.34 of the total amount of sugar). In the above equation n and α depend on the conformation and thus the chromatographic mobility is directly dependent on conformation. A few sugars, such as arabinose and galactose, are exceptions, giving lower R_f values than those calculated by the formula.

4. Acid hydrolysis of glycosides. An enormous amount of factual material exists on the dependence of the rate of acid hydrolysis of glycosides on their structure. Two possible mechanisms for the hydrolysis have been discussed in the literature, one proposed by Bunton and coworkers[50] and Shafizade[51], and the other by Edwards[52].

According to the Bunton–Shafizade mechanism (Scheme 16, *A*) a proton adds to the pyranoside ring oxygen I, followed by a slow (and therefore rate determining for the overall hydrolysis) rupture of the pyranose ring and two further steps to the reaction products. According to the Edwards mechanism (Scheme 16, *B*), developed mainly from work on alkylglycosides, a proton attaches to the oxygen of the substituted hemiacetal hydroxyl IV, followed by the slow scission of an alcohol to form the carbonium or unsaturated oxonium ion VI; this reacts rapidly with water to give the final hydrolysis products. The unsaturated oxonium ion exists in the H1 half-chair conformation. The conversion of the C1 conformation in which most pyranosides exist into the H1 (Scheme 16, VII) is accompanied by a slight rotation of the atomic groups around the 2,3- and 4,5-bonds. Since the rate of hydrolysis is determined by the slow rate of formation of the H1 form, factors which influence the rotation of the atomic groups around the 2,3- and 4,5-bonds have a great significance; as always, large substituents tend to occupy equatorial positions. Edwards' mechanism explains a large amount of experimental material from a



Scheme 16. Mechanisms for the hydrolysis of glycosides: *A*) according to Bunton and Shafizade; *B*) according to Edwards.



Scheme 17. Xylosides (I), glucosides (II), and galactosides (III) in the C1 conformation.

single viewpoint, and is better than Bunton's in this respect[2]. In particular, it explains why alkylheptosides are more stable than alkylhexosides which, in their turn, are more stable than alkylpentosides[53].

Recent studies[54,55] on the kinetics of hydrolysis of phenyl- and chlorophenyl-glycosides have given results in good agreement with Edwards' views on conformations, and are in their turn additional facts which support his mechanism. Phenyl- and *p*-chlorophenyl-glucose, Scheme 17 (II), are hydrolysed less rapidly than the corresponding xylosides, Scheme 17 (I), because of the presence at C_5 of the large substituent CH_2OH, which on the formation of the half-chair form must leave the equatorial position and tend towards the axial position (Scheme 17). On the other hand, the hydroxyl group at C_4, which is axial in the galactosides , Scheme 17 (III), must move to a position close to equatorial when the half-chair form is produced, and this facilitates hydrolysis of the galactosides in comparison with the glucosides.

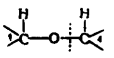
The fact that *p*-chlorophenylglycosides are hydrolysed less rapidly than the corresponding phenylglycosides may be explained by the lower electron density in the benzene ring of the aglycone chlorophenol, and suggests that the proton attaches to the oxygen of the substituted hemiacetal hydroxyl, rather than to the oxygen of the pyranoside ring.

VI. THE CONCEPT OF CONFORMATIONS AS APPLIED TO BIOCHEMISTRY

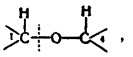
Conformational ideas have been little used in biochemistry.

We shall consider in some detail the work of Meyer and Larner[56] on the mechanism of action of α- and β-amylase. The problem which has been in existence for several decades is why polysaccharides of the starch type with 1,4--glucoside linkages are hydrolysed by α-amylase to α-maltose or its polymers, but by β-amylase to β-maltose.

Meyer and Larner first assumed that the different actions of the amylases are due to different points of attack. If the action of α-amylase is to break the glycoside bridge between the oxygen and C_4,

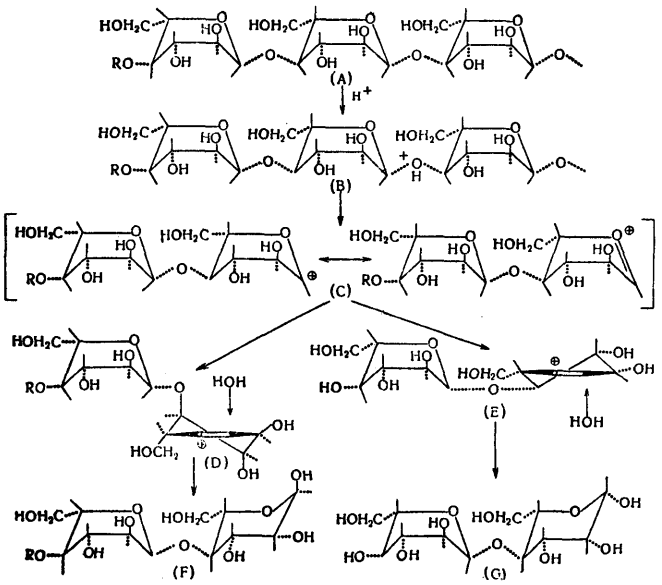


the configuration at C_1 should not change and the product would have an α-hemiacetal hydroxyl. If β-amylase breaks the bond between C_1 and the oxygen,



the reaction is taking place at the centre of asymmetry of C_1, and the configuration may change to give a β-glycoside hydroxyl. To decide this question, glycogen was hydrolysed with α- and β-amylase in $H_2{}^{18}O$; both enzymatically produced sugars were found to contain ^{18}O in the 1-position but not the 4-position. In a control experiment the maltose contained only traces of ^{18}O. Consequently, both α- and β-amylase break the glycoside bond at the same point, between C_1 and the oxygen. To explain the formation of both α- and β-hemiacetal hydroxyls, Meyer and Larner used Edwards' mechanism for the hydrolysis of glycosides (referred to above), with the intermediate formation of unsaturated oxonium ions in the half-chair conformation. Apparently the hydrolysis by α- and β-amylase proceeds as follows (Scheme 18).

The polyglycoside chain of the glycogen with the glucose residues in the B1 boat conformation (A) lies on the surface of the enzyme. A proton attaches to the oxygen bridge to form the saturated oxonium ion (B). Then the chain splits; the right-hand portion of molecule (B) with the new hydroxyl group undergoes no further change (until further attack by the enzyme) and is not shown. The left-hand portion,



Scheme 18. The mechanism of hydrolysis of glycogen at α- and β-amylase.

i.e. the portion split off (maltose in the case of β-amylase, when R = H, and maltose or its homologues in the case of α-amylase) is a carbonium or an oxonium ion (C). This unsaturated unstable ion takes on the more stable C1 conformation, and this occurs by way of a half-chair form with both α- and β-amylase, but because of the surface characteristics of the enzymes, with α-amylase the conversion proceeds through the H1 form (D), and with β-amylase through the 1H form (E). The final result is that the former gives an α- (F) and the latter a β-glucoside linkage (G).

The above mechanism of Meyer and Larner must be corrected in respect of the conformation of the non-reducing glucose residue in maltose (this should have a distorted boat conformation: see Section III). Although the mechanism cannot be considered fully proved, it gives the first satisfactory explanation of the different actions of α- and β-amylase based on modern ideas.

Under the influence of aldolases, the condensation of substances with a primary aldehydic group with aldehydes gives products having a dipolar group of threo-configuration, for example,

dihydroxyacetone phosphate + D-glyceraldehyde ⇌
⇌ D-fructose phosphate.

Hough and coworkers[57] have analysed this effect from the conformational aspect and shown its value in biosynthesis.

Conformational ideas have recently been used by Wallenfels[58] in considering the mechanism of action of galactosidase.

Conformational ideas should have particular value in the analyses of specific immunochemical reactions.

There can be no doubt that since the rate and sometimes even the possibility of chemical reactions depends on conformation this must apply at least equally to biochemical reactions. Clearly, conformations must be taken into account when interpreting the mechanisms of enzyme reactions.

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HOT SYNTHESIS OF COMPOUNDS LABELLED WITH RADIOACTIVE CARBON

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1. METHODS OF SYNTHESISING LABELLED COMPOUNDS

During recent years great attention has begun to be paid to the investigation of physicochemical methods of synthesising labelled compounds, together with direct chemical synthesis and biosynthesis. Methods which have recently been developed are isotopic exchange, exchange synthesis under conditions of irradiation and self-irradiation, radiation synthesis, synthesis in a gaseous discharge, synthesis by means of accelerated ions, and hot synthesis. The last method has now been most thoroughly investigated, and in our opinion is the most promising in several cases.

(a) Simple Chemical Synthesis

The vast majority of the labelled compounds required in science and technology can be obtained by simple chemical synthesis. Only a few natural compounds form exceptions. However, the chemical synthesis of complicated labelled compounds is laborious, while the yield of the products is often low. These difficulties arise from the fact that the starting materials obtained in the nuclear reactor are carbonates in the case of carbon, and elementary tritium or water in the case of hydrogen. A great deal of work has been done on methods of direct chemical synthesis[1-3].

(b) Synthesis by Means of Isotopic Exchange

Synthesis can be achieved by means of isotopic exchange with chemically mobile atoms, such as halogen atoms in organic derivatives, hydrogen, metals in salts and oxides, ligands in complex compounds, etc. If the molecule undergoing labelling contains several identical atoms in identical positions, they are all labelled simultaneously. If the bonds are not identical, the extent to which the radioactive atoms enter into exchange is characteristic of each position, and the specific activity of the compound is not the same at different bonds. In several cases, isotopic exchange can be initiated by irradiation or by self-irradiation. Thus contact of various substances with gaseous tritium is accompanied by the exchange of hydrogen for tritium[3-13]. Exchange has been studied in methane, ethane, toluene, 3,5-dinitrobenzamide, vitamin B_{12}, 4,5-xylylene-1,2--diamine, trinitronaphthoic acid, 4-hydroxyphthalide, 2,4-dihydroxyacetophenone, α-methylglutamic acid, 2-deoxyribose phosphate, imidazoledicarboxyamide, and gibberellic acid.

As a result of the disintegration of tritium in the T_2 molecule, a number of other tritium-labelled products, both simpler and more complex in composition, are formed during the exchange. Methane in the presence of T_2, for example, yields tritium-containing hydrocarbon molecules with 1–6 carbon atoms[4]. The introduction of tritium into organic molecules by contact of the latter with T_2 has been called the Wilzbach method[5].

(c) Radiation Synthesis

The radiolysis of chemical compounds, especially organic compounds, involves the formation of radicals, which interact to yield a mixture of products. If a mixture including substances containing radioactive isotopes is subjected to radiolysis, a mixture of labelled compounds is obtained, among which are present the original molecules, simpler molecules, more complicated molecules, and structural isomers[4].

Radiochemical synthesis can take place both under the influence of external radiation[4] and under the influence of self-irradiation if the substance which acts as donor of radioactive atoms has a high specific activity[3,5-10]. Radiochemical synthesis results in a complex mixture of labelled compounds, which has its advantages and disadvantages. This complicates the isolation of labelled substances, but at the same time makes it possible to obtain a series of compounds by radiation synthesis. In this method it is difficult to predict the intramolecular distribution of the radioactive isotope.

(d) Synthesis by Means of Accelerated Ions

Several workers have shown[13-19] that it is possible to synthesise labelled compounds, for example, to label carbon in organic compounds, by means of accelerated ions containing radioactive atoms. Here it is difficult to expect that a specific tracer will be obtained in a definite position, or that the distribution of radioactive atoms will be the same, within the molecule. The specific activity of the parent substance at a current of the order of 100 μA is a fraction of a microcurie per gramme. It is even lower than the specific activity of the corresponding compounds formed by hot synthesis. The reaction products of accelerated ions are qualitatively similar to those of hot atoms.

(e) Synthesis in an Electric Discharge

Passage of an electric discharge through the vapour of an organic substance generates ions and radicals, which

interact to form new substances. If the discharge passes through the vapour of a radioactive substance or through a mixture of substances, formation of a mixture of labelled compounds can be expected[20-23]. This method has the same advantages and disadvantages as has radiation synthesis.

(f) "Hot" Synthesis†

The term "hot synthesis" is applied to a synthesis resulting from the interaction with surrounding molecules of radioactive recoil atoms obtained in nuclear reactions or by radioactive disintegration. Such interaction yields labelled molecules of the substance within which the recoil atom is produced, more complicated compounds (addition and condensation products), and simpler compounds (decomposition products of the original substance). Hot synthesis is attractive in its practical simplicity. Generation of the radioactive isotope and its introduction into molecules take place in a single process, so that in several cases this method may prove more efficient than other methods. A complex mixture of labelled products is formed, which requires effective and rapid methods of separation. Among such are firstly chromatography, and then fractionation and chemical separation by means of carriers.

2. MECHANISM OF REACTIONS INVOLVING HOT ATOMS

The interaction of recoil atoms with surrounding molecules can be regarded as occurring in three stages.

The first stage involves slowing down of the recoil atoms by collisions with the surrounding atoms and molecules, without the recoil atoms entering chemical compounds. In this stage the recoil atom causes ionisation of the atoms, their electronic excitation, displacement of atoms from their lattice positions, etc., the process which predominates depending on the recoil energy. Electronic excitation is the most probable at high recoil energies, but the energy losses due to this process become unimportant as the recoil atoms slow down, elastic collisions acquiring increasing significance during this period.

The transition to elastic collisions during the slowing down of the recoil atoms takes place gradually. An approximate calculation based on the equation $E = MI/8m$ (where M is the mass of the moving atom, m the mass of the electron, and I the energy of excitation of the electron)‡ shows that ionisation of the medium, for example, by recoil carbon atoms, ceases at energies of the order of 15–20 keV.

Elastic collisions can occur in the range of Rutherford scattering or as between billiard balls. In the former case the transfer of energy takes place in small amounts, so that the range of the recoil atom is large, reaching 10–100 Å with ^{14}C.

The critical energy below which the billiard-ball type of collisions takes place can be found from the equation

$$E_{cr} = 13.6 \frac{2(M_1 + M_2)}{M_2} Z_1 Z_2 \sqrt{Z_1^{2/3} + Z_2^{2/3}},$$

where M_1 and M_2 are the masses of the colliding atoms, and Z_1 and Z_2 their nuclear charges.

For carbon E_{cr} = 6 keV. Above this energy, Rutherford scattering takes place.

The second stage consists in interaction between the recoil atoms and the molecules of the medium in such a way that a molecule (usually excited) or an excited intermediate complex containing the recoil atom is formed.

Depending on the degree of cooling of the recoil atom, interaction takes place within the range of the so-called hot, epithermal, or thermal reactions. Hot reactions have already begun in the range of solid-sphere collisions, for which there is equal probability of any transfer of energy between zero and some maximum value from the recoil atom to an atom of the medium,

When the energy has fallen to 100–200 eV the recoil atom loses the whole of its remaining energy in the last few collisions. For a ^{14}C recoil atom in a hydrocarbon medium the number of such collisions is estimated at five or six.

According to the Seitz–Koehler model of retardation[24-27] described above, a hot zone, in which the temperature is raised to 10^5°K by the dissipation of 100–200 eV of energy, is formed by the ^{14}C recoil atom at a distance of a few hundred Ångström units from the point where it had been produced. The quantity of energy transferable here and the temperature of this region depend on the relative atomic weights of the recoil atom and the atoms of the surrounding medium. The volume of the hot zone and its life-time are determined not only by the energy but also by various properties of the medium, in particular its state of aggregation, thermal conductivity, etc.

The life of a zone with such a temperature does not exceed 10^{-10}–10^{-11} sec. During this short period of time, the disorder characteristic of a liquid may arise at the centre of the hot zone, which in the case of carbon comprises only a few atoms or ions, and as a result any fragments entering this region may approach the recoil atom. In contrast to the model described above, the retardation mechanism suggested by Libby ignores Rutherford scattering at high energies and postulates only solid-sphere collisions for the recoil atoms[28,29]. According to the Libby model, the recoil atoms transfer a great part of their energy within the space of one or more cages by solid-sphere collisions with the atoms forming the walls of the cages. Thus transfer by a ^{14}C atom of energy between 40 000 and 25 eV requires 5–10 collisions in a hydrocarbon medium, resulting in the formation of a hot zone with a temperature of ~ 10^7 °K and a life of ~ 10^{-5} sec, comprising a few hundred atoms or ions; the solid in the zone melts and is mixed up, so that even very remote fragments may approach the recoil atom. Since Libby's theory postulates the transfer of the greater proportion of the energy within the zone of stabilisation of the recoil atom, variation in the initial recoil energy should affect the radiochemical yields of the products. However, experiments with the recoil

† The term "hot" synthesis, as well as the terms "hot" reaction and "epithermal" reaction, will henceforward be used without quotation marks.

‡ The interested reader is advised to consult "Radiation Damage in Solids" by D.S. Billington and J.H. Crawford, O.U.P., 1961, pp. 31 *et seq.* (Ed. of Translation).

atoms ^{14}C having E = 40 keV and ^{11}C having E = 1000 keV did not show this effect, as could be expected on the Seitz–Koehler model for recoil energies exceeding the energy limit of solid-sphere scattering and that portion of the energy which can be transferred in the hot region (100–200 eV for carbon). Limitations in the Libby model are indicated also by other experimental results, the limits of its applicability being governed by the energy range within which Rutherford collisions are insignificant. At low initial recoil energies, at which Rutherford scattering can be disregarded, the Libby model agrees with the postulates of the Seitz–Koehler theory.

The hypothesis of a billiard-ball type of collision can be used to describe the mechanism of the formation of the primary labelled compounds when the energy of the recoil carbon atoms exceeds 25–50 eV. In collisions of this type, ^{11}C and ^{14}C recoil atoms having sufficient kinetic energy can effect elastic replacement of nitrogen, carbon (^{12}C), and other atoms of similar mass in molecules of the medium. On this basis Capron and Oshima showed[30] that such substitution becomes possible only when $E_0 > 2r$ and $r < \frac{1}{2}$, where E_0 is the energy of the recoil atom before the collision, and $r = [(M-m)/(M+m)]^2$ is the minimum fraction of the energy which can remain associated with the recoil atom of mass M after collision with an atom of mass m. Hence substitution is possible provided that $m/M = 0.17$: *i.e.* atoms of the isotopes ^{11}C and ^{14}C can replace atoms of carbon, nitrogen, etc., but cannot replace, by an elastic collision mechanism, hydrogen atoms, for example. The problems of the mass ratio and of the angular distribution of collisions belong to the "energetic" aspect of the consideration of solid-sphere collisions. The mass ratio governs the probability of a complete transfer of energy depending on the masses of the colliding atoms; apart from these factors, the collision frequency must be taken into account in calculating the yield of products of elastic substitution, and this is a function of the number of replaceable atoms, or more precisely of their concentration, dimensions, and steric factors. It has been demonstrated experimentally that the radiochemical yields and specific activities of the substitution products actually depend not only on the mass ratio of recoil and substituted atoms but also on the relative numbers of these atoms in the medium.

In the formation of a substance by a mechanism of elastic collisions, the molecule of the reaction product is obtained by combination of a radical with a recoil atom which has lost all (limiting case) or a considerable part of its energy. In this way a labelled parent molecule is formed as a product of the replacement of other atoms by the recoil atom. Only in the limiting case of zero energy of the recoil atom after the collision is an unexcited molecule formed: in all the remaining cases the product is a molecule having an excess of energy compared with the mean. The excitation may not spread throughout the molecule, but may be localised in some part of it before its decay.

If the recoil atom is cooled in the first stage to lower energies (below 25–50 eV), it can react with the surrounding molecules by a mechanism of inelastic collision, by so-called epithermal reactions[31,32]. This involves energy transfer to the molecule as a whole, and its excitation yields an intermediate complex with excess of energy or an excited molecule.

The energy of excitation is determined by the initial energy of the recoil atom colliding with the molecule and by the proportion of the energy which can be converted into excitation. The latter, as the work of Magee[33,34] has shown, is a function in particular of the relative masses of the recoil atom, the bombarded fragment of the molecule, and the whole molecule.

If during the first stage the collisions result in the recoil atoms being cooled to energies lower than the bonding energies of the atoms in the molecule, it is only in the limiting case that such atoms form unexcited molecules in subsequent thermal chemical reactions. In most cases an excited molecule containing the recoil atom is formed.

The third stage consists in stabilisation of the excited molecule or breakdown of the intermediate complex. Excited molecules formed as a result of hot and epithermal processes will in most cases be stabilised by dissipation of the energy among the surrounding molecules or by the emission of light. Such a process leads to the formation of simple products in which substitution by the recoil atom has occurred. However, reactions involving slight rearrangement, for example, isomerisation, may also occur. In the case of the formation of an intermediate complex by an epithermal mechanism the energy of excitation is large, and transition to the normal, non-excited state involves a fundamental change in the initial molecule, such as its decomposition, combination with other molecules, rupture or formation of double bonds between carbon atoms, etc. Formation of labelled molecules in the epithermal region obviously passes through successive stages of breakdown of the molecules and recombination of the fragments with recoil atoms in the reaction cage.

If the excited molecule decomposes so rapidly that the excitation does not have time to spread throughout the molecule, the result of such a process is formation of a product in which an atom or group of atoms has simply been replaced by the recoil atom.

It has been shown with the simplest molecules that more complicated compounds are obtained practically entirely by thermal reactions, and are suppressed by radical inhibitors[35,36].

Experimental determinations of the composition of the products from reactions involving recoil atoms indicate the final result of all three stages. Few attempts have yet been made to find the reaction products of a recoil atom in the second stage or the mechanism by which the intermediate compounds are transformed in the third stage. An exception is provided by Wolf's papers[37–39], in which the results are interpreted in terms of the formation of an intermediate complex.

The behaviour of the recoil atoms during the first stage, and the proportions of them which react in the hot, epithermal, and thermal regions, depend on the initial energy of the recoil atom and the nature of the surrounding medium, on the masses of its atoms and the structure of its molecules. The governing factors in the second stage are the probability of the formation of an intermediate complex of a particular composition and the structure and degree of excitation of the molecule or complex. Important factors in the third stage are competition between several modes for removal of the excitation energy and the probability of the occurrence of several chemical reactions yielding chemically stable molecules. The radiation stability of the compounds plays a quite significant part in this.

(a) Energy and Charge of Radioactive Carbon Recoil Atoms

In order to obtain ^{14}C-labelled compounds, substances containing nitrogen, alone or mixed with other compounds,

are irradiated with neutrons. Compounds containing the radioactive isotope ^{11}C can be obtained by means of the recoil atoms arising from the nuclear reactions: $^{12}C(n,2n)^{11}C$ and $^{12}C(\gamma,n)^{11}C$. The heat of formation of ^{14}C from nitrogen by the reaction $^{14}N(n, p)^{14}C$ is 0.6 MeV, and that for the formation of ^{11}C by neutron irradiation is $Q = 7.15$ MeV. Hence the recoil energies of the ^{14}C and ^{11}C atoms are respectively $Q/15 = 0.04$ and $2Q/13 = 1.1$ MeV; a similar calculation for the reaction $^{12}C(\gamma,n)^{11}C$ gives a value of the order of 0.5 MeV.[40-43]

Such a high recoil energy of ^{14}C and ^{11}C atoms results in complete rupture of their bonds with the parent molecules and the formation of hot carbon atoms having great kinetic energy. In the case of ^{14}C the speed of the recoil atom corresponds to that of electrons of 1.56 eV energy, the speed of ^{11}C recoil atoms being considerably higher. At such energies and speeds, the carbon recoil fragments must lose those orbital electrons with velocities below what would correspond to the kinetic energies and speeds of the fragments[3]. The outer electrons are stripped by the electrostatic fields of the atoms in the path of the recoil fragment. Owing to this stripping of the outer electrons from the ^{14}C ions formed initially at the instant of splitting off from the parent molecule, the recoil fragments are neutralised after the first few collisions. When the recoil atom has cooled down, it can again acquire extra electrons, thus becoming negatively charged, if ions having a negative electron affinity are present in the surrounding medium. In the case of carbon recoil atoms, the energies at which a neutral fragment can acquire electrons are of the order of 30 keV.

(b) Interaction of Radioactive Carbon Recoil Atoms with Matter

Table 1 gives data on the radioactivity of the reaction products formed by hot ^{14}C and ^{11}C atoms with various substances. Table 2 contains information on the distribution of radioactive carbon in the labelled compounds obtained by hot synthesis. The data in these tables indicate the distribution of radioactive carbon between labelled molecules and individual atomic groupings in molecules.

Substitution forms one of the main reactions of hot carbon atoms. With carbon recoil atoms the replacement of carbon, nitrogen, oxygen, and halogens can occur in collisions of the billiard-ball type. Substitution of hydrogen is possible only by an epithermal reaction mechanism. Whole groups of atoms can also be replaced by the latter mechanism. The yields and the specific activities of the substitution products depend on the relative masses of the colliding atoms and on their relative numbers. If G is the ratio of the number of ^{12}C atoms to the number of ^{14}N atoms from which the ^{14}C recoil atoms are produced, the specific activities of the substitution products are proportional to the ratios $G/(G + 1)$.[2] The maximum values correspond to $G = 1$. The correctness of these conclusions has been demonstrated in the case of several examples[71]. In particular, neutron irradiation of 1-butyltetrazole-5-amine ($G = 1$) and of 1-hexyltetrazole-5-amine ($G = 1.4$) yielded specific activities of 2.0 and 1.2 $\mu c\ mg^{-1}$.

The role of such factors as the frequency and efficiency of collisions are exemplified by the oxalates of nitrogen bases. The distribution of ^{14}C recoil atoms between the base and the oxalate radical has been studied by Zifferero and coworkers[51]. They showed experimentally that a considerable proportion of the parent labelled products is formed by a solid-sphere collision mechanism. Taking the numbers

TABLE 1. Reaction products of carbon recoil atoms.

Irradiated system	Radioactive products	Activity of reaction products		Reference
		%	$\mu c\ g^{-1}$	
Butane + 2-methylpyrazine	n-butane	3.0	–	44
	n-pentane	5.0	–	
	isopentane	5.0		
n-Pentane + 2-methylpyrazine	n-pentane	2.8	0.04	45
	n-hexane	6.5	0.09	
	2-methylpentane	4.3	0.03	
	3-methylpentane	2.1	0.03	
n-Pentane + aniline	light gases	12	–	46
	n-pentane	25		
	isopentane	1	–	
	n-hexane	12	–	
	hexane isomers	6	–	
n-Pentane + aniline or propylamine	light gases	2.1	–	47
	butane	5.7	–	
	neopentane	2.4	–	
	isopentane	3.6	–	
	n-pentane	2.1	–	
	2,2-dimethylbutane	0.1	–	
	2,3-dimethylbutane	0.2	–	
	2-methylpentane	4.5	–	
	3-methylpentane	8.3	–	
	n-hexane	12.2	–	
Methanol + aniline	methane	34.3	–	48
	methanol	15.9	–	
	ethanol	8.4	–	
	n-propanol	9.1	–	
	n-butanol	6.2		
	isopentyl alcohol	4.9		
	higher alcohols	11.3		
	aniline	9.9		
Methylammonium fluoride	light gases	18.5		48
	n-pentylamine	10.0		
	n-hexylamine	1.8		
	3-(isopropylamino)propylamine	4.0		
	tributylamine	21.7		
	ethylamine	16.0		
	n-propylamine	10.0		
Ethylamine	methane	6.8	–	48
	ethylamine	21.5		
	n-propylamine	10.9		
	n-butylamine	12.1		
	di-n-propylamine	10.5		
	t-octylamine	8.2		
	3-(isopropylamino)propylamine	10.1		
	tributylamine	14.0		
	di-2-ethylhexylamine	5.5		
	N-methyldiphenylamine	0.4		
Ethylammonium fluoride	light gases	2.1	–	48
	ethylamine	16.1		
	n-propylamine	14.7		
	n-butylamine	7.8		
	di-n-propylamine	5.0		
	n-hexylamine	3.1		
	t-octylamine	3.5		
	3-(isopropylamino)propylamine	9.8		
	tributylamine	9.8		
	diethylamine	9.0		
	methyldiphenylamine	14.8		
Acetamide	acetic acid	6.44	0.215	49,50
	propionic acid	6.52	2.180	
	acetone	0.13	0.068	
Hydrazinium oxalate	carbon monoxide	3.2	–	51
	carbon dioxide	5.0		
	oxalic acid	10.4		
	formic acid	12.5		
	methylamine	10.7		
	formaldehyde	5.7		

TABLE 1 (cont'd).

Irradiated system	Radioactive products	Activity of reaction products		Reference
		%	$\mu c\ g^{-1}$	
Alanine	alanine	0.2	0.06	38
1,1-Dimethylcyclopentane + 2-methylpyrazine	1,1-dimethylcyclopentane	0.1	–	38
trans-1,2-Dimethylcyclopentane + 2-methylpyrazine	*trans*-1,2-dimethylcyclopentane	0.3	–	38
trans-1,3-Dimethylcyclopentane + 2-methylpyrazine	*trans*-1,3-dimethylcyclopentane	0.4	–	38
Benzene + aniline	methane	1.5	–	48
	benzene	2.5		
	toluene	1.7		
	diphenylmethane	3.2		
	triphenylmethane	2.0		
	polymers	12.2		
Benzene + 2-methylpyrazine	benzene	2.5	0.065	50
	toluene	1.9	0.17	
Benzene clathrate	carbon monoxide	0.2	–	52
	carbon dioxide	0.4		
	oxalic acid	6.7		
	benzene	4.0		
	hydrogen cyanide	2.5		
Benzene clathrate	benzene	1.4	0.63	53
Benzene + aliphatic amines	benzene	2.6	–	54
	toluene	2.25–3.3	–	
Toluene + 2-methylpyrazine	toluene	3.30	0.13	38
	o-xylene	0.96	0.27	
	m-xylene	1.35	2.22	
	p-xylene	0.46	0.13	
	ethylbenzene	0.85	0.12	
Toluene + 2-methylpyrazine	toluene	1.6	0.1	44
	o-xylene	0.33	0.04	
	m-xylene	0.37	0.02	
	p-xylene	0.16	0.04	
	ethylbenzene	0.50	0.06	
Aniline	methane	1.5	–	48
	aniline	3.0	–	
	benzene	0.1		
	toluene	0.7		
	toluidine (*o*, *p*, *m*)	3.2		
	benzylamine	0.8		
	methylaniline	2.0		
	o-methylbenzidine	2.6		
	methyldiphenylamine (*o*, *m*, *p*)	1.6		
Aniline	aniline	2.8	0.10	55
	benzene	0.35	0.03	
	toluene	0.074	0.006	
Methylanilinium oxalate	methylaniline	11.8		56, 57
	oxalic acid	3.3		
Anilinium oxalate	aniline	8.0		56, 57
	oxalic acid	2.7		
Isohexanoanilide	isohexanoic acid	1.0		38
	aniline	2.0		
Phenylalanine	phenylalanine	2.8		58
	aspartic acid	4.7		
	glutamic acid	2.9		
	serine	1.0		
	lysine	1.4		
	α-aminobutyric acid	1.2		
	α-aminovaleric acid	2.0		
	formic acid	4.2		
	propionic acid	1.8		
	malonic acid	2.9		
	succinic acid	1.4		
	glutaric acid	3.6		
	β-phenylpropionic acid	3.7		
Benzamide	benzamide	4.1		60
	acetophenone	0.7		
	benzoic acid	3.8		

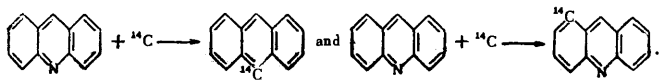
TABLE 1 (cont'd).

Irradiated system	Radioactive products	Activity of reaction products		Reference
		%	$\mu c\ g^{-1}$	
Benzanilide	benzanilide	1.5		60
	benzoic acid	0.4		
	aniline	0.9		
	bibenzoyl	0.9		
	oxalic acid	0.7		
	hydrogen cyanide	2.6		
	carbon monoxide	11.7		
	carbon dioxide	5.0		
Stilbene + azobenzene	stilbene	1.3	0.65	61
Azobenzene	azobenzene	2.3	0.65	55
Naphthalene + hydrazinium oxalate	naphthalene	0.0	–	55
Anthracene + ammonia (liq.)	anthracene	0.009	0.01	55
1-Butyltetrazole-5-amine	1-butyltetrazole-5-amine	14.4	–	61
1-Decyltetrazole-5-amine	1-decyltetrazole-5-amine	1.6	–	61
1-Ethyltetrazole-5-amine	1-ethyltetrazole-5-amine	5.5	–	61
1-Hexyltetrazole-5-amine	1-hexyltetrazole-5-amine	7.7	–	61
1-Phenyltetrazole-5-amine	1-phenyltetrazole-5-amine	1.0	–	61
Pyridine	pyridine	0.5	–	62
Methylpyridine	4-methylpyridine	1.7	–	39
	toluene	0.26		
Pyridinium oxalate	pyridine	2.0	–	56
	benzene	7.6	–	57
	phenol	5.4	–	63
	oxalic acid	1.7	–	
Ethylpyridine	ethylpyridine	1.0	–	38, 64
Ammonium nicotinate	nicotinic acid	4.1	–	65
	benzoic acid	1.5		
	propionic acid	2.3		
	valeric acid	1.5		
	malonic acid	16.3		
	glutaric acid	3.2		
Nicotinamide	nicotinamide	3.4	0.03	38
	benzoic acid	0.4	1.81	
Hydrazide of nicotinic acid	benzoic acid	–	0.43	38
Quinolinium oxalate	quinoline	1.6	–	56, 66
	naphthalene	8.4		
	1-naphthol	2.2		
	oxalic acid	7.1		
	carbon dioxide	0.01		
	carbon monoxide	0.02		
Quinoline	isoquinoline	0	–	67
	quinoline	5.0		
	naphthalene	0.15		
	1-naphthol	0		
	oxalic acid	0		
Isoquinoline	isoquinoline	8.0	–	67
	naphthalene	0.15		
Quinoline oxalate	quinoline	10.0	–	67
	naphthalene	0.2		
	1-naphthol	0.2		
	oxalic acid	0.37		
Isoquinoline oxalate	isoquinoline	10.0	–	56, 57
	oxalic acid	1.5		
1,2-Benzacridine	1,2-benzacridine	4.0	–	68, 69
	1,2-benzanthracene	0.2		
Acridine	acridine	3.5	0.22	38, 70
	anthracene	0.2	0.32	
Reserpine + tetrazoleamine	reserpine	–	0.16	71

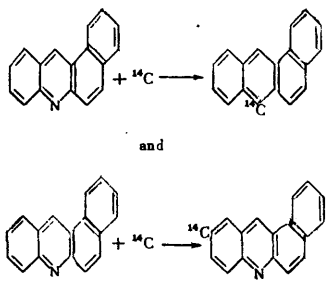
TABLE 2. Distribution of activity in ^{14}C-labelled molecules.

Substance irradiated	Suggested basic mechanism of formation of labelled substance	Product	Activity (%) in given position: theor.	Activity (%) in given position: expt.	Specific activity, $\mu c\ g^{-1}$	Ref.
Acetamide $CH_3.CO.NH_2$	elastic collision, replacement of ^{12}C	acetic acid				
		CH_3	50	38	0.536	49
		$COOH$	50	62	0.840	50
Alanine $CH_3-CH(NH_2)COOH$	ditto	alanine				
		CH_3	33.3	14	—	38
		$CH(NH_2)$	33.3	7	—	
		$COOH$	33.3	79	—	
Benzene C_6H_6	»	benzene				
		C_6H_6	100	100	0.068	50
Toluene $C_6H_5-CH_3$	»	toluene				
		C_6H_5	85.7	89	—	38
		CH_3	14.3	11	—	
Benzamide $C_6H_5-CO-NH_2$	»	benzoic acid				
		C_6H_5	85.7	87.2	—	38
		$COOH$	14.3	12.8	—	
trans-Stilbene $C_6H_5.CH:CH.C_6H_5$ + + azobenzene	»	*trans*-stilbene				
		C_6H_5	42.9	37.5	—	39
		CH	7.1	12.5	—	
		CH	7.1	12.5	—	
		C_6H_5	42.9	37.5	—	
Acetamide $CH_3-CO-NH_2$	elastic collision, replacement of ^{14}N	acetone				
		CH_3	50	40	—	49, 50
		CO	0	20	—	
		CH_3	50	40	—	
Aniline $C_6H_5-NH_2$	ditto	toluene				
		C_6H_5	0	14	—	48
		CH_3	100	86	—	
Azobenzene $C_6H_5-N=N-C_6H_5$	»	benzylideneaniline				
		C_6H_5	0	15	—	61
		CH	100	85	—	
		N	0	0	—	
		C_6H_5	0	0	—	
Methanol CH_3-OH	inelastic replacement of H	ethanol				
		CH_3	100	95	—	39
		CH_2OH	0	5	—	
Pentane $CH_3-(CH_2)_3-CH_3$	ditto	hexane				
		CH_3	100	97	—	39
		$(CH_2)_4$	0	3	—	
		CH_3				
		3-methylpentane				
		$CH_3-CH_2-CH_3$	0	3	—	
		$CH_3\ CH_3\ CH_3$	100	97	—	
Acetamide $CH_3-CO-NH_2$	»	propionic acid				
		CH_3	100	52	3.30	49, 50
		CH_2	0	24	1.44	
		$COOH$	0	24	1.49	
Benzene C_6H_6	»	toluene				
		C_6H_5	0	12	0.024	50
		CH_3	100	88	1.01	
Benzene C_6H_6	»	toluene				
		C_6H_5	0	16	—	19
		CH_3	100	84	—	
Toluene $C_6H_5-CH_3$	»	xylene				
		C_6H_4	0	15	—	38
		$(CH_3)_2$	100	85	—	
		ethylbenzene				
		C_6H_5	0	7	—	
		CH_2	0	13	—	
		CH_3	100	80	—	
Methanol CH_3-OH	thermal replacement of H by fragment containing two carbon atoms	n-propanol				
		CH_3	50	43	—	39
		CH_2	50	55	—	
		CH_2OH	0	2	—	

of ^{12}C and ^{14}N atoms in the molecular volumes of the basic and acidic groups as measures of the probabilities of the ^{14}C entering a given group, these workers calculated the ratio of the activity of the base to that of the acid. With aniline oxalate, for example, the molecular volume of the base is 1.67 times that of oxalic acid and since in the aniline and oxalic acid molecules the ratios of the ^{12}C atoms to the total number of atoms similar in mass to ^{14}C are 6 : 7 and 2 : 6 respectively, the probability of the formation of labelled aniline is 4.3 times that of the formation of the labelled acid. This value agrees comparatively well with the experimental data. With other bases the difference between calculated and experimental values is so large that the assumption of hot substitution probably has little justification in their cases. Among the best studied examples of hot substitutions are the substitution of ^{12}C and ^{14}N in aromatic rings. When acridine is bombarded with neutrons in a nuclear reactor, labelled anthracene and acridine having specific activities of 0.4 and 0.22 $\mu c\ g^{-1}$ of the substance can be isolated[68] from the irradiated specimen. Another paper[70] gives the specific activities of acridine and anthracene as 0.22 and 0.32 $\mu c\ g^{-1}$ of carbon with yields of 0.5 and 0.2% respectively of the total activity. The two products can be formed by replacement of carbon and nitrogen atoms in the original compound by ^{14}C:



In a similar manner neutron irradiation of 1,2-benzacridine yielded labelled 1,2-benzanthracene and the labelled initial product[69], the yields being 4 and 0.2% respectively of the total activity:



The distribution of activity between the products of the above hot reactions is close to the statistical value, in conformity with the character of substitution produced by elastic collision and the closeness of the masses of ^{12}C and ^{14}N to that of ^{14}C.

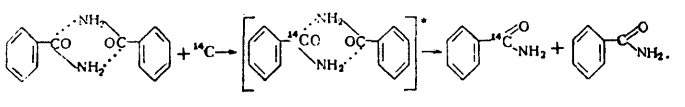
The most probable result of the hot mechanism with carbon compounds is the formation of labelled parent molecules. Cases are known, however, in which the latter are formed[37] by reactions other than hot elastic collisions. Thus several experiments have shown that, in the neutron irradiation of benzene mixed with molecules containing nitrogen, labelled benzene is obtained not only by hot reactions but also by thermal recombination of recoil fragments with free radicals, as shown by the dependence of the yield of labelled benzene on the preserve of radical-acceptors (1,1-diphenyl-2-picrylhydrazyl, etc.). Another example is the formation of labelled products in the irradiation of quinoline and isoquinoline. If it is assumed that the labelled parent compounds and naphthalene are formed

by hot substitutions of ^{14}C for ^{12}C and ^{14}N, the ratio of the yield of quinoline to that of naphthalene, for example, should correspond to the ratio of the number of carbon atoms to that of nitrogen atoms in the quinoline molecule. The yields of labelled compounds obtained by irradiation of isoquinoline and quinoline and its oxalate have been shown[56,67,72] to contradict this hypothesis, and are explained in these papers by the difference in chemical properties between quinoline and isoquinoline, or more precisely by the difference in the bonds and also in the position of the carbon atoms in the molecules of these substances. Such a dependence of the yield of labelled compounds on molecular structure indicates that in this case the labelled molecules of the parent compound are not products of a simple hot substitution.

With azobenzene–stilbene solid solutions a linear relation has been found[61] between the yield of labelled parent compound and the mole fraction. The yield of stilbene did not extrapolate to zero at zero mole fraction of it in the original solution. This suggests that part of the labelled stilbene has arisen as a result of secondary recombination of fragments which had been formed from only the one component, azobenzene: *i.e.* on irradiation of azobenzene–stilbene solutions, part of the parent compound (stilbene) is formed by thermal or epithermal processes involving recombination of the fragments. The deviations of the intramolecular distribution of activity in stilbene from that calculated on the hypothesis that substitution takes place at random also demonstrates the possibility that stilbene can be formed by thermal or epithermal reactions. An important factor is the contribution made by secondary processes, involving the stabilisation of intermediate complexes and excited molecules, to the distribution of activity in products of the postulated hot substitution of ^{14}C atoms for those of similar mass. In aromatic compounds labelled by replacement of ^{12}C and ^{14}N by ^{14}C recoil atoms, for example, the distribution is statistical only to a first approximation, discrepancies always being observed. These deviations show definite regularities.

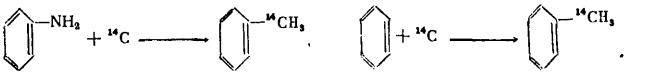
In the formation of labelled toluene from toluene mixed with 2-methylpyrazine and of labelled benzoic acid from benzamide, the deviations from a statistical distribution are of the order of a few per cent higher content of ^{14}C in the ring. A probable cause of this phenomenon in the former case may be removal of the excess excitation energy of the molecules by elimination of the methyl group:

Since this process is especially probable in the case of substitution of carbon in the side-chain, it should lead to a relatively high content of ^{14}C in the ring of toluene. A similar explanation can also be given for benzoic acid obtained from benzamide, the excess excitation energy in this case perhaps being expended also in the rupture of intermolecular hydrogen bonds (bond strength 10–5 kcal × × mole^{-1}); this results in a molecule of benzoic acid being split off without dissociating, and the deviation from a statistical distribution is smaller in this case:

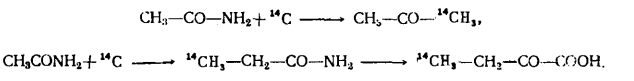


Analogous explanations can be given for the deviations from a statistical distribution of activity in molecules of acetic acid obtained from acetamide, and of labelled alanine from alanine (Table 2).

Replacement of hydrogen by carbon atoms differs both in mechanism and in rules from the hot substitution of atoms of similar mass to carbon. This can be illustrated by results obtained for the irradiation of aniline and of a mixture of benzene with 2-methylpyrazine[48,50]. Labelled toluene is a product in both cases



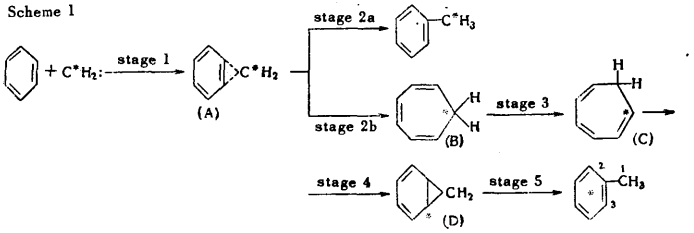
If the substitution of hydrogen in benzene were assumed to take place, like that of nitrogen in aniline, by hot reactions, the yield of toluene from benzene would be six times its yield from aniline. The experimental value of this factor is only 2.7. Irradiation of acetamide provides another example confirming that the substitution of hydrogen by ^{11}C and ^{14}C recoil atoms differs in mechanism from that of nitrogen and inactive carbon atoms. The irradiated acetamide yielded[49] acetone containing 0.13% of the total activity and propionic acid containing 6.52%, the latter being obtained by treating the irradiated mixture with alkalis or acids



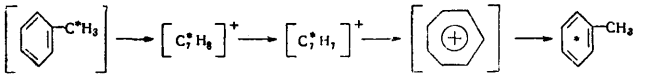
The radiochemical yield of the latter is 50 times that of acetone, whereas the random character of hot reactions would suggest only a threefold difference in yield.

The substitution of hydrogen differs to a considerable extent also from thermal reactions involving radicals. The yield of toluene in the irradiation of benzene is unaffected by the addition of radical-acceptors[37], which tends to refute the possibility that the labelled toluene is formed by thermal recombination of radicals with recoil fragments. According to Wolf, toluene is formed in an epithermal process, independently of additions of radical-acceptors, according to one of the following schemes:

Scheme 1



Scheme 2



In Wolf's view, inelastic collisions result in this case in the formation of an intermediate complex containing seven carbon atoms and possessing sufficient excitation energy for its further conversion into labelled toluene in which the distribution of activity is either fixed or fortuitous. The possibility of the excited methylene reacting with rupture of a C–C bond and formation of a compound of type A

(Scheme 1) is probably not excluded under certain conditions. Interaction of methylene with rupture of a C–H bond has been observed by several investigators[73]. The intermediate compound rearranges to form toluene either by a simple, single-stage process (stage 2a) or along a multistage path including redistribution of hydrogen and rupture of several bonds (stages 2b–5). A more or less uniform distribution of active carbon atoms in positions 1–3 is probable for a multistage process.

Reaction with rupture of a C–H bond may result in the formation of strongly excited toluene. In such a case the toluene molecule can lose hydrogen and ionise to form a tropylium ion $[(C_7H_7)^+]^*$. On losing its excitation energy, this ion is converted into toluene having a uniform distribution of active carbon.

From the above mechanism for the formation of labelled toluene it is evident that the distribution of activity not only among groups of atoms in a molecule but also among groups of molecules (*i.e.* among substances) may depend on the nature of the processes by which the intermediate compound is stabilised.

Epithermal reactions may involve replacement by recoil atoms not only of individual atoms in the molecule but also of entire fragments of molecules, when the yield of labelled products will depend in particular on the size and the structure of the fragment. For example, the yield of labelled benzamide was greater when sulphonated benzamide was irradiated than from the irradiation of benzamide itself. A similar conclusion as to the role of the size of the fragment and the structure of the species was reached from the irradiation of three homologous azobenzenes *p*-ethoxy-*p'*-methoxy-, *p*-methoxy-*p'*-propoxy-, and *p*-ethoxy-*p'*-propoxy-azobenzene. The relative activities of the methoxy, ethoxy, and propoxy groups in the corresponding compounds were 1.00/1.07, 1.00/1.12, and 1.00/1.04.

A method has been suggested[79] for the quantitative measurement of the yields of labelled compounds which is analogous to the calculation of the yields of neutron-capture reactions, *i.e.* the use as the main variables of the flux of recoil atoms and their capture cross-section by components of the medium. The capture cross-section is determined by the chemical properties of the substance, the geometrical dimensions of the fragment undergoing collision, etc. The results can be explained in terms not only of the geometrical dimensions but also of the masses of the fragments colliding with the recoil atom. In fact, in conformity with Magee's conclusions, the fraction of the energy transferred on collision with the recoil atom which is used in increasing the internal energy of the molecule depends on the ratio of the masses of the molecule and the colliding fragment. In particular, for a diatomic molecule

$$\Delta E_{int} = \Delta E_{coll}\, m/(M + m),$$

where ΔE_{coll} is the energy transferred to an atom of mass M on collision with the recoil atom, ΔE_{int} the part of the energy which goes to increase the internal energy of the molecule, m the mass of the molecular residue, and $(M + m)$ is the molecular weight. Thus ΔE_{int} and hence the probability of dissociation of the molecules and its converse, the probability of a labelled molecule being formed without fundamental degradation, depend on the mass ratio of the colliding atom and the rest of the molecule. This relation probably holds also for molecules more complex than diatomic. On this basis the results mentioned above[74] can be explained in just the same way as those on the activity of the alkyl phenyl ethers.

The role of particular processes in the reactions of hot atoms can be analysed with the irradiation of pentane and isopentane (Table 1) as example[47]. In the case of n-pentane the low yield of the labelled starting material (2.1%) indicates that reactions like the hot substitution of carbon atoms are not very probable. A considerably greater part is played by epithermal substitutions of the ^{14}C atom, or fragments containing it, for hydrogen in the pentane molecule, leading to the formation of hexane in yields of up to 12% (with respect to activity).

In considering the distribution of activity among products (radiochemical yield and specific activity) and the distribution of active atoms within molecules of a given kind, account must be taken not only of the nature of the primary reactions of the recoil atoms, leading to the formation of labelled compounds, but also of secondary processes in which excited molecules and intermediate complexes are stabilised. The chemical nature of the molecules and separate fragments, bond strengths, the stabilities of molecules, etc., will play a special part in the distribution of activity at the stage of stabilisation of the intermediate excited complex[64]. Thus in xylenes formed by the irradiation of toluene ~15% of the active carbon is in the ring and 85% in the methyl groups, the greatest number of active carbon atoms being concentrated in the *meta*-position with respect to the first methyl group, and the smallest number in the *para*-position. The difference in radiochemical yields and specific activities of the individual xylenes is probably associated with the greater thermodynamic stability of *m*-xylene. Interpretation of the experimental results is complicated by the fact that the same labelled molecules can be formed by different mechanisms, while the distribution of activity within molecules obtained by different mechanisms will not be the same.

(c) Factors Influencing the Yields of Labelled Products

Temperature. Lowering the temperature has been found[31] to increase the yield of several compounds, which are mainly complicated products of the condensation and cross-linking of molecules, radicals, and fragments. The yield of ^{11}C-labelled benzene from the irradiation of benzene with fast neutrons increases as the temperature is lowered from 0° to -195°. These results are explained[38] by a lengthening, with fall in temperature, of the life of those fragments, the products of hot reactions, which combine with one another in the course of thermal reactions to give benzene. Consequently, temperature has a marked influence on the yields of the products of thermal reactions. Nevertheless, the yield of toluene formed at the same time as benzene, but in the epithermal region, is little affected by temperature. The yields of hot reactions depend still less on temperature. A decrease in yield of the most complicated products with rise in temperature has also been observed[15,16], in the irradiation of cholesterol, paraffin wax, and stearic and benzoic acids with accelerated $^{14}C^+$ and $^{14}CO^+$ ions, in which cases the thermal stabilisation of the fragments containing ^{14}C is similar in character to the thermal reactions with recoil atoms. It is pointed out that the synthesis of complicated labelled compounds should be most efficient at low temperatures.

It is interesting that the yield of labelled products is affected not only by the temperature at which the specimen has been irradiated but also by the processing temperature to which it has been subjected after irradiation[76,77].

Sharman and McCallum observed a variation in the distribution of activity in products, formed by the irradiation of sodium carbonate and of oxalic, glyoxylic, and glycollic acids, with the temperature to which the irradiated preparation had been heated [78].

These phenomena are most often associated with the thermal stability of the products, the effect of annealing leading to disorientation of the molecules in crystal lattices, and the corresponding variation in the rates of thermal recombination. For the carbon isotopes they are similar in character as with the isotopes of other elements.

It follows from this account that, in the choice of temperature of irradiation, due regard must be had to the thermal stability of the specimens. Irradiation at temperatures at which cracking becomes appreciable may substantially change the distribution of activity among the products owing to the change in composition of the irradiated mixture involved in cracking. Furthermore, the choice of temperature of irradiation is important in the synthesis of products formed by thermal reactions.

State of aggregation. The yield of the products of hot synthesis is affected also by the state of aggregation. The difference in the reactions of hot atoms is especially marked between condensed phases and the gas phase: in the latter such processes as, for example, the recombination of fragments and the transfer of energy from excited molecules to the medium become improbable. The phase state does not affect the yield of products obtained by elastic collisions, as in the replacement by a carbon recoil atom of atoms of similar mass. The yields of epithermal and thermal reactions are greatly dependent on the phase state of the irradiated material. On transformation into a solid phase, the probability of energy transfer on collision is markedly changed, and both the cell effect and the probability of the recombination of radicals and recoil fragments, are increased. The difference in thermal conductivity between liquid and solid materials is also important, since the conductivity can determine to a considerable extent the dimensions of the liquid cell [28,27]. The difference in thermal conductivity between different crystalline structures may also play some part. Owing to the greater thermal conductivity and higher melting-points of ionic crystals compared with molecular crystals, for example, the volume of the hot molten zone is considerably smaller in the former. All this makes it possible for recoil atoms in molecular crystals to react with the more remote fragments, which in the case of ionic crystals have insufficient time to diffuse to the recoil atom.

Interesting results have been obtained by Muxart, who found a lower yield of parent compound in the irradiation of liquid quinoline (5.4%) than in that of its solid oxalate (10%). These results were explained by the phase effect in epithermal reactions.

The experimental results confirm the dependence of the yield of labelled products on the phase state. Thus Royland and Libby [43] studied the distribution of activity among the products of the neutron irradiation of solid and liquid specimens of CO_2 and carbonates, and found that on passing from the liquid to the solid state the yield of CO decreased from 95–100 to 50%, while the yield of CO_2 increased under the same conditions from 2–3 to 50%. The increase in the yield of CO in the liquid phase is attributed to an increase in the rate of diffusion of the recoil atom from its track, where it can recombine with oxygen to form CO_2, into the external medium, where it undergoes ordinary thermal reactions with the medium and CO molecules are formed:

$$^{14}C + CO_2 = {}^{14}CO + CO; \qquad {}^{14}C + H_2O = {}^{14}CO + H_2.$$

In the case of the irradiation of benzene with fast neutrons — the nuclear reaction $^{12}C\,(n,2n)\,^{11}C$ — changing from the liquid to the solid state results in a decreased yield of labelled benzene but hardly affects the yield of toluene. Such behaviour can be explained on the hypothesis that formation of toluene takes place at comparatively high energies, whereas that of benzene is a result not only of hot reactions but also of thermal recombination. Toluene is synthesised at energies of 25–50 eV, when the recoil atom transfers to the system so much energy that the solid in a small volume along the track fuses, and the boundary between liquid and solid states of the system disappears.

A considerable quantity of labelled benzene is formed at low energies, so that the phase effect is appreciable, *i.e.* because of the limited diffusion in a solid medium and the short life of the recoil atom, it recombines with fragments from the immediate vicinity. This results in the formation of products differing from benzene. In the solid phase the recoil atom has insufficient time to react with species suitable for the formation of benzene. The interpretation of data for the solid phase must take into account various defects produced by recoil atoms in solids, in particular the intrusion and substitution of atoms, formation of vacancies, and thermal dislocation spikes [26,79]. In view of the different numbers of defects in single crystals and in fine powders, for example, differences can be expected in these cases in the retention and in the dependence of the change in the latter on thermal annealing. Retention should be greater in single crystals than in the powder, but on the other hand, it grows more rapidly on annealing after irradiation in the powder than in the single crystals [80]. Thus the experimental data on phase effects with ^{14}C show that, if the product is formed as a result of hot substitution, the irradiated specimen can be in any state of aggregation. Epithermal reactions occur best when solids are irradiated. Irradiation of liquid phases is the most effective for ensuring a maximum yield in thermal processes.

Recoil energy. It is difficult to reach final conclusions concerning the role of the initial energy of recoil atoms in the synthesis of labelled products. Comparison of data for various recoil atoms obtained from the reactions $^{12}C\,(n,2n)\,^{11}C$, $^{12}C\,(\gamma,n)\,^{11}C$, and $^{14}N\,(n,p)\,^{14}C$ [37,48,50] gives no precise picture, since the experimental conditions varied, among these being the radiation dose, radiation intensity, temperature, phase state of the specimens, and the composition of the irradiated mixtures.

Data are available [37] for solid and liquid benzene on the yield of labelled substances in the nuclear reaction $^{12}C\,(n,2n)\,^{11}C$, and cases have been described of the irradiation of solid benzene with accelerated ions and the irradiation with slow neutrons in a reactor — $^{14}N\,(n,p)\,^{14}C$ reaction — of a mixture of benzene and 2-methylpyrazine (see Table 1). Unfortunately, slight discrepancies in the results of different workers can be attributed not only to the initial energy but also to several other causes. Among these are firstly the dilution of the benzene with 2-methylpyrazine, which reacts with fragments and radicals, thereby affecting the yields of labelled benzene and toluene, that of the former being especially markedly diminished. Results from different sources are difficult to compare also because of the considerable difference in radiation effects, since the total

doses and intensities of irradiation also differed greatly. This view is supported by data on the irradiation of benzene with $^{14}C^+$ ions in an ion-accelerator, the design of which enabled the energy of the ions to be changed and the variation in other parameters to be fixed[19]. The results show that even slight variations in the conditions of irradiation change the yields of labelled benzene from 0.46 to 1.92%, of labelled toluene from 0.20 to 0.94% and of cycloheptatriene from 0.24 to 1.96%. The results of this work on the dependence of radiochemical yields on the energy of the bombarding ions are most complete, although they are fundamentally qualitative in character; they show that a change in the energy of $^{14}C^+$ from 5000 to 90 eV increases the yield of degradation products and decreases that of benzene, toluene, and cycloheptatriene. The cause of this is probably a diminution in the proportion of products of hot substitution at low energies of the ions. The distribution of activity within the toluene molecule (87 ± 5% in the methyl group, 16 – 15% in the ring) shows that the mechanism of the formation of labelled molecules by the interaction of accelerated ions with the medium is analogous to the interaction of the medium with recoil atoms.

In spite of the considerable obscurities associated with the effect of the initial energy with benzene and other compounds labelled with carbon by means of various recoil atoms and ions, it can nevertheless be suggested that the most probable effect would be an increase in the yield of labelled products other than the parent substance on passing from the reactions (γ,n): (n,γ) to the reactions (n,2n) and (n,p), at least partly owing to the more intense decomposition of the medium.

It is interesting that the yield of products may be influenced not only by the energy but also by the charge and configuration of the ion or fragments, since dimensions and hence steric factors can vary considerably, and these must be taken into account in calculating the number of collisions. This is shown especially clearly in the case of stearic acid exposed to $^{14}C^+$ and $^{14}CO_2^+$ ions (see Table 3).

Radiolysis. There are no consistent and verified data on the effect of radiolysis in the stabilisation of carbon recoil atoms. However, it can be expected that radiation effects with ^{11}C and ^{14}C will be similar to those in the stabilisation of recoil atoms of other isotopes. The main ways in which radiolysis affects the distribution of activity among products of hot synthesis are firstly decomposition and other radiation-induced reactions of labelled products, in particular their hydrogenation, or dehydrogenation, polymerisation, etc. An important part is played also by radiation changes in the initial specimens, resulting in the appearance of new radicals, excited molecules, which take part in the stabilisation of recoil atoms. The principal factors causing radiolysis of irradiated systems include, apart from the γ-radiation and the neutrons of the nuclear reactor, elementary particles and recoil atoms, the effect of these last being especially strong since they possess not only great energy but also considerable mass. Study of the way in which the yield of various labelled products depends on the dose and the flux of ionising radiation enables the role of radiolysis in hot synthesis to be established. Table 4 gives data on the yields of stabilisation products of ^{14}C recoil atoms in aniline under various conditions of irradiation. They show that a tenfold change in the n/γ flux intensity ratio produces some change in the distribution of activity. The yields of polymer, of fractions soluble in hydrochloric acid, and of the fraction soluble in benzene are especially strongly affected, but the yields of labelled methane and of the acetic-acid fraction are hardly affected. The influence on the activity of the latter of the duration of irradiation is also very weak.

In 1955 it was found[41,42] that doubling the total dose or intensity of γ-radiation in the exposure of anhydrous Na_2CO_3 to a flux of γ-quanta of energy 23 MeV, which produces the reaction $^{12}C(\gamma,n)^{11}C$, left the distribution of active carbon in the products unchanged. The conclusion that radiolysis is absent is probably correct only for variations in intensity of irradiation within narrow limits. This suggestion is supported by the observation[81] of radiation effects with brominated hydrocarbons.

In view of the considerable influence of radiolysis on the distribution of activity in irradiated systems, the choice of materials for irradiation is very important for the solution of practical problems of hot synthesis. If molecules of the initial substance react directly with hot atoms, the irradiated compound should be stable to radiation, while the conditions of irradiation should guarantee minimum radiation effects. If, however, the labelled compound to be synthesised is a product of interaction of a hot atom with fragments of the initial molecules, which have undergone preliminary radiolysis, it is desirable that the starting material should give the maximum number of such fragments, and the mechanism of the formation of this product should be taken into account in selecting the conditions of irradiation. The chief variables in irradiation are time, intensity, and total dose. Radiation effects due to nuclei and recoil particles can be varied by irradiating heterogeneous systems with particles of different sizes. Increase in their dimensions produces a diminution in the

TABLE 3. Radiochemical yields of products from the irradiation of stearic acid with $^{14}C^+$ and $^{14}CO_2^+$ ions.

Product	Yield on irradiation, %	
	$^{14}C^+$	$^{14}CO_2^+$
Stearic acid	5.7	0.6
Formic acid	2.0	1.0
Formaldehyde	none	1.0
Oxalic acid	none	0.2
3-Oxostearic acid	none	0.3
Activity adsorbed on charcoal	87.2	72.9

TABLE 4. Influence of conditions of irradiation on yields of products formed by reaction of ^{14}C recoil atoms with aniline[48].

Irradiation conditions	*Neutron flux, 10^{-8} counts min^{-1}	2.7	1.3	0.63	0.31	3.4
	Flux of γ-rays, 10^{-3} counts × min^{-1}	2.0	2.0	2.0	2.0	7.0
	Time of irradiation, days	4.3	4.3	4.3	4.3	0.65
Activity	total × 10^{-5} counts min^{-1}	64	31	15	18	12
Activity	CH_4, %	1.5	1.7	1.5	1.5	2
Activity of fractions dissolved in	acetic acid, %	17.0	18.1	17.8	17.5	17.1
	0.1 *N* HCl, %	40.1	39.6	39.3	39.6	36.7
	1.0 *N* HCl, %	13.9	11.7	11.6	11.1	15.1
	6.0 *N* HCl, %	11.4	12.5	—	—	11.3
	12.0 *N* HCl, %	7.1	9.2	—	—	9.1
	benzene, %	3.0	3.3	24.4	26.8	4.2
Activity	insoluble residue, %	6.2	4.0	3.5	3.3	3.8

* These headings in the original paper were respectively: neutron flux, n.cm.$^{-2}$ sec.$^{-1}$ × 10^{-11}; γ-intensity r min^{-1} × 10^{-3}; time (full power), sec. × 10^{-5} (Ed. of Translation).

dose from recoil fragments. However, it is difficult to use this method with the carbon isotopes because of the short range of the recoil atoms. Apart from the radiation effect due to the recoil energy, radiolysis can be produced in irradiated systems by the radiation of the radioactive isotope itself. Table 5 gives data on the degrees of degradation§ of various classes of organic compounds[81]¶. They show that, at moderate values of the degradation factor (5–20), considerable decomposition can be expected only at comparatively high doeses, of the order of 10^6–10^9 rad, which corresponds to considerable specific activities or very prolonged standing.

Table 6 shows the doses of intrinsic radiation of the ^{14}C isotope at definite specific activities and times of storage of labelled preparations[81].

Additives. The yield of labelled products is determined to a considerable extent by the additives present. Their action can differ in mechanism and hence in effectiveness. Inert diluents diminish the yield of products obtained by a mechanism of elastic collisions, and their influence can be calculated. Substances which remove excitation (energy and charge) and thereby prevent the decomposition of labelled molecules and radicals, the yield of which is correspondingly increased, affect mainly the yield of products obtained by epithermal reactions. A study of the radiolysis of hydrocarbon mixtures[82,83] showed that, in a binary mixture, charge is transferred from the component which is excited first (the main component) by the material of lower ionisation potential (additive), and thus the primary component is protected from radiation-induced decomposition. The mechanism by which excitation is degraded may vary. In particular, diffusion of excited solvent molecules, migration of excitation energy to neighbouring molecules, and single-stage transmission of excitation energy to considerable distances, are possible. Effects of this type have been detected in the benzene–toluene, benzene–cyclohexane, benzene–cyclohexene, and cyclohexane–cyclohexene systems. The most efficient additives are acceptors of radicals, which markedly diminish the yields of labelled compounds formed by thermal reactions

TABLE 5. Degrees of degradation of organic compounds.

Compounds	G*	Compounds	G
Saturated hydrocarbons	6–9	Ketones	7
Unsaturated hydrocarbons	14–2000	Carboxylic acids	5
Aromatic hydrocarbons	1	Esters	4
Alcohols	4–12	Halogenated derivatives	4
Ethers	7	Amino-acids	2–30

* G = degradation factor.

TABLE 6. Doses of intrinsic radiation of ^{14}C isotope and degrees of decomposition of organic substances.

Specific activity, counts g^{-1}	Dose after 1 month, rad	Degree of decomposition of substance at $G = 20$, %
1	$7 \cdot 10^4$	—
10	$7 \cdot 10^5$	0.17
100	$7 \cdot 10^6$	1.17
1000	$7 \cdot 10^7$	15.2

Wolf and coworkers[37] have studied the effect of additives on the yield of labelled benzene and labelled toluene from the irradiation of benzene and the activation of carbon by the reaction (n,2n). Additions of quinol were found to have little effect, but addition to the irradiated benzene of the radical-acceptors 1,3,5-trinitrobenzene and especially 1,1-diphenyl-2-picrylhydrazyl greatly diminishes the yield of benzene, that of toluene being slightly increased. The distribution of activity between toluene and benzene is considerably changed in the presence of 2-methylpyrazine, the yield of toluene increasing while that of benzene falls, as in the case of radical-acceptors. The effect of additives has not yet been entirely elucidated. There is little agreement, for example, between the above facts and the results of several workers[37,48,50,53] who obtained identical yields of ^{14}C-labelled benzene and toluene by the irradiation of benzene to which had been added various compounds containing nitrogen: 2-methylpyrazine, aniline, etc. Results given by MacKay and Libby[47] also suggest that the distribution of activity in the products of the irradiation of n-pentane is unaffected by additions of aniline or propylamine. On the other hand, there are indications[84] of a difference in the yields of gaseous and polymeric products of the irradiation of CCl_4 solutions with pyridine and with aniline. The effect of additives is important not only at the instant of localisation of the active atom and formation of the labelled compound, but also during the following moments of existence of the labelled substance in the medium, since it is they which, to a considerable extent, create the conditions under which the products may be either stable or unstable. If a labelled substance is unstable in a given system containing certain components, it will undergo further conversion into a product which is stable under these conditions. All that has been stated above applies to the influence of substances added to the system before irradiation. The action of substances added after irradiation is also important, being based mainly on ordinary chemical interaction, isotopic exchange, and other effects. In general, the distribution of activity in the products should depend on the method of treatment of the irradiated system. Interesting results have been obtained by Wolf *et al.*[54], who found the yield of toluene from benzene to be greatest in solutions in which the amines used as sources of nitrogen contain the greatest quantity of hydrogen in the molecule, data obtained with bis-(3-aminopropyl)amine and 2-methylpyrazine being compared. Further examples are provided by data[85,86] on the distribution of activity in specimens of crystalline Be_3N_2 irradiated in a reactor and then treated in various ways, and also on irradiated acetamide subjected to acid or alkaline hydrolysis.

The available data show that variation in solution pH after irradiation affects not only the yields of individual labelled components but also the intramolecular distribution of activity. However, it is difficult at the present time, owing to the insufficiency of the experimental data, to derive specific rules governing the effect of a method of treatment.

§ This is termed the energy yield, G, by Western authorities. It is the number of molecules changed per 100 eV of energy absorbed in the system (Ed. of Translation).

¶ This reference appears to be incorrect (Ed. of Translation).

The regularities observed in the interaction of recoil atoms and of ions with matter described above make it possible to select the most suitable procedure for the synthesis of labelled compounds. Choice of the initial mixture to be irradiated and the conditions for its subsequent processing to isolate the labelled products is governed not only by the mechanism of formation from the starting material. An individual approach must be made to each irradiated mixture and each product in deciding the question of additives, methods of irradiation and separation, etc. Nevertheless, there are several general principles, attention to which may provide some assistance in carrying out the hot synthesis of labelled compounds.

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THE CHEMISTRY OF THE SILICIDES OF THE RARE-EARTH ELEMENTS

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1. INTRODUCTION

One of the most important conditions for the development of modern technology is the production of new high-temperature materials with special physical and chemical properties — semiconducting, magnetic, nuclear, refractory, emission, and high-temperature strength properties. In this connection the silicides of the rare-earth metals are attracting attention. Compounds of the rare-earth elements are also of theoretical interest, since, unlike the transition metals, in which the *d* levels are being filled, lanthanum and the lanthanides have incomplete inner 4*f* levels, which cannot participate directly in chemical bonding, but which can exert an influence on the nature of the chemical bond formed by the electrons in the outermost levels. In particular, since the 4*f* and 5*d* states are close to one another, the latter may arise in crystals of the compounds as a result of $f \rightarrow d$ transitions.

Because of this and the simultaneous existence, in the silicide lattices, of covalent bonds between the silicon atoms and metallic bonds between the atoms of the metals and silicon, the bonding in silicides is of complex character, and this makes it possible to vary the physical and chemical properties of these compounds over wide limits. Scandium and yttrium resemble the lanthanides extremely closely in many of their properties, their geochemical features, and their behaviour in compounds. These two elements are intermediate between the *d* and *f* transition elements; their silicides exhibit features characteristic both of the silicide phases of transition metals of Groups IV–VIII and of the silicides of the lanthanides.

The problems of the further study of the electronic structure and physical properties of the silicides of the rare-earth elements and the extension of the range of their application makes it necessary to summarise the available information on this group of inorganic compounds.

2. STRUCTURE AND PROPERTIES

The characteristic type of crystal structure shown by the disilicides of the rare-earth metals is the α-$ThSi_2$ structure, in which the silicon atoms form a three-dimensional framework (Fig.1) and the metal atoms are situated in the spaces in this framework (the unit cell contains 4 atoms). This type of structure is produced when the silicon: metal radius ratio $r_{Si} : r_M = k$ is greater than 0.7 and less than 0.8 ($0.7 < k < 0.8$). This corresponds to the silicides of almost all the rare-earth metals, since for the latter $k = 0.69_5–0.75_5$. In this case the significant difference in atomic radii does not favour the close packing of silicon and metal, as in the silicides MSi_2 of the iron disilicide type. Every silicon atom in silicides of the α-$ThSi_2$ type is surrounded by three neighbouring silicon atoms and six metal atoms. The Si–Si distances indicate the existence of covalent bonding (close to $2r_{Si} = 2.35$ Å). The configuration of the bonds corresponds to sp^3 hybridisation. On the other hand, the M–Si distances indicate the absence of covalency, or the existence of weak covalent bonds, between the atoms of metal and silicon in a structure of this type. This bond is apparently metallic in character.

The silicides of lanthanum, cerium, praseodymium, and europium have this type of structure, but the silicides of neodymium, samarium, gadolinium, dysprosium, and yttrium crystallise in a slightly different orthorhombic

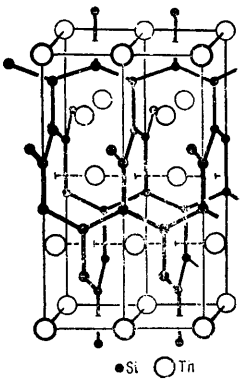

Fig. 1. The crystal structure of α-$ThSi_2$.

TABLE 1. Crystal structures of the silicides of the rare-earth elements.

Silicide	Structural type	System	Space group	Lattice constants, kX			Density, g cm^{-3}	Ref.
				a	b	c		
YSi	CaSi	orthorhombic	D_{2h}^{17}	4.25	10.52	3.826	4.53	2
Y_5Si_3	Mn_5Si_3	hexagonal	D_{6h}^{3}	8.403	—	6.303	—	4
α-YSi_2	α-YSi_2	orthorhombic	D_{2h}^{28}	4.04	3.95	13.23	4.5	3
β-YSi_2	α-$ThSi_2$	tetragonal	D_{4h}^{19}	4.04	—	13.42	—	5
$LaSi_2$	α-$ThSi_2$	tetragonal	D_{4h}^{19}	4.31	—	13.80	5.0	3
CeSi	FeB	orthorhombic	D_{2h}^{16}	—	—	—		2
$CeSi_2$	FeB	orthorhombic	D_{2h}^{16}	4.27	—	13.88	5.45	3
α-$PrSi_2$	α-YSi_2	orthorhombic	D_{2h}^{28}	4.23	4.20	13.68	—	4
β-$PrSi_2$	α-$ThSi_2$	tetragonal	D_{4h}^{19}	4.20	—	13.76	—	3
α-$NdSi_2$	α-YSi_2	orthorhombic	D_{2h}^{28}	4.18	4.15	13.56	4.7	3, 6
β-$NdSi_2$	α-$ThSi_2$	tetragonal	D_{4h}^{19}	4.03	—	13.53	5.84	1, 7
α-$SmSi_2$	α-YSi_2	orthorhombic	D_{2h}^{28}	4.105	4.035	13.46	—	3
β-$SmSi_2$	α-$ThSi_2$	tetragonal	D_{4h}^{19}	4.08	—	13.51	6.26	4
$EuSi_2$	α-$ThSi_2$	tetragonal	D_{4h}^{19}	4.29	—	13.66	—	3
α-$GdSi_2$	α-YSi_2	orthorhombic	D_{2h}^{28}	4.09	4.01	13.44	6.4	3
β-$GdSi_2$	α-$ThSi_2$	tetragonal	D_{4h}^{19}	4.10	—	13.61	5.92	5
α-$DySi_2$	α-YSi_2	orthorhombic	D_{2h}^{28}	4.04	3.95	13.34	6.8	3
β-$DySi_2$	α-$ThSi_2$	tetragonal	D_{4h}^{19}	4.03	—	13.58	—	5

lattice (Table 1), in which, however, the a and b axes differ little from one another, so that Brauer and Haag[1,2] attributed to neodymium disilicide a tetragonal lattice analogous to the lattices of lanthanum, cerium, and praseodymium silicides. The relative positions of the metal and silicon atoms in these structures are the same as those in the α-$ThSi_2$ structure. The transition from tetragonal to orthorhombic lattice at room temperature in the series of disilicides of the rare-earth metals La, Ce, Pr, Nd, ..., the increase in the degree of "orthorhombic character" of the lattice in the series $NdSi_2$, $SmSi_2$, $GdSi_2$, $DySi_2$, *i.e.* the difference between the constants a and b (0.03 Å, 0.07 Å, 0.08 Å, and 0.09 Å respectively), and the reappearance of a tetragonal lattice in $EuSi_2$ and its subsequent replacement by an orthorhombic lattice in $GdSi_2$ can, according to Perri *et al.*[3], be attributed to the effect of the lanthanide contraction. The lattice constants of the disilicides of the rare-earth metals show the same dependence on atomic number as those of the rare-earth metals themselves and their borides, *i.e.* a continuous decrease from $LaSi_2$ to $DySi_2$ (and apparently further, to the end of the lanthanide series), with a sharp increase at $EuSi_2$ (Fig. 2) and, apparently, at $YbSi_2$. A change of this type for metallic Eu and Yb is related to the attraction of an electron from the outer $5d^1$ orbital to fill the vacant state (hole) in the inner $4f^6$ orbital[3].

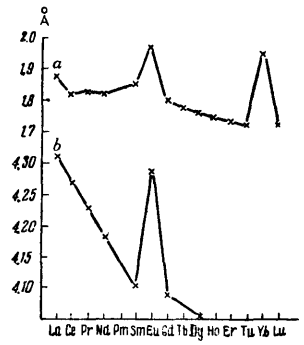

Fig. 2. Dependence of the atomic radii of the rare-earth metals (a) and the lattice constants of their silicides (b) on the atomic number of the elements.

According to Perri *et al.*[5], the lattice of the disilicides of Sm, Gd, Dy, and Y, which is orthorhombic at room temperature, changes above 300°–500° to a tetragonal modification of the α-$ThSi_2$ type, analogous to that of $LaSi_2$ and $CeSi_2$. In the case of $PrSi_2$ the orthorhombic α modification exists only below -120°. The orthorhombic $\rightleftharpoons$ tetragonal transformation temperature increases with increase in the atomic number of the metal. No orthorhombic modification of $EuSi_2$ has been found (Table 1).

The monosilicides of rare-earth metals, known at present for yttrium, lanthanum, and cerium, crystallise in lattices of the orthorhombic-bipyramidal system. Analysis of the silicon : metal radius ratio at which the orthorhombic monosilicides are formed shows that they are produced when the difference in atomic radii is large (k = 0.6–0.9). These complex structures are distinguished by the presence of a chain of covalent bonds between the silicon atoms. The tendency for the structure to become more complex and for covalent bonds to be produced between the silicon atoms as the value of k departs from unity is a general feature of all compounds of transition metals with silicon[8]. However, a marked difference in the radii of the atoms of metal and silicon is not the only condition for the production of orthorhombic lattices in monosilicides of the transition metals and, more particularly, rare-earth metals; a second necessary condition is a certain effective electron concentration, which can be characterised by the ratio Z/ζ†, since the effective electron concentration in the lattice is greater, the greater the total number of valency

† Z is the sum of the number of valency electrons of the metal and silicon, and $\zeta = 1/Nn$, where N is the principal quantum number of the unfilled level and n the number of electrons in this level[9].

electrons of the metal and silicon, and smaller, the greater the acceptor power of the unfilled sub-levels in the atom of the transition metal. Fig.3 [10] shows that the k *vs.* Z/ζ diagram is divided into three regions, the upper and lower corresponding to the orthorhombic monosilicides, and the central to the cubic monosilicides. It follows from this diagram that the orthorhombic monosilicides are formed either when there is a considerable difference in the atomic radii of the metal and silicon, irrespective of the electron concentration, or, in the case where the atomic radii of the metal and silicon are similar, when there is a high electron concentration, requiring a more capacious Brillouin zone. The first case is also characteristic of yttrium and cerium monosilicides.

Examination of the known melting points of disilicides of the rare-earth metals (Table 2) shows that the ratio of these melting points, on the absolute scale, to the melting points both of the metals and of silicon is greater than unity, but as a rule, unlike the case of the borides, it is not much greater than 1. In general, the ratio $T_{M_xSi_y} : T_M$ decreases with increase in the silicon content of the silicide phase. This indicates a weakening of the bonds between the metal atoms in the silicide lattices and is in good agreement with the increase, in the same direction, of the silicon motif in the structure. In this case the $T_{M_xSi_y} : T_M$ ratio also decreases, approaching unity for compounds with the greatest number of Si–Si bonds, *i.e.* those in which the silicon motif is shown to the greatest extent.

This is well illustrated, in particular, by the silicides of rare-earth elements exhibiting a three-dimensional framework of Si–Si bonds (Table 2).

Another noteworthy feature is that for silicides with an orthorhombic lattice (yttrium, gadolinium, and dysprosium disilicides), the ratio of the melting points to the melting points of the corresponding metals is much less than in the case of the disilicides with the tetragonal lattice.

There are almost no data on the heats of formation of the silicides. Brewer and Krikorian [11] estimated the heat of formation of cerium silicide $CeSi_2$ and obtained values in the range 16.6–34.4 kcal per atom of Si (the recommended mean value is 25 ± 10 kcal per atom of Si), or about 50 kcal mole^{-1}. Neshpor [10], on the basis of an analysis of the manometric curves for the preparation of lanthanum mono- and di-silicides *in vacuo* by reduction of lanthanum oxide with silicon, obtained approximate values for the heats of formation of LaSi (30 kcal mole^{-1}) and $LaSi_2$ (44.4 kcal × mole^{-1}). From this, the heat of formation of lanthanum disilicide is ~ 22 kcal per atom of Si, which is close to the corresponding value for cerium disilicide (25 kcal per atom of Si), found by Brewer and Krikorian. The heat of formation of yttrium monosilicide YSi is 32.2 kcal mole^{-1}. [12]

TABLE 2. Melting points of the disilicides of the rare-earth metals.

Silicide	Melting point, °C	$T_{M_xSi_y} : T_M$	$T_{M_xSi_y} : T_{Si}$
YSi_2	1520	1.04	1.04
$LaSi_2$	1520	1.50	1.04
$NdSi_2$	1525	1.39	1.05
$EuSi_2$	1500	1.39	1.03
$GdSi_2$	1540	1.12	1.06
$DySi_2$	1550	1.03	1.06

The electrical conductivity, Seebeck coefficient, and Hall effect have been studied for only a few disilicides [13–16]. The results are given in Table 3, which also gives for comparison the data for the corresponding metals.

The resistivity of the disilicides of the rare-earth metals (Table 3) is considerably greater than that of the corresponding metals and is ~10^{-4} Ω cm, but is considerably less than that of semiconducting silicides such as $CrSi_2$ and $ReSi_2$. [15] The silicides of the rare-earth metals, like the metals themselves, have low Seebeck coefficients. The same is true of the values of the Hall coefficients. In the case of praseodymium disilicide, however, the sign of the Hall effect is the opposite of that for the metal, and this may indicate a significant difference in the nature of the energy spectrum of the electrons in praseodymium and its silicide.

The temperature dependence of the resistance and Seebeck coefficient has been studied for lanthanum disilicide [13,14]. The resistance of $LaSi_2$ (Fig.4) has an anomalous temperature dependence — almost linear, like that characteristic of metallic conductors, and showing an increase with increase in temperature to ~500°, followed by a fairly sharp decrease and changing to a smoother curve with further increase in temperature. The anomalous temperature dependence of the resistance of $LaSi_2$ may be caused either by a change in the mechanism of conductance due to an increase in the La–La distance as a result

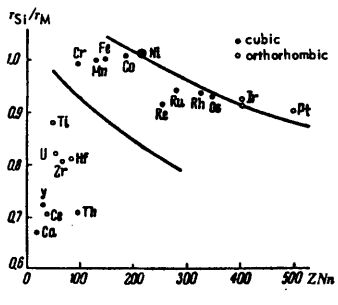

Fig.3. Dependence of the nature of the structure of silicides of transition elements on the ratio $r_{Si} : r_M$ and the product ZNn. [15]

TABLE 3. Electrophysical properties of the disilicides of the rare-earth metals [13–16].

Silicide or metal	Electrical resistivity, μΩ cm	Hall coefficient, $10^8 R$, cm^3 C^{-1}	Absolute Seebeck coefficient, μV deg^{-1}
La	56.8	−8.0	—
$LaSi_2$	236±20	−17.5±0.4	−4.2±0.3
Ce	75.3	+18.1	—
$CeSi_2$	408±20	+19.3±1.0	+7.8±0.5
Pr	68.0	+7.1	—
$PrSi_2$	202±20	−10.7±0.5	−3.2±0.4
$NdSi_2$	349	—	—
$GdSi_2$	263	—	—
$DySi_2$	3020	—	—

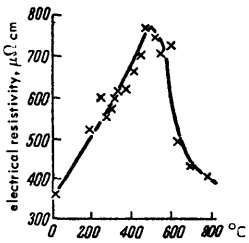

Fig.4. Temperature dependence of the electrical resistivity of $LaSi_2$. [12]

of thermal expansion or by a polymorphic transformation. The latter has been established for $ThSi_2$,[17] whose low-temperature modification is isostructural with $LaSi_2$. Microstructural studies, however, have shown no changes on passing through 500°.

The absolute Seebeck coefficient of lanthanum silicide (Fig. 5) is negative throughout the whole temperature range studied, indicating that the current carriers have negative sign, and passes through a minimum at 500°–600°. At ~500° the curve giving the temperature dependence of the Seebeck coefficient changes sign, like that giving the temperature dependence of the resistance. The Hall constant for $LaSi_2$ at room temperature is negative and has the value -17.5×10^{-5} cm^3 C^{-1}.

Analysis of the temperature dependence of the resistance of lanthanum silicide in the non-linear region shows that it is given by the exponential $\rho_t = \rho_0 \exp(0.19/kT)$, *i.e.* it does not obey either the T^3 (or T^5) law required by theory for $T = \theta$, where θ is the Debye temperature, equal to 502°K for $LaSi_2$, or the $T^{3/2}$ law required by theory for semiconductors with high conductivity[18]. Calculation of the resistance of lanthanum disilicide from Grüneisen's formula[19] for metals does not give satisfactory agreement with experimental data either:

Temperature, °C	0	100	200	300	400	500
Reduced resistivity:						
calculated	0.48	0.71	0.93	0.16	1.37	1.59
experimental	0.67	0.81	0.95	1.10	1.25	1.43

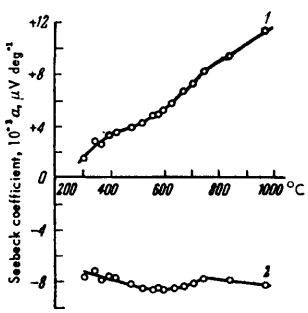

Fig.5. Temperature dependence of the Seebeck coefficient of $LaSi_2$. [12]

All this indicates that the nature of the conductivity in metallic silicides, to which class $LaSi_2$ belongs, is more complex than that for metals. In any case it may be assumed that $LaSi_2$ is a metallic conductor of the n-type from 20° to 500° and a semiconductor, apparently of the p-type, above 500°.[13]

The width of the forbidden gap in the region corresponding to the semiconductor temperature dependence of the conductivity of $LaSi_2$ is ~0.19 eV. This behaviour of lanthanum disilicide cannot be explained by the theory of semiconductors with an impurity zone[6], since it is then difficult to explain the whole course of the temperature dependence of the resistivity of $LaSi_2$ in the region where it is increasing, and also since the width of the forbidden gap in the region of the semiconductor temperature dependence of the resistivity is too small. It may, however, be suggested that the observed nature of the temperature dependence of the resistivity of $LaSi_2$ is related to the anisotropy of its thermal expansion. The latter, as a result of the markedly heterodesmic nature of the interatomic bonds in the lattice of this compound, may lead to a significant change in the nature of the overlap of the energy bands in the valency zone, which at low temperatures is also the conductivity zone. Taking into consideration the electronic structure of semiconducting silicides[19], we may assume that the single *d* electron in lanthanum is used for bonding between silicon atoms at high temperatures. This effect leads to the filling of a band of electronic states, whose production is due to the participation of the silicon atoms in the chemical bonding and to the appearance of an energy gap between this filled band and higher free bands. It is evident that the appearance of a gap between the conducting and non-conducting states in a certain temperature range should lead first to a considerable increase in resistance with increase in temperature and then to its exponential decrease. The low Hall mobility of the current carriers in $LaSi_2$ (Table 4) indicates that the electrons in $LaSi_2$ are bound to a considerable extent, so that even a slight redistribution of electrons may lead to a change in the nature of the conductivity.

Preliminary study of the temperature dependence of the electrical resistance of $CeSi_2$ [13] has revealed its semiconductor character throughout the whole temperature range 20°–1000°.

There are very few data on the magnetic properties of the silicides of the rare-earth metals. Matthias *et al.*[20] observed ferromagnetism in praseodymium disilicide at very low temperatures, its Curie point lying at 10.5°K, but the silicides of Sc, Y, La, Ce, and Nd were found to be paramagnetic down to ~1°K.

TABLE 4. Effective concentration of free current carriers and Hall mobility of the current carriers in silicides of the rare-earth metals.

Phase	Effective concentration of free current carriers, *n*		Hall mobility of the free current carriers, $cm^2 V^{-1} sec^{-1}$
	per cm^3	per molecule	
$LaSi_2$	$2.9 \cdot 10^{22}$	2	0.7—(for La 1.4—)
$CeSi_2$	$3.1 \cdot 10^{22}$	2.3	0.5+(for Ce 2.4+)
$PrSi_2$	$4.4 \cdot 10^{22}$	3.4	0.5—(for Pr 0.5—)

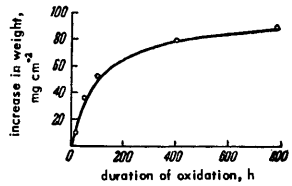

Fig.6. Change in weight of $DySi_2$ specimen during oxidation in air at 1000°. [16]

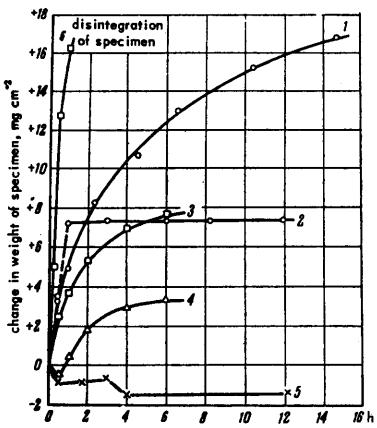

Fig.7. Change in weight during oxidation for the silicides of some transition metals at 1300°: 1) $BaSi_2$; 2) $ReSi_2$; 3) $MnSi_2$; 4) $FeSi_2$; 5) $CrSi_2$; 6) $LaSi_2$.

The hardness of the silicides of the rare-earth metals is much lower than that of the corresponding borides:

Phase	Microhardness $H_{1/2}$, kg mm⁻²	Phase	Microhardness $H_{1/2}$, kg mm⁻²
$LaSi_2$	325	LaB_6	2500
$CeSi_2$	545	CeB_6	2350

This can be attributed both to the considerable weakening of the bond between the metal atoms in the silicides and to the characteristic structural features of the latter, facilitating the shearing deformation characteristic of hardness measurements. The nature of the change in the hardness is exactly analogous to that of the change in the melting points.

Binder [21] gives the bending strength (kg mm^{-2}) of some disilicides: $LaSi_2$ 27.2, $GdSi_2$ 4.4, and $DySi_2$ 6.68.

The resistance of the silicides of the rare-earth metals to oxidation, like that of the silicides of the *d*-transition metals, depends to a marked extent on the nature of the oxide film produced, the volatility of the oxide, and the tendency of the oxide to form silicates with SiO_2. Thus according to Binder's data [21], dysprosium disilicide $DySi_2$ shows a comparatively high resistance to oxidation at 1000° and a marked decrease in the rate of oxidation with time (Fig. 6), whereas Neshpor [12] found that lanthanum disilicide is oxidised extremely rapidly (Fig. 7) with the formation of a grey non-compact oxide film which did not adhere to the specimen surface; the latter also showed considerable cracking. However, Neshpor's experiments were carried out at a higher temperature (1300°). It may be suggested that the difference in the behaviour on oxidation shown by lanthanum and dysprosium disilicides is due to a difference in the tendency to form silicates, since a marked difference in the volatility of these oxides is not to be expected.

According to Brauer and Haag [1], the disilicides of the rare-earth metals are readily decomposed by HF solutions, dilute HCl, and molten $K_2CO_3 + Na_2CO_3$, which is used in the chemical analysis of these compounds.

3. METHODS OF PREPARATION

The chief methods of preparing the silicides of the rare-earth metals are similar to the methods of preparing the borides, and can be divided into the following groups: (1) direct combination of the rare-earth metal and silicon, (2) the reduction of oxides of the rare-earth metals with silicon, and (3) the electrolysis of melts containing the rare-earth metals and silicon.

The direct combination of the rare-earth metals and silicon can be carried out by fusion or sintering. This method appears to have been used first by Vogel [22] for the preparation of cerium–silicon alloys. Brewer and Krikorian [11] used the same method to prepare these cerium–silicon alloys by sintering small pieces of cerium with silicon powder at 1430° (with partial fusion of the specimens). Because of the high affinity of the rare-earth metals for oxygen and nitrogen, the sintering or fusion with silicon should be carried out in an inert atmosphere (argon, etc.), and this makes the method complicated and expensive. In a variation of this method, the reaction between the rare-earth metal and silicon is carried out in molten aluminium, and this method was tested by Brauer and Haag [1] for the preparation of cerium disilicide. An aluminium–cerium alloy containing ~10% Ce was fused with excess silicon in a corundum crucible at 900°, after which the alloy was treated first with acid and then with sodium hydroxide solution. The product obtained in this way, however, was found to be a ternary alloy of approximate composition $Ce_2Al_3Si_2$, so that $CeSi_2$ either is not formed or is formed together with the ternary alloy and is dissolved during the acid–alkali treatment of the fusion products. Thus attempts to prepare silicides by a method similar to Lebeau's copper–silicide method [23], used for the preparation of the silicides of *d*-transition metals, did not give satisfactory results.

Lanthanum disilicide has also been prepared by direct combination of the elements [3].

The reduction of oxides of the rare-earth metals with silicon is at present the most widespread method for preparing the silicides of many rare-earth metals. This method was proposed in its original form as early as 1902 by Sterba [23], who prepared cerium silicide by reducing CeO_2 with silicon:

$$CeO_2 + 3Si = CeSi_2 + SiO_2 .$$

Further tests on this method [1,2] showed, however, that even after 10–40 min at 2000°–2400° in a tubular graphite resistance furnace the product is not $CeSi_2$ but a mixture of

cerium oxide, silicon carbide, and cerium silicate. The formation of the silicate was also observed by Walter[24] in a study of the reaction of CeO_2 with Si at 970°–1700°. Because of this, a vacuum method was developed[1]. This was designed to remove the volatile silicon monoxide, and, in the case of the preparation of cerium disilicide, is represented by the overall reaction:

$$CeO_2+4Si=CeSi_2+2SiO,$$

which according to Brauer and Haag passes through the following stages:

$$CeO_2+Si=Ce+SiO_2,$$
$$SiO_2+Si=2SiO,$$
$$Ce+2Si=CeSi_2.$$

This reaction scheme is not confirmed, however, by the later data of Neshpor and Samsonov[14], who prepared lanthanum silicide by this method. The manometric curve (Fig. 8) for the reaction

$$La_2O_3+7Si=2LaSi_2+3SiO,$$

shows not one pressure jump, as should be the case if Brauer and Haag's scheme (evolution of silicon monoxide) applies, but two. Moreover, the X-ray diffraction patterns of the specimens do not show lines corresponding to any of the modifications of SiO_2. An attempt to attribute the presence of the two pressure jumps to a stage in the reduction involving the formation of the lower lanthanum oxide LaO:

$$La_2O_3+Si \longrightarrow LaO+SiO,$$
$$LaO+Si \longrightarrow LaSi_2+SiO,$$

was also unsatisfactory, since the X-ray diffraction study of the reduction products obtained after the first pressure jump did not show the cubic lattice which should be exhibited by lanthanum monoxide LaO, by analogy with the lower oxides of other rare-earth metals, for example SmO and EuO,[7] and did not show the presence of metallic lanthanum in the reduction product. It was therefore suggested that the reduction takes place in two stages with the formation of lanthanum monosilicide as an intermediate product:

$$La_2O_3+5Si=2LaSi+3SiO,$$
$$2LaSi+2Si=2LaSi_2,$$
$$\overline{La_2O_3+7Si=2LaSi_2+3SiO}.$$

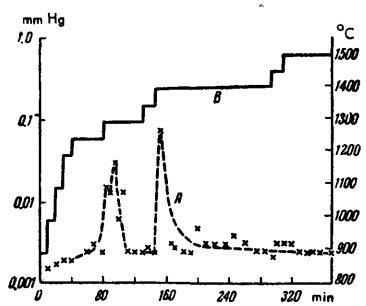

Fig.8. Manometric curve for the reduction of lanthanum oxide with silicon in vacuo[14].

This scheme is confirmed by the presence, in the X-ray diffraction patterns of the low-temperature products, of lines for both monosilicide and disilicide, and also by the results of a thermodynamic treatment of the manometric curve. On the basis of the above scheme, this treatment led to reasonable values for the heats of formation of LaSi and $LaSi_2$.

Brauer and Haag[1] prepared the disilicides of cerium (at 1550°), lanthanum, neodymium, praseodymium, samarium, ytterbium, yttrium, and scandium by reducing the oxides with excess silicon *in vacuo* and removal of the volatile silicon monoxide. The process was carried out in alumina tubes heated in tubular graphite resistance furnaces. The agreement between the compositions of the resulting disilicides and the calculated data is illustrated in Table 5.

Brewer and Krikorian[11] used an analogous method to prepare the silicides of many rare-earth metals, but these authors do not give the conditions and other characteristics of the processes used.

The silicides of lanthanum[14], cerium, and praseodymium have been prepared by the same method from a charge of stoichiometric composition, with heating for 30 min at 1550°–1600° and an initial pressure in the vacuum furnace of 10^{-3} mm Hg.

The vacuum-thermal method of preparing the disilicides of a number of rare-earth metals by reducing the oxides with silicon has also been used by Perri *et al.*[3] The purity of the oxides of lanthanum, cerium, praseodymium, samarium, europium, gadolinium, dysprosium, and yttrium was 99–99.5%, and that of the neodymium oxide was 95%. The reduction reactions were carried out in alumina boats *in vacuo* with continuous evacuation at 1100°–1600°. The optimum temperatures for the preparation were 1200°–1300° for $SmSi_2$ and 1400°–1550° for YSi_2 and $DySi_2$; increase in temperature above 1600° led to reaction with the material of the boat and contamination of the silicides.

Attempts by the same authors to prepare silicides by reducing the oxides with silicon in a medium of hydrogen did not give satisfactory results, due to the formation of films of silicon oxide on the silicide particles, giving products contaminated with considerable quantities of oxygen.

The electrolysis of melts. This method is analogous to the method for preparing borides, developed in detail by Andrieux. It was first used in 1865 by Ulik[25], who electrolysed fluoride melts. It was later applied to mixtures of CeO_2, SiO_2, and CaO by Sandlar[4]. This method has been studied in greatest detail by Dodero[26] for the case

TABLE 5. Chemical analysis of specimens obtained by reducing oxides of the rare-earth metals with silicon.

Silicide	Metal, %		Silicon, %	
	calc.	expt.	calc.	expt.
$LaSi_2$	71.23	70.9	28.7	28.8
$CeSi_2$	71.43	72.1	28.57	27.6
$PrSi_2$	71.57	71.3	28.43	27.6
$NdSi_2$	71.99	70.7	28.01	27.8
$SmSi_2$	72.83	72.4	27.17	26.8
YSi_2	61.31	62.4	38.69	37.6

of the preparation of cerium and lanthanum silicides by the electrolysis of fused mixtures of oxides of the rare-earth metal, silicon, and calcium carbonate, chloride, and fluoride. A disadvantage of the method is that the silicides are usually contaminated with silicates, whose removal requires complex tedious operations, and this makes the electrolysis of melts unsuitable for the preparation of the silicides of the rare-earth metals.

4. SILICIDES OF SCANDIUM, YTTRIUM, AND THE LANTHANIDES

Scandium silicides. The first attempts to prepare scandium silicides by reducing scandium oxide with silicon *in vacuo* were made by Brauer and Haag[1], but the products could not be satisfactorily identified by X-ray diffraction methods. Preliminary analysis of the X-ray diffraction patterns showed that they differed considerably from those of the tetragonal disilicides of lanthanum and yttrium.

The experiments of Samsonov *et al.*[27] on the preparation of scandium mono- and di-silicides by reducing Sc_2O_3 with 98% silicon according to the reactions:

$$Sc_2O_3+5Si=2ScSi+3SiO,$$
$$Sc_2O_3+7Si=2ScSi_2+3SiO,$$

at 1100°–1900° showed that the X-ray diffraction patterns of the products of the reduction designed to produce $ScSi_2$ and those obtained at 1100°–1500° are identical, whereas those for the products at 1600°–1700° show some differences and are less distinct, apparently due to decomposition of the products with the liberation of silicon. The X-ray diffraction patterns of the products of the reduction designed to produce ScSi differ from the above patterns. Neither the first nor the second X-ray diffraction patterns could be identified. Chemical analysis of the products of the reduction designed to produce ScSi gives a composition close to this formula, but the products of the reduction designed to give $ScSi_2$ have a composition close to the formula Sc_3Si_5. A silicide of this composition is known for uranium, but the structure found for α-USi_2 has been attributed to it.

Yttrium silicides. The existence of three yttrium silicides, YSi, Y_5Si_3, and YSi_2, has been established. The latter is obtained by reducing yttrium oxide at 1400°–2250°[3] with silicon *in vacuo*[1,21]. The silicide YSi_2 crystallises in an orthorhombic lattice with the space group D_{4h}^{28} characteristic of the low-temperature α-modifications of the disilicides of the lanthanides (Table 1); β-YSi_2 has a tetragonal lattice of the α-$ThSi_2$ type (space group D_{4h}^{19}). The $\alpha \rightarrow \beta$ transformation takes place at 450°. The physical properties of YSi_2 have not been studied; it has been established, however, that it is paramagnetic down to 1°K.[19]

The monosilicide YSi was prepared[28] by arc melting and has a composition close to the stoichiometric. X-Ray diffraction study shows that YSi has an orthorhombic lattice belonging to the space group $Cmcm(D_{2h}^{1})$, similar to the CrB structure[29] and identical with the CaSi structure. The silicide Y_5Si_3 has a hexagonal lattice of the Mn_5Si_3 type[30].

Lanthanum silicides. The existence of two silicide phases — the monosilicide LaSi and the disilicide $LaSi_2$ — has been established in the lanthanum–silicon system.

Dodero[26] prepared lanthanum disilicide by the electrolysis of a mixture containing La_2O_3 10, SiO_2 30, $CaCO_3$ 50, CaF_2 78, and $CaCl_2$ 20 g at 1100° with a current of 30 A. After electrolysis for 1 h a pear-shaped deposit consisting of silicates with lanthanum silicide inclusions formed on the cathode. Since the chemical and mechanical separation of the resulting mixture is difficult, it is recommended that the electrolysis be carried out with a water-cooled aluminium cathode by the contact method; as electrolysis proceeds, the temperature is increased and the pear-shaped deposit drops into the melt, where the silicide collects in a fairly pure conglomerate. It is treated with 5% NaOH to remove free silicon.

Purer lanthanum silicide $LaSi_2$ is obtained by reducing lanthanum oxide with silicon *in vacuo*[1,3,21]. This process has been studied in greatest detail by Neshpor and Samsonov[14], who prepared lanthanum disilicide from a charge of stoichiometric composition, calculated on the assumption that the reaction

$$La_2O_3+7Si=2LaSi_2+3SiO$$

takes place.

To establish the optimum conditions for the reaction, the charge was formed into briquettes, placed in the graphite heater of a vacuum resistance furnace, and heated at temperatures in the range 1200°–1600° for 30 min at each temperature. The initial pressure in the furnace was 10^{-3} mm Hg. The extent to which the reaction had proceeded was found by chemical analysis and X-ray diffraction, and also from the value of the ratio $\gamma = (G_1/G_2) \times 100\%$, where G_1 is the weight of product which would be obtained if the reaction went to completion according to the equation and G_2 the actual weight of reaction product obtained at each temperature. Values of $\gamma \leq 100\%$ correspond to more or less complete reaction. The results of the chemical analysis and X-ray diffraction study of the products obtained at different temperatures are given in Table 6 and Fig. 9.

The data in Table 6 show that the reaction with silicon begins at temperatures below 1250°. The quantity of free silicon decreases fairly rapidly with increase in temperature, but even at 1580° the reaction product still contains oxygen, whose concentration can be estimated approximately from the difference 100 - (La + Si_{total}). The X-ray diffraction data show that $LaSi_2$ has appeared in the reaction products at 1250°, and the concentration of this phase increases with temperature. In addition to $LaSi_2$, however, the X-ray diffraction patterns show the presence of

TABLE 6. Chemical and phase composition of the products of the reduction of lanthanum oxide by silicon (duration of reaction 30 min).

Temperature, °C	γ, %	Chemical composition, %					Phase composition
		La	Si_{total}	Si_{free}	$Si_{combined}$	100−(La+Si_{total})	
—	—	71.3*	28.7*	—	28.7*	—	$LaSi_2$
1250	104	53.0	37.25	22.3	19.25	9.75	
1260	101	51.0	36.80	22.1	18.87	11.61	$LaSi_2$, Si, phase X
1370	87	50.5	30.6	13.65	19.65	9.9	
1400	75	61.4	28.75	1.6	27.6	9.85	
1490	72	67.3	27.2	1.3	26.3	5.5	$LaSi_2$, phase X
1580	78.7	65.0	28.8	—	—	6.2	

* Calculated composition of $LaSi_2$.

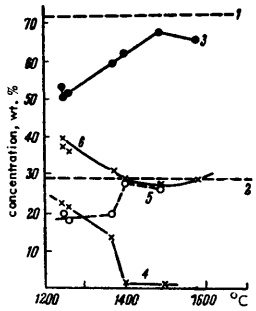

Fig. 9. Temperature dependence of the composition of the products of the reduction of lanthanum oxide with silicon:
1) and 2) concentration of La and Si, respectively, in $LaSi_2$. Experimentally determined concentrations of La and Si in the reaction products:
3) La; 4) Si_{free}; 5) $Si_{combined}$; 6) Si_{total} (duration of reaction 30 min [14]).

a phase X, whose concentration is a maximum in the low--temperature products and decreases with increase in the reaction temperature.

Change in the duration of the reaction leads to the results shown in Fig. 10. Heating was continued until the pressure in the furnace was approximately equal to that at the start of the reaction. A sharp increase in pressure, corresponding to the vigorous evolution of SiO, is observed from 1400°. Table 7 gives the results of the chemical analysis and X-ray diffraction study of the reaction products and also shows the time required for the pressure in the furnace to reach a value close to the initial value. Fig. 11 gives the temperature dependence of the composition and the time required for the reaction to proceed to an appreciable extent.

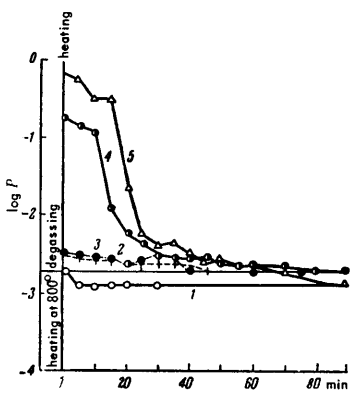

Fig. 10. Isotherms for the pressure in the furnace during the reduction of lanthanum oxide by silicon [14]:
1) 1150°; 2) 1250°; 3) 1375°; 4) 1490°; 5) 1600°.

TABLE 7. Dependence of the chemical and phase composition of the products of the reduction of lanthanum silicide with silicon on the temperature and duration of heating *in vacuo*.

Temperature, °C	Time, min	γ, %	Chemical composition, %					Phase composition
			La	Si_{total}	Si_{free}	$Si_{combined}$	100 − (La + Si_{total})	
1150	30	120	50.0	40.25	26.0	19.25	9.75	$LaSi_2$, Si, phase X
1250	45	118	50.7	40.3	24.4	21.08	9.00	
1375	70	75	66.5	28.9	3.6	26.3	4.6	
1490	90	81	63.75	31.0	2.7	29.1	5.25	$LaSi_2$, phase X
1600	100	53.5	70.20	28.4	0	28.4	1.4	$LaSi_2$

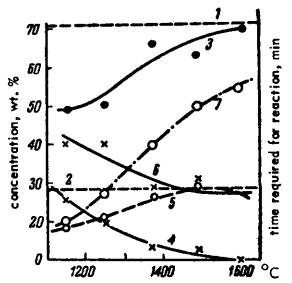

Fig. 11. Temperature dependence of the composition of the products of the reduction of lanthanum oxide with silicon and the temperature dependence of the time required for the reaction [9]. Symbols as in Fig. 9;
7) time, h.

These results show that the optimum conditions for the preparation of lanthanum disilicide are obtained at 1600° for 1.5 h. Under these conditions, pure lanthanum oxide gives a silicide of composition: La 70.9, $Si_{combined}$ 28.1, and C (from the graphite heater) 0.15%.

A manometric study of the reduction process indicated that phase X, formed at relatively low temperatures, is lanthanum monosilicide.

Pure lanthanum disilicide $LaSi_2$ can also be obtained by the direct reaction between lanthanum and silicon [3].

Lanthanum disilicide is known in only one crystalline modification — a tetragonal form for which the following lattice constants have been given:

a, Å	*c*, Å	*c*/*a*	References
4.280	13.747	3.21	1
4.374	13.565	3.12	31
4.31	13.80	3.21	3

The most reliable data are those of Perri *et al.*[3], and these are generally accepted.

The data obtained by Neshpor and Samsonov [14] and Binder [21] for the resistivity of $LaSi_2$ differ considerably, the values being 536 and 273 μΩ cm respectively. The electrical conductivity of $LaSi_2$ changes character at 500°.

Below 500° $LaSi_2$ is an *n*-type metallic conductor and above 500° a *p*-type semiconductor. Like scandium and yttrium disilicides, $LaSi_2$ is paramagnetic down to 1°K. It is oxidised extensively in air at 1300°. Lanthanum silicide differs from the other silicides of the rare-earth metals in its relatively low hardness (31 R_A [21]‡) and a bending strength§ of $\sigma_{bending}$ = 27.2 kg mm^{-2}.

Cerium silicides. The equilibrium diagram of the cerium–silicon system was first studied by Vogel[22], who detected one silicide phase — the monosilicide CeSi — and constructed a tentative diagram. The existence of a second silicide phase $CeSi_2$ was then discovered[1,23,32], and later Brewer and Krikorian[11] made a fairly detailed study of the system. X-Ray diffraction study of the alloys, which they prepared by sintering metallic cerium with silicon powder, showed the presence of phases with nominal formulae $CeSi_{0.35}$ (Ce_3Si), $CeSi_{0.5}$ (Ce_2Si), and $CeSi_{0.75}$. The phase $CeSi_{0.35}$ is detected in the alloys containing unreduced CeO_2, the phase $CeSi_{0.5}$ in alloys containing 33–37 at.% Si, and the phase $CeSi_{0.75}$ in alloys with 40–45 at.% Si.

Brewer and Krikorian also confirmed the presence, in addition to these phases, of the disilicide $CeSi_2$ with tetragonal lattice and constants a = 4.175 ± 0.002 Å and c = = 13.878 ± 0.006 Å (the specimens of $CeSi_2$ were contaminated with up to 5% C), which differ slightly from the results of Brauer and Haag[1] and Zachariasen[32] and more significantly from those of Perri *et al.*[3] and Binder[21]. The latter are now generally accepted:

a, Å	c, Å	c/a	References
4.175	13.848	3.32	11
4.16	13.90	3.34	32
4.156	13.84	3.33	1
4.27	13.88	3.26	3.21

According to Parthé[28], cerium monosilicide, CeSi, has an orthorhombic lattice of the FeB type. No phase transformations have been observed in $CeSi_2$.[5] Part of the cerium–silicon diagram, constructed from results from various sources[11,22,33], is shown in Fig. 12.

$CeSi_2$ can be prepared directly from the elements at 1430°[22] or by electrolysis of fused mixtures of CeO_2, SiO_2, and CaO[4] or of CeO_2, SiO_2, CaF_2, and $CaCl_2$,[26] but is usually prepared by reducing cerium oxide with silicon *in vacuo* at 1550°–1600° with subsequent extraction of silicon if excess of the latter is used in the reduction[1,3,21].

Thus Brauer and Haag[1] prepared cerium disilicide from CeO_2 + Si mixture with excess silicon (1 : 7) by heating in an alundum tube placed in a tubular graphite furnace at 1550°, with evacuation of the silicon monoxide with a vacuum pump. The reaction was assumed to be complete when a fairly sharp drop in pressure was observed. The reaction products were treated with 2 *N* sodium hydroxide solution until evolution of hydrogen stopped.

Cerium disilicide is slightly harder than lanthanum disilicide. Its electrical resistivity at room temperature is ~400 μΩ cm, and preliminary results[14] indicate that in the range 20°–1000° $CeSi_2$ has a negative temperature coefficient of resistivity, *i.e.* it exhibits semiconducting properties. It is paramagnetic down to ~1°K.[19]

‡ R_A means Rockwell A superficial hardness.

§ Transverse rupture strength at room temperature (Ed. of Translation).

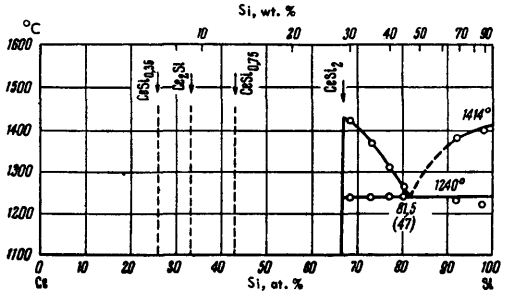

Fig.12. Equilibrium diagram of the cerium–silicon system[33].

Brewer and Krikorian[11] made a preliminary study of the phase compositions of some alloys in the Ce–Si–C system. An X-ray diffraction investigation of an alloy containing C 25, Ce 25, Si 50%, obtained from the elements by sintering at 1330° for 44 min, revealed the phase $CeSi_2$ and another phase, whose composition and structure was not determined[7]. Cerium carbides CeC, Ce_2C_3, and CeC_2 were not detected. The alloys obtained were greyish brown. The Ce–Si–C alloys decomposed in air with the liberation of acetylene.

Praseodymium silicides. Praseodymium has been shown to form one silicide phase — the disilicide $PrSi_2$ — which has an orthorhombic lattice of the YSi_2 type (α-$PrSi_2$) up to -120° and the tetragonal lattice of the $ThSi_2$ type (β-$PrSi_2$), characteristic of the disilicides of the rare-earth metals, above -120°. The transformation is accompanied by extremely small changes in the constants *a* and *c*.

$PrSi_2$ has the lowest resistivity in the $LaSi_2$–$CeSi_2$–$PrSi_2$ series, the value being ~200 μΩ cm, and is as yet the only disilicide for which ferromagnetism has been detected at very low temperatures[19]; its Curie point is 10.5°K.

Praseodymium disilicide is prepared by reducing praseodymium oxide with silicon *in vacuo* at 1550°–1600°.[1,3]

Neodymium silicides. Perri *et al.*[3] report an orthorhombic structure for neodymium silicide, and Brauer and Haag[1] a tetragonal structure. Although there are no published data on phase transformations in $NdSi_2$, it may be assumed that the compound exists in the α- and β-modifications characteristic of the neighbouring disilicides of praseodymium and samarium. $NdSi_2$ is obtained by reducing neodymium oxide with silicon *in vacuo*[1,3,21]. According to Binder[21], the resistivity of $NdSi_2$ is ~350 μΩ cm and the bending strength has the low value of 6.2 kg mm^{-2} at 20°. Neodymium disilicide is paramagnetic down to 1°K.[19]

Samarium silicides. Samarium disilicide is known in two crystalline modifications: α-$SmSi_2$ and β-$SmSi_2$, with lattices of the YSi_2 orthorhombic and $ThSi_2$ tetragonal types respectively and a transformation temperature of 380°. $SmSi_2$ is prepared by reducing samarium oxide with silicon *in vacuo* at 1550°–1600°.[1,3] According to Perri *et al.*[3], the optimum temperature of formation of $SmSi_2$ by this method lies in the range 1200°–1300°.

Europium silicides. Europium forms the disilicide $EuSi_2$, which exists in the tetragonal modification. No orthorhombic modification of $EuSi_2$ has been detected[5], even below -150°. Europium disilicide is prepared by reducing europium oxide with silicon *in vacuo*[1,21].

The lattice constants of $EuSi_2$ are anomalous, being much higher than those of the disilicides of the neighbouring elements samarium and gadolinium. This is apparently due to the bivalency of europium in the disilicide and is discussed in detail above (p.703). $EuSi_2$ melts at a lower temperature (1500°) than the disilicides of the other lanthanides.

Gadolinium silicides. Gadolinium forms one silicide, known in two crystalline modifications: the orthorhombic α-$GdSi_2$ and the tetragonal β-$GdSi_2$, with transformation temperature[5] 400°.

The calculations of Perri *et al.*[3] of the structure factor of gadolinium silicide showed that agreement between the calculated and experimental values is obtained only by assuming for the silicide phase the composition $GdSi_{1.3}$. The pyknometric density of this silicide is 5.94 g cm^{-3}, whereas the density calculated for $GdSi_2$ is 6.43 g cm^{-3} and that for $GdSi_{1.4}$ 5.92 g cm^{-3}. Chemical analysis showed an Si : Gd atomic ratio of 1.47. On this basis it was suggested that a gadolinium silicide phase $GdSi_{1.4}$, with a certain homogeneity range, exists.

Gadolinium silicides are prepared by reducing gadolinium oxide with silicon *in vacuo* at 1550°–1600°.[3,21] The reduction of gadolinium oxide with silicon[27]:

$$Gd_2O_3+Si \longrightarrow GdSi_2+SiO\,,$$

takes place in 40 min at 1500° in a vacuum resistance furnace with graphite heater, to give a product containing 26.8% Si (calculated for $GdSi_2$: Si 26.3%) and 0.8–0.9% C. X-Ray diffraction study showed that the lattice corresponds to the structure of orthorhombic $GdSi_2$.

Binder[21] noted that $GdSi_2$ exhibits a range of homogeneity, whose width was not defined precisely. The resistivity of $GdSi_2$ is ~260 $\mu\Omega$ cm. Its bending strength is the lowest of any disilicide yet studied and amounts to only 4.4 kg mm^{-2}.

There are no data on silicides of terbium, holmium, erbium, thulium, and lutetium.

Dysprosium silicides. Dysprosium disilicide exists in two crystalline modifications: the orthorhombic α-$DySi_2$ and the tetragonal β-$DySi_2$, with the $\alpha \rightarrow \beta$ transformation at 540°.[5] Like the disilicides of the other lanthanides, $DySi_2$ is prepared by reducing the oxide with silicon *in vacuo*[21]. According to Perri *et al.*[3], the optimum temperature for the reduction is 1400°–1500°. The properties of this disilicide have been studied in more detail than those of the disilicides of the other later lanthanides (Tb... Lu), since it has possible uses in nuclear technology, in counters and tracers.

The density of the orthorhombic modification of $DySi_2$, determined by X-ray studies, is 6.80 g cm^{-3}, with the assumption that it has the orthorhombic lattice characteristic of the disilicides, with four atoms in the unit cell. This value differs considerably, however, from the pyknometric value of 5.10 g cm^{-3}, and this has been attributed to the existence of a large number of vacant sites. This is also indicated by the high resistivity of $DySi_2$, the value being 3020 $\mu\Omega$ cm, which is greater by one order of magnitude than that of other lanthanide disilicides. $DySi_2$ has a positive temperature coefficient of resistivity, of the same order of magnitude as that of metals. According to Binder and Steinitz[16], dysprosium disilicide is extremely hard (89 R_A), and its bending strength at room temperature is 6.68 kg mm^{-2}.

$DySi_2$ is stable in boiling water, treatment for 16 h leading to no measurable change in weight of the specimens. $DySi_2$ is extremely stable to oxidation at 1000° (Fig.6):

Duration of oxidation, h	Change in weight, mg cm^{-2}
0.5	+2.60
1	+4.34
18	+21.4
42	+35.8
66	+44.5
96	+52.2
398	+80.0
782	+90.8

Even after prolonged oxidation at 1000°, the disilicide specimen remains hard and compact, and retains its silvery colour.

Articles made of $DySi_2$ can be produced either by hot pressing or by making use of its relatively low melting point of 1550° and sintering the previously compressed objects. The sintered articles can be shaped with silicon carbide wheels and cut with abrasive wheels or by electro-impulse methods. The usual precautions necessary when working with hard and brittle materials must be taken.

Ytterbium silicide. An attempt has been made to prepare ytterbium disilicide by reducing ytterbium oxide with silicon at 1550°–1600°.[1] However, X-ray diffraction study of the specimen was impossible; preliminary results showed that the ytterbium silicide was of indefinite composition, $YbSi_x$ obtained in this work crystallised in a lattice different from that of the other tetragonal lanthanide disilicides. In our opinion, the X-ray diffraction pattern shows a similarity to those of the orthorhombic modifications of the disilicides.

5. USES

The fields of applications of the silicides of the rare-earth metals have not yet been fully determined, but examination of their physicochemical properties reveals the following possible uses.

The comparatively high heat resistance of some silicides, combined with the high neutron-capture cross-section of elements such as Gd and Eu indicates their possible use, either directly or as additives in other alloys, as materials for various neutron-absorbing devices in nuclear-energy technology[16]. The half-lives of the silicides of some metals in the radioactive state, for example, dysprosium, are convenient for practical purposes, and this makes it possible to use them for the construction of dosimeters and counters[21]. The semiconducting properties of some of the silicides (those of lanthanum and cerium), combined with their chemical stability, makes it possible to use these silicides as semiconducting materials for use at high temperatures or in aggressive media. The comparatively low

thermodynamic stability of the silicides and the high affinity of the components for oxygen reveals a possible application for deoxidising in metallurgy and as special hardeners for introducing the rare-earth metals into various types of glass. Individual silicides are probably of interest as scale-resistant components in alloys with high-temperature strength.

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THE MOLECULAR STRUCTURE OF 1,3,5-TRIAZINE AND ITS DERIVATIVES

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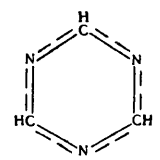
1. INTRODUCTION

One of the sensational scientific achievements of recent years has been the long awaited discovery of free symmetrical triazine. It has turned out that this compound was first obtained by Nef[1] as early as 1895, but owing to errors in determining its molecular weight, he ascribed to this substance an incorrect structural formula, regarding it as a dimer of hydrocyanic acid. This view was shared by other investigators for more than half a century (see, for example, Hinkel and Summers[2]).

It was only in 1953 that Grundmann and Kreutzberger[3] again determined the molecular weight of the product described by Nef, and found, to their surprise, that it was a trimer of hydrocyanic acid, its molecular structure being that of symmetrical triazine (I):



(I)

Intensive research on the physicochemical properties of 1,3,5-triazine gave an immense amount of information, not yet fully systematised, which enables a fairly complete picture to be obtained of its molecular structure, which is of considerable theoretical importance.

Many derivatives of 1,3,5-triazine are of no less theoretical and practical interest. Thus melamine (2,4,6-triamino-1,3,5-triazine), cyanuric acid (2,4,6-trihydroxy--1,3,5-triazine), cyanuric chloride (2,4,6-trichloro-1,3,5--triazine), and several others have become of definite and

TABLE 1. Additional conventional notation for fractional bond orders (examples).

Type of bond	Bond order: graphical symbol	Bond order: numerical symbol
Weak bond	·····	$n=\frac{1}{\infty}$
Weaker than single	⌒	$n<1$
Single	—	$n=1$
Stronger than single	·····	$n>1$
Bond order $1\frac{1}{3}$	≡	$n=1\frac{1}{3}$
Weaker than $1\frac{1}{3}$	≡	$n<1\frac{1}{3}$
Stronger than $1\frac{1}{3}$	≡	$n>1\frac{1}{3}$
"Sesqui-bond" ($1\frac{1}{2}$)	=	$n=1\frac{1}{2}$
Weaker than $1\frac{1}{2}$	=	$n<1\frac{1}{2}$
Stronger than $1\frac{1}{2}$	=	$n>1\frac{1}{2}$
Double bond	=	$n=2$
Weaker than double	=	$n<2$
Stronger than double	=	$n>2$
Triple bond	≡	$n=3$
Weaker than triple	≡	$n<3$

continually increasing importance in the plastics, paper, paint, pharmaceutical, and several other industries. These compounds, discovered in the dawn of organic chemistry (melamine was discovered by Liebig[4] in 1831, cyanuric acid[5] in 1828), are now produced in quantities of many tons. The chemical properties of 1,3,5-triazine derivatives and associated technological problems are discussed in detail in several monographs and reviews[6,7].

The peculiar molecular structure of these substances makes them also of great theoretical interest. This aspect is hardly considered in the reviews which have been cited.

The present review discusses the molecular structure of 1,3,5-triazine and its derivatives in the light of work on the determination of interatomic distances and the investigation of vibrational and electronic spectra.

Since almost all the compounds under consideration contain fractional chemical bonds, the classical method of graphical representation of molecular structure is not always adequate. We shall therefore use a system of extra conventional symbols suggested by one of us[8]. This system is based on two principles: (1) division of the line representing the bond into a number of parts equal to the denominator of the fractional part of the bond multiplicity; and (2) the use of arcs to denote weakening or strengthening of the bond (in the former case the arc is convex towards the line denoting a σ-bond, while in the latter case it is convex in the opposite sense).

The most frequent cases of fractional bond multiplicity and their symbols are shown in Table 1. Plus and minus signs are used, as is customary, to denote partial positive and negative charges, and also a partial radical state. Weak partial charges are placed in circles, stronger partial charges in parentheses.

A detailed description and examples of the use of this additional conventional notation have been published previously[8]. The present review gives further examples of the usefulness of introducing a definite system of additional symbols, enabling a single structural formula to represent the detailed structure of molecules containing conjugated bonds (both with $\pi-\pi$ and with $n-\pi$ conjugation).

2. INTERATOMIC DISTANCES AND BOND MULTIPLICITY

Up to the present time, very few data have become available on interatomic distances in 1,3,5-triazine and its derivatives. Results obtained by individual investigators often vary among themselves by an amount exceeding the experimental error. In several cases data on interatomic distances are inconsistent with general theoretical ideas. Fresh, more reliable and more exact data are required.

Table 2 summarises published information on interatomic distances in these compounds. The most reliable and unambiguous values are those for melamine, cyanuric chloride, and cyanuric acid; the remaining data require critical examination.

The C–N interatomic distance in free 1,3,5-triazine (I) is of great theoretical significance, being the only example of the "sesqui-bond" [bond order 1.5 (Ed. of Translation)] $C_{sp^2}-N_{ps}$. Therefore the discrepancy in the experimental results[9,10], making it necessary to choose the "best" value on the basis of other considerations, is very unfortunate. Since the C–N distances in 1,3,5-triazine cannot be greater than the length of the corresponding bond in cyanuric chloride (II) and should be considerably less than the $C-N_r$ distance in melamine†, the results of Wheatley's X-ray measurements[9] must be accepted as the more likely to be correct. The mean length of the C–N "sesqui-bond" has been taken[17] as 1.325 Å.

The C–Cl distance in cyanuric chloride is almost equal to that in chlorobenzene[18] (1.69 ± 0.03). The decrease in the C–Cl distance compared with its value in alkyl chlorides[19] is considerably greater than the decrease due to the change in valency state of the carbon atom, which in this case (transition from sp^3 to sp^2 state) is estimated[20] at about 0.02 Å. The remainder of the decrease in interatomic distance must be ascribed to the interaction of the 1,3,5-triazine ring with the chlorine atom, as shown in the structural formula (II).

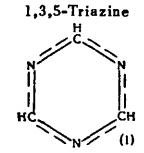
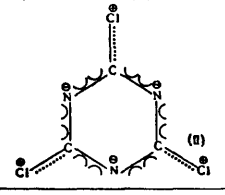
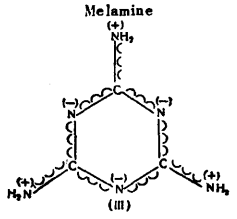
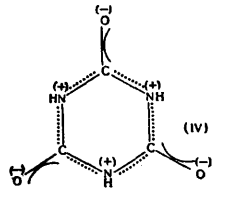
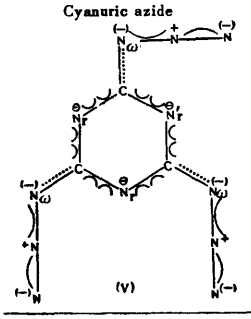
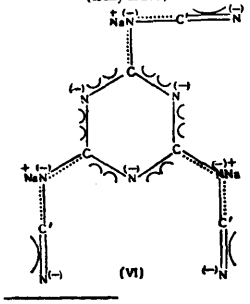
The length of the C–N bond in cyanuric chloride is very close to 1.5. The order‡ of this bond[17] is close to 1.43. On the hypothesis that the sum of the multiplicities of the bonds associated with a carbon atom is 4,[17,21] we can estimate the multiplicity of the C–Cl bonds in cyanuric chloride as close to 1.15.

Some explanations require that positive charges shall be written on the chlorine atoms. The physical significance of these symbols is that they indicate a decrease in the negative charge on the chlorine atom resulting from the electrical dissymmetry of the C–Cl bond caused by interaction of the ring π electrons with lone electron pairs on the chlorine atom.

† Here and subsequently, the subscript "r" indicates a cyclic nitrogen atom, and "ω" a nitrogen atom outside the ring.

‡ The term "bond order", or more precisely "bond multiplicity", will be applied to the number of pairs of electrons associated with a given bond[20].

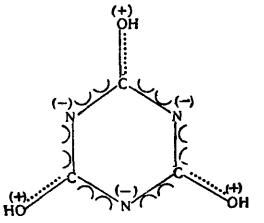
TABLE 2.

Compound	Bond length, r, Å	Bond order, n	Method of determination	Ref.
1,3,5-Triazine  (I)	$C-N_r$ 1.319±0.005 C—H 1.00	1.5	X-ray	9
	$C-N_r$ 1.338±0.001		rotational structure of Raman spectrum	10
Cyanuric chloride (2,4,6-trichloro-1,3,5-triazine)  (II)	$C-N_r$ 1.33±0.02	1.43	electron diffraction	11
Melamine  (III)	$C-N_r$ 1.33±0.01	1.35	ditto	11
	$C-N_\omega$ 1.37±0.03	1.25		
	$C-N_r$ 1.33—1.35	1.35	X-ray	22
	$C-N_\omega$ 1.35—1.36	1.30		
	N—H...N 3.00—3.10			
Cyanuric acid  (IV)	$C-N_r$ 1.36±0.06	1.23±0.15	ditto	15
	C—O 1.28±0.06	1.42±0.22		
	N—H....O 2.80			
	$C-N_r$ 1.36±0.02	1.29±0.07	»	13
	C—O 1.28±0.03	1.42±0.15		
	N—H....O 2.80			
Cyanuric azide  (V)	$C-N_\omega$ 1.38	1.22	»	14
	$C-N_r$ 1.38	1.22		
	$C-N_r$ 1.31	1.53		
	$N_\omega \diagdown\!\!\diagup {}^{+}N$ 1.26			
	$^{+}N-N$ 1.11			
Sodium tricyanomelaminate (trihydrate)  (VI)	$C-N_r$ 1.34—1.35	1.35—1.30	»	12
	$C-N_\omega$ 1.40	1.15		
	1.32	1.30		
	1.21	2.20		
	(1.34—1.35)*	(1.35—1.30)		
	1.36—1.33	1.30—1.40	calculated[21]	21
	(1.32)	(1.30)		
	1.17	2.70		

* Accepted values are in parentheses.

The interaction between π electrons of the triazine ring and the lone pairs on the nitrogen atoms in the melamine molecule is so strong that it leads to almost complete equalisation of the lengths and multiplicities of the C-N bonds. Only a slight difference in bond lengths, and especially the arrangement of the hydrogen atoms, enable us to assume that, in the crystalline state, melamine is in the amino-form. Published methods[23] for preparing the imino-form ("isomelamine") have been shown[22] to give the same amino-form as do all other methods for preparing melamine.

A notable feature of the structure of cyanuric acid is the absence of conjugated bonds in the 1,3,5-triazine ring and the presence of three carbonyl bonds (oxo-form). It is difficult to decide directly from the interatomic distances to what extent the structure of cyanuric acid is close to the oxo-form or to the hydroxy-form (VII), since in both cases intermediate values are observed for the bond lengths. Determination of bond multiplicities from the hybrid bond length/multiplicity curves shows that the observed interatomic distances correspond to formula (IV), not (VII). Thus the benzenoid structure with $\pi-\pi$ conjugation proved less advantageous than the structure having carbonyl bonds. This is explained[24] by the fact that the carbonyl bond is energetically more favourable than the multiple C–N bonds, while the loss in $\pi-\pi$ conjugation is to a considerable extent balanced by strong $n-\pi$ conjugation.



(VII)

The data on interatomic distances in cyanuric azide (V) probably contain an error: there are absolutely no reasons why the C–N distances in the ring should be different. The mean, 1.34–1.35 Å, of the distances given[14] is most probable, corresponding to a bond multiplicity of 1.35–1.30.

Among the interatomic distances in sodium tricyanomelaminate[12] those of $C-N_\omega$ and C...N (Table 2) are doubtful. Actually, calculation of the sums of the bond multiplicities gives 3.65–3.85 for the ring carbon atoms and 3.50 for the nitrile carbon atoms, instead of the expected 4. If the interatomic distances in the ring are regarded as correct, and the sum of the bond multiplicities given by the carbon atoms is taken as 4, the orders of the C–N and C≅N bonds are easily found to be 1.30–1.40 and 2.70 respectively. Hence from the hybrid bond relationship we obtain interatomic distances of 1.36–1.33 and 1.17 Å.

The general conclusion which follows from the data considered here is that the observed interatomic distances differ markedly from the lengths of "pure" single, double, and triple bonds. The difference can be measured by determining from the curve the multiplicity (order) of the given bond. In several cases it is possible, from the postulate that the aggregate multiplicity of the bonds emanating from a carbon atom is 4, to assess the correctness of the results obtained or to predict interatomic distances which have not yet been measured.

It is curious also that the 1,3,5-triazine ring, like the benzene ring, can act either as a donor or as an acceptor of electrons.

3. VIBRATIONAL SPECTRA

A great deal of information has now accumulated on the infra-red spectra of 1,3,5-triazine and its derivatives. However, owing to the experimental difficulties associated with the absence of suitable solvents and the impossibility of obtaining stable liquids, available data on the Raman spectra are confined to 1,3,5-triazine, cyanuric acid, and cyanuric chloride.

Table 3 shows the vibrational properties of 1,3 5-triazine molecules (symmetry D_{3h}).

Experimental results on the infra-red and Raman spectra of 1,3,5-triazine and its deuterated derivatives are given in several papers [26-28].

The frequencies were assigned on the basis of calculations using Urey–Bradley potential functions [29] and a valence-force model [30] (Table 4), the frequencies being numbered after Herzberg [31].

Two frequencies of class A_2' are forbidden in the spectrum of 1,3,5-triazine, and one E″ frequency is not observed because of its very low intensity; calculated values of these frequencies are given in Table 4. The class A_1' frequencies 1132 and 992 cm^{-1}, class E′ frequencies 1555, 1410, and 675 cm^{-1}, and the A_2'' frequency 735 cm^{-1}, which are characteristic and appear in the spectra of derivatives, are assigned to vibrations of the 1,3,5-triazine ring [28].

Table 5 traces the frequencies of these vibrations in the infra-red spectra of various 1,3,5-triazine derivatives having D_{3h} symmetry.

It is evident from Table 5 that all the characteristic frequencies persist in the spectra of the most varied derivatives. The A_2'' frequency falls roughly in conformity with increase in multiplicity of the C–N bonds in the ring.

Special interest attaches to investigations of the vibrational spectrum of cyanuric acid (IV), which first enabled the prolonged controversy about its molecular structure to be settled. The first investigation of the Raman spectra by Kahovec and Kohlrausch [32] showed that, in the solid state, cyanuric acid exists not in the hydroxy-form (VII), as many had supposed [33], but in the oxo-form (IV). This conclusion was subsequently confirmed by numerous investigations [15,34-38] of the infra-red spectra. The basis for such a conclusion was the intense absorption band with $\nu_{max} \simeq 1710$ cm^{-1}, which is clearly due to the characteristic vibration of the carbonyl group.

It is interesting that the carbonyl frequency in cyanuric acid is appreciably higher than in urea [39] (1686 cm^{-1}), although the interatomic distance and hence the multiplicity of the carbonyl bond are similar in these molecules ($r_{C=O}$ is 1.262 Å in urea [40] and 1.28 Å in cyanuric acid [14]). This may be due [37] to mechanical causes, such as strain in the ring.

An attempt at assigning frequencies in the vibrational spectrum of cyanuric acid was made by Newman and Badger [15], but their investigation cannot be accepted as complete or reliable, since the assignment of several frequencies is open to doubt.

The spectrum of cyanuric acid contains more than one absorption band within the range of N–H vibrations, which is probably consistent with the idea that more than one type of hydrogen bond is present [15,41]. The intensity and position of the NH-frequencies depend on the mode of preparation of the specimen (as a sublimed layer, a paste with a fluorinated oil, or a plate with KBr or NaCl). Padgett *et al.* [38] explained the observed variations by complex formation involving both an anion and a cation.

TABLE 3*.

Symmetry class	No. of vibrations	Symmetry of vibrations c_3	σ_x	σ_z	c_y	Activity of vibrations: Raman spectra RS**	IRS***	Character of vibrations
A_1'	3	s	s	s	s	p	ia	in plane
A_1''	0	s	as	as	s	v	ia	out of plane
A_2'	2	s	as	s	s	v	ia	in plane
A_2''	2	s	s	as	as	v	M_z	out of plane
E′	5	e	e	s	e	dp	$M_\perp$	in plane
E″	2	e	e	as	e	dp	ia	out of plane

* The symbols used in Table 3 are taken from Kohlrausch's book [25].

** Raman spectra.

*** Infra-red spectra.

TABLE 4.

Infra-red spectrum (gas) light	Infra-red spectrum (gas) heavy	Raman spectrum (liquid) light	Raman spectrum (liquid) heavy	Assigned to [30]
—	—	3042(10) *p*	2293	$\nu_1(A_1')$
—	—	1132(8) *p*	1077	$\nu_2(A_1')$
—	—	992(7) *p*	987	$\nu_3(A_1')$
—	—	1617.0 *	1586*	$\nu_4(A_2')$
—	—	1251 *	951*	$\nu_5(A_2')$
3056	2280	3042(10) *d*	2288	ν_6 (E′)
1556	1530	1555(3) *d*	1523	ν_7 (E′)
1410	1283	1410(2) *d*	1282	ν_8 (E′)
1174	931	1176(2) *d*	935	ν_9 (E′)
675	667	676(6) *d*	663	ν_{10} (E′)
737	577	—	—	$\nu_{11}(A_2'')$
830	861	—	—	$\nu_{12}(A_2'')$
—	—	1031*	846*	ν_{13} (E″)
—	—	340(4) *d*	309	ν_{14} (E″)

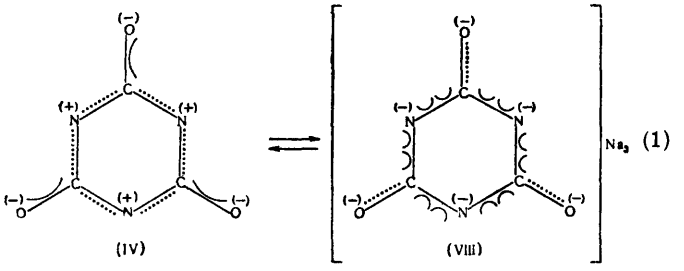
* Calculated results.

TABLE 5.

Compound	Symmetry of vibration E′	E′	A_2''	E′	Ref.
1,3,5-Triazine	1555	1410	735	675	26,30
Trideutero-1,3,5-triazine	1530	1284	667	577	30
Trimethyl-1,3,5-triazine	1560	1410	775	—	26
Triethyl-1,3,5-triazine	1560	1387	785	—	26
Cyanuric chloride	1510	1268	735	705	—
Trimethoxy-1,3,5-triazine	1565	1390	814	—	37
Melamine	1560	1434	813	730	46,37
Hexadeuteromelamine	1534	1211	810	—	46
Trisodium cyanurate	1530	1410	828	—	41

No investigations have been made of the vibrational spectra of cyanuric acid in solution, apart from Ito's work[42] on the Raman spectra. He explained the observed changes in the spectra of cyanuric acid in acid and in alkaline solutions by tautomeric changes, although examination of the electronic spectra shows that ions of the tautomeric forms are produced. The frequencies cited by Ito show poor agreement with those obtained from the spectra of the crystals.

Formation of a salt of cyanuric acid involves a redistribution of electron density[41,43,44] accompanied by an increase in multiplicity of the ring C–N bonds and a decrease in that of the C–O bonds. In other words, the structure of the salts corresponds to an ion of the hydroxy-form of cyanuric acid:



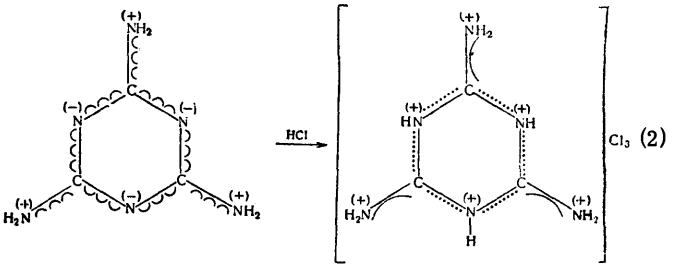
(IV) (VIII) (1)

In agreement with the above scheme (1), the carbonyl band has disappeared from the spectrum of the trisodium salt, and absorption bands characteristic of the 1,3,5-triazine ring (listed in Table 5) have appeared.

In addition to the spectra of the salts, the infra-red spectra of the "amides" of cyanuric acid have been well studied, the spectra of the "triamide", melamine (2,4,6--triamino-1,3,5-triazine)[34,37,45,46], in especial detail.

The infra-red spectrum of melamine contains four absorption bands in the region of the N–H vibrations: two narrow bands of higher frequency 3470 and 3425 cm^{-1}, and two broad bands of lower frequency 3335 and 3120 cm^{-1}. Finkel'shtein[37] assigned the first two bands to antisymmetric and symmetric vibrations of NH_2 groups forming a weak hydrogen bond, while the second pair were assigned to corresponding vibrations of NH_2 groups forming a strong hydrogen bond. Such an assignment explains the frequencies and the form of the absorption bands, and agrees with the view that two types of hydrogen bond are present in cyanuric acid. Jones and Orville-Thomas[46] have given a different assignment of the frequencies: the band at 3470 cm^{-1} was assigned to an antisymmetric vibration of the NH_2 group, the 3425 cm^{-1} band remained unassigned, the 3335 cm^{-1} band was assigned to a symmetric vibration of the NH_2 group, and the 3120 cm^{-1} band was interpreted as a combination band (NH_2 deformation vibration 1640 cm^{-1} plus C–N stretching vibration 1540 cm^{-1}). It can be objected to such an assignment that it is difficult to explain the difference in half-width between antisymmetric and symmetric vibrations of NH_2 groups, while the intensity of the 3120 cm^{-1} band is too great for a combination band. Although the final solution to this problem remains for the future, the observed absorption is linked in both papers with the presence of NH_2 groups of the amino-form of melamine. Such an explanation is consistent both with determinations of interatomic distances and with an examination of the rest of the vibrational spectrum of melamine, in which it is easy to identify all the characteristic bands of the triazine ring (see Table 5).

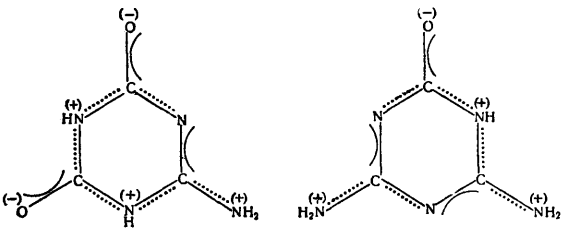
Examination of the infra-red spectra[43] and especially the electronic spectra of salts of melamine shows that salt formation is accompanied by a redistribution of electron density such that the multiplicity of the cyclic $C-N_r$ bonds is diminished, while that of the $C-N_\omega$ bonds outside the ring increases, as shown in the scheme (2).



(III) (IX) (2)

Thus melamine trihydrochloride can be regarded as a salt of the imino-form of melamine.

The infra-red spectra have been studied also of the other amides of cyanuric acid: ammelide — 2-amino-4,6--dihydroxy-1,3,5-triazine (X) — and ammeline — 2,4-diamino-6-hydroxy-1,3,5-triazine (XI)[37,47] (see Section 4). The presence of intense bands in the neighbourhood of 1700 cm^{-1} definitely indicates that these compounds have the oxo-structure in the crystalline state. The frequencies associated with the triazine ring fall slightly in the sequence: melamine, ammeline, ammelide. Salt formation takes place according to scheme (1) by reaction with alkalis, and according to scheme (2) by reaction with acids.



(X) (XI)

Among the halogenated derivatives, the vibrational spectra of the mono-, di-, and tri-chlorotriazines have been most fully studied[26,44,45,47–49]. All the spectra show quite distinctly the characteristic absorption bands of the 1,3,5--triazine ring, which are shown in Table 5 for the case of trichlorotriazine. The successive introduction of chlorine atoms greatly affects the band around 1450 cm^{-1}, and to a less extent the bands at 790 and 1560 cm^{-1}. The 847 cm^{-1} band observed in the spectra of the di- and tri-chlorinated derivatives is assigned to a vibration involving the chlorine atoms.

Among other derivatives of 1,3,5-triazine, the spectra have been studied of trimethoxytriazine[37,44], substituted melamines[45], and methoxy-derivatives of triazine[47].

The results obtained from the investigation of the vibrational spectra of 1,3,5-triazine derivatives agree well with data on the molecular structure from determinations of interatomic distances. Especially valuable results have been obtained for cyanuric acid, its amides, and its salts, which have enabled the structure of these molecules to be established for the first time.

4. ELECTRONIC SPECTRA

Investigation of the ultra-violet absorption spectra of 1,3,5-triazine derivatives started more than half a century ago with the work of Hartly[50], who was the first to obtain the spectrum of cyanuric acid in aqueous solution.

Attempts at a theoretical calculation of the delocalisation energy[51] and the electronic spectra[52-54] of 1,3,5-triazine were undertaken long before Grundmann and Kreutzberger identified this compound. Owing to imperfections in the theory and inadequate experimental data, such calculations were, of course, unable to give an accurate prediction of the electronic spectrum of the triazine. Only subsequent improvement in the theoretical equipment enabled an approach to be made to calculating the electronic spectrum of 1,3,5-triazine (Table 6).

As can be seen from Table 6, the origin of the first absorption band is not absolutely clear. Several authors assign it to the triplet $n \rightarrow \pi^*$ ($^1A_1' \rightarrow {}^3A_1'$) electronic transition, whereas other workers assign it to a $\pi \rightarrow \pi^*$ ($^1A_1' \rightarrow {}^1A_2''$) transition. The latter assignment maintains the analogy[60] with the spectrum of benzene, in which the only absorption band in the near ultra-violet range relates[61] to the electronic–vibrational transition $\pi \rightarrow \pi^*$ ($^1A_{1u} \rightarrow B_{2u}$).

The most detailed examination of the problem of assigning electronic transitions by Brinen and Goodman[62] showed that the $n \rightarrow \pi^*$ and $\pi \rightarrow \pi^*$ transitions should have similar energies, and probably constitute one absorption band.

Experimental investigation[63] showed the electronic spectrum of 1,3,5-triazine in the near ultra-violet to consist of two bands. The first of them has a sharp maximum at 272 mμ, while the second is located at the limit of sensitivity of quartz spectrophotometers (200–230 mμ), and was not detected in other work[64]. The same applies to the work of Paoloni[65], who detected a second short-wave band in the spectrum of trimethyl-1,3,5-triazine which is absent from the spectra of other alkyltriazines[66,67].

TABLE 6.

Lower excited level		Ref.
symmetry	λ, mμ*	
A_1''	256	54
$^3A_1'$	292	55
$^1A_2'$	234	56
$^1A_2'$	229	57
—	315	58
$^3A_1'$	337	59
Experimental results: origin of band	320	
maximum of band	272	

* For the sake of uniformity and clarity, values in this column have been converted by us from eV into mμ.

Thus only one band can be regarded as reliably established in the spectra of 1,3,5-triazine and its derivatives; the second short-wavelength band requires more careful investigation.

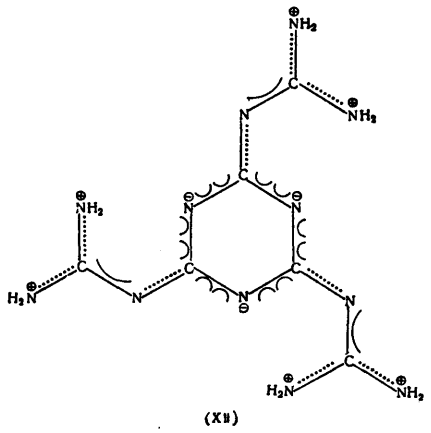
Data on the absorption of trisubstituted triazine derivatives having D_{3h} symmetry are collected in Table 7. A noteworthy feature is the regular shift in band I towards shorter wavelengths accompanied by a decrease in its intensity, roughly in conformity with the decrease in multiplicity of the cyclic C–N bonds (see Table 2). In the spectrum of melamine this band is already represented by a barely perceptible "shoulder" on the background of the intense band III. The existence of such absorption can also be explained by the presence of an ionic form. Band I is absent from the spectrum of cyanuric acid, in which the multiplicity of the bonds in the ring is a minimum. Such behaviour of band I supports its assignment to a $\pi \rightarrow \pi^*$ transition ($^1A_1' \rightarrow {}^1A_2'$). Dewar and Paoloni[71] reached a similar conclusion, after having made the first attempt at a quantum-mechanical calculation of melamine.

The presence of band II in the absorption spectra of 1,3,5-triazine derivatives requires to be verified and more closely specified, as mentioned above. At the present time, therefore, it is pointless to consider it in detail. Little can be said also about the most intense band III, since experimental data on this band are lacking for such fundamentally important compounds as 1,3,5-triazine and its alkyl derivatives.

TABLE 7.

1,3,5-Triazine derivative	Band I		Band II		Band III		Solvent	Ref.
	λ	ε	λ	ε	λ	ε		
Triazine	267	768	221	213	—	—	methanol	63
	268	791	221	137	—	—	acetonitrile	63
	272	881	222	146	—	—	cyclohexane	63
	272	890	—	—	—	—	isooctane	64
Calculated data	292							55
Trimethyltriazine	248	692	227	554	—	—	water	65
	256	795	227	476	—	—	methanol	65
	256	795	—	—	—	—	methanol	66
	264	701	227	289	—	—	cyclohexane	65
Triethyltriazine	259	696	—	—	—	—	methanol	66
Tributyltriazine	259	690	—	—	—	—	methanol	66
Trichlorotriazine	255	680	—	—	—	—	methanol	54
	256*	600	—	—	196.5	450000	water	68
Trimethoxytriazine	258	521	—	—	137	42 000	water	64
Tri(hydroxymethylamino)triazine	250	weak	—	—	213	50 000	water	54
Tris(dihydroxymethylamino)triazine	250	weak	—	—	213	50 000	water	54
Melamine	236	weak	—	—	208	51 000	water	68,69 70,71
Trisdimethylaminotriazine	232	weak	—	—	208	56 000	water	54
Trisdiethylaminotriazine	230	weak	—	—	210	55000	water	68
Cyanuric acid	absent		absent		<170	—	water	68

Where conjugation of the 1,3,5-triazine ring with C=N double bonds occurs, the sole example of which is provided by triguanidinotriazine (XII), a very intense absorption band[72] appears having λ_{max} = 261 mμ and $\epsilon_{max} \simeq 64000$.



(XII)

Triguanidinotriazine not only possesses a greater number of interacting π-electrons than 1,3,5-triazine, but also differs in symmetry, which may be reduced from C_{3h} as far as C_s depending on orientation. It is evidently advisable to regard triguanidinotriazine as a separate chromophore, since different selection rules operate here, and the electron transitions are different in character.

The same applies to the absorption spectra of derivatives of 1,3,5-triazine containing benzene[73-76] and naphthalene[77] rings, the spectra of which differ in character from those of derivatives of the original triazine.

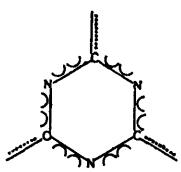
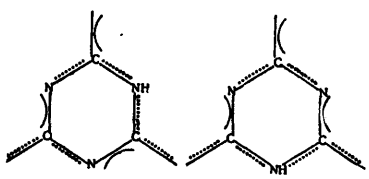
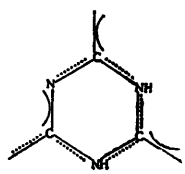
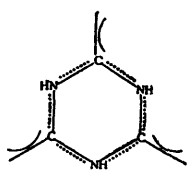
Changes in the shape of the electronic shell can have a great influence on the nature of the electronic spectrum as is shown by the examples of mono- and di-substituted 1,3,5-triazine[54] (Table 8).

Table 8 gives data on amino-substituted triazines in which the amino-group interact very strongly with the

TABLE 8.

1,3,5-Triazine derivative	Band I		Band II		Band III	
	λ	ε	λ	ε	λ	ε
2-Amino-	261	1960	220	16230	215	25 000
2-Amino-4,6-dichloro-	260	1990	224	15250	215	20 000
2,4-Diamino-	259	3620	absent		205	34 500
2,4-Diamino-6-methyl-	255	3435	absent		205	35 000
2,4,6-Triamino-	236	weak	absent		208	51 000

TABLE 9.

Diagram of molecule	Symmetry	Band	2,4,6-Triamino-1,3,5-triazine (melamine)		2,4-Diamino-6-hydroxy-1,3,5-triazine (ammeline)		2-Amino-4,6-dihydroxy-1,3,5-triazine (ammelide)		2,4,6-Trihydroxy-1,3,5-triazine (cyanuric acid)	
			λ	ε	λ	ε	λ	ε	λ	ε
	D_{3h}	I	236	very low	230	4700	230	7300	228	7500
		III	206	47 200	—	—	—	—	—	—
 a b	C_s, C_{2v}	I	236	10 100	228	7500	226	8500	222	7500
		II	210	35 000	202	22 000	198	21 000	198	16 000
		III	190	4000	170	40 000	185		—	—
	C_s	I	230	22 000	230	19 800	220	12 500	215	10 500
		III	—	—	196	45 000	180	38 000	182	35 300
	D_{3h}	III	weak absorption without maxima down to λ < 170 mμ							

1,3,5-triazine ring. Although the marked differences produced in the spectra on successive replacement of the hydrogen atoms of the triazine by amino-groups are quite clearly evident in Table 8, the lack of data on absorption in the vacuum ultra-violet range does not allow a complete picture to be obtained of the influence of amino-groups.

Considerably more complete information is available on the absorption spectra of cyanuric acid and its amides, ammeline (XI), ammelide (X), and melamine (III) (Table 9). The changes occurring in the absorption spectra of these compounds in acid and alkaline media were previously linked by several workers[69,70,78,79] with tautomeric changes of the lactam–lactim type. Later work[81,82] has shown, however, that ionisation takes place at the same time, so that the final result of the process is the ion of the corresponding tautomeric form.

Table 9 shows diagrams of the molecular structure of these molecules or ions omitting the charges and external atoms. Data on the absorption spectra of neutral molecules, the structures of which have been reliably established from their infra-red spectra[37,43], are given diagonally across Table 9, inside the rectangles formed by the heavy lines. The horizontal rows in the table correspond to successive replacement of amino- by hydroxy-groups (moving from the left to the right). The vertical columns correspond to successive increase in positive charge on the cations or a corresponding decrease in negative charge on the anions (moving down the table).

The data in Table 9 show a clear similarity in the spectra of ions and molecules over a whole horizontal series, indicating a similarity in molecular structure expressed by a diagram common to the whole series.

Hence it can be seen that the formation of positive ions is accompanied by the elimination of one double bond from the ring, whereas the formation of negative ions introduces an additional double bond into the ring. Thus the structure of the corresponding ion can be readily established from that of the neutral molecule.

It follows also from Table 9 that the character of the absorption of amino- and hydroxy-derivatives of 1,3,5-triazine is determined solely by the distribution of the electron cloud of the triazine ring. The presence of charges and differences in external functional groups somewhat distort the shape of the absorption curve, but the general character of the spectrum remains unchanged.

Similarity in absorption spectra can probably be traced in several other derivatives of 1,3,5-triazine. For example, there is a striking analogy between the spectra of monoamino-1,3,5-triazines (Table 8) and the second series in Table 9. Here, with the same general character of the spectra (three maxima), the difference consists solely in a shift in the wavelengths of the absorption maxima.

Apart from the electronic absorption spectra, increasing attention has been paid recently to research on the luminescence of 1,3,5-triazine[83,84] and its derivatives[85]. Further development of research in this field, as on other types of electronic spectra, undoubtedly promises to give much new information from which details of the electronic structure of these molecules can be assessed.

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Although problems of the molecular structure of 1,3,5-triazine and its derivatives, in particular of the most important of their amino- and hydroxy-derivatives, have now been solved in the sense of the relative arrangement of the atoms having been established, questions associated with the nature and the properties of the bonds which are formed remain open to a considerable extent. The information required for solving these problems too is now being rapidly collected. As far as spectroscopic investigations are concerned, this process is accelerated by their great practical value. Thus ultra-violet and infra-red spectra have already been employed for a long time for analytical purposes[80,86-90], directly for the solution of purely technological problems, and also for studying various physico-chemical properties (for example, ionisation constants and thermodynamic functions). New data are accumulated mainly by extending the range of substances studied. However, it is more important for the development of theoretical research to make exact investigations of a limited number of compounds having the simplest structure. The simplest representative of this class of compounds, 1,3,5-triazine itself, requires accurate determination of the ultra-violet spectra, including the vacuum ultra-violet, and study of the microwave spectrum in order to ascertain the exact interatomic distances.

The collection and extension of experimental data will undoubtedly require the development of theoretical methods and concepts, for which 1,3,5-triazine is almost as important as benzene has been in its time. The theoretical papers containing calculations on 1,3,5-triazine which are now appearing represent the first steps in the creation of a modern theory of molecular structure. All the effort which has been put into the study of the structure of its derivatives is justified by their great value in modern technology, which promises to contribute greatly to an understanding of the origins of the properties which they confer on plastics (incombustibility, heat-resistance, stability, etc.) and the possibility in due course of combining these properties.

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FLASH SPECTROSCOPY, A METHOD FOR INVESTIGATING RAPID PHOTOCHEMICAL REACTIONS

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1. INTRODUCTION

The mechanism of most chemical reactions involves the formation as intermediate products of free atoms, radicals, diradicals, and radical-ions, which determine the subsequent character of the reactions.

The method of flash spectroscopy, proposed by Norrish and Porter, has been used since 1949 to study rapid photochemical reactions effected by free radicals and also to investigate the primary intramolecular processes of excited molecules. Work on flash spectroscopy was reviewed in 1954 by one of us[1]. As new possibilities have been opened up for the method and a considerable amount of research has been published since then, it has appeared necessary to prepare a fresh survey.

Let us describe briefly the principle of the method of flash spectroscopy. Reaction is initiated by a momentary high-intensity discharge in a flash lamp. The changes occurring in the illuminated system are studied by means of the absorption spectra in the ultra-violet, visible, and near infra-red regions, the spectra being recorded photoelectrically or photographically (each method has its advantages).

The absorption spectra are photographed by using a second, less powerful lamp, which is triggered at a certain time, determined by a timer, after discharge of the first, powerful flash lamp (see Fig.1). The photographic method is convenient in preliminary investigations when the whole spectral range is recorded, and also in the simultaneous measurement of relative intensities at different wavelengths. Furthermore, the lifetimes of the reaction intermediates are determined from a series of spectra obtained at different times after discharge of the main lamp. However, it is less convenient in kinetic investigations, where the photoelectric method is especially useful.

The photoelectric method, unfortunately, allows measurements to be made only over a very narrow range of wavelengths. Usually, both methods are employed for recording spectral changes.

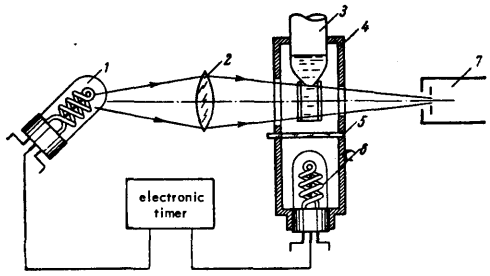

Fig.1. Optical arrangement for spectrosopic measurements with two flash lamps: 1) ISS-250; 2) condenser; 3) cell; 4) jacket; 5) ZhS-18 light filter; 6) ISS-250; 7) spectrograph.

Several arrangements have been suggested for the photographic recording of a spectrum using only one lamp[2] (see Fig.2); in several cases the reaction vessel and the flash lamp are combined as a single unit[3,4].

Lamps of varying power are used depending on the nature of the investigations. The lamps are designed on the general principle that a quartz tube into which are sealed electrodes (usually of tungsten) is filled with an inert gas (argon, krypton, xenon). The flash produced by the discharge of high-voltage condensers gives a high-intensity light flux with a flash of duration 10^{-4} sec or less. Recently Brody and Rabinowitch[5] have produced a lamp in which the flash duration is of the order of 10^{-9} sec. Information on the types of flash lamps manufactured in the Soviet Union is given by Marshak[6].

By means of flash lamps a light flux can be obtained having an energy of the order of 10^6 W sec, corresponding to a flux of 10^{23} quanta per flash. In this way large changes are produced photochemically, and thereby one of the main difficulties in photochemical investigations is overcome.

The method of flash photolysis can give very high concentrations of free atoms and radicals, as a result of which it becomes possible to investigate their reactions in many chemical systems. Reactions lasting for 1–3 μsec can be studied in this way.

In spite of the broad possibilities of flash spectroscopy in the ultra-violet, visible, and near infra-red regions of the spectrum for the identification of free atoms, radicals,

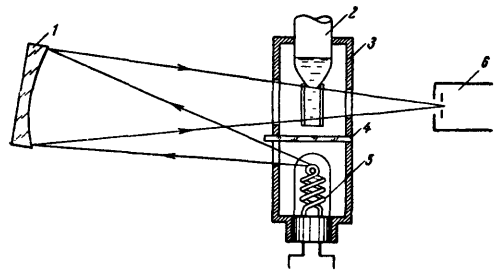

Fig.2. Optical arrangement for spectroscopic measurements with one flash lamp: 1) mirror; 2) cell; 3) jacket; 4) ZhS-18 light filter; 5) ISS-250; 6) spectrograph.

and diradicals in a reaction mixture, this method has substantial limitations. It is quite difficult to determine several reaction intermediates because their absorption spectra are in the far ultra-violet or because they have no specific absorption for comparison with other compounds. In several cases, moreover, it is difficult to obtain direct information on many changes occurring in the molecule under the influence of light. For this purpose it would be useful to examine the infra-red region of the spectrum. However, scanning is very slow in present-day infra-red spectrometers, and it is probably for this reason that they have not been used in flash photochemistry. They will no doubt be employed in the future, when the rate of scanning has been increased.

A recently described method for investigating short-lived ions, radical-ions, and electrons produced in flash photolysis using an electric field is worth considering. The formation of a short-lived triphenylamine radical-ion in hexane has been demonstrated in this way[7,8]. Concentration of ions as low as 10^{-7} M with lives as short as 10^{-13} sec can be detected by this method[8].

A mass-spectroscopic method, by which the spectra of substances can be determined every 50 μsec[9], has also been successfully employed to analyse the intermediate products formed in flash photolysis. With keten, CH_2CO, for example, this method has shown that the CH_2 formed by photolysis reacts with the initial CH_2CO with a very high probability. The reaction product C_3H_4O exists for several hundred microseconds.

Photochemical flash initiation of reactions is very convenient because the photochemical system can be exposed to light of definite wavelength, and thereby only a definite molecule or even part of it can be excited, which greatly facilitates the theoretical interpretation of the results. Use of sensitisers enables photochemically inactive systems to be excited, so that the range of application of photochemistry is extended. Photochemical initiation has advantages over the use of sources of ionising radiation, with which it is difficult to effect selective absorption of the incident energy by definite components of the system. Further, ionising radiation, without giving any appreciable advantage in the concentration of the free radicals formed, produces a large variety of excited molecules and atoms, as well as ions, which greatly complicate the process under investigation. Furthermore, the solvent cannot remain inert in the radiation method of initiation. This is not generally the case with flash photolysis.

Successful study of processes involving interaction between radiation and matter requires the use of both radiation-chemical and flash-photolytic initiation as complementary methods. This enables a bridge to be built between two allied branches of chemistry, photochemistry and radiation chemistry.

Since flash spectroscopy is at the same time a method of initiating and of recording free radicals and excited molecules, it has enabled a successful start to be made on investigating the rapid processes described below, which determine the kinetics of most chemical reactions.

2. IDENTIFICATION AND REACTIONS OF FREE RADICALS

Flash photolysis was first applied to the photochemical breakdown of simple or more complicated substances in the gaseous state, in the first instance of the halogens: chlorine[10-12], iodine[13-16], and bromine[13-17]. It was possible by absorption spectroscopy to follow the formation of the free atoms and their subsequent recombination. The reaction of chlorine atoms with oxygen was studied, a new radical ClO being formed, the absorption spectrum of which was later obtained in the photolysis of ClO_2.[18]

The absorption spectra of radicals were obtained in a similar manner by the flash photolysis of the compounds listed in Table 1.

The life of the resulting free atoms and radicals varies between quite wide limits, from fractions of a millisecond to several minutes, *i.e.* it depends on their nature. For example, the radical ClO has a life of 4×10^{-3} sec, while that of the CS radical is 2 min. The reactions of excited oxygen atoms and molecules, obtained in the flash photolysis of ozone, have also been studied[32].

However, in the photochemical flash decomposition of several organic compounds, such as keten[33], acetaldehyde[34,35], biacetyl[34], acetone[34,36,37], diethyl ketone[38], methyl iodide[39], azomethane[40], tetraethyllead[41], and benzene[4,42], a steady-state concentration of radicals could not be obtained, owing to the formation of stable end-products of the photochemical reactions by the occurrence of secondary reactions between the initially formed radicals at high concentrations of the latter.

Although the early work on flash photolysis was carried out with gases, as already noted, at the present time most effort is devoted to the photolysis of liquid systems. This is partly because a large amount of energy is evolved during photolysis, being the excess energy of the photodecomposition products and also the energy evolved on recombination of the atoms and radicals. The energy which

TABLE 1. Radicals formed in flash photolysis.

Substance	Radicals found from absorption spectra	References
CS_2	CS, S_2	10, 11, and 12
NH_3	NH_2* and NH	3, 19, 20, 21, 22
N_2H_4	NH_2 and NH	22, 23
HN_3	NH_2, NH, and N_2	24
PH_3	PH_2, PH, and P_2	3, 22, 25
NOCl	NO	26
B_2H_6	BH	3, 22
SiH_4	SiH	3, 22
HCN	CH, C_2, and CN*	3, 22
CH_3CN	CH, C_2, and CN	3, 22
S_2Cl_2	S_2, SCl	27
H_2O	OH	3, 22
H_2S	SH	19, 20
D_2S	SD	19, 20
C_6H_6	CH, C_2, and C_3	3, 22
CH_3CHO	HCO	22, 28, 29
CH_3CDO	DCO	28, 29
$C_6H_5CH_3$		
$C_6H_5CH_2NH_2$	$C_6H_5CH_2$	30
$C_6H_5CH_2OH$		

* In subsequent investigations the absorption spectra of the radicals NH_2 and CN were obtained in low intensity, under conditions of continuous illumination but with a long absorption path[31].

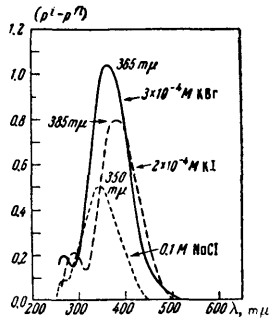

Fig. 3. Absorption spectra of dihalogen ions produced by flash illumination of aqueous solutions of NaCl, KI, and KBr at pH 6.0: 1) Cl_2^-; 2) I_2^-; 3) Br_2^-.

is liberated may produce substantial changes in the course of the reaction, and it is extremely difficult to establish the nature of the effect.

To eliminate the thermal effect in gaseous systems, a considerable amount of an inert gas is usually introduced (partial pressure of gas up to 1 atm). Thus in an investigation by the flash method of the rate of recombination of iodine atoms[15,16] the calculated rise in temperature after introduction of the inert gas was ~1°, although the percentage decomposition into atoms was ~50%: *i.e.* the effect of temperature gradient could be neglected. However, introduction of a foreign gas may cause additional phenomena affecting the course of the reaction, and associated mainly with energy-transfer processes.

In liquid systems, owing to their great heat capacity, the temperature rise during photolysis seldom exceeds a fraction of a degree, which is insignificant.

Intensity measurements on the absorption bands can be used to determine the relative concentrations of the radicals, and from these the rate constants of the reactions in which they take part can be calculated. As an example, photolysis of aqueous solutions of NaCl, KBr, and KI involved the intermediate formation of the dihalide ions, *i.e.* Cl_2^-, Br_2^-, and I_2^- respectively[43] (their spectra are shown in Fig. 3).

The flash photolysis of potassium iodide solutions has been investigated in greater detail. The I_2^- ions are formed by the reaction

$$I + I^- \underset{k_1'}{\overset{k_1}{\rightleftharpoons}} I_2^- \qquad (1)$$

and are removed by the following bimolecular reactions

$$2I \xrightarrow{k_2} I_2, \qquad (2)$$

$$I + I_2^- \xrightarrow{k_3} I_3^-, \qquad (3)$$

$$2I_2^- \xrightarrow{k_4} I_3^- + I^-. \qquad (4)$$

Breakdown of the I_2^- ion was found to be kinetically second order, being greatly dependent on the concentration of I^- ions. Analysis of the results showed which of the reactions (1) or (4) was responsible for the breakdown of the I_2^- ion. The constant of reaction (4) was found to have the maximum value: $K_4 = 2k_4 = (7.7 \pm 1.5) \times 10^9$ mole^{-1} sec^{-1}, whereas the minimum value $K_1 = k_1/k_1' = 1.2 \times 10^4$.

High-intensity flash illumination of some solutions results in the appearance of intermediate products having variable life times. In solutions of bromine and iodine in carbon tetrachloride and hexane, for example, absorption appears in the range 280–330 mμ, lasting for 70 μsec or less[43]. In aqueous $KBrO_3$ solutions, after the flash, absorption is observed in the range 350–390 mμ, which is due to the radical $BrO_3\cdot$ (~10 μsec), while absorption in the neighbourhood of 460 mμ is due to a $BrO\cdot$ radical (duration of existence 1 μsec)[44,45]. A long-lived intermediate was also observed in the photodecompositionn of oxalato-complexes of iron, cobalt, and uranyl[46]. Aqueous solutions of aromatic hydroxy-compounds show a short-lived (15 μsec) shift in the electrolytic dissociation equilibrium

$$R\cdot OH + H_2O \overset{h\nu}{\rightleftharpoons} RO^{-*} + H_3O^+.\ ^{42}$$

When in the ground state the resulting ion RO^- recombines with the H_3O^+ ion to form the original compounds.

3. STUDY OF THE TRIPLET STATE

Under certain conditions dyes and aromatic compounds show, in addition to fluorescence, a prolonged afterglow or phosphorescence, which can sometimes continue for several seconds. This phenomenon is well developed when the molecules are trapped in various organic and inorganic matrices or even when they are attached to the surface of adsorbents, and especially at low temperatures.

It follows from the occurrence of phosphorescence that the molecules of the dyes and aromatic compounds contain, in addition to an excited state (with the normally short life of 10^{-8}–10^{-9} sec), an intermediate long-lived metastable state (lying below the excited level), into which the molecule can pass from the excited state[48].

Terenin advanced and justified the view[49] that the metastable electronic state is a triplet–diradical (bivalent) state having two unpaired electrons differing from the singlet excited and ground state, in which all the electrons are paired.

The important role of the triplet state of molecules in the occurrence of many photochemical reactions is now generally recognised, especially in photooxidation and photoreduction processes, but up till now the triplet state has not been taken into account in considering thermal reactions, although this state can become populated at low temperatures. The transition of several substances to a triplet state is favoured by illumination with a high-intensity flash.

Thus the spectra of solutions of aromatic compounds freed from oxygen show a diminution of the singlet state and the appearance of new absorption bands. These disappear about 10^{-2}–10^{-5} sec after the termination of photolysis, the absorption due to the singlet state regaining its original value[50]. The new absorption bands are due to molecules in a triplet state, the transition to which is effected by the flash illumination; the probability of the transition is independent of the nature of the solvent or its viscosity.

Fig. 4 shows the absorption spectra of anthracene before and after the flash. Table 2 gives the frequencies of the triplet spectra of several organic compounds.

The quenching of molecules in the triplet state does not occur exactly according to a first-order law, which indicates that quenching can take place by collision between two molecules in this state[50,51]. The mechanism of quenching is a radiationless transition of the molecule from the triplet state to the upper vibrational levels of the singlet ground state Within certain limits transition is independent of the concentration of the substance (with anthracene between 2×10^{-6} and 10^{-3} M), but it diminishes with increase in viscosity of the solvent. Experimental data indicate that the probability of the transition to the triplet state may exceed that of the transition from the triplet to the singlet ground state by a factor of 10^4. This phenomenon has not yet received a theoretical explanation.

Anthracene molecules in the triplet state are quenched considerably more strongly in the presence of oxygen or nitric oxide. The effect of paramagnetic ions on triplet naphthalene molecules in ethylene glycol has also been investigated[51]. The ions Cu^{2+}, Ni^{2+}, Co^{2+}, and Mn^{2+} have a strong quenching effect. The diamagnetic ions Zn^{2+} and Ca^{2+}, as also the paramagnetic ions Ce^{3+}, Nd^{3+}, and Gd^{3+}, do not have an appreciable quenching effect[51].

By means of the flash technique[52] a triplet diradical state has been observed also in the vapours of aromatic compounds. The probability of the transition from the excited singlet to the triplet state was found to be independent, within wide limits, of the pressure of the inert gas, and to vary little with different states of aggregation, its value for aromatic compounds being of the order of 10^6–10^9 sec^{-1}. The probability of a transition from the triplet state to the singlet ground state also depends little on the pressure of the inert gas, but is greatly dependent on the state of aggregation. In the vapour phase this probability is of the order of 10^4–10^5 sec^{-1}, whereas for most aromatic molecules in a solid medium it ranges from 10^3 to 10^{-1} sec^{-1}.

During the flash photolysis of the vapours of such aromatic compounds as toluene, ethylbenzene, benzyl chloride, benzylamine, benzyl alcohol, etc., identical electronic absorption spectra, due to the free benzyl radical, are observed[53]. Benzyl radicals and also radicals obtained from other compounds have a life which is shorter than 10^{-4} sec, indicating a high efficiency of recombination.

TABLE 2. Band maxima of triplet–triplet absorption.

Compound	In hexane[50], cm^{-1}	In liquid paraffin[50], cm^{-1}	In vapour (CO_2 gas)[52]	
			temp., °C	cm^{-1}
Naphthalene	24 210 25 640 27 210	(1) 24 100 25 550 26 880 (2) 38 500	50	25 180 26 550 27 930 29 340 30 900
1-Methyl-naphthalene	23 700 25 130	23 700 25 060 26 320	40	24 720 26 410
Anthracene	23 790 25 130	(1) 21 370 (2) 23 580 24 940 (3) 35 700	120	24 810 26 230
Phenanthrene	(1) 19 230 19 670 (2) 20 790 22 060 23 500	—	200	21 880 23 250 24 590
Naphthalene	from 20 400 to 25 000	(1) 21 000 (2) 21 740 23 320 25 000 (3) 31 900 (4) 35 030	160	23 630 24 900
1,2-Benzanthracene	20 620 22 200 23 260	(1) 18 520 (2) 20 620 21 690 23 010 24 100 (3) 31 750	200	broad band from 21 740 with maximum at 22 120
Pyrene	24 330 25 840 27 100	(1) 19 250 20 700 (2) 24 040 25 220 26 910 (3) 27 780	100	25 350
Fluorene	broad band from 25 000 to 29 400	—	95	20 410 broad band from 26 300 to 31 250 with maxima at 28 360 and 30 230
Triphenylene	(1) 23 360 24 750 (2) 28 900	—	200	24 390

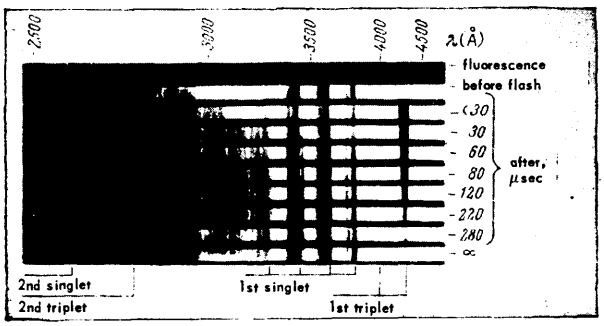

Fig. 4. Series of absorption spectra of triplet state of anthracene in hexane.

The formation of these radicals is due to the weak bond in the side-chain and their relatively high stability. Subsequently, these and other radicals were obtained by the continuous illumination of frozen solutions at a low light intensity, when their survival time reached many hours[54].

Transitions to the triplet state and the formation of radicals have been detected by a similar spectroscopic method in solutions of albumin, ovalbumin, amino-acids, and phenol[55–57], rhodopsin[58], and also quinones (benzoquinone, acetophenone, derivatives of anthraquinone), acridine, and other compounds[59–62].

Solutions of derivatives of anthraquinone and acridine showed momentary selective fading of their main absorption band under the influence of flash illumination[60]. These compounds were subject to reversible decolorisation which show delayed fluorescence in the adsorbed state, indicating the presence of a nearby triplet level. These compounds also sensitise the photooxidation of organic compounds[60].

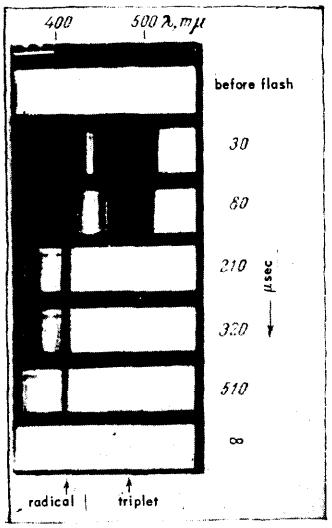

Fig. 5. Absorption spectra of triplet state and radical of duroquinone.

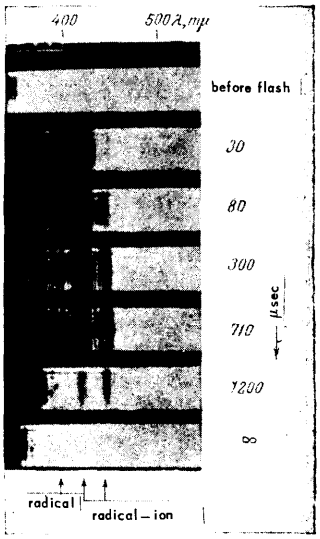

Fig. 6. Absorption spectra of radical and radical–ion of durosemiquinone (in ethyl alcohol).

The momentary reversible fading of several anthraquinone and acridine derivatives under the influence of a high-intensity flash is explained by the accumulation of excited molecules in the triplet diradical state.

This postulate was confirmed for the sensitisers of anthraquinone derivatives, duroquinone and benzophenone, which exhibit strong absorption by intermediate forms (triplet state and radical–ions)[61,63,64]. Thus with duroquinone the semiquinone radical and, under special conditions, the semiquinone radical–ion were detected[61] together with the triplet form (see Figs. 5 and 6). Flash spectroscopy has also established that it is an $n \rightarrow \pi^*$ transition, not $\pi \rightarrow \pi^*$, which is photochemically active in sensitised reactions[62].

Temporary and reversible fading in the main absorption band is observed also when solutions of Methylene Blue or thionine in sulphuric acid are exposed to a flash source, with the appearance of strong absorption in the range 360–440 mμ, which disappears after less than 30 μsec. This absorption is ascribed to the triplet state of the dye. Under different conditions of illumination (shorter ultra-violet rays) another intermediate product, the semiquinone radical of the dye[65], is formed. The appearance of two absorption bands after flash illumination has been observed also with eosin solutions; these last for different times, and are due to the dye in a triplet state and to the semiquinone radical of the dye[66]. A triplet form appears in fluorescein solutions after exposure to a flash, and as it decays radicals appear (bearing positive and negative charges)[67]. With thin films of solid organic dyes, for example, Crystal Violet, eosin, Rhodamine B, Methylene Blue, and erythrosin, momentary fading was observed, on exposure to high-intensity flashes, under vacuum conditions both at +20° and on cooling with liquid air[60,68]. With thin films of Crystal Violet, trypaflavine, and Rhodamine B, the life of the decolorised form of the dye was found to be $(0.8–1.0) \times 10^{-3}$ sec, while with Methylene Blue and eosin it was $(1–1.5) \times 10^{-3}$ sec (at -180°).

4. INVESTIGATION OF EXPLOSIVE REACTIONS

The flash technique has been successfully employed to investigate the explosive oxidation of hydrogen and several hydrocarbons with oxygen. It has proved possible not only to obtain the absorption spectra of the reaction intermediates (free radicals and atoms) but also to measure their relative concentration throughout the reaction. Several complicated radicals, which do not emit light and hence are not detected in the flame emission spectra, were observed from the absorption spectra. Moreover, it is difficult from the emission spectra of the radicals and atoms to follow rapid changes in their concentrations, and hence to analyse the whole course of the combustion. The flash technique enables the mechanism of burning to be established with sufficient precision.

In order to study the process of combustion by the flash technique, however, simultaneous initiation of the reaction (ignition) throughout the reaction vessel is necessary. This is achieved by adding a photosensitiser, which under the influence of the high-intensity flash breaks down into free radicals and atoms, and these initiate the chain reaction. If, however, a reactant in the explosive reaction forms free radicals and atoms on absorption of light from the flash lamp, there is no need for a sensitiser. In the explosive oxidations of hydrogen and hydrocarbons with oxygen, the sensitiser used is nitrogen dioxide (at a pressure of 0.75 mm), which is half-decomposed by the flash, and has almost completely disappeared after 0.8×10^{-3} sec.

The mechanism of the photolysis of nitrogen dioxide is as follows:

$$NO_2 + h\nu \rightarrow NO + O.$$

The following secondary reaction is also possible:

$$O + NO_2 \rightarrow NO + O_2.$$

It is assumed that, since N_2O and O_2 are formed

in equivalent quantities, reaction takes place also between "hot" NO* molecules and the initial NO_2:[9]

$$NO_2 + NO^* \rightarrow N_2O + O_2.$$

The absorption spectra of the radicals OH and NO are observed[69] in the reaction between hydrogen and oxygen sensitised with nitrogen dioxide. The most interesting is the OH radical, the intensity of whose spectrum is high immediately after the flash, then falls rapidly. The relative concentration of OH radicals was found to diminish with increase in the pressure of hydrogen. In the presence of nitrogen as inert gas, the concentration increases insignificantly, but the survival time of the OH radicals becomes much longer. Excess of oxygen has a similar effect to nitrogen.

Formation of OH radicals in this reaction takes place immediately after the photochemical decomposition of the nitrogen dioxide:

$$O + H_2 \rightarrow OH + H.$$

In the presence of excess of hydrogen there is a rapid decrease in the number of OH radicals:

$$OH + H_2 \rightarrow H_2O + H;$$

but in the absence of hydrogen:

$$OH + OH \rightarrow H_2O_2 \text{ or } OH + OH \rightarrow H_2 + O_2.$$

Formation of the HO_2 radical was not detected spectroscopically in these experiments, probably because this radical cannot exist for a long time in the presence of hydrogen, with which it reacts:

$$HO_2 + H_2 \rightarrow H_2O_2 + H;$$

and perhaps also because it has no characteristic spectrum in the range studied.

In the explosive oxidation of acetylene[70], ethylene[71,72], ethane, and methane[71] with oxygen sensitised by nitrogen dioxide, the absorption spectra of a series of radicals: OH, CH, C_2, C_3, CN, and NH, were obtained with all the hydrocarbons. Quantitative measurements of the absorption spectra of these radicals were obtained only in different stoichiometric mixtures, which is quite understandable.

From the variations in the relative concentrations of different radicals, *i.e.* their formation and disappearance throughout the reaction as a function of the pressure of the reactants and the time, it was possible to establish exactly the kinetics of the explosive oxidations. As example we can cite the kinetics of the explosive photochemical reaction of acetylene with oxygen (see Figs. 7 and 8), which takes place in the following stages: (1) an induction period lasting from 0 to 3×10^{-3} sec, at the end of which OH radicals begin to appear; (2) a period in which diatomic radicals, OH, CH, and C_2, are formed (in the presence of nitrogen dioxide the radicals CN and NH are also produced), of duration $\sim 10^{-4}$ sec; (3) a period of reaction between hydrogen and oxygen with the formation of the OH radical and the disappearance of all the remaining intermediate radicals, lasting for $\sim 10^{-4}$ sec; (4) a period of slow reaction of the atoms and radicals remaining from periods (2) and (3), with formation of the final reaction products. The most important reactions are those of the OH radical with hydrogen and with carbon monoxide.

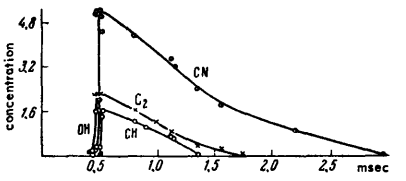

Fig. 7. Concentrations of various radicals as a function of time at pressures of 10 mm O_2 + + 13 mm C_2H_2 + 1.5 mm NO_2.

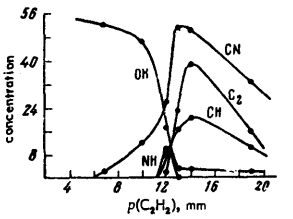

Fig. 8. Maximum concentrations of radicals as a function of the pressure of acetylene. Oxygen pressure 10 mm, NO_2 pressure 1.5 mm.

All explosive reactions involving the oxidation of hydrocarbons are fundamentally homogeneous as a result of the simultaneous initiation of reaction (ignition) throughout the space, which is produced by the sensitiser radicals. However, the formation of a large number of diatomic radicals during the reaction is accompanied by intense emission of light lasting several microseconds, due to the formation of shock waves passing through the reactant gases and causing detonations in the vessel. Addition of tetraethyllead to the reaction mixture was found to lengthen the induction period and almost completely to destroy the strong emission. Tetraethyllead promotes the homogeneity of explosive oxidations in a gaseous medium[73,74] by reacting with the oxidised intermediate products and forming lead oxide. This diminishes the source of spontaneous ignition causing detonation in the second period. Furthermore, the lead oxide terminates chain reactions leading to explosion.

Subsequently a study was made of the explosive combustion of hydrogen sulphide, which is effected in the absence of a sensitiser. The absorption spectra of the radicals SH and OH were obtained in the initial stage of the reaction, these then forming the final reaction products H_2O and SO_2. A strong emission of wavelength $\lambda > 2000$ Å was noted in this reaction, this being ascribed to an excited sulphur dioxide molecule[75].

Similar experiments, using very brief high-intensity flashes (15 μsec or less[42]), were made on the combustion of benzene, propane, and acetaldehyde.

Investigations have also been made on the oxidation of phosphine and methyl iodide by oxygen[76,77], and also of ammonia, hydrogen, hydrogen chloride, methane, and water by ozone[78].

It was mentioned earlier that the flash illumination of endothermic reaction systems ($H_2 + O_2$, etc.) causes explosions. This proved to be true also of many other endothermic substances [79], as, for example, nitrogen iodide, which decomposes under the influence of a flash of light as follows:

$$NH_3 + NI_3 \xrightarrow{h\nu} N_2 + 3HI,$$

$$3HI + 3NH_3NI_3 \rightarrow 2NH_4I + 1.5N_2 + 4.5I_2.$$

Several nitrides, carbides, azides, perchlorates, and other compounds are decomposed explosively by flashes of light. In the case of very thin layers of silver nitride only impressions can be obtained since the light produces photochemical action only where it is incident, which cannot extent to other parts of the layer.

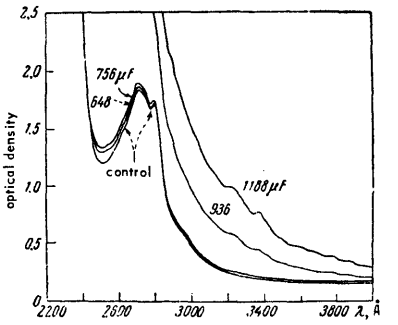

Fig. 9. Effect of energy of flash on pyrolysis of mineral oil. Absorption spectra of oil samples after exposure to flashes of various energies (648, 756, 936, and 1188 μF at 4 kV).

5. HETEROGENEOUS FLASH INITIATION OF THERMAL REACTIONS

In the investigation of thermal reactions, a considerable rise in temperature of the system is often required for a brief period. However, it is quite difficult to achieve this. The action of an intense flash of light on a transparent gaseous, liquid, or solid thermal conductor containing finely dispersed opaque solid particles (carbon, metals) produces a marked rise in temperature of the sytem. After a flash of a few milliseconds, for example, finely divided tungsten powder was observed to vaporise explosively in a vacuum. This indicates that the temperature in the illuminated system was of the order of several thousand degrees. Carbonisation, explosion, vaporisation, fusion, pyrolysis, and other thermal processes can be initiated in a similar manner. Extremely interesting results have been obtained by the flash initiation of thermal reactions. For example, gaseous methane and tungsten (25 mm of wire, dia. 7.5 μ) were exposed to the flash from a lamp of energy 25 J. Deposition of carbon was observed, as well as the formation of H_2, C_2H_6, C_2H_4, and C_2H_2. A control sample (without the wire) underwent no change. Calculation of the quantity of hydrogen formed showed that 400 volumes of methane decomposed per unit volume of the wire. Since methane does not absorb in the near ultra-violet or the visible region, the reaction investigated was a typical example of heterogeneous sensitisation. Experiments with non-absorbing systems (CH_4–O_2, H_2–O_2) were analogous, irradiation resulting in explosions. Initiation of the pyrolysis of mineral oil containing molybdenum (particle diameter < 74 μ) or carbon (particle diameter < 36 μ, 0.03% by weight) by a flash of 7500 J gave the oil a jet-black colour (formation of carbon of particle diameter ~100 Å), and on exposure to a mercury lamp (3661 Å) the oil showed a light blue fluorescence. Examination of the dependence of the pyrolysis of oils on the flash energy showed the presence of a threshold energy (see Fig. 9).

The heterogeneous flash initiation of a reaction has been used also to diminish the period of exposure in studying the photodegradation polymers [80]. On the illumination of a polyethylene film into which had been introduced a tungsten wire (130 μ), pyrolysis of the polymer was observed, the number of molecules of gas evolved per gramme of polymer being proportional to the square root of the number of flashes. It is interesting that pyrolysis does not occur in the vicinity of fluorescent impurities accidentally present in the polymer.

In heterogeneous photolysis the energy of the whole spectrum of the lamp can be utilised for the excitation. This allows systems which absorb little if at all to be initiated and hence intermediate compounds can be studied which are not found in photochemical reactions. A disadvantage of the method is the formation of a very reactive surface, which complicates interpretation of the results and comparison with processes of homogeneous sensitisation.

6. INVESTIGATION OF THE PHOTOREACTIONS OF CHLOROPHYLL

Application of the flash technique, with photographic and spectrophotometric recording of the spectra, to the study of the primary photoreactions of chlorophyll has enabled their detailed mechanism to be revealed. Spectroscopic measurements have been carried out in the near ultra-violet and the visible regions of the spectrum. The main absorption bands of chlorophyll (660–645 mμ and 460–470 mμ) were found to be momentarily and reversibly decolorised in solutions free from oxygen (in ethanol, methanol, acetone, benzene, pyridine, and other solvents) by powerful flashes of light [60,68,81–88]. The lifetime of the decolorised form is 1.5×10^{-4} sec with chlorophyll *a*, 1.3×10^{-3} sec [81] to 10^{-3} sec [85] with chlorophyll *b*, and 10^{-3} sec [60,68] with chlorophyll *a* + *b*.

Reversible fading was observed also in frozen solutions of chlorophyll (at -190°) under steady illumination [83]. Here the decrease in absorption in the above regions of the spectrum was accompanied by an increase in the ranges 740–700 and 500–480 mμ.

Similarly, new absorption bands appear in the spectrum of solutions of decolorised chlorophyll during flash illumination (see Fig. 10). Use of lamps giving flashes of duration 10^{-3} sec resulted in quite strong absorption at 525 mμ [81,82,85,86]. With lamps giving shorter flashes, however, new absorption bands were observed, the most intense being at 460 ± 5 mμ with chlorophyll *a*, 480 ± 5 mμ with chlorophyll *b* [84,87,88], and at 460 mμ with pheophytin *b*. [87] Momentary reversible bleaching was found also in both absorption bands (665–680 and 345–360 mμ) with the chlorophyll analogues magnesium and zinc phthalocyanines and metal-free phthalocyanine [60,68],

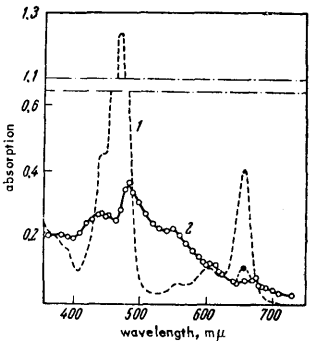

Fig.10. Absorption spectrum of chlorophyll *b*: 1) before flash; 2) after flash from lamp.

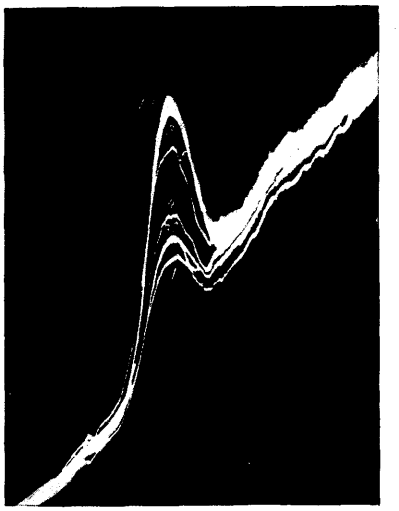

Fig.11. Microdensitometer tracings of absorption spectra of a solution of magnesium phthalocyanine in pyridine. Spectrum from flash lamp at intervals after illumination with lamp No.1: 1) 20 μsec; 2) 50 μsec; 3) 200 μsec; 4) 300 μsec; 5) 800 μsec; 6) 2500 μsec; 7) 4000 μsec; 8) 0.01 sec; 9) 0.1 sec; 10) 1 sec.

and the life of this form (see Fig. 11) was found to be $(0.8-1.0) \times 10^{-3}$ sec. With magnesium phthalocyanine new absorption bands were discovered with maxima at 410 and 400 mμ,[87] and also the appearance of a band at 560 mμ, which is ascribed to a photoreducing form of the pigment in the absence of foreign reducing agents[89]. Phthalocyanines containing copper, iron, or cobalt, as well as iron and copper pheophytinates, did not show reversible bleaching under the influence of light flashes.

Solutions of chlorophyll and magnesium and zinc phthalocyanines in ethanol and acetone showed considerably weaker reversible bleaching in the presence of water than in the dry solvents. It was also found that the long-wavelength absorption bands of the pigments were considerably more intense in the moist than in the dry solvents, in agreement with published data on the action of traces of water on the spectrum of the pigments[83,90]. The converse rule is observed with pyridine, ether, toluene[60,68], and benzene solutions[87].

Momentary reversible decolorisation is observed with pigments in other states of aggregation (frozen solutions at -180°, thin solid films, and adsorbed on silica gel[60,68]).

Reversible fading of the red absorption band of chlorophyll occurs also in homogenised solutions of chloroplasts, and in leaves and algae, in which an intermediate form having an absorption maximum at 525 mμ was detected[91-93].

The suggestion is made in all the papers that the momentary reversible decolorisation of molecules of chlorophyll and its derivatives and analogues under the influence of a high-intensity flash of light is caused by the accumulation of excited molecules in a metastable triplet level. This is also indicated by the fact that oxygen prevents decolorisation, since it strongly deactivates such a state. The presence of a nearby metastable triplet level in the above pigments is indicated by the phosphorescence which has been found in frozen solutions of chlorophyll *a* and *b*,[94-98] and also by the strong quenching effect of oxygen on the fluorescence of the pigments[60,98].

However, the transition of pigment molecules to a metastable triplet state is accompanied by formation of their photoproducts, which have characteristic absorption bands depending on the experimental conditions: 470 mμ with the primary photoreducing form of the pigment, the radical-ion of the semiquinone[99]; and 525 mμ with the secondarily reduced, hydrogenated (semiquinone) form of the pigment[100,101].

The flash spectroscopy of the pigments has enabled the primary photochemical act of photosynthesis accomplished in plants to be established. After having absorbed a quantum of red light, the chlorophyll first passes from an excited to a metastable triplet state possessing greater reactivity and a long life, which determines its chemical properties in the further reactions of photosynthesis.

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OVERLAP INTEGRALS AND APPROXIMATE ESTIMATES OF THE ENERGIES OF CHEMICAL BONDS

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1. INTRODUCTION

Estimation of the strength of a chemical bond constitutes one of the most important problems of theoretical chemistry, since in several cases there are no reliable experimental data on bond energies.

However, quantum-mechanical calculations of these quantities are very complicated, and there is no great certainty that the results obtained are correct. Therefore approximate, semiquantitative calculations, which enable comparative assessments to be made[1], now play a great part in quantum chemistry.

A simple method for the quantum-mechanical estimation of the strength of a chemical bond is the use of overlap integrals. These integrals may also be used to solve several other chemical problems, and we therefore think it necessary to bring them to the attention of a wide circle of chemists.

Overlap integrals are the simplest of all molecular integrals. If the state of an electron in an atom A is described by the wave function χ_A, and that in an atom B by the function χ_B, the overlap integral of these two functions is

$$S_{AB} = \int \chi_A \chi_B \, d\tau. \qquad (1)$$

Integration is carried out with respect to the coordinates of one electron over the whole configurational space. Only non-orthogonal wave functions can overlap, their degree of non-orthogonality being a measure of their overlap; therefore overlap integrals are still termed also "non-orthogonality integrals".

The energy of a bond can be regarded as roughly proportional to the overlap integral[2], since it consists mainly of the exchange energy. If, however, the expression is written down for the exchange integral in the case of the formation of the simplest molecule H_2^+, it is evident that almost all its terms contain overlap integrals as cofactors:

$$H_{12} = H_{21} = \int \chi_A \left(E_0 + \frac{1}{R} - \frac{1}{r_B}\right) \chi_B dr =$$

$$= E_0 \int \chi_A \chi_B dr + \frac{1}{R} \int \chi_A \chi_B dr - \int \chi_A \frac{1}{r_B} \chi_B dr =$$

$$= E_0 S + \frac{1}{R} S - K, \qquad (2)$$

where E_0 is the energy of the hydrogen atom, R the internuclear distance, r_B the instantaneous distance between the electron and the nucleus B, and K the resonance integral.

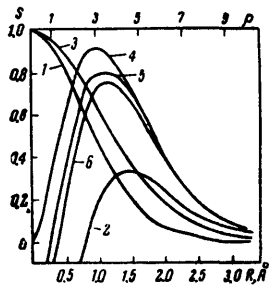
The following semiempirical formula has been suggested for the exchange integral $H_{ij} = \int \chi_a^2 \chi_b^2 (1/r_{12}) d\tau_1 d\tau_2$, which presupposes that the latter is proportional to the overlap integral S_{ij}:

$$H_{ij} = \frac{1}{2} F_x S_{ij} (H_{ii} + H_{jj}), \qquad (3)$$

where H_{ij} and H_{jj} are integrals representing the energy of the electron in the i-th or the j-th orbital in the field of the nuclear skeleton of the molecule and the remaining valence electrons, and F_x is an empirical correction, its value being 1.67 for a σ bond and 2.00 for a π bond[3]. The exchange energy calculated according to this formula agrees well with experimental data for several compounds[3,4].

Hence it can be seen that overlap integrals vary in the *same* sense as exchange integrals, *i.e.* in the *same* sense as the energies of chemical bonds.

However, overlap integrals cannot be "absolute" measures of the energy of a chemical bond or other characteristics of chemical interaction in a molecule. Whether it is more advantageous for the molecular orbital formed by the overlapping of atomic orbitals to be occupied by one or two electrons cannot be determined from an examination of the overlap integrals.



Variation in overlap integrals with change in internuclear distance for various bonds between two carbon atoms: 1) between 2s orbitals; 2) between $2p\sigma$ orbitals; 3) between $2p\pi$ orbitals; 4) on linear hybridisation; 5) on trigonal hybridisation; 6) on tetrahedral hybridisation.

Therefore all conclusions based on the change in value of the overlap integrals are usually valid only for sufficiently similar compounds. Here we can detect several interesting regularities and make some predictions. But caution must be exercised in transferring all this to other compounds.

In the calculation of overlap integrals, atomic orbitals are most often taken in the form of Slater functions. Exact expressions for atomic orbitals, obtained by the self-consistent field method, are employed only for rigorous calculations. The Slater orbitals have the following form

$$\chi_A = Y(\theta, \varphi) r^{n-1} e^{-\frac{Z'}{n'} r}, \qquad (4)$$

where $Y(\theta, \varphi)$ is the angular function, and Z' and n' are the effective charge and the effective quantum number calculated according to definite rules[5]. Calculation of overlap integrals presents no difficulty if χ_A and χ_B are taken to have the form (4), since detailed tables exist for computing the expressions resulting from the integration[5]. There are also special tables of overlap integrals, which are very convenient to use[6,7]. The integrals are tabulated in the form of functions of two parameters depending on the internuclear distance (R) and the difference in electronegativity between the interacting atoms. These parameters are denoted by ρ and t:

$$\rho = \frac{1}{2} \frac{R}{a_H} (\mu_A + \mu_B); \quad t = \frac{\mu_A - \mu_B}{\mu_A + \mu_B}; \quad \mu = Z'/n', \qquad (5)$$

where a_H is the Bohr radius.

An overlap integral is a function which depends on the form of the atomic orbitals, the internuclear distance, and the parameter t. Such integrals vary between 0 and +1 or -1†. With increase in R they fall off very rapidly to zero. Increase in the parameter t in the positive or the negative direction also markedly diminishes the value of the overlap integral, maximum overlap occurring when $t = 0$. The overlap of the orbitals depends also on the type of bond – σ, π, or δ – formed between them. The Figure illustrates the overlap integrals for various bonds.

† The overlap integral can be negative when the positive part of one atomic orbital overlaps the negative part of the other. This occurs, for example, in the formation of σ bonds from p or f orbitals, in which positive and negative lobes are oriented in opposite directions along the line of the bond.

When the overlap integral is used as a criterion of bond strength, it is usually assumed that a σ bond is sufficiently strong if its overlap integral is about 0.4. The overlap integrals for π and δ bonds have values of at least 0.2.

2. ESTIMATION OF CHEMICAL BOND STRENGTH BY MEANS OF OVERLAP INTEGRALS

Pauling's well-known criterion of bond strength starts from the postulate that the radial parts of the wave functions involved in bond formation are equivalent. It is formulated thus: "... for s-p hybridisation the bond energy is closely proportional to S^2, with S the magnitude of the angular part of the bond orbital in the bond direction"[2].

The overlap integral is a clearer criterion of chemical bond strength, since it takes into account the overlap in both angular and radial parts of the atomic orbitals, and is furthermore a function of the interatomic distance, which allows the variation in energy with change in distance to be assessed. Therefore the overlap integral is a more precise measure of the strength of a chemical bond.

A systematic comparison of overlap integrals with energies and other properties of chemical bonds was first undertaken by Mulliken and his collaborators[8] using data on simple compounds of elements in the short periods of Mendeleev's system.

Mulliken uses, in addition to overlap integrals, the concept of the reduced internuclear distances ξ, defined by the relation: $\xi = R/(r_A + r_B)$. On putting $r = n' a_H/\mu$, we obtain, when $n'_A = n'_B = n'$, $\xi = (1 - t^2)\rho/2n'$, where n', μ, ρ, and t have the same significance as in Eqns. (4) and (5), a_H being the Bohr radius. If the Slater orbitals represent correctly the actual motion of the electrons, $\xi = 1$ should correspond to the maximum bond strength at the equilibrium distance. Hence ξ also may be a characteristic of the chemical bond, but it is cruder than the overlap integral, since it takes account only of the radial overlap. The greater is ξ, the smaller is the overlap integral.

Table 1 compares values of R, ξ, and overlap integrals for several homopolar bonds between atoms of elements in the Short Periods I and II (according to Mulliken).

These data show that, in agreement with Pauling's criterion, the overlap integrals for the hybrid sp orbitals are larger than those for the purely s and p orbitals. On the other hand, the overlap integrals are larger for $s-s$ bonds than for $p-p\sigma$ bonds (apart from O_2 and F_2, in which ρ is very large); this contradicts Pauling's criterion, according to which a $p'-p\sigma$ bond is always more stable than an $s-s$ bond by a factor of $\sqrt{3}$. The overlap integrals for linear and trigonal hybridisation are larger than that for tetrahedral hybridisation (according to Pauling the converse should be true). This is confirmed by data on the C–H interatomic distances in ethane, ethylene, and acetylene, which are 1.11, 1.07, and 1.06 Å respectively[9]. With low values of ρ, the overlap integral is greater for $p\pi$ bonds than for $p\sigma$ bonds, because in this case the Slater $p\pi$ orbitals are more exact than the $p\sigma$-orbitals, and therefore the general variation of the overlap integrals for the $p\sigma$ bonds is somewhat distorted‡. The value of ξ increases monotonically with increase in atomic number, the greatest

‡ This provides an example of the inexactness of the Slater functions, showing clearly that they must be used with caution, as otherwise it might be wrongly concluded that in a multiple bond the π component is stronger than the σ component.

TABLE 1.

Bond	R, Å	ξ	Overlap integrals for various bonds (at t = 0)					
			s−s	pσ−pσ	pπ−pπ	hybridisation: linear sp	trigonal sp^2	tetrahedral sp^3
H—H	0.74	0.70	0.75					
Li—Li	2.67	0.82	0.59	0.05	0.55			
B—B	1.52	0.94	0.50	0.30	0.33		0.80	
B=B	1.76	1.08	0.40	0.33	0.24		0.74	
B=B⁻	1.92	1.02	0.44	0.32	0.28			0.73
C≡C	1.21	0.93	0.54	0.29	0.33	0.88		
C=C	1.34	1.03	0.44	0.32	0.27		0.77	
C—C	1.54	1.18	0.34	0.33	0.19			0.65
N≡N	1.095	1.01	0.45	0.32	0.28			
N=N	1.24	1.15	0.36	0.33	0.22			
N—N	1.47	1.36	0.25	0.29	0.13			
O=O	1.21	1.30	0.28	0.31	0.15			
O—O	1.47	1.58	0.16	0.23	0.07			
F—F	1.435	1.77	0.11	0.17	0.05			
Na—Na	3.08	0.87	0.48	0.03	0.58			
Al—Al	2.50	1.08	0.32	0.33	0.35			
Si=Si	2.04	1.03	0.35	0.30	0.371			
Si—Si	2.32	1.17	0.26	0.37	0.28			
P≡P	1.89	1.10	0.31	0.36	0.31			
P—P	2.20	1.28	0.20	0.38	0.21			
S=S	1.89	1.24	0.23	0.38	0.22			
S—S	2.10	1.38	0.16	0.36	0.16			
Cl—Cl	1.99	1.281	0.21	0.291	0.101			

deviations in its value from unity being observed with O_2, F_2, Cl_2, and S_2.

Mulliken found similar relations for heteropolar bonds, with the difference that the overlap integral in this case depends on the parameter t, which is roughly proportional to the electronegativity difference $\varkappa_A - \varkappa_B$. We shall not give these results, since they do not differ fundamentally from the data in Table 1.

Overlap integrals make it possible to estimate the interaction between electrons in different orbitals. Table 2 gives values of the integrals for the P—O bond (R = 1.64 Å) for phosphorus and oxygen orbitals having different quantum numbers.

As can be seen from Table 2, the overlap integral between a valency orbital of one atom and an inner orbital of another may be as much as 10% of the overlap integral of the valency orbitals, which must be taken into account in the more exact quantum-chemical calculations. Nevertheless, the overlap between two inner orbitals of the interacting atoms is very slight. Thus the overlap integrals for 1s orbitals in the bonds Li—Li, C=C, and F—F and for 2s, $2s'-2p\sigma$, and $2p\pi-2p\pi$ orbitals in the Na—Na, Si=Si, and Cl—Cl bonds are almost zero. Finally, the overlap integrals show that the overlap in ionic bonds is negligible (in the NaF molecule the overlap integral for the $2s-2p\sigma$ orbitals is 0.019).

Overlap integrals allow an estimate to be made of the relative strength of bonds in molecules in which not all the bonds are equivalent. In the PCl_5 and PF_5 molecules, which have the structure of a trigonal bipyramid, for example, the P—X bonds in the direction of the principal axis of symmetry are found to be weaker than the equatorial bonds[10]. This result does not contradict experimental data on the interatomic distances and the frequencies of P—X stretching vibrations in these molecules. Use of Pauling's criterion to assess the relative strength of the bonds in these molecules led to the opposite result, which did not agree with the experimental data.

For the direct estimation of the energy of a chemical bond Mulliken suggested the so-called "magic formula"[11], which for a polyatomic molecule can be written in the form:

$$D_0 = \sum X_{ij} - \frac{1}{2}\sum Y_{kl} + \frac{1}{2}\sum K_{mn} - P + E_R, \qquad (6)$$

where ΣX_{ij} is the exchange energy over all bonding pairs of electrons, ΣY_{kl} and ΣK_{mn} represent the energy of non-bonding pairs of electrons (the term with the minus sign represents repulsion, and that with the plus sign attraction), P is the energy of promotion, *i.e.* the energy required to transfer the electrons of an atom to the valency state, E_R the energy of ionic interaction, and D_0 the dissociation energy of the molecule (disregarding zero-point vibrations).

This formula is a generalisation of formulae for simple molecules (such as H_2^+, H_2, He_2^+), which result from calculations by the molecular orbital or valence bond methods. As already state, exchange integrals are usually proportional to overlap integrals. Furthermore, the exchange energy is proportional to the ionisation potential of the valence electron. This makes it possible to write the following approximate expression for the term X_{ij}:

$$X_{ij} = A_j S_{ij} \bar{I}_{ij} / [1 + S_{ij}] \qquad (7)$$

where $\bar{I}_{ij}$ is the mean ionisation potential, S_{ij} the overlap integral, and A_j an empirical parameter whose value is 0.65 for $s-s$ bonds, 1.0 for most σ bonds, and 1.5 for π bonds.

The electron—electron repulsion energy Y_{kl} can also be expressed in terms of an overlap integral and an ionisation potential

$$Y_{kl} = \nu A_k S^2 \bar{I}_{kl}, \qquad (8)$$

where ν is an empirical parameter.

Eqns. (7) and (8) give quite good agreement for the simplest molecules. Thus the dissociation energy of H_2 calculated according to Eqn. (7) is 4.07 eV, which is less than the experimental value by only 0.69 eV. Table 3 shows the variation in the electron—electron repulsion energy for two

TABLE 2

Overlap of outer orbital of one atom with inner orbital of the other for the P—O bond				
Overlapping orbitals	$2s_P - 2s_O$	$2s_P - 2p\sigma_O$	$2p\sigma_P - 2p\sigma_O$	$2p\pi_P - p\pi_O$
Overlap integral	0.017	0.029	0.022	0.004
Overlap of outer orbitals for the P—O bond				
Overlapping orbitals	$3s_P - 2s_O$	$3s_P - 2p\sigma_O$	$3p\sigma_P - 2p\sigma_O$	$3p\pi_P - 2p\pi_O$
Overlap integral	0.24	0.20	0.23	0.14

TABLE 3.

R/a_H	2.01	2.51	3.01	4.01	5.01
Overlap integrals	0.275	0.161	0.091	0.049	0.0075
Y_{kl} from Eqn. (8)	2.61	0.85	0.77	0.01	0.0018
Y_{kl}, theoretical	2.31	0.81	0.26	0.025	0,0023

TABLE 4.

Molecule	Optimum effective Z	D, kcal	
		from Eqn. (9)	expt.
H_2	0.611	98.0	109.8
Li_2	1.30	26.2	26.0
Na_2	1.88	18.2	17.0
K_2	2.13	14.8	12.0

He atoms calculated by means of Eqn. (8). The agreement with more rigorous theoretical calculations is quite satisfactory [8].

In order to calculate for more complicated molecules, all the terms in the "magic formula" must be taken into account, and variable parameters must be introduced. Mulliken calculated from Eqn. (6) the dissociation energy of the molecules CH, O_2, N_2, F_2, Li_2, CH_4, C_2H_6, C_2H_4, and C_2H_2. By a suitable choice of coefficients, satisfactory results were obtained. It must be especially emphasised that, if calculations are being applied to a new type of compound, the "magic formula", like other similar formulae, cannot give *a priori* any certainty that the results obtained are correct. This formula has not, therefore, been widely used.

Still simpler formulae can be chosen. For example, we suggest the following:

$$D = \left(\frac{Z^2}{R} - \frac{2ZS}{(1+S)^2}\right) \times n^{-2}, \qquad (9)$$

where n is the principal quantum number, the term Z^2/R represents repulsion between atoms, and the second term represents exchange interaction. Eqn. (9) does not give sufficient weight to repulsion between inner electrons, and therefore it, too, is unsuitable for "absolute" calculations, but represents the variation in energy in a series of similar compounds quite correctly, especially if the effective charge Z is varied. Table 4 gives dissociation energies for molecules of the alkali metals which we have calculated from Eqn. (9).

It is evident from the above that calculations based on simplified formulae using only overlap integrals cannot give good quantitative results even for comparatively simple compounds, let alone complicated compounds. But they can be employed relatively successfully for the qualitative assessment of the properties of chemical compounds.

3. USE OF OVERLAP INTEGRALS TO EXPLAIN THE PROPERTIES OF COMPOUNDS CONTAINING *d* ELECTRONS

Compounds of the transition metals having valence *d* electrons are of considerable interest to chemists, and we shall therefore discuss the application of overlap integrals to these compounds separately.

A good example of how the overlap integral and the "magic formula" enable a qualitative explanation to be given of the properties of molecules is provided by the work of Jaffé and Doak on the stability of organometallic compounds [12]. They compared values of the overlap integrals and the mean ionisation potentials for the element–carbon (E–C) bonds, and also values of X_{ij}, which represents the exchange energy in the magic formula, calculated by means of Eqn. (7). On comparing these quantities and also values of the ionic interaction energy $E_{\overline{IR}}$, it is possible to divide metals into three groups according to their ability to form bonds with carbon, as can be seen from Table 5.

The following conclusions can be drawn from Table 5. The metals Na, Mg, and Al should give quite strong M–C bonds, since the corresponding overlap integrals are quite large, and the term X_{ij}, representing the exchange energy, is very considerable. However, this applies also to the non-metals of this period, Si, P, Cl, and S, with the difference that with them the E–C bonds should be still stronger.

Metals of a transition period should not form stable bonds with carbon, since S_{ij} and X_{ij}/A are considerably smaller with them. The ionic interaction energy is also low.

The metals Zn, Ga, and Ge and non-metals As, Se, and Br should give stable organometallic compounds, the bonds they form with C being almost completely covalent.

The metals K and Ca, it would seem, should not form M–C bonds, since their overlap integrals and X_{ij} are of the same order as with the transition metals. But the organometallic compounds of these metals are quite stable. This is because in this case the M–C bond is to a considerable extent ionic, since the term $E_{\overline{IR}}$, representing the ionic interaction energy, is quite large. All these conclusions are confirmed by experiment§.

Overlap integrals are of great help in ascertaining the role of *d* electrons in simple and multiple bonds. Pauling's criterion shows that *d* orbitals should give more stable bonds than do *s* or *p* orbitals, since they are more concentrated in definite directions. The overlap integrals, which take into account the radial components, give a more

TABLE 5.

Elements	Mean overlap integral	Mean ionisation potential, $\overline{I}$	Exchange energy, X_{ij}/A	Ionic interaction $E_{\overline{IR}}$
Na	0.397	5.11	2.67	4.0
Mg, Al, Si, P, S, Cl	~0.4—0.6	~6—10	~3.6—5.7	~2.6—0.0
K	0.145	4.32	1.14	4.41
Ca	0.244	6.09	1.94	3.42
Sc, Ti, V, Cr, Mn, Fe, Co, Ni, Cu	~0.3—0.4	~6—7.5	~2.5—3.0	~0.5—0.6
Zn, Ga, Ge, As, Se, Br	~0.5—0.6	~8—11	~4	~0.5—1.0

§ We have been speaking throughout of an M–X bond; if, however, the bonding molecular orbitals are formed by *d* orbitals of a transition metal and π orbitals of the ligands, such organometallic compounds may be very stable, for example the various "metallocenes". The above considerations are not applicable to such compounds, for they contain no localised M–C bonds.

precise answer. This is especially important with multiple bonds, to which Pauling's criterion is not applicable.

By means of overlap integrals Jaffé [13] showed that d electrons can form not only σ and π but also δ bonds, with overlapping of all four lobes of each d orbital.

In complexes, π and δ bonds are found quite often, and their reality is demonstrated by the shortening of the interatomic distance and by calculation of the corresponding overlap integrals. In the $[OsNCl_5]^{2-}$ ion, for example, the Cl atom located *trans* to the nitrogen atom is linked with the osmium by a δ bond, which shortens the Os–Cl distance by 0.27 Å. [14,15] The overlap integral of this δ bond is about 0.20. The δ bond is formed from a d_{xy} orbital of the Os occupied by a pair of electrons and a free d_{xy} orbital of the *trans* Cl atom, belonging to the same point group.

The overlap integrals show that multiple bonds are more advantageous in an octahedron and a square than in a tetrahedron, since in this last case they are conjugated to a less extent. This results in a decrease in the total overlap in the tetrahedron of 20% compared with the square and the octahedron (for molecules having the same ligands [13]).

Overlap integrals can be used also in discussing compounds having f electrons. Coulson and Lester compared the overlap integrals of the p, d, and f orbitals of uranium with NO_3^- groups in the $[UO_2(NO_3)_6]^{4-}$ ion, and showed that participation of f electrons is necessary for the formation of molecules having D_{6h} symmetry [16].

Examination of the overlap integrals between various orbitals of uranium and oxygen in the uranyl ion UO_2^{2+} leads to the conclusion that the d orbitals of uranium may form σ and π bonds with the oxygen atoms, whereas such bonds involving f electrons should be far weaker [17].

In computing overlap integrals involving d orbitals it is important to determine correctly the effective charges for d electrons, since Slater's rules often do not give good results, especially with elements of Short Period III. Several modifications of these rules exist which give better results [18]. In comparing overlap integrals for different bonds, it is necessary that the effective charges should be computed according to the same rules, as otherwise the results will not be comparable.

4. DETERMINATION OF THE AMOUNT OF IONIC CHARACTER IN BONDS BY MEANS OF OVERLAP INTEGRALS

Overlap integrals can provide quite a convenient measure of the ionic character of a polar bond. Let us consider the ratio of such an integral in a real molecule to that in a hypothetical comparison molecule: *i.e.* let us compare the real molecule with a molecule consisting of the same atoms for which $t = 0$ (the bond is assumed to be ideally covalent), while the internuclear distance is the sum of the covalent radii of the atoms forming the bond. The "degree of ionisation" i of bonds involving s or p electrons is determined from the equation

$$i = 1 - \frac{\sum A_j S_j - \frac{1}{2}\sum A_{j'}(S_{j'})^2 + 0.82\sum S_k}{\sum A_j S'_j - \frac{1}{2}\sum A_{j'}(S'_{j'})^2 + 0.82\sum S'_k}, \qquad (10)$$

where A has the value 1 for S_{s-s}, 1.72 for $S_{s-p\sigma}$ and $S_{p\sigma-p\sigma}$, and 0.82 for $S_{p\pi-p\pi}$. The term $\frac{1}{2}\Sigma A_{j'}(S_{j'})^2$ represents the repulsion of non-binding electrons. The numerator relates to the real molecule, and the denominator to the comparison molecule.

By this method Batsanov and Durakov calculated the degrees of ionisation of the bonds in 32 hydrides and halides [19]. They obtained results which agreed quite well with those obtained from measurements of the dipole moments [20].

5. USE OF OVERLAP INTEGRALS TO DETERMINE THE MOST ADVANTAGEOUS HYBRIDISATION OF ATOMIC ORBITALS IN A MOLECULE

The most widespread method for determining hybrid orbitals as a linear combination of the original atomic orbitals consists in finding the angles θ and φ at which the value of the function is a maximum. The atomic orbitals are selected according to the symmetry of the molecule [21], the difference in the radial components of the orbitals being neglected.

Overlap integrals permit a more objective assessment of the most advantageous hybridisation in any actual compound, since they take into account not only differences in angular and radial components of the atomic orbitals but also the interatomic distances in the molecule.

How the radial components of the Slater s, p, and d orbitals can differ may be shown by two examples. With nickel ($3d^94p$) the maximum value of the radial component for the $3d$ orbital is at 1.25 atomic units, while for the $4s$ or $4p$ orbitals it is at 3.7 atomic units. With sexivalent sulphur ($3s3p^33d^2$) the maximum values of the radial components are 1.46 and 5.45 atomic units for the $3p$ ($3s$) and $3d$ orbitals respectively [22].

Overlap integrals give different relations for the relative stabilities of various configurations from those given by the Pauling criterion based on the maximum values of the angular components of hybrid functions. According to Pauling, the octahedral configuration d^2sp^3 should be more stable than the tetrahedral sp^3 by a factor of 1.5, and than the square sdp^2 by a factor of 1.2. The square configuration should be more stable than the tetrahedral by a factor of 1.35.

Calculation of the overlap integrals for nickel compounds with $\rho = 6.0$ and $t = 0$ shows the octahedral configuration to be more stable than the tetrahedral by only 15%, and than the square by 10%. The variation in the overlap integrals with different values of ρ and t shows that the overlapping of the hybrid orbitals of nickel with the orbitals of the ligands is in most cases the same in different molecular configurations [22]. This, however, occurs also with compounds of other elements.

In conclusion, let us consider the possibility of constructing hybrid orbitals taking into account their maximum overlap with the orbitals of the ligands [23]. This method, which can be termed the "maximum overlap method", gives a set of bonding and non-bonding hybrid orbitals in the form of a linear combination of atomic orbitals for the given molecular configuration.

Let us consider a molecule MX_k. Let us represent the valence orbitals of the central atom by Φ_1, Φ_2, ..., Φ_n, and those of the ligands by Θ_1, Θ_2, ..., Θ_n ($n \geqslant k$). We try to

find hybrid orbitals of M in the LCAO form¶: $\Psi_j = \sum_{i=1}^{n} a_{ij}\,\Phi_i$ such that the sum of the overlap integrals of all the resulting hybrid orbitals with the corresponding orbitals of the ligands

$$\sum_{i=1}^{k} \langle \Psi_i \Theta_i \rangle = \sum_{i=1}^{k} \sum_{j=1}^{k} a_{ij} \langle \Phi_i \Theta_i \rangle$$

should be a maximum.

First we consider the overlap of all the valence orbitals of the central atom with all those of the ligands which can form bonds with the central atom. Then the set of linear equations is solved to find the coefficients for bonding and non-bonding orbitals taking into account their normalisation and mutual orthogonality. The number of equations depends on the number of bonds in the molecule and on the number of valence orbitals of the central atom.

In the ClF_3 molecule, for example, the chlorine atom has nine valence orbitals, comprising one s, three p, and five d orbitals, occupied by seven electrons. The molecule has a T-shaped structure (symmetry C_{2v})[24]. Of these seven electrons, three take part in forming three σ bonds with three fluorine atoms, while the remaining four occupy in pairs two non-bonding σ orbitals which are orthogonal to all the bonding orbitals. The overlap matrix for this molecule is as follows (disregarding the difference in the radial components of the sp and d orbitals of the chlorine).

$R =$

	Θ_1	Θ_2	Θ_3
s	1	1	1
p_z	$\sqrt{3}$	0	0
p_x	0	$\sqrt{3}$	$-\sqrt{3}$
d_{z^2}	$\sqrt{5}$	$-1/2\sqrt{5}$	$-1/2\sqrt{5}$
$d_{x^2-y^2}$	0	$1/2\sqrt{15}$	$-1/2\sqrt{15}$
p_y	0	0	0
d_{xy}	0	0	0
d_{xz}	0	0	0
d_{yz}	0	0	0

Inspection of this matrix shows that the overlap of the p_y, d_{xy}, d_{xz}, and d_{yz} orbitals of the chlorine with all the ligands is zero; hence they are not involved in forming hybrid bonding orbitals. The p_z, p_x, d_{z^2}, and $d_{x^2-y^2}$ orbitals of the chlorine can take part in the formation of σ bonds.

Five linear combinations are formed from these five orbitals. Three of them will be bonding σ orbitals, and two non-bonding. The latter are found from the condition of minimum overlap with all the fluorine atoms. The three bonding σ orbitals are then constructed, orthogonal to the non-bonding orbitals. The last stage of the calculations by the maximum overlap method consists in finding those linear combinations of bonding orbitals which would have maximum overlap with all the ligands.

The calculation shows that these three best hybrid σ orbitals of Cl, corresponding to maximum overlap with all the p orbitals of the F atoms, are as follows[23]

$$\psi_1 = 0.385s + 0.588p_z + 0.708d_{z^2} + 0.089d_{x^2-y^2},$$

$$\psi_2 = 0.708p_x + 0.316s + 0.039p_z - 0.278d_{z^2} + 0.568d_{x^2-y^2},$$

$$\psi_3 = -0.708p_x + 0.316s + 0.039p_z - 0.278d_{z^2} + 0.568d_{x^2-y^2},$$

One electron from the Cl atom and one from each of the F atoms are placed in each of these three orbitals, which yields three σ bonds.

The value of the method consists in the fact that it enables us to find the orbitals which are most advantageous from the point of view of their maximum overlap, not for an abstract configuration but for an actual molecule, taking into account its structure, interatomic distances, and effective charges on the atoms.

Molecular orbitals found by the maximum overlap method are no less accurate than those calculated with self-consistency, provided that proportionality between overlap and exchange integrals is observed[25]. In general they can be successfully employed as starting orbitals for further calculations by the self-consistent field method.

Recently the maximum overlap method has been generalised by replacing the condition that the sum of the overlap integrals should be a maximum by the condition that the sum of their squares should be a maximum[25,26]. This general statement of the problem does not require proportionality to be postulated between the total energy of the molecule and the overlap. However, additional data are then required on the relation between energy and overlap, which considerably diminishes the practical value of the method.

On the assumption of proportionality between energy and overlap, both maximum conditions (of the sum or of the sum of the squares of the overlap integrals) yield identical results.

¶ LCAO = linear combination of atomic orbitals.

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